Amar Safdar *Editor*

Principles and Practice of Cancer Infectious Diseases

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Editor

Principles and Practice
of Cancer Infectious Diseases

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This book is dedicated for promoting excellence in care and well-being for the patients with cancer.

Preface

Patients with cancer are highly susceptible to infections. These infections are inclined to be difficult to prevent, diagnose, and treat. There are a variety of reasons for this which will be discussed in detail in the chapters of this book. The intent for this book is to provide a comprehensive review of the ever changing spectrum of the management of infectious diseases in this complex population of patients. The changes in patient demography, near-constant global migration of contagious infections, emerging resistance to standard antimicrobial therapy, and the impact of expanding repertoire of antineoplastic therapies including the anticancer biologics and stem cell transplantation have influenced these changes. This book will provide a detailed guide for assessment of risk factors for various infections, evaluating prognosis among susceptible oncology patients with complex issues related to management of opportunistic infections. Strategies to promote hosts' immune response underscore the future measures based on perspicacious insight in the disease pathogenesis; interaction between the pathogen and host's immune function and inflammatory response are given prominent discussion throughout the book. I hope the reader will become acquainted with common and less often encountered infections and importantly, develop a keen knowledge of conditions that might be mistaken as infectious diseases in patients undergoing treatment for neoplastic diseases.

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Part I
Overview and Special Population

Chapter 1
Infections in Patients with Cancer: Overview

Amar Safdar, Gerald Bodey, and Donald Armstrong

Abstract Patients with neoplastic disease are often highly susceptible to severe infections. The following factors influence the types, severity, and response to therapy of these infections: (1) Changing epidemiology of infections; (2) cancer- and/or treatment-associated neutropenia; (3) acquired immune deficiency states such as cellular immune defect; (4) recent development of new-generation diagnostic tools including widely available DNA amplification tests; (5) effective intervention for infection prevention; (6) empiric or presumptive therapy during high-risk periods; (7) availability of new classes of highly active antimicrobial drugs; (8) strategies to promote hosts' immune response; and (9) future measures. This introductory chapter intended for the reader to become familiar with the important historical milestones in the understanding and development in the field of infectious diseases in immunosuppressed patients with an underlying neoplasms and patients undergoing hematopoietic stem cell transplantation.

Keywords Cancer • Infection • Neutropenia • Immune defects • Diagnosis • Therapy

Patients with neoplastic disease are often highly susceptible to severe infections. These are inclined to be difficult to prevent, diagnose, and treat. There are a variety of reasons for this which will be discussed in detail in the chapters of this book. We will introduce this volume by reviewing the history and background of such infections, where we believe major advances have been made and what we believe will be necessary to effectively prevent and manage such infections in the future. The following factors influence the types, severity, and response to therapy of these infections: (1) Changing epidemiology of infections; (2) cancer- and/or treatment-associated neutropenia; (3) acquired immune deficiency states such as cellular immune defect; (4) recent development of new-generation diagnostic tools including widely available DNA amplification tests; (5) effective intervention for infection prevention; (6) empiric or presumptive therapy during high-risk periods; (7) availability of new classes of highly active antimicrobial drugs; (8) strategies to promote hosts' immune response; and (9) future measures.

Historical Perspective

The introduction of chemotherapeutic regimens has expanded the population at risk, since many of these agents affect host defenses, most often causing neutropenia. However, even in acute leukemia, the malignancy with the highest frequency of infection, very little was published about infectious complications until the second half of the twentieth century. The paucity of published data is illustrated by a book on acute leukemia, published in 1958, which made no mention of infectious complications [1]. Indeed, at that time, some physicians attributed fevers in leukemia patients to a general hypermetabolic condition caused by the neoplasm.

By the 1950s, several antineoplastic agents became available which caused at least transient improvement in some malignant diseases. Nitrogen mustard caused responses in Hodgkin disease, aminopterin caused responses in acute leukemia, and methotrexate cured choriocarcinoma in women. The subsequent use of multiple drug combinations in acute lymphocytic leukemia and Hodgkin disease represented major advances [2]. Another important advance was the use of platelet transfusions to control and prevent hemorrhage in acute leukemia patients with thrombocytopenia [3]. In an autopsy study, the frequency of hemorrhage as a cause of death in acute leukemia patients decreased from 67 to 37% due to the use of platelet transfusions [4]. Unfortunately, infection remained a major cause of death. There have been many reviews of the subjects over the years, some with international contributors and continuity which are references here [5–11].

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Epidemiological Factors

Exposures to organisms in the distant as well as recent past should be considered in patients with neoplastic disease. Latent infections may be activated in the presence of waning immunity whether it be due to the disease itself or to the treatment. The classic example of this is reactivation of latent tuberculous in patients with treatment-induced helper T-cell dysfunction. Additional latent infections which may be activated, for example, are histoplasmosis, coccidiomycosis, disease caused by the Herpes group of viruses, toxoplasmosis, strongyloidiasis, and others. These demand consideration and many such as TB, herpes simplex, and strongyloidiasis can be effectively treated prophylactically. Recent travel or residence and hospitalization may expose patients to organisms which may incubate such as malaria after travel to an endemic area or colonization due to drug-resistant bacteria such as *Klebsiella*, *Pseudomonas,* and *Stenotrophomonas* species acquired during a previous hospitalization. Questions to investigate epidemiologic factors should include exposures at home along with work, habits, and hobbies. Also, a detailed history of recent and remote travel and recreational activities may provide clues for an otherwise improbable diagnosis. All of these can be a source of infection, some of which can be avoided with appropriate patient education.

Hosts' Susceptibility

It is not surprising that the frequency of infection is related to the type of underlying malignancy and most infections occur in patients who are failing to respond to their cancer therapy. Surveys in the 1960s found that about 80% of patients with acute leukemia, 75% with lymphoma, but less than 40% of patients with metastatic carcinoma developed infection [12, 13]. There are a wide variety of factors that may impact on the susceptibility of cancer patients to infection [11]. Local factors such as tumor masses that may obstruct the bronchial tree or urinary tract and necrotic tumors in the gastrointestinal tract can result in infection. In an autopsy study of children with metastatic carcinoma, 80% of cases of pneumonia were associated with pulmonary metastases, aspiration, or tracheostomy [14]. Antibiotic therapy is often of limited efficacy in these types of tumors, unless the local predisposing factor can be removed.

Immunological Factors

Neutropenia is the most important predisposing factor and can be due to the disease or its therapy. While there were some reports of the role of neutropenia in infection, a detailed

analysis of 52 patients with acute leukemia was published in 1966 [15]. This study demonstrated that the risk of infection was related to the degree and duration of neutropenia. The risk increased when the neutrophil count was less than 1,000/mm^3, but increased substantially when it was below 500/mm^3. Also, the risk of developing infection increased the longer the duration of neutropenia. One hundred percent of episodes of severe neutropenia (<100 PMN/mL) lasting 3 weeks or longer were accompanied by identifiable infection compared to 65% of episodes lasting one week. Neutropenia diminishes the likelihood of detecting characteristic manifestations of infection. One study compared physical findings of infection in a group of patients with severe neutropenia with a group with adequate neutrophil counts [16]. Only 8% of patients in the former group with pneumonia were able to produce purulent sputum compared to 84% in the latter group. Similarly, among patients with urinary tract infections, pyuria was found in 11 and 97%, respectively. In an autopsy study, it was demonstrated that many pulmonary infections were not detected on routine chest radiographs antemortem [17]. Likewise, among patients with gram-negative bacillary pneumonia, 85% of those with initially abnormal chest radiographs had >1,000 neutrophils/mL, whereas 81% with normal roentgenograms had <1,000 neutrophils/mL [18]. The lack of signs of infection in febrile neutropenic patients impairs the physician's ability to determine whether or not fever is due to infection. In one study of fever in neutropenic patients, physicians were required to conclude whether infection was present or not before instituting therapy [19]. The physician's initial diagnosis (infection or fever of unknown origin) was incorrect in 33% of the cases.

White blood cell (WBC) transfusions were initiated in an effort to improve the outcome of infections in severely neutropenic patients. Since it was difficult to collect sufficient neutrophils from normal donors, initially, patients with chronic myelogenous leukemia with high neutrophil counts were used as donors [20]. Later, the development of the continuous cell separating machine made it possible to collect adequate cells from normal donors [21]. Studies demonstrated that there was a direct relationship between the number of cells transfused and the increment in the recipient's neutrophil count. In one study of 128 neutropenic patients who had fever unresponsive to antibiotic therapy, 49% responded after WBC transfusions, including patients with pneumonia and gram-negative bacillary septicemia [22]. Unfortunately, potential adverse effects occurred in some recipients. In one study when WBC transfusions were administered with amphotericin B, 64% of patients developed acute dyspnea, respiratory deterioration, and new pulmonary infiltrates compared to only 6% of patients who did not receive amphotericin B [23]. Several other studies failed to observe this toxicity. Another potential adverse event primarily for bone marrow transplant recipients was

acquisition of cytomegalovirus (CMV) infection [24]. Reports of graft-versus-host disease (GVHD) in a few recipients has led to routine irradiation transfused cells, but questions have been raised about adverse effects of radiation on the function of the transfused neutrophils. In a review of seven prospective randomized trials of WBC transfusions in neutropenic patients with infection, it was concluded that the transfusions were of some benefit in five studies but the number of patients in each study was small [25]. A problem with many was the ignoring of the number of neutrophils administered; hence, some patients received an inadequate dose. The use of WBC transfusions diminished by the 1980s because there was inadequate evidence of their efficacy from prospective comparative studies. However, there has been a resurgence of interest in increasing available neutrophils since recombinant myeloid growth factor granulocyte-colony-stimulating factor (G-CSF) has become available. Administration of G-CSF to donors improves the number of neutrophils collected as well as increases their activity against infection [26].

Protected Environment. Because of the risk of infection during periods of chemotherapy-induced neutropenia, efforts were made to provide a sterile environment for these patients. The first type of unit was a bed surrounded by a plastic canopy with filtered air (Fig. 1.1). Later, laminar air flow rooms were designed [27]. These units provided filtered air, sterile water supply, sterile room, specially prepared food, and toilet facilities. The patients were given specifically prepared "sterile" food and prophylactic oral and topical antibiotics. These rooms, air, food, and patients were carefully monitored for microbial contamination [28, 29]. The program reduced the frequency of infection and permitted the use of more

intensive chemotherapy in the premyeloid growth factor era. Unfortunately, more intensive chemotherapy in this setting did not result in higher remission rates for several malignancies including acute leukemia [30], lymphoma [31], and sarcoma [32]. One review of protected environment entitled "Protected Environment are discomforting and expensive and do not offer meaningful protection" summarized the discussion as follows "The one constant in almost every controlled study is that life has not been prolonged, remission induction increased, nor remission prolonged" [8].

In the late 1940s and early 1950s, patients with neoplasms were originally found to be infected with organisms from the flora in their nasopharynx and the gastrointestinal tract due to neutropenia caused by their disease or subsequent therapy. Exceptions were those with cellular immune defects due to the neoplasm such as Hodgkin's disease, who might present with cryptococcosis or those with multiple myeloma who might present with pneumococcal septicemia because of their decreased production of normal immune globulins. In the neutropenic patient, the organisms invading from the nasopharynx were usually *Streptococcus pyogenes* or *Staphylococcus aureus* (penicillin susceptible). From the orointestinal tract, *Escherica coli* and *Klebsiella* or *Proteus* species were responsible; these bacteria were sensitive to most available antibiotics during early 1950s. Gradually, but steadily, resistance developed in most of the organisms except *S. pyogenes*. *S. aureus* resistant to penicillin and *Pseudomonas aeruginosa* resistant to all antimicrobials except polymyxin appeared in the late 1950s [4, 33, 34]. Antimicrobial resistance developed over the years among the orointestinal isolates and the Gram-positive cocci increased to become predominate by the 1980s with MRSA and penicillin-resistant
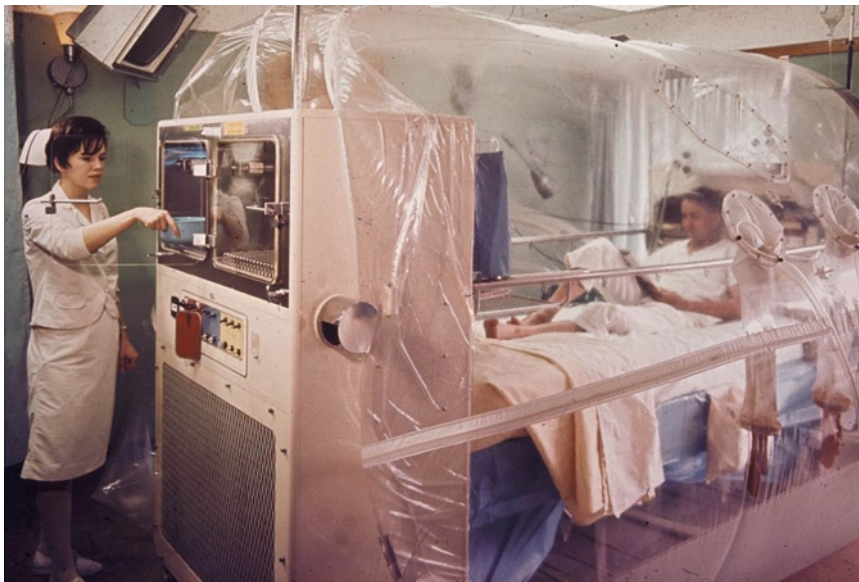
Fig. 1.1 First type of protective environment for severely neutropenic patients. Note, sleeves in the side of canopy to perform tasks on patient and chambers at the foot that irradiated items placed into unit

alpha streptococci appearing. Many of the effective anticancer treatment regimens result in neutropenia so that these types of infection remain a major problem in patients with neoplastic disease.

In contrast, patients with cellular immune defects due to their basic disease or its therapy are prey to a different array of organisms. Predisposing diseases include Hodgkin's disease, T lymphocyte lymphomas and leukemias, and hairy cell leukemia. Various transplantation procedures and GVHD along with treatments for them including cyclosporine, antithymocyte globulin, tacrolimus and adrenocorticosteroids induce defects which result in such opportunistic infections. The diseases are due to organisms from all categories including *Salmonella* spp., *Histoplasma capsulatum*, *Leishmania* spp., and CMV. In the early 1980s and with the advent of the AIDS epidemic, investigators with access to laboratories where T cells could be measured began systematic studies that revealed that patients with levels in the 200 range or lower would develop one or more of these opportunistic infections, especially PCP. It became apparent that as the T cells fell, it could be predicted which organisms would cause disease [8, 35]. Now with the measurements of endogenous cytokines, T-cell subset populations, and functional analysis, this is even more predictable and offers opportunities for treatment and prevention.

B-cell defects have been well described occurring in certain groups of patients with certain underlying neoplastic diseases such as multiple myeloma and chronic lymphocytic leukemia or those after bone marrow transplantation. In these instances, the organisms to be anticipated are *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Neiseriae meningitimus,* or late after transplantation, Echoviruses. Vaccine studies in this group of patients and others are underway to try to achieve protection.

An altered integument allows access to a large variety of organisms to invade patients with neoplastic disease. Areas at risk include the entire orointestinal tract where chemotherapy-induced mucusitis with ulcers allow organisms' entry into tissues and the bloodstream. Intravascular catheters allow direct entry into the bloodstream and other catheters such as bladder, intraperitoneal or intracranial devices are sources of infection especially in the neutropenic patient. In addition, life-threatening infections may result from infusion of blood products or transplanted organs. These may vary from HIV and HTLV-I [36] to *Salmonella* spp., *Candida* spp., and *Trypanasoma cruzi* among others.

Knowing the immunological defect in a patient with neoplastic disease suspected of having an infection is extremely important. From the clinical picture, the appropriate tests can be done to confirm the diagnosis, and if indicated, empiric therapy can be started. A fine example of this is the empiric therapy of the neutropenic patient with appropriate antibiotics for anticipated organisms in the clinical setting such as a

particular hospital. In the early 1960s, a clinical study from the NCI documented the association of the fall of the neutrophil count with the rise of the severe infections [15]. An example of a population at risk for a specific infection due to an immune defect was the prevention of Pneumocystis pneumonia in children with acute lymphoblastic leukemia carried out at St. Judes Hospital in Memphis TN [37]. Almost 100% protection was achieved. Knowledge of the perturbations in immune function following bone marrow transplantation has enabled clinicians to use preemptive therapy for suspected infections such as those caused by CMV.

Finally, immune defects involving innate and adaptive immune responses may occur in patients who have received prolonged courses of chemotherapy, neoadjuvant antineoplastic monoclonal antibody therapy, or immunosuppressive agents for treatment of GVHD following allogeneic stem cell transplantation.

Diagnostic Evaluation of Infection

There have been remarkable advances in diagnostic tests for the evaluation of infection in the past five decades, especially in diagnostic microbiology allowing us to make earlier and more specific microbial diagnoses. Gram stains, invented in 1884 by Hans Christian Gram in Denmark, and variations on dye techniques are still routine and useful for early presumptive diagnoses, but immunological methods using direct fluorescent antibody stains have been developed and are regularly used especially for viruses. In unusual circumstances such as suspected polyoma virus infection, electron microscopy may be used. New culture methods include isolator lysis centrifugation tubes which are used for continuous around-the-clock monitoring employing a fluorescent carbon dioxide detection system. An automated broth system can be used for quantitation by colony counts of centrifuged sediments and these systems are more sensitive for the isolation of some fungi, mycobacteria and *Bartonella* species. In addition, the broth can be examined by nucleic acid probes and HPLC for rapid organism identification. Automated broth Minimum Inhibitory Concentration (MIC) antimicrobial susceptibility tests yield more rapid results which can be entered into online computer systems for clinicians and recorded for antimicrobial susceptibility patterns for hospital infection control. To help select antimicrobial regimens for empiric therapy, these data can also be available for local and national Health Departments as well as the hospital.

Polymerase chain reaction (PCR) techniques to recognize copies of nucleic acid fragments in various specimens have been developed and are being used. Many are undergoing FDA approval and some may be available only in special laboratories. These techniques may well replace earlier tests

using antigen detection by poly or monoclonal antibodies and chemical tests for specific cellular elements such as arabinatol, beta D-glucan, or galactomanans of fungi.

Antibody tests are much easier to perform since the enzyme-linked antibody (ELISA) test has replaced the compliment fixation (CF) test, and for specificity, the Western blot has become the "gold standard". However, for cancer patients and those following allogeneic stem cell transplantation, serologic diagnosis may provide limited information regarding active versus remotely acquired disease. Furthermore, a negative serology cannot be interpreted with certainty due to potential defects in B-cell function.

Radiologic testing with CT scans and MRIs has better defined anatomic lesions for presumptive diagnoses, and recent advances in safe tissue sampling can be used by interventional radiology techniques for specific diagnoses. Bronchoalveolar lavages have virtually replaced open lung biopsies for investigating pulmonary lesions; however, similar to diagnostic reliability of serologic diagnosis, a negative BAL sample smear or culture dose not exclude the possibility of opportunistic lung infection. Radioactive labeling of the patient's own neutrophils and injecting them for localizing foci of infection can sometimes be helpful as can technetium scans. Efforts to localize infected sites using antibody for specific organisms are presently under study and this method could also offer treatment opportunities. Similarly, PET scan are now commonly used for tumor burden and disease recurrence monitoring; this new technology appears promising as an adjuvant diagnostic tool.

Pathogens of Interest

Most infections occurring in patients with nonhematological malignancies are caused by organisms commonly associated with the site of the tumor or nosocomial pathogens except when on chemotherapy. Infections in patients with hematological malignancies are usually caused by organisms that are prevalent in association with specific deficiencies in host defense mechanisms or are due to nosocomial pathogens. Only a few examples will be presented in this discussion, primarily focused on those infections prevalent in neutropenic patients.

Bacterial Infections

Early studies of infection in patients receiving chemotherapy for hematological malignancies found that *S. aureus* developed resistance to penicillin. It became the predominant cause of fatal infection in neutropenic patients [4]. Once effective antibiotics became available for treatment of penicillin-resistant *S. aureus*, gram-negative bacilli emerged as the most common cause of fatal infections. *Pseudonomas aeruginosa* became a major cause of infections, especially among neutropenic patients [29, 37, 38]. Although polymyxin B and colistin were very active in vitro against the pathogen, they were ineffective for therapy in neutropenic patients and were of limited benefit in other patients. Their efficacy in neutropenic patients depended upon the recovery from neutropenia. The availability of carbenicillin, the first β lactam with anti-pseudomonal activity, had a dramatic impact on the therapy of life-threatening *Pseudomonas* infections [39]. Other gram-negative bacilli emerged as significant pathogens, including *Klebiella* spp. and *Serratia marcescens*. Cephalothins were the first β lactam available for the treatment of some of these infections [40]. Over the years, multiplicity of antibiotics has been developed including potent broad-spectrum cephalosprosins, carbapenims, and fluoroquinolones [41]. Despite these important advances, bacterial infections remain a serious threat to cancer patients, due in large part to the ability of organisms to develop resistance to multiple antibiotics. Recent increase in nonpseudomonal nonfermentative Gram-negative bacteria such as *Stenotrophomonas maltophilia* has been associated with difficult-to-treat healthcare-associated infections; these bacteria may also cause less severe community-acquired infections [42]; high-dose trimethoprim-sulfamethoxazole remains the treatment of choice, although occasionally a multidrug-resistant organism poses a serious challenge [43]. Emergence and spread of extended-spectrum beta-lactamases (ESBL) *Enterobacteriaceae* and recently identified carbapenemases producing *Klebsiella* species (KPC) and spreading to other gram-negative disease-associated bacteria herald alarming limitation in choice for effective antimicrobial therapy against these new groups of MDR-gram-negative bacterial infections [44].

Listeria monocytogenes was one of the first bacterial infections reported as occurring more frequently in patients with cellular immune defects [8, 45] and it continues to be a problem [46]. It soon became apparent that *Salmonella* spp., *Nocardia asteroids*, and *Rhodococcus equi* were also opportunistic bacterial pathogens in this setting. *Mycobacterium hemphilum* [47] was thereafter established as a *Mycobacterium* to be anticipated in T-cell-deficient patients, in addition to the classic example of *M. tuberculous* [48] and subsequently *M. avium-intracellulare* complex.

Principles of Antibiotic Therapy in Neutropenic Patient

This discussion will be limited to general principles. Discussion of specific antibiotic therapies is presented in other chapters of this book. After multiple antibiotics became

available and the potential for emergence of resistance became apparent, it became the standard practice to withhold antibiotic therapy in the febrile patient until the infecting pathogen was identified. However, early studies of antibiotic therapy for fever in neutropenic patients clearly indicated the importance of instituting antibiotic therapy promptly to neutropenic patients when they become febrile. It has been demonstrated that mortality rates increase substantially if therapy is not administered promptly. The choice of initial antibiotic therapy should provide broad-spectrum antibacterial coverage against gram-positive cocci and gram-negative bacilli. Most infections are caused by aerobic gram-negative bacilli and anaerobic infections tend to be uncommon. It is of critical importance for physicians caring for neutropenic patients to be aware of the common pathogens causing infections at their hospitals and their antimicrobial susceptibilities so that appropriate antibiotic regimens will be selected. Antibiotics that are bactericidal should be selected when possible. The greatest experience has been obtained with broad-spectrum β lactams and aminoglycosides. Aminoglycosides are less effective as single agents in neutropenic patients and should not be used alone [49].

Some studies have indicated that synergistic combinations that provide high serum cidal levels such as a β lactam plus an aminoglycoside are more effective than single agents [50]. However, aminoglycosides have potential nephrotoxicity, which are more prevalent in the elderly and patients with cancer such as multiple myeloma or cancer therapy induced reduced renal reserves.

Various regional, national, and international groups have met and are still meeting to study questions of treatment and how to conduct studies to evaluate treatment of bacterial infections. These have included The Infectious Diseases Society of America [51], The European Organization for Research and Treatment of Cancer [52], and The Immunocompromised Host Society [53]. For empirical antibacterial treatment, it is evident that regimens should be aimed at the most prevalent organisms with reliable knowledge of their susceptibility infecting the patient at a given hospital. It must be stressed that continued efforts at prevention, e.g., scrupulous hygiene, are most important.

Patients with fever of unknown origin that persists after several days of broad-spectrum of antibiotic therapy represent a difficult problem. Careful reevaluation and collection of additional appropriate diagnostic tests need to be performed and additional therapeutic measures should be considered. These may include other antibacterial, antifungal, or antiviral agents. Antifungal agents should be given serious consideration in these patients. Some investigators have advocated that antibiotic therapy be continued in patients with documented infections until the neutrophil count recovers. There is considerable evidence to indicate that this is unnecessary and can encourage superinfection. A more appropriate approach is to discontinue the therapeutic agents, watch carefully.

Mycobacterial Infections

Tuberculous is a well-recognized, albeit uncommon, complication even in patients with severe cellular immune defect [48]. Patients with solid organ cancer may be as susceptible to active *Mycobacterium tuberculous* infection as patients with hematologic malignancy and those undergoing hematopoietic stem cell transplantation [54]. It remains important to realize that tuberculous, being an indolent disease, may be mistaken for a slowly progressing neoplasm and may lead to unnecessary large excisions that can be avoided by initial fine needle aspiration and biopsy of the suspected mass [55].

Nontuberculous mycobacterial disease due to slow-growing mycobacteria is on the rise. Cancer patients with *Mycobacterium intracellulare* lung infections are often postmenopausal women [56], with a selective defect in interferon gamma production or presence of interferon gamma inhibitor [57, 58]. Rapidly growing mycobacterial (RGM) lung disease is uncommon and mostly seen in patients undergoing chemotherapy and in individuals with pervious pulmonary involvement with cancer [59]. *Mycobacterium chelonae* and *Mycobacterium fortuitum* were the prominent RGM associated with lung disease [59, 60]; recently, *Mycobacterium abscessus* has been a predominate RGM pulmonary pathogen [61]. *M. abscessus* infections are difficult-to-treat due to high level of drug-resistance [61] and issues related with drug intolerance. Patients with severe cellular immune defects have significantly poor outcome with disseminated RGM end-organ infection [62], with the exception of *Mycobacterium mucogenicum* catheter-associated infection that responds to prompt removal of the infected catheter and a short course of combination antimicrobial therapy [61].

Fungal Infections

Fungal infections emerged as a significant complication of patients with hematological malignancies after effective chemotherapy became available. The major predisposing factors to these infections were determined to be prolonged neutropenia and adrenocorticosteroid therapy, which interferes with macrophage function. These infections are also prevalent among HSCT recipients who develop graft vs. host disease and receive adrenocorticosteroid therapy.

As early as the mid-1950s, an increasing proportion of patients with acute leukemia developed fungal infections, predominantly candidiasis and aspergillosis [63]. In recent years, infections caused by Zygomycetes, *Fusrium* species, and *Scedasporium* species have become increasingly frequent [64, 65].

There are multiple species of *Candida*, with different antifungal susceptibilities and patterns of infection [56, 66–68]. Superficial candidiasis occurs in cancer patients receiving radiation therapy and those with impaired T-cell function. Infections involved the oropharynx, esophagus, larynx, urinary tract, and gastrointestinal tract and serve as the origin of disseminated infection, especially in those with neutropenia and long-term intravenous catheters. Disseminated infection is often difficult to diagnose because there may be few signs and symptoms except fever and progressive debilitation and the organism is often not cultured from blood specimens. About 10% percent of patients have multiple skin lesions [69]. There is a chronic form of disseminated candidiasis that occurs in neutropenic patients, which persists after neutrophil recovery and is characterized by persistent fever, debilitation, weight loss, and in some patients, hepatosplenomegaly and right upper quadrant pain [70–72].

Mortality rates have been as high as 70% among patients treated with amphotericin B. Fluconazole prophylaxis has been associated with a significant increase in drug-resistant *Candida krusei* and *Candida glabrata* breakthrough disseminated infections [73–75]. Other alternatives are lipid formulations of amphoterician B and echinocandins. Neutrophil recovery is a critical factor in recovery from candidiasis. Prolonged therapy with fluconazole has been effective for chronic candidiasis and recent experience suggests that anti-inflammatory agents may be useful.

Aspergillosis. The major sites of infection are the lungs and sinuses. Disseminated infection is uncommon. Infection is acquired by inhalation of spores and epidemics have occurred during construction in hospitals. The hyphae invade blood vessels causing thrombosis and infraction and can erode through facial planes, cartilage, and bone. Patients with pulmonary infection may present with symptoms suggesting acute pulmonary embolism. Characteristic nodular infiltrates can be detected on pulmonary CT scans "Halo sign" when radiographs are normal [76]. Culture specimens are often negative, but blood galactamannan tests are helpful in establishing the diagnosis and evaluating treatment response [77]. Sinus infections often present with black eschars on the nose or palate. Progressive infection causes proptosis, endophthalmitis, or cerebral infraction. Therapy consists of effective new *Aspergillus* active triazole-based drugs such as voriconazole and posaconazole, and echinocandins such as caspofungin and micafungin in combination or as a single agent [78]. Lipid formulations of amphoterician B are also used in combination with other mold-active drugs. Neutrophil recovery and discontinuation of systemic immunosuppressive therapy, especially adrenal costicosteroids, are important for recovery from the infection. Surgical resection of the infected tissue may benefit some patients and resection of residual cavitary lesions may be necessary to prevent pulmonary hemorrhage and late-recurring bacterial superinfections.

Patients at risk of developing cryptococcosis have impaired cellular immunity or are receiving adrenal corticosteroids; hence, patients with CLL or lymphoma or HSCT recipients are at greatest risk. Infection is acquired by inhalation of organisms; hence, the lung is the primary site of infection, although less than 40% of infected patients present with symptoms of pneumonia. The infection can progress rapidly leading to death. Over 50% of cancer patients develop meningitis and some have widely disseminated infection. The latex agglutination test detects cryptococcal antigen in cerebrospinal fluid or blood of infected patients [79]. Optimal treatment consists of initial systemic therapy with amphotericen B plus low-dose flucytosine [80]; for patients with mild-to-moderate infection, high-dose oral fluconazole may be given for maintenance therapy.

Zygomycosis, caused by molds of the order Mucorales, are increasing in frequency [81]. These infections share the same characteristics as aspergillosis, but mortality rates exceed 70% despite amphotericin B therapy. Newer azoles such as posaconazole may be effective therapy [82]. Over 80% of *Trichosporon* infections are disseminated and the organism can be cultured from blood specimens of most patients. Other infections include endophthalmitis, pneumonia, meningitis, and osteomyelitis [83]. Optimal therapy may be a combination of amphotericin B and fluconazole, but the mortality rate is high in neutropenic patients despite therapy; high-dose voriconazole may be effective in patients with disseminated or hepatosplenic *Trichosporon* species infection [84]. Breakthrough *Trichosporon* infection may occur in patients receiving mold-active drugs such as echinocandins or oral broad-spectrum triazoles [85, 86].

Fusarium spp. cause infections predominantly in the sinuses and lungs. Fusariosis like *Aspergillus* species infection are angioinvasive; pulmonary nodular or mass-like disease is indistinguishable from other mold infections [87]. About 75% of infections in neutropenic patients disseminate and the organism often can be cultured from blood specimens. Nearly half of patients are fungemic and up to 80% or more present may develop multiple (>10) nodular skin lesions that develop necrotic center; skin biopsy is diagnostic and should be performed promptly. Mortality remains high despite the availability of highly active triazole drugs against this organism [87].

Unresolved immune suppression continues to influence treatment response among cancer and hematopoietic stem cell transplant (HSCT) recipients with systemic fungal disease [88]. Various strategies including donor granulocyte transfusions in patients with severe neutropenia have not shown significant improvement in outcomes in recent clinical trials [89]. Combined therapy using effective antifungal agents plus recombinant cytokines to boost macrophage, helper, and cytotoxic lymphocyte functions have been explored; a nonrandomized study using granulocyte-macrophage colony-stimulating

factor (GM-CSF) and interferon gamma (IFNγ) which were safe and appeared to have a favorable impact in patients receiving donor granulocyte transfusions [90]. Safety of IFNγ has been a concern due to potential cytokine-induced graft compromise and/or GVHD in recipients of allogeneic HSCT; these concerns were not observed in our patients with life-threatening fungal infections [91], although larger, randomized studies are needed to explore this important issue further. Similarly, drugs that may promote pathogen-directed immune capture by introducing configurational changes in these pathogens are being explored [92, 93].

Viral Infections

For many years, little attention was focused on viral infections in cancer patients due to the lack of rapid diagnostic tests and effective therapy. For example, only in recent years have community respiratory viral infections been recognized as potentially serious to immunocompromised patients. Table 1.1 lists most of these viral infections and available therapy. Many acute viral infections represent reactivation of long-standing latent infection.

Human herpes viruses are among the most common causes of viral infections in cancer patients and are associated with significant morbidity and mortality in severely immunocompromised hosts. Herpes simplex viruses cause oropharyngeal and esophageal disease and may disseminate to other organs. Reactivation of varicella-zoster virus occurs mainly in patients with leukemia and lymphoma and can result in localized infection (shingles), disseminated cutaneous infection, pneumonia, encephalitis, hepatitis, or small bowel disease [94]. CMV infection is most often due to reactivation of latent infection, but has also been attributed to transmission by white blood cell transfusions [24, 95]. It is a special risk to HSCT recipients who may receive infected tissue. CMV may cause hepatitis, meninoencephalitis, pneumonitis, or gastroenteritis [96, 97]. The disease has immunosuppressive effects that increase the risk of other infection. Prophylaxis or preemptive therapeutic strategies are necessary for patients undergoing stem cell transplantation [98]. Epstein–Barr virus can cause a fulminant fatal lymphoproliferative disorder in occasional patients following allogeneic stem cell transplantation. Immunocompromised cancer patients occasionally develop interstitial pneumonitis, encephalitis, or hepatitis due to human herpes virus 6 infections.

Progressive multifocal leukoencephalopathy is a demyelinating disease of the brain caused by the JC virus which occurs infrequently among patients with CLL and Hodgkin disease. The disease is due to reactivation of latent infection that is prevalent in normal adults. Symptoms include visual disturbances, speech defects, and mental deterioration leading to dementia and coma with 80% of patients dying within one year. Parvovirus B19 may cause anemia in cancer patients which may be followed by severe polyarthritis. Most patients have been infected with polyomavirus (BK) virus that persists in the genitourinary tract and is a major cause of hemorrhagic cystitis in HSCT recipients [99].

Community respiratory viral infections cause about 30% of respiratory infections in cancer patients during winter and spring and can be a serious threat to transplant recipients and patients with acute leukemia who may develop viral pneumonia or superinfection with bacteria or fungi [100, 101]. Epidemics have occurred in transplant and leukemia units. Some of these patients have very prolonged viral shedding after resolution of symptoms. Viruses causing infection include influenza A and B, respiratory syncytial virus (RSV), parainfluenza (PIV), and adenovirus. In stem cell transplant recipients following PIV and RSV infections, pulmonary obstructive defects were recently recognized; these may be severe and complete resolution may take longer than 12 months after the initial viral infection [102]. Novel respiratory viruses recently recognized to cause serious life-threatening disease include human metapneumovirus, human cornonavirus NL63 and HKU1, agent of severe acute respiratory syndrome (SARS), and human bocavirus [103, 104]. Adenovirus also causes gastrointestinal infection, hepatitis, hemorrhagic cystitis, pancreatitis, and encephalitis; fatal disseminated adenovirus infections are seen in adults and pediatric patients with profound cellular immune defects such as cordblood transplant recipients with GVHD [105].

Parasitic Infections

Neuro-hepatic toxoplasosis is more common in cancer and transplant recipients in the northeastern United States, whereas strongyloidiasis infestation rates are mostly seen in habitants of southeast and south-central US states. Similarly, amebiasis and giardiasis are infrequently seen in patients from rural residences who consume water from shallow contaminated wells. Latent *Toxoplasma gondii* infection is difficult to diagnose on the bases of travel, food consumption, or history of domestic feline exposure; serology may be diagnostic, although in patients with B-cell defects PCR analysis may be needed. Malaria is mostly seen in patients traveling to endemic regions without prophylaxis or receiving ineffective chemoprophylaxis due to drug-resistant strains of *Plasmodium* species. "Airport malaria" has also been seldom reported in patients who reside near airports with frequent international flights. Transfusion malaria has been observed in patients with neoplastic diseases and should be considered and explored in the presence of unexplained fever [106]. Chaga's disease has also been transmitted by transfusions

Table 1.1 Infections causing pneumonia in cancer patients based on the underlying immune defect

Immune defect	Bacteria	Fungi	Parasites	Viruses
Granulocytopenia	*Staphylococcus aureus*	*Aspergillus fumigatus;* and other *Aspergillus* spp.		Herpes simplex virus I and II
	Streptococcus pneumoniae	Non-*Aspergillus* hyalohyphomycosis		Varicella-zoster virus
	Streptococcus species	Such as *Pseudallescheria boydii, Fusarium solani.*		
	Pseudomonas aeruginosa	*Mucorales* (zygomycoses)		
	Enterobacteriaceae	Dematiaceous (black) fungi such as *Alternaria*		
	Escherichia coli	*Bipolaris, Curvularia, Scedosporium apiospermum*		
	Klebsiella species	*Scedosporium prolificans*		
	Stenotrophomonas maltophilia			
	Acinetobacter species			
Cellular immune	*Nocardia asteroides* complex	*Aspergillus* and non-*Aspergillus* filamentous molds	*Toxoplasma gondii*	Cytomegalovirus
Dysfunction	*Salmonella typhimurium* spp.	*Pneumocystis jiroveci* (*P. carini*)	*Microsporidium* spp.	Respiratory viruses
	Salmonella enteritidis	*Cryptococcus neoformans*	*Leishmania donovani*	Influenza A and Influenza B
	Rhodococcus equi	Endemic mycoses due to *Histoplasma capsulatum*	*Leishmania infantum*	Parainfluenza type-3
	Rhodococcus bronchialis	*Coccidioides immitis, Blastomyces dermatitidis*	*Strongyloides stercoralis*	Respiratory syncytial virus
	Listeria monocytogenes	*Penicillium marnefie*		Adenovirus
	Mycobacterium tuberculous			Varicella-zoster virus
	Nontuberculous mycobacteria			HHV 6
				JC and BK virus
				Parvovirus B19
				SARS-associated coronavirus?
				Paramyxovirus?
				Hantavirus?
Humoral immune	*Streptococcus pneumoniae*	*Pneumocystis jiroveci* (*P. carini*)?	*Giardia lamblia*	VZV
Dysfunction	*Haemophilus influenzae*		*Babesia microti*	Echovirus
Splenctomy	*Neisseria meningitidis*			Enterovirus
	Capnocytophaga canimorsus			
	Campylobacter			
Mixed defects	*Streptococcus pneumoniae*	*Pneumocystis jiroveci* (*P. carini*)	*Toxoplasma gondii*	Respiratory viruses
	Staphylococcus aureus	*Aspergillus* spp.	*Strongyloides stercoralis*	Influenza
	Haemophilus influenzae	*Candida* spp.		Parainfluenza
	Klebsiella pneumonia	*Cryptococcus neoformans*		Respiratory syncytial virus
	Pseudomonas aeruginosa	*Mucorales* (zygomycoses)		Adenovirus
	Acinetobacter spp.	Endemic mycoses (severe systemic dissemination)		VZV
	Enterobacter spp.			
	Stenotrophomonas maltophilia			
	Nocardia asteroides complex			
	Listeria monocytogenes			
	Legionella spp.			

Patients with mixed immune defects include recipients of allogeneic hematopoietic stem cell transplant; acute or chronic graft versus host disease; myelodysplastic syndrome; adult T-cell leukemia lymphoma; antineoplastic agents like cyclophosphamide, fludarabine, and HHV6: Human herpesvirus 6 *L. donovani* and *L. infantum* may lead to serious visceral leishmaniasis. *L. donovani* is seen in Africa and Asia, *L. infantum* is seen in Africa, Europe, Mediterranean, and Central and South America. VZV is rarely associated with systemic dissemination in patients with humoral immune defects, or even those with mixed immune dysfunctions. *Strongyloides stercoralis* may lead to serious, life-threatening hyperinfection syndrome in patients with marked cellular immune defects

causing fevers and pericardial effusions [107]. This disease may become more common as the number of potential donors coming from endemic areas increases and also the reduvid bug appears to be moving north into southwestern states. Screening donors may become necessary. A recent increase in fatal *Babesia* species infection reported since

November 2005 in the US has raised concerns of this rare intraerythrocytic parasite disease [108].

Hydated cyst due to *Echinococcus granulosus* and *E. multilocularis* and neurocycticercosis is difficult to distinguish from cystic brain tumor or bacterial or fungal brain abscess. Liver hydated cyst may present as polymicrobial bacterial abscess in patients from the developing world.

End-Organ Infection

Septicemia including disseminated infection and pneumonia are the most common sites of infection; urinary tract, skin, and central nervous system infection occurs less commonly. The site of infection is often related to the site of the primary tumor, a metastasis, or a surgical procedure. Septicemia is most likely to occur in patients with impaired host defenses. The frequency of infection has been determined in several autopsy studies.

Pneumonia

The management of pneumonia in the cancer patient is often frustrating and difficult. The spectrum of potential pathogens is exceptionally broad including those that infect normal hosts and those that occur predominately in immunocompromised hosts; predisposing factors include deficiencies in host defense mechanisms such as neutropenia or hypo IgG, bronchial obstruction or ulceration due to tumor, mucosal damage due to chemotheapeutics agents, and the use of mechanical ventilation. Cancer patients may develop pulmonary infiltrates due to noninfectious causes such as hemorrhage, radiation pneumonitis, and leukoagglutinin reaction. Several neutropenia patients are unable to produce adequate inflammatory responses and thus may fail to produce persistent sputum, develop clinic signs and symptoms, or develop abnormalities on chest radiographs.

In a study of gram-negative bacillary pneumonia in cancer patients (most of whom had hematological malignances), only 64% had abnormal radiographs at the onset of their pneumonia and 20% never developed abnormalities [109]. Identification of the infecting pathogen is often difficult. Adequate sputum specimens are often not available. The diagnostic yield from invasive procedures such as bronchoalveolar lavage is suboptimal. Biopsies are often contraindicated because of the risk of hemorrhage due to thrombocytopenia or coagulopathies. The use of CT scans and blood tests such as galactomannon detection for Aspergillosis have improved diagnostic capabilities [76].

Abdominal Infections

A wide variety of infection agents may infect the gastrointestinal tract due to obstruction, ulceration, and other factors. This discussion will focus on two infections with potentially serious consequences in neutropenic patients: typhlitis and perianal infections. Typhlitis or neutropenic enterocolitis is characterized by well-demarcated ulcers, hemorrhage, and large masses of organisms with few inflammatory cells usually limited to the cecum, but can be more extensive. Computed tomography scans provide superior images of the intra-abdominal organs and may be able to diagnose subclinical small bowel perforations, infected collections, and pneumatosis intestinalis, a serious complication which requires intense bowel management and presents as surgical dilemma [110]. Bacteremia occurs in 70% of patients. Therapy consists of broad-spectrum antibiotics, and anti-*Candida* agents, bowel rest, and decompression are important [110].

Perianal infections are most common in patients with acute monocytic leukemias. The prominent symptoms are fever and pain on defecation. Lesions often arise adjacent to a hemorrhoids and are indurated and ulcerated, often with extensive necroses. It is important to evaluate for recrudescent Herpes virus infections and perirectal abscess. Evaluation of surgical intervention may be obtained if there is not a prompt response to antimicrobial therapy or if a drainable focus is identified.

Catheter-Related Infections

Most cancer patients receiving antineoplastic therapy have indwelling central venous access. Catheter infections are an important cause of delay in chemotherapy, hospitalization, cost of care, and deaths [111, 112]. Coagulase-negative *Staphylococcus* (CoNS) and other skin gram-positive bacteria are common pathogens. Catheter removal reduces risk of infection recurrences [113], and in patients with high-grade bacteremia or candidemia with or without hemodynamic compromise, the catheter should be removed immediately. A thorough evaluation for underlying endovascular infection such as septic thrombophlebitis may yield a source of persistent bacteremia, lack of complete response, and influence duration of systemic antimicrobial therapy. Factors that influence antimicrobial choice include (a) penetration of drug in the biofilm, (b) antimicrobial activity within the biofilm, and (c) activity against the nonplanktonic stationary phase of the microorganisms [114]. A detailed discussion of this important topic is presented in two chapters.

This introductory chapter intended for the reader to become familiar with the important historical milestones in the understanding and development in the field of infectious

diseases in immunosuppressed patients with an underlying neoplasm and patients undergoing hematopoietic stem cell transplantation.

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Chapter 2
Infections in Hematopoietic Stem Cell Transplant Recipients

Georg Maschmeyer and Per Ljungman

Abstract The risk of infection among allogeneic hematopoietic stem cell transplant (aHSCT) recipients is determined by patient age, underlying disease, the complications that occurred during preceding treatment regimens, the selected transplantation modality, and the severity of graft-versus-host disease. Immunological reconstitution after hematopoietic recovery has an impact on the type of posttransplant infectious complications, and infection-related mortality is significantly higher postengraftment than during the short posttransplant neutropenia. As different pathogenetic and epidemiological backgrounds of infections occur following aHSCT, three consecutive time periods posttransplant are separately described: the early posttransplant period (preengraftment, comprising 3 weeks), the intermediate posttransplant period (3 weeks to 3 months), and the late posttransplant period (later than day + 90).

Keywords Allogeneic • Hematopoietic stem cell transplant • Early infection • CMV • Late infections • Graft-versus-host disease

Introduction

Fever and Infection After Allogeneic Hematopoietic Stem Cell Transplant

The risk of infection among allogeneic hematopoietic stem cell transplant (aHSCT) recipients is determined by patient age, underlying disease, the complications that occurred

during preceding treatment regimens, the selected transplantation modality, and the severity of graft-versus-host disease (GvHD) [1, 2]. In comparison with patients undergoing high-dose chemotherapy and autologous stem cell transplantation, recipients of aHSCT are at a much higher risk of infection also after hematopoietic reconstitution, due to delayed recovery of T-cell and B-cell functions. Immunological reconstitution after hematopoietic recovery has an impact on the type of posttransplant infectious complications [3, 4], and infection-related mortality is significantly higher postengraftment than during the short posttransplant neutropenia. After nonmyeloablative conditioning, there is a lower risk of severe and fatal infections in the early posttransplant period [5–9]. Because of different pathogenetic and epidemiological backgrounds of infections, three consecutive time periods posttransplant are separately described: the early posttransplant period (preengraftment, comprising 3 weeks), the intermediate posttransplant period (3 weeks to 3 months), and the late posttransplant period (later than day + 90) (Fig. 2.1).

Early Posttransplant Period (Preengraftment; Earlier than Day +21)

Epidemiology of Infections During Neutropenia Posttransplant

Almost all patients receiving myeloablative conditioning regimens develop fever during neutropenia, and most of these febrile episodes are due to infections. The risk of severe bacterial or fungal infection in the early posttransplant period is markedly reduced when nonmyeloablative conditioning has been used. Clinical signs of infection apart from fever may be absent or discrete, and an infectious focus frequently will not be identified by clinical examination, microbiological, or imaging techniques. The differential diagnosis of non-infectious causes of fever, such as transfusion reactions,

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Viral

Herpes simplex virus

Respiratory viruses*

Cytomegalovirus•, Human herpesviruses 6,7

Varicella zoster virus, Epstein Barr virus, BK/JC viruses

Bacterial

Gram positives, Gram negativesΔ

Encapsulated bacteria

Fungal

Candida spp.

Aspergillus spp.◊

Parasitic

Toxoplasma gondii

Pneumocystis carinii

Risk factors

| Mucositis Organ dysfunction Neutropenia and other immune defects | Acute graft-versus-host disease (GVHD) and therapy for this condition Mucocutaneous damage (GVHD) Cellular immune dysfunction Immunomodulating viruses | Chronic GVHD and therapy for this condition Mucocutaneous damage (GVHD) Cellular and humoral immune dysfunction Hyposplenism, decrease in opsonization Decrease in reticuloendothelial function |

Preengraftment **Immediate postengraftment** **Late postengraftment**

Fig. 2.1 Infections following allogeneic hematopoietic stem cell transplantation (from Up to Date v18.3, Anaissie E, Marr KA, Thorner AR, 2010)

drug-related adverse events, allergy, and acute GvHD, must be considered.

Infections in neutropenia after aHSCT may be life-threatening. Bacterial pathogens account for about 90% of infections during this phase. Epidemiological factors relevant for bacterial infections are shown in Table 2.1. Bacteremia, often related to central venous catheters (CVCs) and/or severe mucositis, occurs in up to 30% of patients after aHSCT, with the majority being caused by Gram-positive pathogens, predominantly coagulase-negative staphylococci, corynebacteria, and alpha-hemolytic streptococci [10–14]. Rarely, viridans streptococcal bacteremia may cause toxic shock and acute respiratory distress, potentially resulting in fatal outcome. Gram-negative infections are less frequent, but typically associated with higher morbidity and mortality. Gram-negative pathogens may enter the bloodstream via mucosal damage in the gastrointestinal tract of patients. Beyond that, fungal infection may occur in up to 15% of patients [15], and herpes simplex virus (HSV) infections emerge in this early posttransplant period unless acyclovir prophylaxis is given.

Table 2.1 Epidemiological aspects of bacterial infections after hematopoietic stem cell transplantation (HSCT)

- Similar spectrum as neutropenic patients after intensive chemotherapy
- Lower risk of severe and fatal infections early post-TxP after non-myeloablative conditioning
- Short neutropenia±mucositis after autologous HSCT: infections comparable to other patients with short-term neutropenia, but Gram-positive pathogens more frequent
- Allogeneic HSCT: critical role of immune reconstitution
  - Slow after T-cell depletion
  - Slow after mismatched donor
  - Slow/absent with significant graft-versus-host disease
  - Chronic GvHD: functional asplenia

Diagnostic Procedures

- Afebrile patient.
  - Daily clinical exam+body temperature at least three times daily.
  Note: antipyretic medication (steroids; analgesics such as metamizole).

- Serum C-reactive protein (CRP) twice weekly.
- *Aspergillus* antigen (GM) ≥twice weekly.
- First fever.
  - Update physical exam, blood cultures, clinical chemistry, CRP, interleukin-6 (IL-6), and thoracic computed tomography (CT) scan; other measures according to clinical findings (see below).
- Persistent fever.
  - Update physical exam, blood cultures, clinical chemistry, CRP, IL-6, and thoracic CT scan; consider abdominal ultrasound or magnetic resonance imaging (MRI).
  - Check results of antigen testings.
- Fever + pulmonary infiltrates.
  - Bronchoscopy + bronchoalveolar lavage (BAL) =>microscopy + culture for bacteria; test for *Mycobacterium tuberculous* (MTB), *Pneumocystis*, cytomegalovirus (CMV), respiratory viruses, adenovirus, *Aspergillus* + other fungi; check for *Aspergillus* GM; optional: *Aspergillus*-PCR and MTB-/*Pneumocystis*-PCR.
- Fever + signs of inflammation at CVC.
  - Blood cultures from peripheral vein and from CVC.
  - Follow-up cultures in case of cultures positive for *Staphylococcus aureus* and *Candida* spp.
- Fever accompanied by skin lesions.
  - Blood cultures.
  - Biopsy (=>histopathology and *nonfixated* =>microbiology).
- Neurological symptoms ± fever.
  - Cerebrospinal fluid (CSF) =>human herpes virus-6 (HHV-6); *Aspergillus* GM; CMV; HSV, VZV.
  - Fundoscopy.
  - Cranial MRI.
- Fever + abdominal symptoms.
  - *Clostridium difficile* toxins; noro-/rotaviruses; CMV; adenovirus; Epstein–Barr virus (EBV).
- Perianal infiltrate/abscess.
  - Beware of results from inappropriate microbiological diagnostics suggesting monomicrobial etiology.
- Fever + increasing "liver function tests" =>viral (hepatitis B virus (HBV), varicella zoster virus (VZV); CMV, etc.), *Candida*?
  - Liver ultrasound or CT or MRI (preferred) [16].
    NB: *Pneumocystis jiroveci* typically accompanied by lactate dehydrogenase rise

If causative microorganisms have been isolated from blood, urine, or CSF culture, follow-up cultures should be obtained to document microbiological eradication, whenever possible.

Since conventional chest radiography is insensitive and has a low negative predictive value for detecting pulmonary infiltrates in neutropenic patients, multislice or high-resolution CT of the lungs should be obtained early in neutropenic patients and particularly in those not responding to initial

Table 2.2 Pulmonary infections and noninfectious complications following allogeneic HSCT

	Early <90 days	Late (>90 days)
Infectious (pneumonia)	Bacterial, fungal, viral, protozoal pathogens	Bacterial, fungal, viral pathogens
Noninfectious	Pulmonary edema	Restrictive lung disease
	Idiopathic pneumonia syndrome	Constrictive bronchiolitis
	Diffuse alveolar hemorrhage	Lymphocytic interstitial pneumonitis
	Engraftment syndrome	
	Delayed pulmonary toxicity syndrome	
	Secondary pulmonary alveolar proteinosis, pulmonary veno-occlusive disease	

antimicrobial therapy [17]. Differential diagnoses to pulmonary infiltrates posttransplant are shown in Table 2.2.

Antimicrobial Therapy in Patients with Neutropenic Fever After Allogeneic Stem Cell Transplantation

Fever of more than 38.2°C, or fever of 38.0°C lasting for an hour or longer, or that recurs within 24 h should give reason for immediate broad-spectrum antibacterial treatment. Microbiological identification of an underlying pathogen is achievable in about one third of all patients. Therefore, it has become an accepted clinical practice to initiate broad-spectrum antimicrobial treatment empirically, or preemptively in the presence of specific clinical or radiological signs or symptoms. For selection of empiric antibacterial therapy in patients with febrile neutropenia, local antimicrobial resistance pattern must be taken into account.

Initial empirical regimens should be active against enterobacteriaceae, *Pseudomonas aeruginosa*, *S. aureus,* and streptococci. Clinical trials that investigated single-agent regimens in patients with neutropenic fever included only few patients after allogeneic stem cell transplantation. Patients with severe mucositis should not be given single-agent ceftazidime because of the risk of bacteremia due to viridans streptococci, whereas piperacillin-tazobactam, imipenem, or meropenem appear appropriate.

In the case of skin infections or venous catheter infections, prompt addition of a glycopeptide antibiotic to the initial empiric regimen should be considered. Stopping the administration of glycopeptides should be considered, if no multiresistant Gram-positive bacteria have been identified.

In febrile neutropenic patients with pulmonary infiltrates, prompt preemptive addition of a systemic antifungal active against *Aspergillus* spp. is recommended [16].

Second-Line Empiric Antimicrobial Regimens in Patients with Neutropenic Fever After Allogeneic Stem Cell Transplantation

If a causative infectious agent has been identified, modification of the empirically started antibacterial therapy according to the in vitro susceptibility pattern should be considered. In case of clinical nonresponse after 72–96 h of full-dose antibacterial treatment, modification of the antimicrobial regimen must be discussed and diagnostic procedures be repeated. Particularly in patients given a prednisone equivalent at a dose of >2 mg/kg/day, broad-spectrum systemic antifungal treatment should be part of the second-line treatment.

Duration of Antimicrobial Treatment

Antimicrobial treatment may be discontinued if all of the following conditions are met: defervescence for at least 48 h, negative cultures, no clinical or radiological evidence of an infection, and neutrophil recovery to above 1,000/μL.

If infections have been microbiologically proven, it is advisable to repeat the initial diagnostic procedures, in order to document the microbiological response (e.g., blood cultures, CSF cultures, urine cultures, stool cultures, bronchial secretions in case of ventilated patients, smears). In some cases, narrowing the antimicrobial spectrum can be acceptable.

Early Fungal Infections After Allogeneic Stem Cell Transplantation

Epidemiological aspects of invasive fungal infections in transplant patients are listed in Table 2.3. In this patient population, the incidence rate of systemic mycoses can be as high as 15%, or higher under certain circumstances [15]. Increased risk is expected in patients with a previous history of invasive fungal infection, long-lasting severe neutropenia, previous episodes of prolonged neutropenia, severe skin and mucosal damages due to conditioning treatment, transplantation outside of a laminar air flow unit, age >45 years, intensive immunosuppression as part of the conditioning regimen or for prophylaxis, and/or treatment of GvHD [18]. Apart from specific local epidemiological conditions, *Candida* and *Aspergillus* species are predominant pathogens.

Fever unresponsive to broad-spectrum antibiotic treatment may be the only early symptom of a systemic fungal infection. In patients with pulmonary *Aspergillus* infection, pleuritic chest pain, cough, or hemoptysis may occur. Blood cultures may occasionally grow *Candida* species. *Aspergillus*

Table 2.3 Risk factors of invasive fungal infection in patients after allogeneic SCT

Early fungal infection (<40 days after SCT)
- Previous history of invasive fungal infection
- Long-lasting neutropenia
- Advanced malignancy/previous neutropenia
- Severe skin and mucosal damages due to conditioning treatment
- Transplantation outside of LAF unit
- Age >45 years

Intensive immunosuppression as part of the conditioning regimen
- Immunosuppression as prophylaxis and/or treatment of GvHD

Late fungal infection (>40 days after SCT)
- Immunosuppression due to GvHD and its treatment (corticosteroid or other more intensive immunosuppressive treatments)
- Transplants from unrelated donors or family donors mismatched for HLA class I and/or class II antigens
- Cytomegalovirus infections and antiviral therapy
- Age >45 years

spp. detected in clinical specimens (such as saliva or throat swabs) from neutropenic patients are likely to indicate incipient invasive infection. At the same time, even if moulds have been isolated from BAL specimens, it may be difficult to distinguish between contamination and true invasive pulmonary infection, whereas in cases of documented invasive pulmonary aspergillosis, cultures from BAL are often negative. Serial screening of blood samples for *Aspergillus* galactomannan or beta-D-glucan as well as for fungal DNA by polymerase chain reaction (PCR) may be helpful for early initiation of broad-spectrum systemic antifungal treatment.

Antifungal agents frequently used in this situation are liposomal amphotericin B and caspofungin, both being licensed for empirical treatment of refractory neutropenic fever. If, however, thoracic CT scan shows typical findings indicative of invasive aspergillosis, voriconazole might be the first choice, as in case of probable or proven aspergillosis. Antifungal treatment is continued at least until neutrophil recovery and resolution of clinical and radiological signs of infection.

Other mould infections such as zygomycosis and fusariosis are rare, but increasingly reported in patients post-aHSCT, and in case of suspected zygomycosis, liposomal amphotericin B would be the preferred choice.

Early Viral Infections After Allogeneic Stem Cell Transplantation

Virus infections can occur during the period before hematopoietic engraftment. HSV reactivates frequently in this early period unless acyclovir prophylaxis is given, and the clinical symptoms are frequently uncharacteristic [19]. Acyclovir-resistant viruses have been reported in different

patient series to occur in up to 10% and should be suspected if mucositis is prolonged in patients on acyclovir prophylaxis [20, 21]. Respiratory viral infections especially caused by RSV, parainfluenza, and influenza can occur early and are frequently due to nosocomial transmission within the transplant unit and therefore infection control procedures should be in place during times due to community outbreaks of these viruses [22–27]. Lower respiratory tract infection due to RSV and parainfluenza are associated with significant mortality. Patients, who are HBV DNA positive or HBsAg positive, before aHSCT are at risk for severe hepatitis and should be given prolonged antiviral prophylaxis [28–30].

Intermediate Posttransplant Period (3 Weeks to 3 Months)

Specific Epidemiology of Infections in the Intermediate Posttransplant Period

In the majority of allogeneic stem cell transplant recipients, infections emerge later than day +50 posttransplant. After hematopoietic reconstitution, a severe combined quantitative and functional deficiency in the T and B lymphocyte compartment persists. If T-cell depletion has been used, or if HLA-incompatibility between recipient and donor had to be accepted, immunodeficiency will be prolonged after transplantation. Immunodeficiency comprises impaired T helper cell function, immunoglobulin synthesis, and cytotoxic T cell response. Despite normalization of white blood cell counts, compromised granulocyte functions, primarily impairment of chemotaxis and phagocytosis, may persist.

Bacterial and Fungal Infections in the Intermediate Posttransplantation Period

In 14% of patients, bacteremia occurs after hematopoietic engraftment, with a mortality rate comparable to that before and after engraftment. Among blood culture isolates, Gram-positive pathogens (staphylococci in particular) are predominant, with the focus being identified in more than 50% of patients. Venous catheter infections are the cause for more than 30% of bacteremias, and fever and chills within the first hour after start of fluid infusion typically are indicating a catheter-related bacteremia. Other more frequent infections during the intermediate posttransplant period are pneumonias, preferably caused by *Streptococcus pneumoniae*, *Klebsiella* species, and *P. aeruginosa*, or by filamentous fungi such as *Aspergillus*. Among less frequent bacterial

pathogens relevant during this period are *Listeria monocytogenes* and *Legionella pneumophila*. While listeriosis may origin from products made from unpasteurized milk, the latter typically is related to the use of showers or jacuzzis after the water has been resting in the pipes for a longer period of time. In patients who are treated with tumor necrosis factor antagonists such as infliximab, a dramatic increase in the risk of invasive fungal infections must be considered [31, 32]. Apart from aspergillosis, some rare forms of invasive mycosis caused by *Fusarium* spp., zygomycetes, resistant *Candida* spp., *Pseudallescheria boydii* (or its asexual form, *Scedosporium apiospermum*), and others may occur during this time period [33]. Typically, patients with fusariosis have skin lesions and positive blood cultures, while zygomycetes cause clinical syndromes resembling aspergillosis.

Viral Infections

Viruses are common causes of infections during the period from engraftment to day +90 after HSCT. The classic viral pathogen during this period is CMV called "the troll of transplantation." CMV reactivates in 60–70% of pretransplant seropositive patients and primary infections occur in up to one third of seronegative patients with seropositive donors [34]. Established end-organ CMV disease is still associated with significant morbidity and mortality. Therefore, preventive strategies either by antiviral prophylaxis or preemptive therapy should be used [35, 36]. Antiviral prophylaxis has been less used, but new antiviral agents might make this strategy more attractive. Monitoring with sensitive assays such as pp65 antigenemia or quantitative PCR in blood is indicated in all aHSCT recipients to allow early initiation of antiviral therapy with ganciclovir or valganciclovir [35].

Epstein-Barr Virus (EBV) also reactivates very frequently after aHSCT, but rarely causes end-organ disease [37]. However, EBV-driven posttransplant lymphoproliferative disease (PTLD) is a complication with high mortality unless treated [38–41]. This complication is more commonly seen in EBV seronegative patients receiving grafts from EBV seropositive donors and in patients having delayed immune reconstitution such as after a T-cell-depleted or HLA-mismatched stem cell transplantation. PTLD frequently causes unspecific symptoms frequently with fever and lymphadenopathy and is associated with high levels of EBV in blood [39, 40, 42–44]. Rituximab (anti CD20 antibody) given either as preemptive therapy or as therapy for established PTLD is most likely effective, although no controlled trial has been performed [45–49].

Adenovirus infections can cause multiorgan disease including pneumonia, encephalitis, hepatitis, gastroenteritis, and hemorrhagic cystitis. Severe adenovirus disease is more frequently seen in children especially after transplant

procedures resulting in delayed reconstitution of the immune system such as haploidentical transplants or mismatched cord blood grafts and monitoring for adenovirus in blood might be indicated in such patients [50–57]. Cidofovir is a potentially effective antiviral agent, but is associated with nephrotoxicity [58–60].

Other viral pathogens potentially important during this period after HSCT are HHV-6 associated with encephalitis and bone marrow suppression [61–66], BK-virus infections associated with hemorrhagic cystitis [67, 68], and respiratory viruses.

Late Period After Allogeneic Stem Cell Transplantation (Later than Day +90)

Specific Epidemiology of Infections During the Late Posttransplant Period

In the late posttransplant period, immune reconstitution usually advances, particularly in patients who have received a transplant from an HLA-identical family donor. These patients often show full hematopoietic reconstitution and early immune reconstitution. If no relevant GVHD emerges, prophylactic immunosuppression will typically be discontinued. Patients with a CD4-count of >200/μL blood and normalized serum immunoglobulin levels can be considered as immunocompetent without an increased risk of opportunistic infections. However, in the case of chronic GvHD, which may occur in more than 30% of patients, a severe combined cellular and humoral immunodeficiency will persist for a prolonged period of time. Mucosal damage, functional deficiencies of granulocytes (especially impaired chemotaxis), functional asplenia, and qualitative as well as quantitative T- and B-cell deficiencies pave the way to a significantly increased susceptibility to infections in these patients. In particular, bacterial infections of the respiratory tract constitute a major cause of death [69]. Life-threatening infections are typically caused by encapsulated bacteria such as *S. pneumoniae* or *Haemophilus influenzae*. Sinusitis, otitis media, and pharyngitis may indicate such infections in the late posttransplant period. Patients among this risk group presenting with signs of infection should receive immediate antibacterial treatment.

An important pathogen of interstitial pneumonia in the late phase after allogeneic stem cell transplantation is *P. jiroveci* [70]. Without specific prophylaxis, about 30% of patients with chronic GvHD develop *Pneumocystis* pneumonia, which can take a fatal course in up to 15% of patients and prophylaxis given for at least 6 months (and longer in patients with chronic GvHD) is recommended to all patients. In regions with relatively high prevalence rates, mycobacterial infections should be taken into consideration as well [71, 72].

Late Viral Infections After Stem Cell Transplantation

Late-occurring CMV infection and disease have become more frequent during the last decade. These are associated with delayed and incomplete reconstitution of specific immunity, primarily of T-cells, and occur more commonly in patients experiencing severe GvHD [73, 74]. Prolonged monitoring and repeated antiviral therapy are needed in such patients, although toxicity from antiviral therapy and development of resistant CMV strains are important considerations [34, 36]. The possibility to reconstitute specific immunity by adoptive transfer of T-cells has been explored by several groups.

VZV is an important pathogen after HSCT. Primary varicella – chickenpox – occurring in seronegative patients is an important complication especially in children. Preventive measures should be taken after exposure and i.v. acyclovir therapy given if the infection develops. VZV can reactivate also early after aHSCT, but infections are more commonly seen during the late posttransplant period. The clinical manifestations vary from localized herpes zoster – shingles – to visceral disseminated disease associated with high mortality [75–77]. Visceral disease including CNS disease can occur without cutaneous manifestations and can therefore be difficult to diagnose. Early initiation of antiviral therapy with intravenous acyclovir is crucial when visceral or disseminated VZV disease is suspected. Localized shingles can often be treated with orally given valacyclovir or famciclovir [37]. In many centers, longterm prophylaxis given for at least one year after HSCT is used to prevent VZV reactivations [78, 79].

Respiratory viruses, especially influenza, can also be severe late after HSCT. Yearly vaccination against influenza is therefore recommended [80]. RSV and parainfluenza infections have been associated with late respiratory compromise presumably through immune-mediated mechanisms [81, 82].

HBV infection can reactivate in previously HBV-infected patients, especially during prolonged treatment for GvHD. Reactivation can result in a potentially severe acute hepatitis and patients should be carefully monitored, and if signs of HBV reactivation develop, be given antiviral therapy [28–30].

Late Fungal Infections After Stem Cell Transplant

Fungal infections during late transplant period are discussed in detail in Part III.

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Chapter 3
Infections in Patients with Hematologic Malignancies

Genovefa Papanicolaou and Jayesh Mehta

Abstract Hematologic malignancies are a heterogeneous group of diseases with differing clinical manifestations, disease course, response to therapy, and long-term outcome. More intensive therapies are also being extended to older age groups and to patients with significant comorbidities, which were traditionally excluded from such treatment. These intensive treatment approaches are associated with multiple complications; infections from a wide variety of pathogenic and opportunistic organisms being amongst the commonest and the most serious. Infections affect quality of life, delay potentially saving chemotherapy and pose a substantial burden for the health care system and remain an important cause of death. In this chapter we outline the common immune defects and associated infections frequently seen in patients with hematologic malignancies.

Keywords Leukemia • Lymphoma • Multiple myeloma • Infections • Serious • Immune dysfunction • New chemotherapy • Old age

Introduction

Hematologic malignancies are a heterogeneous group of diseases with differing clinical manifestations, disease course, response to therapy, and long-term outcome. Response to therapy and long-term survival has improved significantly over the last few decades as a result of the development of more intensive and effective treatment approaches [1, 2]. These intensive treatment approaches are associated with multiple complications in patients with hematologic malignancies. Infections from a wide variety of pathogenic and opportunistic organisms are amongst the commonest and the most serious [2–5]. The availability of new, broad-spectrum antimicrobial agents has improved outcomes – but has also

resulted in alterations in the types of infections seen. Hersh et al. noticed this trend almost half a century ago [6]. Over the study period, infections were amongst the major causes of death in 70% of the acute leukemia patients who died. Fatal staphylococcal infections declined by 85% over the period but fatal fungal infections tripled.

Microbiologically or clinically documented infection develops in 60–80% of patients undergoing induction chemotherapy for acute leukemia. Up to 50% of patients with chronic lymphocytic leukemia suffer from recurrent infections. Infections affect quality of life, delay potentially saving chemotherapy, pose a substantial burden for the health care system and remain an important cause of death for patients with hematologic malignancies [7–14].

Immune Host-Defects in Hematologic Malignancies

Under normal circumstances, the immune system consists of multiple layers that each contribute to protection against infection. Redundancy at the cellular and signaling level limits the potential for microbes to escape this defensive system, and modest compromise of one layer of immune defense may not be readily apparent. In patients with hematologic malignancies, the redundancy of the immune system has been severely compromised. Innate immune defenses like mucosal integrity, neutrophil and monocyte function, and numbers may be compromised as a result of cytotoxic therapy or steroids. In many cases, the underlying disease or therapy has compromised or even eliminated the adaptive immune system (i.e., antibody generation and T-cell responses). The underlying immune defect often plays a major role in defining the type and clinical presentation of many infections. For example, infection by *Streptococcus pneumoniae* often presents as fulminant sepsis in splenectomized patients [15, 16]. Community respiratory viruses causing self-limited upper respiratory infections in healthy individuals have been associated with high mortality in patients with leukemia [17]. Prevention of infection is

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Table 3.1 Infections control: close attention to all potential sources of infection [18]

Environment
- Ventilation and construction: *Aspergillus*
- Water*: Legionella pneumophila*
- Environmental surfaces: *Clostridium difficile,* VRE
- Invasive medical devices

Health care workers
- Hand washing
- Isolation technique
- Preemptive barrier precautions

Visitors

Contact with food, flowers, toys

Table 3.2 Role of host defenses on patient response: neutropenia significantly worsened response rates in patients with invasive aspergillosis [19]

Neutropenia status	Patient response to therapy		
	Aspergillus fumigatus	*Aspergillus terreus*	*P* value
No neutropenia	53% (8/15)	50% (4/8)	0.01
Neutropenia resolved	50% (4/8)	44% (4/9)	0.01
Persistent neutropenia	10% (1/10)	6% (1/15)	0.01

paramount for the most vulnerable patients. Close attention is paid to all potential sources of infection including the environment, health care workers, and visitors (Table 3.1) [18].

Immune recovery plays an important role on the outcome of infection (Table 3.2) [19–21].

A useful initial approach is the recognition of the major predisposing factors broadly classified as: (1) granulocytopenia and qualitative defects of phagocytes; (2) cellular immune dysfunction; (3) humoral immune dysfunction and (4) impaired mucosal integrity. More than one predisposing factors may be present at any given time. Classic associations between specific immune defects and types of infectious pathogens are helpful to guide the initial approach to the patient. Table 3.3 shows the predominant pathogens associated with major immune defects.

Neutropenia

Neutrophils are the first line of defense against pyogenic bacteria and fungi. The lack of inflammatory response due to the absence of neutrophils may result in rapid progression of infection in the absence of signs and symptoms. The relationship of granulocytopenia and risk of infection is well-established. It is widely appreciated that risk of infection increases very little until the granulocyte count drops below 500/mm^3 and rises rapidly as the count approaches 0 [22]. The severity and duration of neutropenia are important determinants of the type of infectious complications (Fig. 3.1).

Patients whose neutropenia persists for 10 days or longer are at high risk not only for acute bacterial infections, but also for secondary infections due to fungi and viruses. The risk of infection is more pronounced in patients who have a rapidly falling granulocyte count than in patients who have a prolonged stationary granulocyte count such a in myelodysplastic syndrome [23].

The bacterial pathogens isolated from neutropenic patients at the early stages of neutropenia tend to originate from the patients' endogenous flora. Gram-negative enteric organisms, α-hemolytic streptococci and enterococci are associated with oral and gastrointestinal mucositis. Skin related pathogens (staphylococci, coagulase negative staphylococci, and *Corynebacterium* spp.) are associated with line infections (Table 3.3).

The most common sites of infection are the bloodstream followed by lung and GI tract. Seeding of infection from the bloodstream may lead to localized abscesses that may become clinically apparent after neutrophil recovery (Fig. 3.2). Fever with mucositis and abdominal pain raises suspicion of neutropenic enterocolitis (typhlitis).

Since the mid-1980s, 60–70% of bacteremias associated with a single organism are caused by Gram-positive organisms [24–26] (Fig. 3.3). An increase in Gram-positive and polymicrobial infections is noted over the 15-year period of study.

The rise in the incidence of multiresistant organisms among patients with hematologic malignancies may reflect broader trends observed in nosocomial pathogens [27, 28].

The 30-day mortality rates for neutropenic patients with bacteremia approach 30% [13, 29, 30]. Polymicrobial bacteremia and fungemia have been associated with highest mortality rates [31]. Viridans streptococcal bacteremia has been associated with a toxic-shock-like syndrome with hypotension maculopapular rash palmar desquamation, and acute respiratory distress syndrome [32–34].

Persistent fever in a neutropenic patient despite broad spectrum antibiotics should raise suspicion for fungal infection. Prior to the implementation of preemptive antifungal therapy, up to 50% patients treated for leukemia were found to have a fungal infection at autopsy [35]. Empiric antifungal therapy has substantially reduced the incidence of fungal infections during neutropenia [36]. Only the minority of fungal infections is diagnosed antemortem (Fig. 3.4).

The likelihood of patients requiring systemic antifungals during neutropenia has changed over the years due to changes in our use of antifungal prophylaxis (Table 3.4).

The predominant fungal pathogens in neutropenic patients are shown on Table 3.3. *Candida* remains the most common yeast causing bloodstream infection (Fig. 3.5). In a recent study, the incidence of candidemia in patients with hematologic malignancies was approximately 20 episodes per 1,000

Table 3.3 Predominant pathogen association with selected host immune defects

Host defense	Bacteria	Fungi	Viruses	Other

Neutropenia	Gram-positive
	  Staphylococci (CoNS, *S. aureus*)
	  Streptococci (α-hemolytic, Group D)
	Anaerobes
	  Anaerobic streptococci
	  Clostridium spp.
	  Bacteroids spp.
		Candida spp.
		Aspergillus spp.
		Trichosporon spp.
		Fusarium spp.
		Mucor		

Cellular dysfunction	*Legionella* *Salmonella* *Nocardia* Mycobacteria (TB and atypical) Live bacteria vaccine (BCG)	*Cryptococcus* *Histoplasma* *Coccidioides* *Candida* spp. *Pneumocystis*	Herpes viruses VZV, CMV, HSV, HHV6, EBV Respiratory viruses Live virus vaccines	*Toxoplasma* *Cryptosporidium* *Strongyloides*

Humoral dysfunction	Gram positive
	  S. pneumoniae
	  S. aureus
	Gram-negative
	  H. influenzae
	  Neisseria spp.
	  Enteric organisms
			Enteroviruses
			Live vaccine viruses
				Giardia

Anatomic disruption				

Upper GI	Mouth flora
	  α-Hemolytic streptococci
	  Anaerobic *Peptostreptococci*
		Candida	Herpes simplex	

Lower GI	Gram-positive (Group D streptococci)
	Enteric Gram-negative organisms
	Anaerobes
	  Bacteroides, *Clostridium* spp.,
	    Group D streptococci
		Candida		

Skin	Gram-positive
	  Staphylococci
	  Corynebacterium spp.
	Gram-negative
	  Pseudomonas spp.
	  Enteric Gram-negative
	Mycobacteria
	M. abscesses fortuitum,
	  Mycobacterium chelonei
		Candida
		Aspergillus		

Splenectomy	Gram-positive
	  S. pneumoniae
	  DF2 bacillus
	  Capnocytophaga canimorsus
	Gram-negative
	  H. influenzae
	  Salmonella spp.
	  Neisseria meningitidis
				Babesia

patient days despite antifungal prophylaxis. Non-albicans species predominated with *Candida tropicalis* and *Candida parapsilosis* accounting for 40% of all isolates. An increase in the frequency of fluconazole-resistant *Candida* species including *Candida glabrata* and *Candida krusei* has been noted in several studies possibly as a result of antifungal prophylaxis with fluconazole [37, 38]. A complication of

candidemia is chronic disseminated candidiasis (hepatosplenic candidiasis). The only symptom may be persistent fever after resolution of neutropenia. Numerous target lesions in the liver and spleen may be apparent by CT imaging [39] (Fig. 3.6).

Infections by filamentous fungi, *Aspergillus* being the most common, are an important cause of mortality in patients
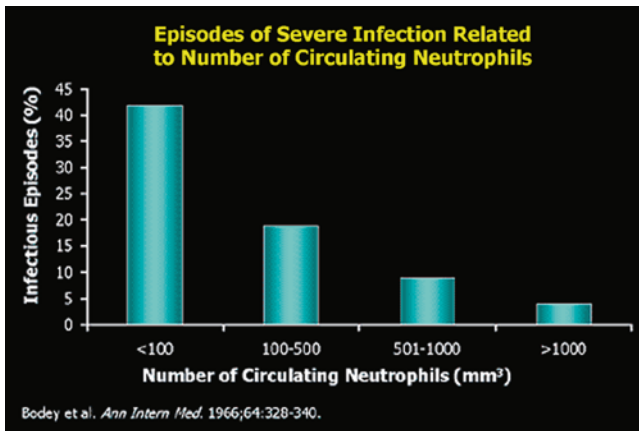
Fig. 3.1 Episodes of severe infection related to numbers of circulating neutrophils. Bodey et al. examined the occurrence of severe infection in 52 patients with acute leukemia treated at the National Institutes of Health from 19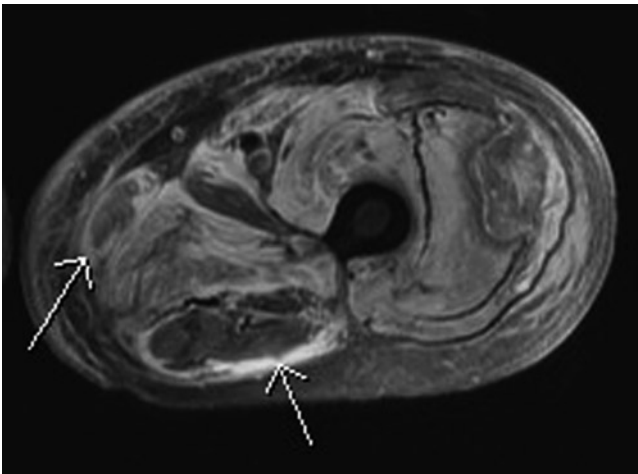59 to 1963. The risk of developing severe infection at a given neutrophil count was calculated form the number of severe infections occurring per 1,000 days at each neutrophil count. When severe neutropenia was present 43 episodes of severe infection were observed per 1,000 days

Fig. 3.2 MRI of thigh of a patient with lymphoma after neutrophil recovery form intensive chemotherapy. Multiple abscesses are shown in proximal/mid left. Diffuse edema and enhancement is noted in the muscles, along the fascia and subcutaneous issues. Aspirate of the abscess grew *Pseudomonas aeruginosa*

with hematologic malignancies [3, 40, 41]. The lungs are the most common site of infection followed by the sinuses. Aspergillosis of the central nervous system (CNS) may result from hematogenous dissemination with mortalities approaching 100% (Fig. 3.7) [42].

Zygomycosis is much less common than aspergillosis, but a rising trend has been noted increased use of prolonged antifungal prophylaxis with agents active against *Aspergillus*, such as voriconazole (Fig. 3.8) [43, 44].

Other molds previously thought to be contaminants or colonizers have been recognized to be causing invasive
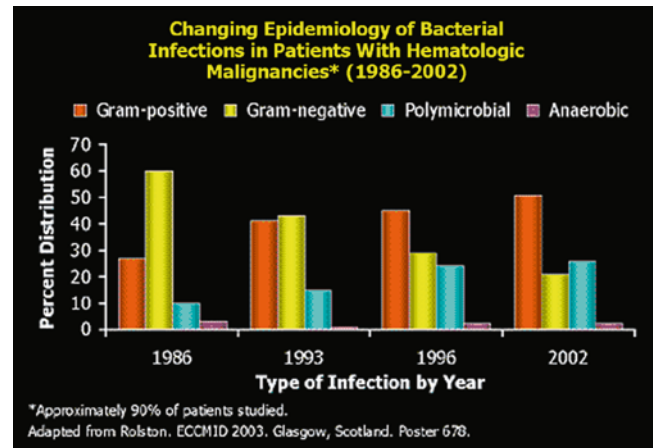
Fig. 3.3 Changing epidemiology of bacterial infections in patients with hematologic malignances. An increase in Gram-positive and polymicrobial infections is noted over the 15-year period of study
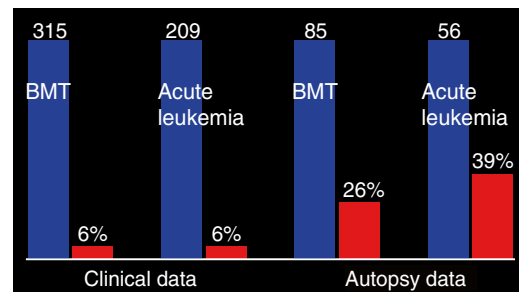
Fig. 3.4 The incidence of fungal infections is underestimated due to our inability to establish the diagnosis antemortem. *Left*: Number of patients dying after allogeneic bone marrow transplantation or induction/salvage therapy for acute leukemia (*blue bars*) over a 12-year period at the Royal Marsden Hospital, UK and percentage in whom fungal infections were clinically suspected (red bars). *Right*: Autopsy data: The subset of patients who had autopsy (*blue bars*) and percentage in whom fungus was detected (*red bars*)

mycoses in severely immunosuppressed patients. Sinusitis with emerging fungal pathogens including Fusarium and dark-walled molds are being recognized with increasing frequency [45].

Qualitative Phagocyte Defects

Chemotaxis, cell activation, phagocytosis, and intra- or extracellular killing by oxygen-dependent and oxygen-independent pathways may be compromised in the presence of adequate cell numbers.

Intrinsic functional defects of granulocytes exist in patients with acute leukemia, myelodysplastic syndromes and preleukemic states [46]. From a clinical perspective such patients with borderline granulocyte count should be approached as if they had absolute neutropenia.

Table 3.4 Changes in the incidence of presumed/confirmed fungal infection with changes in antifungal prophylaxis

Stage of disease	Royal Marsden Hospital, UK, 1992–1995		Northwestern Memorial Hospital, Chicago, IL, 2002–2005	
	Antifungal prophylaxis	% of patients requiring systemic antifungal therapy	Antifungal prophylaxis	% of patient requiring systemic antifungal therapy
A. Acute Myelogenous Leukemia				
Within 6 weeks of induction	Nystatin	44%	Fluconazole	13%
Autograft in CR1	Nystatin	31%	Fluconazole	8%
Allograft in CR1	Nystatin	51%	Voriconoazole	15%
B. Multiple Myeloma				
Within 12 weeks of induction	None	4%	Fluconazole	0%
Early autograft	Nystatin	9%	Fluconazole	0%
Allograft for relapsed disease	Nystatin	67%	Voriconazole	0%

Percentage of patients requiring systemic antifungals during treatment for acute myelogenous leukemia (A) or multiple myeloma (B) over a 12-year period (Courtesy of Dr. Jayesh Mehta)
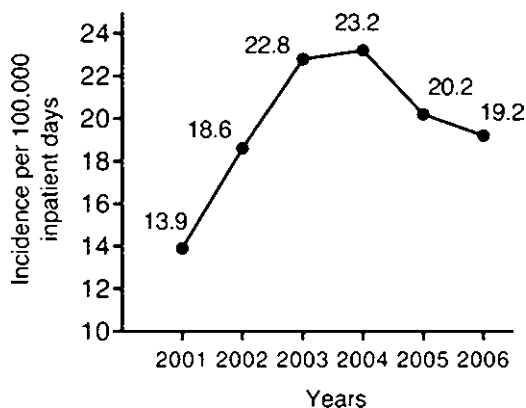
Fig. 3.5 Incidence of candidemia among patients with hematologic malignancies during 2001–2007 at the M.D Anderson Cancer Center. A slight decrease in the incidence of candidemia was observed during the last 2 years of the study. Seventy-six percent of infections were caused by non-albicans species. The attributable during the study period was 19%

Fig. 3.6 Hepatosplenic candidiasis in a patient with acute myelogenous leukemia in remission. The patient developed persistent fever after four cycles of chemotherapy and associated prolonged neutropenia. CT of the abdomen: Multiple hypodense lesions in the liver. Liver biopsy showed granulomatous necrosis with yeast forms consistent with *Candida*

Leukemia and lymphoma are associated with intrinsic defects in monocyte function. Circulating monocytes are precursors for alveolar and lamina propria macrophages, the mucosal cells that play an important role in earliest defense against pulmonary and intestinal infection [47]. Although the exact relationship between circulating monocytes and infection has not been explored it is reasonable though to hypothesize that these cells would make an important contribution in the defense against bacterial or fungal infections.

Treatment modalities such chemotherapy, corticosteroids, radiation or growth factors may result in phagocyte dysfunction. The major effect of corticosteroids on granulocyte function appears to be impairment of chemotaxis which decreases localized inflammatory response. In vitro, steroids inhibit phagocytosis, microbicidal activity and antibody dependent cytotoxicity. In addition, a number of monocyte functions are impaired including chemotaxis, bactericidal activity, and production of interleukin-1 and TNF-α. Use of Corticosteroids predisposes to infections by pathogens that depend on phagocyte function such as *Staphylococcus aureus*, *Enterobacteriaceae*, and *fungi*. The risk of infection increases when the adult equivalent of prednisone 20–40 mg/day or higher is administered for longer than 4–6 weeks.

Steroids may also enhance susceptibility to infection though delay in wound healing, increased skin fragility, and impairment of lymphocyte function.
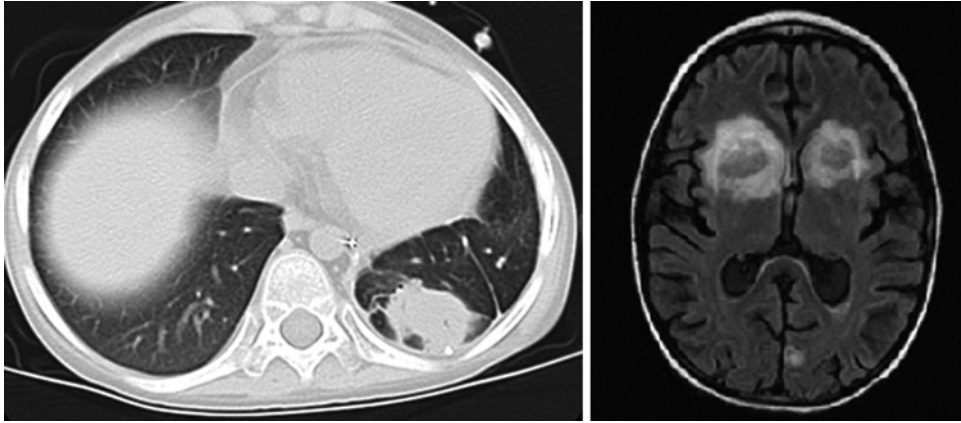
Fig. 3.7 Disseminated aspergillosis in a child with leukemia; *Left*: Chest CT demonstrating cavitary lesion. Biopsy showed septate hyphae. *Right*: MRI showing bilateral frontal lobe ring enhancing lesions
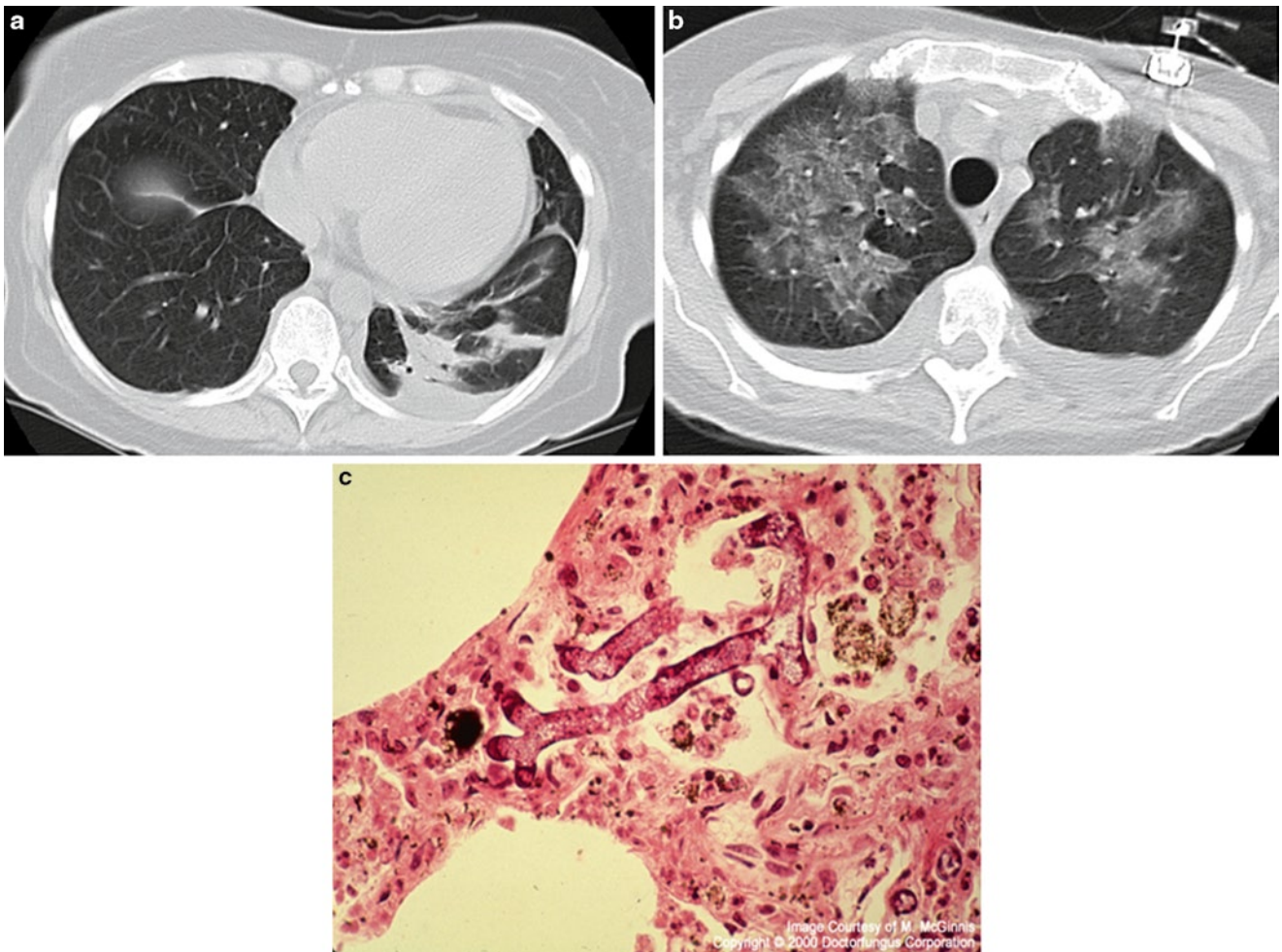
Fig. 3.8 Influenza and Mucor pneumonia in a heavily treated patient with lymphoma. Initially the patient presented with influenza infection and a left lung consolidation (**a**). Several weeks after empiric treatment with voriconazole the patient presented with respiratory distress and diffuse interstitial infiltrates (**b**). Sputum culture grew *Aspergillus* spp. and *Mucor* spp. Nasopharyngeal cultures were persistently positive for influenza A. Autopsy showed broad nonseptate hyphae consistent with zygomycosis (**c**)

Cellular Immune Dysfunction

Intrinsic defect in cellular immunity is the hallmark of immune dysfunction seen in lymphoma. T-cell function is required for macrophage activation and subsequent microbicidal activity. In the absence of functional T-cells, intracellular pathogens may survive and replicate inside macrophages. The pathogens causing infections in patients with impaired T-cell immunity include a broad array of intracellular bacteria, fungi, DNA viruses, and protozoa (Table 3.2).

Endemic fungi like *Histoplasma* or *Coccidioides*, or parasites like *Strongyloides stercoralis* may reactivate and cause severe disease during intense chemotherapy. A variety of opportunistic pathogens like atypical mycobacteria, Nocardia (Fig. 3.9), or toxoplasma may cause disseminated disease in patients with impaired T-cell immunity.

Lymphoreticular malignancy and corticosteroid therapy seem to be a major factor for infection by the opportunistic fungi *Cryptococcus* spp. and *Pneumocystis jiroveci* (Fig. 3.10).

The most common manifestation of cryptococcal infection is meningitis though primary pneumonia, fungemia, and cutaneous or visceral dissemination may occur.

Protective immunity against most viruses is highly dependent on virus-specific, MHC-restricted T-lymphocytes. Infections by the herpes viruses including herpes simplex (HSV), Varicella-zoster virus (VZV), and cytomegalovirus (CMV) are almost exclusively due to reactivation. HSV infections range from 15% among CLL patients treated with fludarabine to 90% of patients with acute leukemia. Mucocutaneous HSV disease will frequently present with an atypical appearance and can mimic other pathogens. The

incidence of VZV infections ranges from 2% in patients with CML receiving imatinib to 10–15% in patients with CLL receiving fludarabine or alemtuzumab to 25% of patients with Hodgkin's lymphoma. More than 80% of VZV infections present with localized disease. Patients who are VZV naïve are at risk for primary infection with either wild type or vaccine strains and should be counseled about the risk of developing such an infection. T-cell depleting agents (e.g., alemtuzumab) and aggressive chemotherapy (e.g., hyper-CVAD and acute leukemia induction) appear to increase the incidence of CMV infection and disease [48].

Fulminant hepatitis B may occur during immunosuppression in patients with active hepatitis B [49, 50]. Disseminated disease caused by vaccination with live viruses such as varicella and polio and or bacteria such as BCG have been reported [51].

Humoral Immune Dysfunction

Multiple myeloma and chronic lymphocytic leukemia are associated with intrinsic defects in humoral immunity. Immunoglobulins and complement provide opsonic, lytic, and neutralizing activities essential for protection against bacterial pathogens. Impaired humoral immunity is a risk factor for recurrent infections from polysaccharide-encapsulated bacteria such as *S. pneumoniae*, *Haemophilus influenzae*, or *Neisseria* spp. Pyogenic infections by enteric Gram-negative organisms and staphylococci are also frequently encountered (Table 3.3).
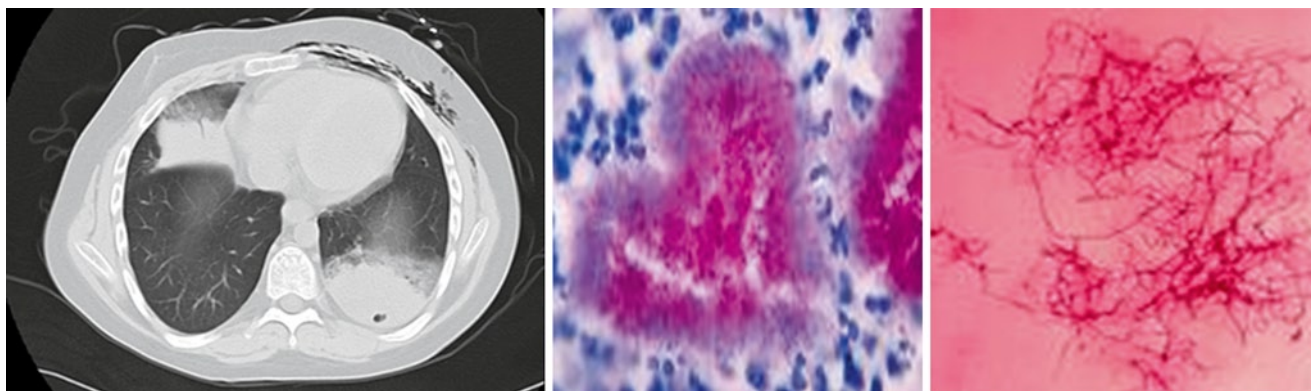
Fig. 3.9 Pulmonary nocardiosis in patients with lymphoma treated with high dose steroids, CT Chest (*right*) showed consolidation with cavitation in the right middle lobe and left lower lobe (*left*). At autopsy bilateral pneumonia and pulmonary abscesses were noted (*middle*) with colonies of filamentous micro-organisms morphologically consistent with *Nocardia* species (*right*)

Fig. 3.10 Patient with lymphoma treated with Alemtuzumab and steroids presenting with shortness of breath. CT of chest showed nodular and interstitial infiltrates. Septate hyphae consistent with *Aspergillus* and *Pneumocystis* were noted at autopsy

The sites of infection are most frequently the upper respiratory tract, the urinary tract, or the skin. Septicemia occurs less frequently, but it does cause significant morbidity and mortality.

Normal humoral immune function is essential for the control of enteroviruses in the acute viremic phase. Chronic carriers of Hepatitis B are at risk for severe Hepatitis B reactivation after treatment with rituximab, a monoclonal antibody against B-cells [52]

Splenic Dysfunction

The spleen removes opsonized and non-opsonized microorganisms form the circulation and is the principal organ for the production of antibody to polysaccharide antigens. Splenectomized patients have decreased levels of IgM and properdin, and may be deficient in other phagocytosis promoting peptides. Splenectomized patients are highly vulnerable to bacterial infections by *S. pneumoniae* and *H. influenzae*, as well as *Neisseria* spp. and *Capnocytophaga canimorsus* (Table 3.2). Overwhelming infection after splenectomy occurs in 6.9% of post splenectomy patients with 50% of the infection-related deaths occurring within the first 3 months post splenectomy. Even overwhelming infection may present with subtle symptoms. Asplenic patients with

underlying hematologic malignancy who present with fever should be managed initially as potentially septic.

Mucosal Impairment

Mucosal immunity of the gastrointestinal, sinopulmonary, and genitourinary tracts constitute the first line of host defense against invasion of these barriers by microorganisms. Oral and gastrointestinal mucositis is a frequent complication of treatment of patients with hematologic malignancies ranging from mild erythema and soreness to ulcerations with hemorrhage. The pathophysiology of mucositis is complex, involving initial damage by oxygen free radicals, followed by upregulation of proinflammatory cytokines and microvascular damage. This ultimately leads to ulceration, which is exacerbated by bacterial, viral, and fungal colonization [53–55]. In neutropenic patients, more than 80% of microbiologically documented infections are caused by organisms that are part of the endogenous flora and about one-half of the etiologic agents are acquired by the patients subsequent to hospital admission [56, 57].

Immune Defects in Specific Malignancies

The recognition of the principal immune defect enables us to assess the relative risk for specific pathogens. The predominant immune defects associated with most common hematologic malignancies and their treatments are listed on Table 3.5. Multiple immune deficits can coexist in the same patient.

Acute Leukemia

Severe and prolonged neutropenia and mucositis are the major immune defect in patients with acute leukemia undergoing intensive chemotherapy. Intensive induction chemotherapy or consolidation chemotherapy for acute leukemia are usually followed by 2–4 weeks or 8–12 days of neutropenia respectively. Fever develops in the vast majority of patients with neutropenia. An organism is identified in approximately 50% of the cases. The most common infections and causative agents during the neutropenic phase in acute leukemia are listed on Table 3.3.

Patients with acute lymphoblastic leukemia, hairy cell leukemia, and mycoses fungoides have an intrinsic impairment in cellular immunity. These patients are susceptible to opportunistic pathogens like *P. jiroveci* and reactivation of

Table 3.5 Predominant immune defects associated with common hematologic malignancies

Disease		Host defense impairment					
		Neutropenia	Phagocyte defects	Cellular immunity	Humoral immunity	Splenic dysfunction	Anatomic disruption
AML	Disease	+++	+	−	−	−	±
	Treatment	+++		+	+	−	+++
ALL	Disease	+++	+	+	−	−	±
	Treatment	+++		++	++	−	+++
Hairy cell leukemia	Disease	++*	+	±	±	−	±
	Treatment	++		+	++	If splenectomy	±
CLL	Disease	±	+	±	+++	±	±
	Treatment	++		++	++	++	+
CML	Disease	±	+	−	−		±
	Treatment	±		±	−		±
Myeloma	Disease	±	+	±	+++		±
	Treatment	± to ++		++	++		± to +
Lymphoma	Disease	−	+	+++	±	±	±
	Treatment	± to +++		++	++	If splenectomy	± to +++
MDS	Disease	++	+	−	±		±
	Treatment	++		+	−		

++ to +++: Significant; +: known; ±: not prominent;* also monocytopenia

latent viruses primarily varicella zoster and herpes simplex (Table 3.5) [58].

Chronic Lymphocytic Leukemia

In chronic lymphocytic leukemia, an intrinsic defect in the clonal B-cells leads to unbalanced immunoglobulin chain synthesis resulting in hypogammaglobulinemia. Impairments in cellular immunity, the complement system, and variable neutropenia depending on the extent of marrow involvement may also contribute to susceptibility to infections [59].

The incidence of infection correlates with the duration and the stage of disease as well as with the serum levels of immunoglobulins (particularly IgG). Up to 50% of patients with CLL experience recurrent infections [59]. The 25-year risk for severe infection was 26% in one cohort of 125 patients analyzed over 10 years [60]. In patients treated with conventional chemotherapy, infections are likely to be mainly bacterial; including *S. pneumoniae, S. aureus*, and enteric Gram-negative organisms. Opportunistic infections such as *Pneumocystis* and fungal infections are uncommon as cellular immunity is preserved in the early stages of disease [59].

Treatment with purine analogues (fludarabine and clofaradine) usually results in prolonged lymphopenia [59, 61]. Reactivation of HSV or VZV occurs approximately in 10–15% of patients treated with fludarabine [62–64]. The relative risk of infection related to cell-mediated immunity deficit is increased when fludarabine is combined with corticosteroids or alemtuzumab treatment [59, 61, 65]. The

incidence of infection in patients treated with Alemtuzumab appears higher in pretreated patients compared to patients receiving alemtuzumab as first line single agent [66–74]. Although the majority or infections occur within the first 3 months of treatment some infections were reported up to 180 days post treatment [75, 76]. The addition of the anti B-cell antibody rituximab to nucleoside analogue based therapy does not appear to increase the risk of early or late infections [77, 78].

Myeloma

In multiple myeloma, the intrinsic immune deficits are a reduction in polyclonal immunoglobulin synthesis and a failure to make appropriate antibody responses post immunization. Cell-mediated immunity is intact unless patients are treated with corticosteroids of cytotoxic chemotherapy. The degree of humoral immunity impairment is related with the stage of disease [79]. Patients who have responded to chemotherapy and are in the "plateau phase" are at a low risk [80].

Infection is the most common cause of death among patients with multiple myeloma, accounting for 20–50% of all deaths. The sites of infections and causative pathogens are reviewed in Table 3.5. Most infections in newly diagnosed patients and during the first cycles of chemotherapy are caused by *S. pneumoniae, S. aureus* and *H. influenzae*, or *Neisseria* spp. In patients with renal failure, relapsed and/or refractory advanced disease, more than 90% of the infectious episodes are caused by Gram-negative bacilli or *S. aureus* [81]. Patients treated with bortezomib, particularly in

combination with dexamethasone or cytotoxic agents, have a high incidence of varicella-zoster infections and prophylaxis with acyclovir is indicated [82]. An increased incidence of Aspergillosis has been reported after intensive chemotherapy and associated neutropenia [83].

Strategies for the prevention of infection in patients with myeloma include prophylactic antibiotics, passive immunization with polyclonal or specific immunoglobulins, and vaccinations.

Lymphoma

Impaired cellular immunity is the predominant intrinsic host immune defect in patients with Hodgkin's disease and non-Hodgkin's lymphomas. In addition, cytotoxic agents administered alone or in combination with steroids are major causes of impaired T-cell immunity. Fludarabine or Alemtuzumab (MabCampath®) result in profound and prolonged depletion of lymphocytes. Radiation can result in impaired T-cell immunity especially when given in combination with other immunosuppressive agents. Some degree of cellular dysfunction may persist even in patients who have been in remission for several years [84]. The most common sites and pathogens associated with impaired cellular immunity are reviewed in Table 3.3.

In patients with T-cell lymphoma, bacterial sepsis is the most common infectious complication and accounts for about 50% of all deaths [85, 86]. Cutaneous bacterial infections in particular due to *S. aureus* are the most common followed by cutaneous herpes simplex and VZV, bacteremia, bacterial pneumonia, and urinary tract infection [87]. In patients with T-cell lymphoma treated with alemtuzumab, CMV (CMV reactivation) is the most common viral infection followed by HSV and VZV [88, 89]. A high incidence of mold infections has also been reported [88]. Patients with HTLV-1 associated T-cell lymphoma are at increased risk of infection with *S. stercoralis* and possibly with *Mycobacterium tuberculous* and leprosy [90].

Summary

Over the last two decades, the increasing intensity of chemotherapeutic regimens and improved survival of patients with hematologic malignancies have lead to an increased population of highly immunocompromised individuals. Our evolving understanding of the immune system, sensitive diagnostic methods, and effective antiinfectives have led to an overall improvement in the incidence of infections and associated mortality. The relentless selective pressures on pathogens have led to shifts in the epidemiology of infections. A multidisciplinary team consisting of oncologists, infectious disease clinicians, and basic scientists is required to address the constantly evolving challenges of infections in patients with hematologic malignancies.

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Chapter 4
Infections in Solid Tumor Patients

Alison G. Freifeld

Abstract Over 90% of the 1.4 million new cases of cancer diagnosed in the United States in 2008 were due to solid tumors, with predominant sites being lung, breast, prostate, colorectal, bladder, and uterine cancers. While it is clear to practicing oncologists that solid tumor patients are generally at lower risk for infection-related complications overall, infections are certainly not rare in this population. Common foci include intravascular catheter-related bacteremia, pneumonias, wound and skin/soft tissue infections, and fever associated with chemotherapy-induced neutropenia. Nonetheless, there is little published data examining the incidence or characteristics of infections in solid tumor patients. This is not only because infection is relatively uncommon in solid tumor patients but also because sites, pathogens, and severity will vary, to a large extent, with tumor location, natural history, and the type and intensity of anticancer therapy. This variability precludes a neat summary of all the bacterial, viral, and fungal infections that occur in the solid tumor group as a whole. Instead, observational series and anecdotal reports have lead to the recognition of patterns of infection that may be considered "typical" for specific solid tumor types, or that are associated with certain antitumor treatment regimens. The goal of this chapter is to familiarize the physician with these infection profiles, so they may identify and manage them promptly and effectively.

Keywords Infection • Neutropenia • Catheter-related infections • Postsurgical wound infections • Bacteremia • Colon cancer • Breast cancer • Lung cancer

Introduction

Over 90% of the 1.4 million new cases of cancer diagnosed in the United States in 2008 were due to solid tumors, with predominant sites being lung, breast, prostate, colorectal, bladder, and uterine cancers [1]. Hematologic malignancies accounted for less than 10% of new cancers in the same year (approximately 5% lymphomas, 3% leukemias, and 1.5% multiple myelomas), yet the levels of morbidity, mortality, and overall healthcare resource utilization among patients with hematologic cancers far exceed those for solid tumor patients [2, 3].

Duration of hospitalization and inpatient mortality tends to be significantly greater in leukemic patients with fever and neutropenia than for those with solid tumors [3]. In a recent multicenter European study, bloodstream infections were found to be nearly 3 times more common in lymphoma and leukemia patients with fever and neutropenia than in patients with solid tumors [4]. While it is clear to practicing oncologists that solid tumor patients are generally at lower risk for infection-related complications overall, infections are certainly not rare in this population. Common foci include intravascular catheter-related bacteremia, pneumonias, wound and skin/soft tissue infections, and fever associated with chemotherapy-induced neutropenia. Nonetheless, there is little published data examining the incidence or characteristics of infections in solid tumor patients. This is not only because infection is relatively uncommon in solid tumor patients but also because sites, pathogens, and severity will vary, to a large extent, with tumor location, natural history, and the type and intensity of anticancer therapy. This variability precludes a neat summary of all the bacterial, viral, and fungal infections that occur in the solid tumor group as a whole. Instead, observational series and anecdotal reports have led to the recognition of patterns of infection that may be considered "typical" for specific solid tumor types, or that are associated with certain antitumor treatment regimens. The goal of this chapter is to familiarize the physician with these infection profiles, so they may identify and manage them promptly and effectively.

Infection Risks and Pathogens

In the patient with hematologic malignancy, normal immune mediator cells are replaced by malignant clones that fail to perform protective immunologic tasks. Serial cycles of

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intensive chemotherapy with corresponding prolonged periods of neutropenia further contribute to profound immunologic compromise that allow for opportunistic infections to advance. By contrast, defects in immune responses are far less frequent among solid tumor patients whose immune function is unaffected by the underlying disease, and less intensive cytoreductive therapies are more common.

Breeches in physical defense barriers are a common predisposing factor leading to infection in the solid tumor patient. Tumor infiltration across tissue planes with obstruction of a normally patent conduits of body secretions, such as colon, biliary tract, or bronchus, can lead to postobstructive infections. Tumor debulking or diagnostic surgeries with attendant anatomic disruptions and poor surgical wound healing will also contribute risks. Radiation therapy can also lead to tissue fragility and damage and impaired wound healing. Concurrent use of chemotherapy that enhances the radiosensitivity of tumors increases the chance of mucosal injury and neutropenia [5]. Disruptions of skin and mucous membrane integrity allow for skin and gastrointestinal commensals such as staphylococci, streptococci, enteric Gram-negative bacilli, and Candida species to gain access to surrounding tissue or to the bloodstream. These components of colonizing flora are common etiologies of infections in the solid tumor patient (Table 4.1).

Cytotoxic chemotherapy for solid tumors will often occur in repeated cycles, as with hematologic cancer treatments, but the attendant periods of chemotherapy-induced neutropenia are comparatively very mild (rarely yielding an absolute neutrophil count <100/mm^3) and brief, usually lasting a few days (and usually less than 1 week) with each cycle. Since the depth and duration of neutropenia are factors that dictate infection risk in cancer patients, it follows that solid tumor patients are less prone to documented invasive infections during neutropenia. This is particularly true in the case of invasive mold infections such as aspergillosis, which is vanishingly rare among solid tumor patients. Mold infections classically typically develop in the setting of profound (absolute neutrophils <100/mm^3) and prolonged neutropenia

lasting more than 2 weeks and accordingly, they occur almost exclusively among patients with acute myeloid leukemia (AML) and very rarely in those with less intensively treated hematologic malignancies such as lymphoma and multiple myeloma, and almost never in solid tumor patients [6, 7]. Similarly, viral infections such as adenovirus, BK virus, or EBV-associated lymphoproliferative disorders, which take advantage of the immune dysregulation post allogeneic stem cell transplant, are distinctly rare in solid tumor patients. This is because the critical T-cell mechanisms controlling these infections are less profoundly impaired after chemotherapy for solid tumors compared with more intensive regimens given for acute leukemia or stem cell transplants [8]. In general, the spectrum of pathogens that commonly cause infections in solid tumor patients is narrower and more representative of "normal flora" than in patients undergoing treatment for hematologic malignancies. In the latter group, antibiotic resistant and hospital acquired pathogens such as Enterococcus, VRE, Pseudomonas, and beta-lactamase-producing Gram-negative bacilli are more likely to occur.

Infections Associated with Specific Cancers and Treatments (Table 4.2)

Lung Cancer

Cancer of the lung (small cell 10%, nonsmall cell 90%) was the leading cause of cancer mortality in the United States in 2009, resulting in 28% of all cancer deaths [1]. Surgical resection is a common initial approach to lung cancers, with adjuvant or neoadjuvant chemotherapy and/or radiation also being administered, depending on the location, extent, and tumor type. Despite aggressive multimodality approaches to management, infections are fairly uncommon after lung cancer surgery and/or chemotherapy. Among 1885 patients retrospectively reviewed from 1992 to 2003 in Japan, lung

Table 4.1 Comparison of common pathogens in solid tumor and hematologic malignancy patient groups

Pathogens	Solid tumor patients	Hematologic tumor patients (e.g., AML, stem cell transplant recipients)
Gram-positive bacteria	• Coagulase negative Staphylococci • Occasionally other Gram positives	• Coagulase negative Staphylococci • VRE and MRSA acquired in the hospital • Bacillus
Gram-negative bacteria	• Enteric Gram negatives	• Enteric Gram negatives • Pseudomonas and resistant Gram-negative bacilli acquired in the hospital
Fungi	• Occasional oral thrush • Occasional candidemia associated with catheters	• Invasive candidiasis often prevented with prophylaxis but candidiasis associated with catheters occasionally occurs • Aspergillus and other molds occur almost exclusively in hematologic malignancy patients with GVHD and/or prolonged neutropenia

Table 4.2 Infectious complications associated with various solid tumor malignancies and treatment regimens

Solid tumor type	Potential infectious complications
Lung	Pneumonia
	Lung abscess
	COPD exacerbations
Breast	Skin/soft-tissue infections at surgical site
	Cellulitis in setting of lymphedema after axillary node dissection – now uncommon since sentinel node biopsy is standard of care
GI	Postoperative anastamotic leak or peritonitis
	Intra-abdominal abscess
	Hepatic abscess
Head and Neck	Wound infection due to surgical and/or radiation therapy tissue disruption
	Esophagitis initiated by radiation therapy, with fungal or viral superinfection
CNS	Temozolomide and steroids increase risk for *Pneumocystis jirovecii* pneumonia

cancer surgery was complicated by postoperative respiratory infections in fewer than 4%, with approximately 3% pneumonia cases and 1% having empyemas, usually with associated bronchopleural fistulas [9]. Multivariate analysis showed that age 75 years or older, decreased lung function as measured by FEV1%, advanced pathologic stage, and induction chemotherapy were independent risk factors for pneumonia. Pneumonia was also identified in only 5% of advanced lung cancer patients treated with cytotoxic chemotherapy alone, and again, older age and impaired pulmonary function were risk factors [10]. These risks are predictable since a significant proportion of patients with lung malignancy are of older age and have underlying chronic obstructive lung disease (COPD) as a consequence of prolonged cigarette smoking. Death due to pneumonia is distinctly uncommon, however, accounting for less than 1% of lung cancer mortality in a study of treatment-related toxicities during the 1990s [11].

Lung cancer is an important cause of nonresolving pneumonia in adults, often resulting from partial or complete obstruction of an airway by endobronchial tumor growth. Bacteria normally inhaled and then cleared by mucociliary action in the bronchial tree are, instead, trapped and overgrow distal to the blockage to cause a postobstructive pneumonia. Slow or delayed resolution of the infection despite seemingly adequate broad-spectrum antibiotic therapy is a hallmark of this process, in which mechanical clearance of pathogens is impaired [12]. In a study of 35 adults with nonresolving pneumonia, bronchoscopy revealed bronchoalveolar or adenocarcinoma as the cause in 4 (11%) [13]. Unlike simple pneumonias, segmental or lobar atelectasis is characteristic of postobstructive pneumonia as air is reabsorbed from portions of the lung distal to the obstructing lesion. Postobstructive pneumonias in the lung cancer patient are often polymicrobial. Oropharyngeal bacteria such as anaerobic and microaerophilic streptococci have traditionally been presumed to be the cause.

However, studies have suggested that *Staphylococcus aureus* and enteric Gram-negative bacilli are more prevalent contributors to respiratory infections in lung cancer patients, including postobstructive pneumonia and lung abscess [14, 15]. Alterations in oropharyngeal colonizing flora, with a transition from predominantly Gram-positive bacteria to Gram-negative enteric organisms, have been documented to occur commonly with the environmental pressures of illness, antibiotics, and/or chemotherapy in cancer patients; this change in oral flora is reflected in the bacterial profile of subsequent pneumonias in these patients [16]. Unless adequate treatment is provided, postobstructive pneumonias may progress to lung abscess or empyema. A broad spectrum antibiotic regimen, including Gram-negative, staphylococcal, and anaerobic coverage, should be instituted, with heed paid to the emergence of resistant bacteria in patients who have been in hospital settings. Clindamycin combined with a cephalosporin, piperacillin-tazobactam, or a carbapenem are acceptable antibiotic options. Effective therapy also requires relief of the obstruction by surgery, irradiation, and/or chemotherapy in order to allow drainage of the affected lung tissue.

Surgical resection is integral to the management of most nonsmall cell lung cancers, but postoperative infections, including empyema and pneumonia, appear to be rare [9]. Infection risk postoperatively is related to age older than 75 years, low FEV1%, advanced pathologic stage, and the use of induction chemotherapy. COPD is a common comorbid condition in lung cancer patients, and exacerbations may be frequent in the postsurgical stage or during chemo- or radiation therapy. Aspiration pneumonia, superinfection of necrotic tumor, and unusual opportunistic infections such as *Pneumocystis jerovicii* pneumonia or influenza pneumonia can also complicate lung cancer treatment [17]. Tuberculous infection with inflammation and scarring has been posited as a cofactor in the development of lung cancer, but proof of this concept has not been established [18]. In recent years, the coexistence of TB and lung cancer has been reported infrequently and exclusively from countries in southeast Asia, where TB is endemic [19, 20]. In these recent reports, it appears that coexisting respiratory TB does not appreciably alter the clinical course of lung cancer patients if antituberculous therapy is used properly.

Breast Cancer

Local skin and soft-tissue infections that involve the breast and/or arm are the most frequent infectious events seen in breast cancer patients, and these infections typically occur following surgery for tumor resection. For most women with stage I or II breast cancer, breast-conservation therapy (lumpectomy/partial mastectomy plus radiation therapy) is as effective as mastectomy and is now a common practice [21].

Breast cellulitis occurring months to years (226 days median time to onset) after breast-conservation therapy has been noted to occur in approximately 8% of women, as a novel complication of this approach. By contrast, the older surgical approach of modified radical mastectomy with axillary lymph node dissection was often complicated by chronic ipsilateral arm lymphedema and occasionally by recurrent bouts of streptococcal cellulitis in the affected arm [22]. The relatively long time period between breast conservation surgery and the onset of breast cellulitis has earned the moniker "delayed breast cellulitis" for this infection. Characterized by diffuse breast erythema, edema, tenderness, and warmth occurring more than 3 months after surgery, delayed breast cellulitis is generally responsive to prompt treatment with antistreptococcal antibiotics [23]. Antibiotic treatment should not be withheld in these patients' pending results of blood or tissue cultures, since a pathogen will rarely be isolated.

Colon Cancer

There is longstanding recognition that bloodstream infections due to certain gut organisms, particularly *Clostridium septicum* and *Streptococcus bovis*, may be harbingers of an occult colon cancer [24–26]. Tumor perforation through the colonic mucosa, typically in the ascending colon, is considered the point of entry for these pathogens. Rarely, myonecrosis with atraumatic gas gangrene may complicate *Clostridium septicum* sepsis, while endocarditis has been associated with *Streptococcus bovis* infections arising from occult colonic tumors [27, 28].

When sepsis or other serious infection due to these pathogens occurs without an obvious underlying etiology, there should be a high index of suspicion for associated colonic malignancy and colonoscopy is warranted.

Partial or complete bowel obstruction is a common presentation of primary colon cancer occurring in about 15–20% of patients at diagnosis [29, 30]. Fever and abdominal pain are typically associated with obstructing tumor masses. Bacterial translocation of enteric organisms from the gut lumen has been implicated as a possible source of fever and sepsis in patients with obstruction. In one clinicopathologic study, bacterial translocation to mesenteric nodes (identified by culture of biopsy specimens from surgery) occurred more frequently in colon cancer patients with large bowel obstruction than in those without obstruction (14 of 36 patients vs. 16 of 218 patients; $P < 0.001$) [31]. Both aerobic and anaerobic bacteria were found to translocate in this study, and translocation of bacteria predisposed to postoperative septic complications including bacteremia and intra-abdominal abscess ($P < 0.05$). Tumor perforation through the bowel wall with subsequent local intra-abdominal abscess formation is a very rare complication of intraluminal colon cancer [32]. Despite the frequency of obstructing colonic malignancies, only about 5% of patients have documented bacteremia or abscess in this setting [30, 32, 33].

Surgical resection is a mainstay of early colorectal cancer management. The incidence of postsurgical infections is approximately 10%, with most related to anastamotic leaks and intra-abdominal abscesses [33]. Nonetheless, in a comparison of 59 colon cancer patients with a leak or an abscess with 118 matched controls, the presence of leak or an abscess was not shown to impact the outcome at 5 years; however, these complications were associated with increased overall cancer-specific mortality and local recurrence in patients who underwent resection for rectal cancer [34]. Postoperative wound infection has also been found to be significantly more frequent in cases where the tumor site was the rectum rather than colon [35]. Wound infections after surgery for colorectal surgery are also decreased by the use of laparoscopic approach rather than open surgery, and by high-pressure washing of the wound before abdominal closure. Broad-spectrum antibiotic prophylaxis given before elective colorectal surgery is effective in reducing the incidence of postoperative surgical wound infections by at least 75% [36]. Single doses of regimens with broad spectrum activity against aerobic and anaerobic bacteria, such as ertapenem or a cephalosporin plus metronidazole, are as effective as multiple doses of antibiotics. It is essential to time antibiotic delivery to achieve maximal serum levels at the time of surgery, generally about 1–2 h prior to incision.

Other infrequent infection-related complications of surgical management include bacteremia, enterocutaneous or enterovaginal fistula, catheter infection, urinary tract infection, peritonitis, and pneumonia. An interesting observation made in the late 1980s was the finding that homologous blood transfusions given around the time of colorectal cancer surgery may be associated with a significant increase in the risk for developing wound infections or any of these other aforementioned infectious complications [33, 37]. However, larger retrospective follow-up studies failed to detect this link. Leukocytes depletion of blood products by filtration (now routine) appears to significantly lower the risk of infection and other complications in patients undergoing gastrointestinal surgery [37, 38].

Bevacizumab, an antibody that targets vascular endothelial growth factor (VGEF), inhibits tumor growth by inhibiting angiogenesis. In combination with chemotherapy, bevacizumab appears to extend progression-free survival and overall survival in patients with advanced colorectal malignancies. Rare, but important adverse effects of the antiangiogenesis antibody include gastrointestinal perforation and poor wound healing [39]. Clearly, serious infectious complications, such as sepsis or wound infection, may ensue from these unusual adverse effects of bevacizumab therapy (Table 4.3).

Table 4.3 Monoclonal antibodies used to treat solid tumors and their potential infectious complications

Bevacizumab	Poor wound healing, colon perforation, with intra-abdominal sepsis
Trastuzumab	infection

GU Cancers

Urogenital cancers including renal cell, prostate, and urothelial bladder cancer are typically treated with cytoreductive chemotherapy and/or special surgical interventions, although infectious complications occur infrequently. Fewer than 5% of urogenital cancer patients were noted to develop a documented infection during chemotherapy-related neutropenia in one large study [40]. Typically, those infections were associated with mechanical abnormalities such as urinary diversion or hydronephrosis or during severe neutropenia, when the absolute white blood cell count fell below 500/mm³. Antimicrobial prophylaxis for standard chemotherapy regimens in this setting is therefore not recommended. The use of antimicrobial prophylaxis prior to "clean-contaminated" urologic surgery for diagnosis (i.e., prostate biopsy) or tumor resection is somewhat controversial because of the paucity of good clinical trial data. However, it is generally recommended that patients undergoing prostate biopsy, transurethral resection of bladder tumor, or manipulation of bowel segments for urinary diversion in patients with bladder cancer receive a brief course of antibiotic prophylaxis to decrease infectious complications [41–43].

An ileal conduit or a neobladder (ureterosigmoidostomy) is typically created to provide urinary diversion following cystectomy for bladder cancer. Bacteriuria is an expected finding in patients with an ileal neobladder, with at least 80% developing bacterial growth in urine cultures at some point. This must be distinguished from a true urinary tract infection because simple bacteriuria does not require antibiotic treatment. True urinary tract infection, with attendant fever and malaise and urinary bacterial concentrations of >10⁵/ml, affects a significant proportion of patients following urinary diversion. Symptoms from the lower urinary tract may not be prominent in this group, so clinical suspicion is key to the diagnosis [44].

Antibiotics appropriate for urinary bacterial isolates should be administered for a 14-day course. Notably, the level of white blood cells in the urine may not correlate with the presence or absence of bacterial growth in urine cultures in samples from ileal conduits, suggesting that neutrophil inflammatory responses of ileal mucosa to the presence of bacteria differ from those of the bladder [45].

Percutaneous renal radiofrequency (RF) ablation is a well-established minimally invasive therapeutic option for the treatment of selected patients with renal cell carcinoma. Major complications are rare and include hematuria, internal hemorrhage, and unintended thermal injury to the ureter or other organs during ablation. Several patients with ileal conduits who underwent percutaneous renal RF ablation and developed infectious complications have been described: a renal abscess and a calyceal-cutaneous fistula [46]. Postablation syndrome characterized by low-grade fever (without infectious etiology), pain, and malaise following the procedure is reported in about one third of patients [47].

Bacillus Calmette-Guerin (BCG) is a live attenuated strain of *Mycobacterium bovis* that has been used to treat bladder carcinoma since 1976, and has been associated with disease eradication in more than two thirds of patients with early stage disease [48]. The precise mechanisms of action are unknown, but intravesical instillation of BCG triggers a variety of local immune responses, which appear to induce antitumor activity. Due to its success, BCG bladder instillation is widely employed. Although the mycobacterial strain is attenuated, side effects include fever (2.9%), granulomatous pneumonitis and/or hepatitis (0.7%), sepsis (0.4%), and a variety of local and disseminated BCG infections [49, 50]. A number of cases of mycotic vascular infections of large arteries secondary to *M. bovis* infection after intravesical BCG therapy have been reported, especially involving the abdominal aorta [51, 52]. Psoas and pancreatic abscesses, vertebral osteomyelitis, and aortoduodenal fistula have also been reported [53–55]. BCG sepsis or vascular infection is characterized by high fevers, chills, hypotension, and confusion occurring beyond the first day or two after installation. Disseminated intravascular coagulopathy, respiratory failure, and hepatic dysfunction may occur as well. Documentation of positive blood cultures is rare and treatment should be started based upon clinical suspicion. Treatment of serious *M. bovis* infections is with isoniazid (INH) and rifampin (RIF) for at least 6 months. The addition of prednisone 40 mg daily until fever resolves has been advocated to reduce the inflammatory component and may improve survival [49, 50].

CNS Cancer

The prolonged use of high-dose corticosteroids and radiotherapy in patients with primary brain tumors yields severe lymphocyte depletion that increases the risk of life-threatening opportunistic infections, particularly due to *Pneumocystis jerovici* pneumonia (known generally as "PCP") [56, 57].

Tapering of corticosteroid doses appears to be a predisposing factor for the development of (or "unmasking" of) Pneumocystis pneumonia symptoms in these patients [58]. Patients frequently present with nonspecific symptoms, such as a dry cough, slowly progressive dyspnea, and high fevers without clear etiology. Unlike patients with HIV/AIDS, cancer patients with PCP are more likely to present with the abrupt onset of dyspnea and hypoxia. Chest X-ray

may be normal during the early stages of PCP, but typical diffuse bilateral interstitial infiltrates subsequently develop in most cases. Definitive diagnosis requires demonstration of *P. jiroveci* cysts in the sputum or bronchoalveolar lavage by silver stain or other method. Trimethoprim-sulfamethoxazole at high doses is the mainstay of treatment for PCP.

Temozolomide, an oral alkylating agent, has emerged as an important therapeutic advance in the management of malignant gliomas in the past decade. However, opportunistic infections have been observed due to profound lymphopenia that accompanies temozolomide long-term use, probably exacerbated by concurrent corticosteroid administration. *Pneumocystis jiroveci* pneumonia is a well-described adverse effect of temozolomide treatment for brain tumors, and prophylaxis with inhaled pentamidine or twice weekly oral trimethoprim-sulfamethoxazole is recommended during concomitant temozolomide and radiotherapy, or when CD4 lymphocyte counts decrease below 200/mm^3 [59]. Rare cases of cryptococcal meningitis, listeria brain abscess, and disseminated strongyloidiasis have also been reported in association with temozolomide therapy [57, 60, 61].

Summary

Infectious complications are considerably less frequent among solid tumor patients than those with hematologic malignancies. Nonetheless, they are not rare and the clinician must be aware of the syndromes and pathogens that are particularly associated with specific cancers and treatment regimens. It is emphasized that antimicrobial prophylaxis is rarely indicated in patients being treated with routine chemotherapy regimens. Instead, a heightened sense of suspicion and appropriate microbiologic and/or radiographic testing are the key to evaluating fever and diagnosing infections in the solid tumor population.

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Chapter 5
Infections in Patients with Hematologic Malignancies Treated with Monoclonal Antineoplastic Therapy

André Goy and Susan O'Brien

Abstract The advent of monoclonal antibody therapy heralded a new era in oncology. In 1997, rituximab became the first monoclonal antibody for the treatment of cancer following its approval for patients with B-cell non-Hodgkin's lymphoma. The potential risks of any pharmacotherapy should be considered alongside the obvious benefits. Recently, concerns have emerged over the possible increase in infectious complications associated with monoclonal antibodies compared with traditional chemotherapy. Due to the nature of the malignancies that they target, most of the monoclonal antibodies currently in use for the treatment of hematologic cancers are directed at specific surface markers on B or T cells. Consequently, the risk of infectious complications with these monoclonal antibodies is of particular concern and a comprehensive review of these complications is presented in this chapter.

Keyword Infections • Rituximab • Alemtuzuma • Daclizuma • CMV • Viral hepatitis

Introduction

The advent of monoclonal antibody therapy heralded a new era in oncology. In 1997, rituximab became the first monoclonal antibody for the treatment of cancer following its approval for patients with B-cell non-Hodgkin's lymphoma (NHL). The majority of monoclonal antibodies used in oncology bind to cell surface receptors present on malignant cells. It was hoped that the development of monoclonal antibodies would result in a more favorable tolerability profile than that offered by systemic cytotoxic chemotherapies by providing a more targeted therapy. Since rituximab, several monoclonal antibodies have demonstrated efficacy as well as

relatively good tolerability profiles in a range of solid and hematologic tumor types. Hence, eight other monoclonal antibody therapies have subsequently received approval for the treatment of various cancers (four in hematologic malignancies) and over 100 are currently in clinical development [1].

The potential risks of any pharmacotherapy should be considered alongside the obvious benefits. Recently, concerns have emerged over the possible increase in infectious complications associated with monoclonal antibodies compared with traditional chemotherapy [2–4]. Due to the nature of the malignancies that they target, most of the monoclonal antibodies currently in use for the treatment of hematologic cancers are directed at specific surface markers on B or T cells [5]. Consequently, the risk of infectious complications with these monoclonal antibodies is of particular concern.

Interaction of Monoclonal Antibodies with the Immune System

Common targets for monoclonal antibodies in hematologic malignancies include CD20, CD33, CD52, and the α-chain of the interleukin-2 receptor (IL-2Rα), also known as the CD25 antigen. CD52 is a panlymphocytic cell surface antigen expressed on normal and malignant B- and T-lymphocytes, natural killer cells, but also macrophages and monocytes with relatively high density [5]. CD20 and IL-2R expressions are more limited, with CD20 expressed mainly on pre-B and mature B lymphocytes with weak expression on a subset of T cells and IL-2R expressed only on activated lymphocytes (Fig. 5.1) [5–8]. The CD33 antigen is expressed on most hematopoietic stem cells, on mature and immature myeloid cells, and on erythroid, megakaryocytic, and multipotent progenitors, but not on lymphoid cells [9, 10]. Monoclonal antibodies targeting these receptors can lead to the depletion of normal as well as malignant cells [11, 12]. As outlined in Fig. 5.1, B and T cells are an integral part of the immune system and are essential for the activation of humoral and cell-mediated immunity.

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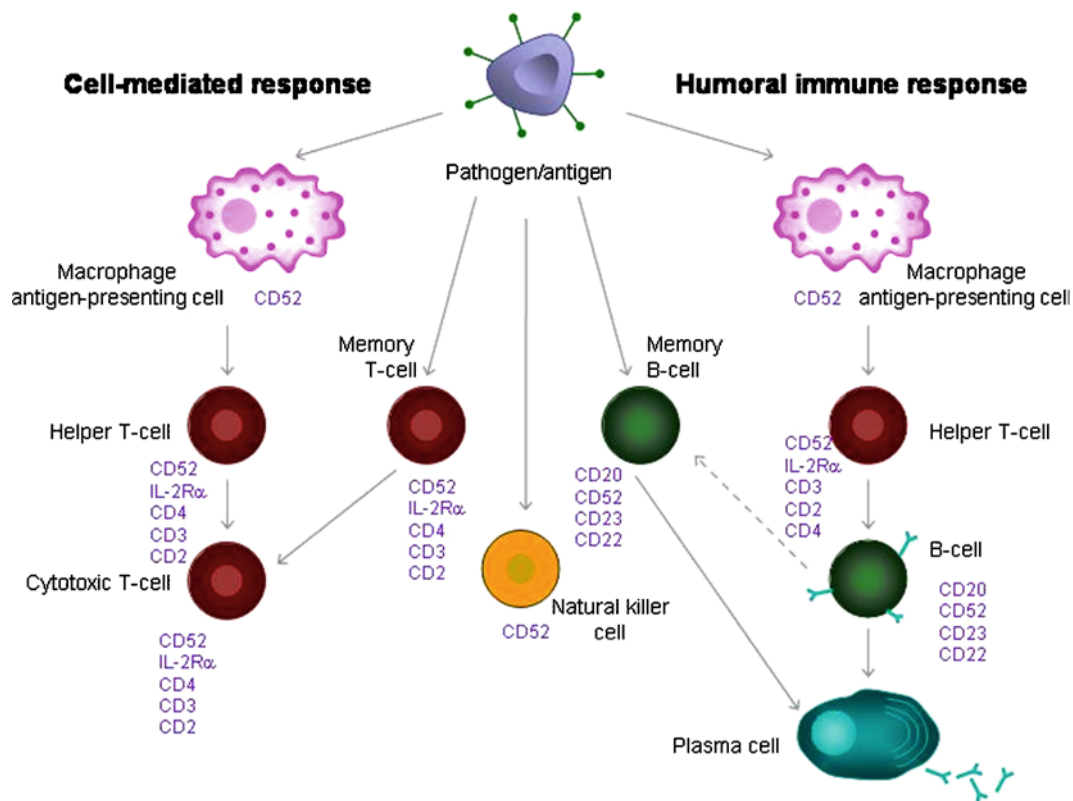
Fig. 5.1 Schematic overview of immune response and cell surface receptor targets for monoclonal antibody therapy

One monoclonal antibody, infliximab, does not bind to a cell surface receptor; rather it binds with high affinity to the soluble and transmembrane forms of tumor necrosis factor (TNF)-α. TNF-α plays an important role in immunity by activating a number of immune cells and inducing the local inflammatory response. Infliximab inhibits TNF-α binding to the cellular receptors [13], and a single dose results in a sharp and substantial decline in the levels of C-reactive protein and IL-6 [14].

Treatment of patients with a monoclonal antibody directed against CD20, CD33, CD52, IL-2Rα, or TNF-α, therefore, may compromise the immune system and increase the risk of opportunistic and nonopportunistic infections, such as pneumonia and reactivation of hepatitis B virus (HBV) [11, 15–17]. Immunosuppression resulting from the depletion of the body's reserve of B and T cells through monoclonal antibody therapy can be profound and prolonged [18]. Moreover, patients with hematologic malignancies are already at risk of infection as a result of immune dysfunction inherent in the underlying disease process and other risk factors such as prior cytotoxic chemotherapy. In addition, it is important to note that polymorphisms of leukocyte IgG receptors (FcγR) may also predispose patients to a higher risk of infection, although precise relationships are unclear [19]. For example, the FcγRIIa-R/R131 genotype has been linked to greater susceptibility to *Streptococcus pneumoniae* [20, 21], while

other studies have reported no such association [22], and the FcγRIIa-R/R131–FcγRIIIb-NA2/NA2 genotype combination has been shown to be associated with high frequencies of meningococcal disease [23].

The aim of this chapter is to evaluate the incidence of infectious complications associated with the monoclonal antibodies most commonly used for the treatment of hematologic malignancies. A summary of the current evidence for the risk of infectious complications associated with monoclonal antibodies in hematologic malignancies is given in Table 5.1.

Anti-CD20 Antibodies

Rituximab

Rituximab was the first treatment of its kind to be approved for a hematologic malignancy and is perhaps the most comprehensively studied monoclonal antibody. The combination of rituximab with chemotherapy regimens has revolutionized the treatment of patients with indolent and aggressive B-cell NHL, providing the first improvement in overall survival vs. chemotherapy alone in 30 years [3, 24–30]. As a result, rituximab in combination with chemotherapy has become the

Table 5.1 Infections and associated complications reported during monoclonal antibody therapy for hematological malignancies

Treatment	Target	Infection complications	Overall infection rate
Rituximab	CD20	Bacterial infections, e.g., sepsis	≈30%
		Fungal infections, e.g., *Pneumocystis*	
		Viral infections, e.g., CMV/HBV/HCV/TB reactivation, VZV and PML	
Tositumumab	CD20	Bacterial infections, e.g., sepsis, pneumonia	13–45%
		Viral infections, e.g., herpes zoster, herpes simplex II	
Ibritumomab tiuxetan	CD20	Bacterial infections, e.g., sepsis, pneumonia	≈29%
		Viral infections	
Alemtuzumab	CD52	Bacterial infections	>50%
		Fungal infections	
		Viral infections, e.g., CMV infection/reactivation	
Gemtuzumab ozogamicin	CD33	Bacterial infections	28–36% (grade 3/4)
		Fungal infections, e.g., pulmonary aspergillosis	
Lumiliximab	CD23	Bacterial infections, e.g., pneumonia	15%
		Viral infections, e.g., parainfluenza virus	
Inotuzumab ozogamicin	CD22	Unknown	More data needed
Zanolimumab	CD4	Bacterial infections	49%; more data needed
		Fungal infections	
		Viral infections	
Muromonab-CD3	CD3	Bacterial infections	21–50%
Siplizumab	CD2	Viral infections, e.g., EBV	More data needed
Denileukin diftitox	IL-2R	Bacterial infections; more data needed	≈30%
Daclizumab	IL-2Rα	Bacterial infections	95%
		Fungal infections	
		Viral infections, e.g., CMV reactivation, respiratory viral infections, EBV	
Basiliximab	IL-2Rα	Bacterial infections	>75%
		Invasive fungal infections	
		Viral infections, e.g., CMV reactivation	
Tocilizumab	IL-6	Bacterial infections, e.g., pneumonia	More data needed
		Viral infections, e.g., herpes zoster	
Infliximab	TNFα	Bacterial infections, e.g., TB, *Listeria*	≈80%
		Invasive fungal infections, e.g., endemic mycoses, *Candida*	

CMV cytomegalovirus; *EBV* Epstein–Barr virus; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *VZV* varicella zoster virus; *PML* progressive multifocal leukoencephalopathy; *TB* tuberculous

new standard of care in aggressive CD20-positive B-cell NHL [31]. Rituximab has recently been shown to improve progression-free survival in patients with previously untreated or relapsed chronic lymphocytic leukemia (CLL) [32, 33] and has demonstrated efficacy in patients with HIV1-associated B-cell NHL [34] and posttransplant lymphoproliferative disorder [35].

Rituximab binds to the CD20 antigen on B lymphocytes leading to cell lysis, which may be mediated by complement-dependent cytolysis (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and/or direct induction of apoptosis [36, 37]. It has also been suggested that killing of malignant B cells by rituximab may result in a "vaccinal" effect, i.e., priming of lymphoma antigen-specific T-cell responses, leading to antilymphoma immunity that remains long after the initial antibody-induced cytotoxicity [38, 39]. The relative importance of each of these mechanisms to the therapeutic effects of rituximab needs further clarification; however,

there is convincing evidence that direct induction of apoptosis by rituximab may occur before other proposed mechanisms (e.g., ADCC) are triggered [40]. ADCC is considered to be of particular interest as response to rituximab appears to depend on patients' FcγR genotype [41–43]. The observation that rituximab-induced B-cell depletion still occurs in mice that lack certain complement factors indicates that the exact role of CDC remains to be determined [44].

Rituximab-induced B-cell depletion is rapid and sustained, with peripheral B-cell depletion occurring 24–48 h after the first administration of rituximab in patients with relapsed low-grade B-cell NHL and persisting for 6–9 months after the completion of therapy [18]. Normalization of B cell counts appears to result from repopulation with naïve B cells, which exhibit a deficiency in expression of CD27, a memory B cell surface marker [45]. In addition to inducing B-cell depletion, rituximab treatment is associated with significantly reduced circulating immunoglobulin levels (IgM and IgG),

persisting for 5–11 months after rituximab administration and falling below the normal range in 14% of patients [18]. More research examining the effects of rituximab on the immune system is needed, although early evidence has indicated that T cells are minimally affected and protective titers against immunized pathogens generally appear to be preserved [46].

The most common side effects of rituximab treatment typically occur during the first infusion and can include fever, chills, nausea, itching, cough, throat swelling, hypotension, and transient bronchospasm [15]. Occurrence of these reactions depends on the rate of rituximab infusion, but they usually develop within 30–120 min from the start of infusion [36, 47]. Tumor lysis syndrome (TLS) is a rare but potentially fatal adverse event observed within 12–24 h of the first infusion of rituximab in patients with a high number of circulating tumor cells (>25,000/mm^3) or high tumor load; TLS prophylaxis is recommended in high-risk patients [15, 36].

Prolonged or delayed secondary hypogammaglobulinemia can arise as a result of rituximab retreatment, prolonged scheduling (especially in the maintenance setting in indolent B-cell NHL), or after high-dose therapy following stem cell transplantation [48–51]. Rituximab has also been associated with an impaired secondary humoral response to recall antigens [52] and an altered B-cell repertoire during immunologic reconstitution [53]. In a study of patients with B-cell NHL who received rituximab as an adjuvant to autologous SCT, recovery of memory B cells was delayed and exhibited abnormal cell marker expression and function, indicating that naive B cells may fail to differentiate into plasma cells [53]. Expansion of functionally immature B cells and decreased memory B cells may contribute to an immunodeficient state in patients recovering from rituximab-mediated B-cell depletion, particularly following repeated treatment [54]. Evidence suggests that this immunodeficiency may lead to infectious complications associated with rituximab.

Rituximab is increasingly being used for long-term maintenance therapy with delayed relapse and increased progression-free survival. A rational maintenance schedule has been proposed as single infusions of rituximab 375 mg/m^2 given every 3–4 months to maintain serum levels above the threshold for response of 25 μg/mL [55], the 3-month schedule is being used in ongoing clinical studies such as the Eastern Cooperative Oncology Group (ECOG) 4402 (RESORT) study [39]. Other rituximab schedules for maintenance therapy have been shown to provide significant benefit in patients with lymphoma, including 4 weekly infusions every 6 months and single infusions every 2–3 months [56]. Such long-term maintenance treatment raises added concerns of prolonged exposure and B-cell depletion in increasing the risk of infectious adverse events.

Rituximab-Associated Infection

Randomized controlled trials performed to date have provided conflicting evidence on the incidence of infection in patients treated with rituximab plus chemotherapy vs. chemotherapy alone. A pooled analysis of data from 356 rituximab-treated patients indicated an overall incidence of infection of approximately 30%, with bacterial infection accounting for 19% of cases and viral infection accounting for 10% [15]. In an interim analysis of an open-label, Phase II trial investigating 6 cycles of dose-dense rituximab 12×375 mg/m^2 plus CHOP-14 (R-CHOP-14) in elderly patients with diffuse large B-cell lymphoma (DLBCL), 7 of the first 20 patients (35%) developed grade 3/4 infections and there were seven cases of interstitial pneumonia, some of which were related to CMV reactivation [57]. Compare this with another randomized trial of 6 vs. 8 cycles of "standard" R-CHOP-14 in elderly patients where the rate of grade 3/4 infection was 28 and 35%, respectively, and it appears that the rate of infection may be increased by using dose-dense rituximab. By contrast, lower rates of grade 3/4 neutropenia (17.5%) and grade 3/4 infections (16%) were observed in a phase II, open-label study of R-CHOP administered every 14 days for the treatment of patients with DLBCL who were younger than 70 years [58]. Therefore, the risk of infection appears to be greater in elderly patients than their younger counterparts.

Randomized controlled Phase III trials performed in patients with a variety of indolent and aggressive lymphomas have failed to demonstrate a significant increase in the infection rate in patients treated with rituximab-based regimens (Table 5.2). Similar conclusions were drawn from a meta-analysis of four randomized controlled trials [30] and a retrospective analysis of infection rates in 160 patients with CLL following fludarabine–cyclophosphamide treatment with or without rituximab [59]. Interestingly, adding rituximab to CHOP therapy has generated confounding evidence for myelosuppression, with some Phase III trials reporting no differences between the groups [3, 29, 60, 61] and others reporting a significantly increased risk of granulocytopenia in the rituximab arms [26, 62].

Studies investigating the impact of long-term maintenance therapy with rituximab on risk of infection have also yielded inconsistent findings. In a recent meta-analysis of five randomized controlled maintenance trials, the risk of both infection and neutropenia was significantly increased during rituximab maintenance therapy in patients with lymphoma [63]. Updated data from a European Organization for the Research and Treatment of Cancer (EORTC) Intergroup trial of rituximab in remission induction and maintenance, with a median follow-up of 6 years, also described how rituximab maintenance was associated with a significant increase in grade 3/4 infections: 9.7 vs. 2.4% (p=0.01). Seven of 167

Table 5.2 Infection rates in published phase III randomized controlled trials comparing treatment with vs. without rituximab

Treatment	Type of malignancy	Infection-related death rate (%)	Overall grade 3/4 infection rate (%)	Reference
Rituximab+CHOP (n=202)	DLBCL	NR	12	Coiffier et al. [31];
CHOP (n=197)		NR	20	Feugier et al. [3]
Rituximab+CHOP-like chemotherapy (n=404)	DLBCL	0.74	7	Pfreundschuh
CHOP-like chemotherapy (n=403)		0.25	8	et al. [29]
Rituximab+CHOP (n=267)	DLBCL	3.0	17	Habermann
CHOP (n=279)		2.5	16	et al. [61]
Rituximab+CHOP-14 (n=578)	Aggressive B-cell NHL	NR	31	Pfreundschuh
CHOP-14 (n=570)		NR	30	et al. [28]
Rituximab+CHOP (n=99)	HIV1-associated NHL	15	NR	Kaplan et al. [2].
CHOP (n=50)		2	NR	
Rituximab+CVP (n=162)	FL	NR	NR	Marcus et al. [197]
CVP (n=159)		NR	NR	
Rituximab+CHOP (n=223)	FL	1.8	5	Hiddemann
CHOP (n=205)		2.0	7	et al. [26]
Rituximab+MCP (n=105)	FL	NR	7	Herold et al. [25]
MCP (n=96)		NR	8	
Rituximab+CHVP-IFN (n=175)	FL	NR	3.4	Salles et al. [198]
CHVP-IFN (n=183)		NR	1.1	
Rituximab+CHOP (n=234)	FL	0.4	NR	van Oers et al. [60]
CHOP (n=231)		0.4	NR	
Rituximab+FCM (n=66)	FL and MCL	NR	1.4	Forstpointner
FCM (n=62)		NR	1.8	et al. [24]
Rituximab+CHOP (n=62)	MCL	6	5	Lenz et al. [62]
CHOP (n=60)		3	6	

CHVP-IFN cyclophosphamide, doxorubicin, etoposide, prednisolone, interferon-α2a; *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, given in a 21-day cycle; *CHOP-14* CHOP given in a 14-day cycle; *CVP* cyclophosphamide, vincristine, prednisone; *DLBCL* diffuse large B-cell lymphoma; *FCM* fluradabine, cyclophosphamide, mitoxantrone; *FL* follicular lymphoma; *MCL* mantle cell lymphoma; *MCP* mitoxantrone, chlorambucil, prednisolone; *NHL* non-Hodgkin's lymphoma; *NR* not reported

patients discontinued rituximab maintenance because of toxicity, which was mostly recurrent infection [64]. However, other results from long-term rituximab therapy have contradicted these findings. No increased risk of major infection was observed over 5 years in patients with relapsed follicular lymphoma in a prospective single-arm study of autologous stem cell transplant combined with in vivo rituximab graft purging and posttransplant rituximab maintenance [49] and only mild infectious toxicity was seen in patients with relapsed B-CLL treated for 1–3.5 years [65].

In patients with HIV1-associated conditions, the addition of rituximab to standard treatment regimens has been associated with increased neutropenia and a higher rate of infectious complications compared with standard therapy alone, particularly in patients with low CD4 cell counts (<50 cells/μL). In a Phase III study comparing cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with or without rituximab, Kaplan and colleagues [2] observed a trend towards greater risk of neutropenia (62 vs. 48%), febrile neutropenia (31 vs. 24%), and treatment-related infectious diseases (13 vs. 2%) in patients with HIV1-associated lymphoma receiving R-CHOP vs. those receiving CHOP. Treatment-related infection led to the death of 8 of the 22 patients (36%) in the R-CHOP group who had a CD4 count of <50 cells/μL compared with 5 of the 77 patients (6%) with CD4 counts of ≥50 cells/μL. HIV1-related opportunistic infections in the R-CHOP group included *Candida albicans* (n=1), *Pneumocystis carinii* pneumonia (PCP; n=3), cytomegalovirus (CMV; n=2), esophageal candidiasis (n=1), and *Mycobacterium avium* (n=1); there were no opportunistic infections in the CHOP group. Spina and colleagues conducted a pooled analysis of three studies in 74 patients with HIV1-associated B-cell NHL, three-quarters of whom were receiving concurrent highly active antiretroviral therapy [66]. Adding rituximab to cytotoxic therapy resulted in grade 3/4 neutropenia in 78% of patients and a high rate of infectious complications (31%) including CMV retinitis (n=3), cryptosporidiosis (n=3), pulmonary tuberculous (n=2), PCP (n=1), and salmonellosis (n=1).

Certain infectious complications should be particularly borne in mind when initiating rituximab therapy. These include reactivation of HBV and hepatitis C virus (HCV), CMV infection, and progressive multifocal leukoencephalopathy (PML). Routine serologic screening, particularly for HBV and CMV, should be conducted prior to initiation of rituximab therapy and patients be carefully monitored for development of viral infections throughout treatment [67]. Prophylaxis with lamuvidine to prevent HBV reactivation is recommended throughout treatment and for at least 6 months after completion of therapy as late reactivations have occurred [68]. Prophylaxis for other viral infections is generally not recommended due to the toxicity associated with antiviral agents. Standard of care for the treatment of viral infections includes lamuvidine for HBV reactivation and ganciclovir for CMV.

Hepatitis B and C

Reactivation of HBV is a well-recognized complication of chemotherapy in inactive carriers, i.e., those testing positive for the HBV surface antigen (HBsAg), as well as in patients with chronic HBV infection. Reactivation occurs spontaneously in 14–50% of these individuals, and the rate could be even higher in patients with hematologic malignancies. HBV reactivation is therefore a concern in patients treated with immunosuppressant therapy such as rituximab, particularly in regions where HBV is endemic. In a review of 64 cases of viral infection after rituximab treatment for patients with lymphoma, HBV infection was the most commonly observed infection, occurring in 25 patients (39%), 13 of whom died as a result of hepatic failure [17] (Fig. 5.2). Among these 25 infected individuals, 13 had HBV reactivation (HBsAg positive) and eight had developed primary HBV infection (HBsAg-negative); the HBsAg status prior to rituximab therapy was unknown in the remaining four patients. More recently, Yeo and colleagues analyzed the rate of HBV reactivation among 104 patients with CD20-positive DLBCL who underwent chemotherapy with or without rituximab [69]. Among 46 patients who were HBsAg-negative and HBV-positive, 25 were treated with CHOP and the remainder with R-CHOP. HBV reactivation occurred in five R-CHOP-treated patients, but in none of those treated with CHOP alone. Notably, reactivation occurred up to 170 days following the last dose of R-CHOP, in line with previous reports of late HBV reactivation [68], suggesting that administration of antiviral therapy should continue for at least 6 months after completion of chemotherapy. Prophylactic lamivudine has been shown to reduce the risk of HBV reactivation in HBV carriers receiving rituximab-containing regimens for lymphoma [70–72]. Once HBV is reactivated, lamuvidine treatment is much less effective – over 50% of
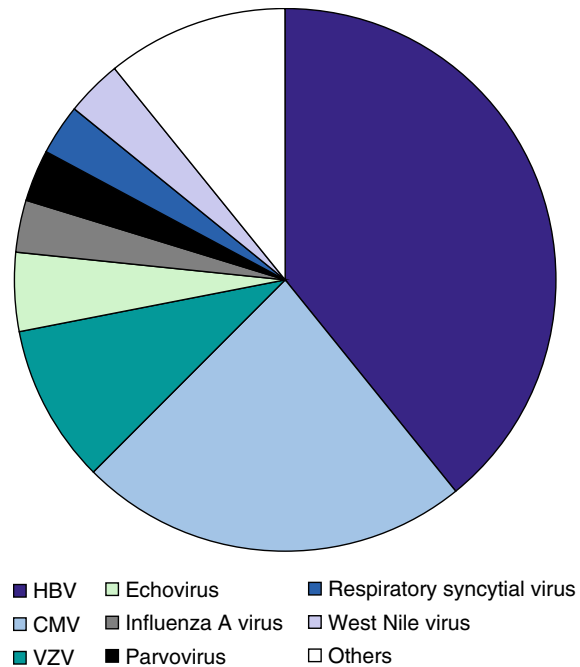
Fig. 5.2 Rituximab-related viral infections in patients with lymphoma (*n* = 64) [17]. *HBV* hepatitis B virus; *CMV* cytomegalovirus; *VZV* varicella zoster virus

such patients died in one report – illustrating the importance of preemptive treatment [17].

The incidence of HCV reactivation is less well defined. Most HCV-infected individuals experience chronic infection that may potentially lead to cirrhosis and hepatocellular carcinoma. HCV infection is now known to be associated with B-cell lymphoproliferative disorders, including mixed cryoglobulinemia, B-cell NHL, marginal zone lymphoma (splenic, nodal and extranodal), small lymphocytic lymphoma/ CLL, lymphoplasmacytic lymphoma, and DLBCL [73, 74]. The direct role of HCV infection in the genesis of these B-cell lymphoproliferative disorders remains unclear, but epidemiologic and molecular observations have recently suggested that HCV may be the causative agent in some cases of B-cell NHL [75]. Reactivation or worsening of HCV in patients receiving chemotherapy or immunochemotherapy has also been reported [76], although this appears to be much less common than HBV reactivation. Nonetheless, careful monitoring of these patients, which can reveal increased HCV RNA load during or after chemotherapy, is recommended [77].

Cytomegalovirus

CMV is a major cause of morbidity and mortality in immunocompromised individuals [78, 79]. CMV infection has been less widely reported than HBV infection in

rituximab-treated patients; however, Aksoy and colleagues [17] did identify 15 cases of this challenging infection in their literature review, including one patient who had received rituximab alone to treat lymphoma 10 years after a kidney transplant and would therefore be immunosuppressed [80]. In a study of 46 patients with relapsed indolent or high-risk aggressive B-cell NHL, of whom 17 received rituximab before autologous hematopoietic stem cell transplantation (HSCT), Lee and colleagues [81] reported CMV infection in three rituximab-treated patients, two of whom developed CMV disease. The risk of developing CMV infection after autologous HSCT was higher in rituximab-treated patients (17.6 vs. 0%; $p = 0.045$, two-sided Fisher's exact test). Nevertheless, all patients with CMV disease recovered after ganciclovir and CMV-specific immunoglobulin therapy.

Progressive Multifocal Leukoencephalopathy

PML — a rare and devastating neurologic disease involving areas of demyelination in the central nervous system — is classically associated with profound immunosuppression. PML is caused by reactivation of the latent JC virus (JCV) that is present in up to 80% of adults, leading to the death of myelin-producing oligodendrocytes. A state of immunodeficiency is the main risk factor for JCV reactivation and development of PML, with the most common causes comprising HIV infection, hematologic malignancy, and post-transplant immunosuppressive therapy [82]. There is no specific antiviral treatment currently available for PML; successful treatment of PML with cidofovir appears to be limited to isolated cases [83–86]. If the accompanying underlying immune deficit can be reversed, PML mortality is in excess of 95% [87].

Isolated cases of PML have been reported among patients undergoing rituximab treatment after autologous peripheral blood stem cell transplantation. PML has recently been reported in patients treated with rituximab-based chemoimmunotherapy for lymphomas as well as for rheumatologic diseases [88]. The first two cases of PML were reported by Goldberg and colleagues [78] in patients with lymphoma who had undergone high-dose therapy followed by stem cell transplantation. More cases have since been reported, including a series of 52 cases of PML in patients with lymphoma, most of whom had been treated with cytotoxic chemotherapy plus rituximab [89].

Hence, while the risk of PML associated with rituximab remains uncertain because of confounding factors, particularly the complicated immunosuppressive regimens used in hematological cancers and prior stem cell transplantation, careful prescribing and continued vigilance are warranted with this agent [88].

Other Infections

Other infections anecdotally associated with rituximab administration include varicella zoster virus [90, 91], PCP [92–94], adenovirus [95], parvovirus B19, [96, 97] and bronchiolitis obliterans with organizing pneumonia (BOOP) [98, 99]. These occur at greatly reduced frequency compared with the infections discussed above. Among 64 cases of severe viral infection, Aksoy and colleagues reported six cases of varicella zoster virus infection compared with 25 cases of HBV. Isolated cases of enteroviral [100, 101] and echoviral infections [102, 103] have also been observed in patients undergoing treatment with rituximab.

Late Neutropenia

Late-onset neutropenia (LON) has been reported with rituximab-containing chemotherapy in patients with hematological cancers such as follicular lymphoma and NHL, particularly in those receiving autologous HSCT and high-dose regimens [104–106]. LON is generally an infrequent adverse effect of standard-dose chemotherapy, although it may be more common following high-dose chemotherapy and stem cell transplantation [105]. Rituximab-induced LON appears to be associated with a lack of granulopoiesis in the bone marrow that occurs when B-cell depletion in peripheral blood is maximal [107]. Although the exact mechanism of rituximab-induced LON is unclear, it has been proposed that it may be related to excessive B-cell recovery stimulated by increased serum levels of the cytokine BAFF [107], and that disruptions in stromal-derived factor-1 levels during rapid B-cell expansion reduce neutrophil migration from the bone marrow [108]. LON has also been attributed to rituximab-induced reactivation of parvovirus B19 infection [109]. This adverse effect has been reported to occur at least 4 weeks after the last dose of treatment, but can be resolved with granulocyte colony-stimulating factor [106] or intravenous immunoglobulin.

Other Approved Indications

Rituximab is also approved for the treatment of moderate-to-severe rheumatoid arthritis (RA) as B cells are believed to act at multiple sites during the pathogenesis of this disease. Similar to what is seen in B-cell NHL patients, significant and sustained peripheral B-cell depletion occurs in patients with RA, generally lasting for at least 6 months with subsequent gradual recovery. In a meta-analysis of data from three randomized clinical trials, a

greater incidence of serious infections was observed with rituximab compared with placebo (2.3 vs. 1.5%), although the difference was not statistically significant [110]. The serious infections reported with rituximab comprised bronchopneumonia (one fatality), septic arthritis, pyelonephritis, gastroenteritis, epiglottitis, cellulitis, and acute hepatitis B.

Anti-CD20 Radioimmunoconjugates

Radioimmunoconjugates combine the targeted action of an antibody with the cytotoxic activity of a radioisotope, the latter conferring particular clinical benefit in radiosensitive hematologic cancers such as B-cell NHL [37]. Two radioimmunoconjugates are currently approved for the treatment of patients with CD20 antigen-expressing relapsed or refractory, low-grade or follicular NHL, including patients with rituximab-refractory disease: ^{131}I-tositumomab [111] and ibritumomab tiuxetan [112]. These agents are associated with reversible, radiation-related myelosuppression that has a late-onset and sometimes results in severe cytopenia, particularly neutropenia. With both radioimmunoconjugates, B-cell counts fall soon after treatment (median time to nadir of 4–7 weeks), with recovery to normal range occurring after approximately 6 months [113, 114]. There are no apparent clinical consequences of the transient B-cell depletion and no significant reductions in T cells or serum immunoglobulin levels [113, 114].

Tositumomab

Tositumomab is a murine antibody that results in very low rates of complete response when administered as monotherapy. In order to improve its efficacy, tositumomab has been conjugated with iodine-131 (^{131}I) to give ^{131}I-tositumomab.

Although grade 3/4 neutropenia has been reported to occur in almost two thirds of patients with B-cell NHL treated with ^{131}I-tositumomab, resultant infections are generally mild [111]. Infection rates of 13–45% have been observed in studies of patients with relapsed or refractory B-cell NHL [115–117]. Serious infections are uncommon, with an overall rate of 4.3% recorded in the ^{131}I-tositumomab safety database [118]. Indeed, grade 3/4 infections were observed in only 2% of 89 patients with follicular B-cell NHL treated with ^{131}I-tositumomab after initial therapy with CHOP [119]. In previously untreated patients with advanced follicular lymphoma, grade 3/4 hematologic toxicities were reported in 45% of these patients, with grade 4 neutropenia in 5% of patients and no infection-related hospitalizations [113].

Ibritumomab Tiuxetan

Ibritumomab tiuxetan is also a murine antibody, which, in its therapeutic form, is conjugated with yttrium-90 (^{90}Y). Treatment with ibritumomab tiuxetan requires two IV infusions of low-dose rituximab (250 mg/m^2) to be given before administration of ^{90}Y-ibritumomab tiuxetan on Day 1 and Day 7, 8, or 9 of the treatment schedule in order to deplete circulating B cells and improve biodistribution of the radioisotope and preferential delivery to tumor sites.

Available evidence suggests that ^{90}Y-ibritumomab tiuxetan may be associated with a similar rate of infection to rituximab. In an analysis of five clinical studies in which 349 patients with relapsed low-grade B-cell NHL were treated with ^{90}Y-ibritumomab tiuxetan, infection was reported in 29% of patients, including grade 3/4 infections in 5% [120]. Hospitalization as a result of infection was necessary in 7% of patients due to febrile neutropenia (2%), urinary tract infections (1%), sepsis (1%), pneumonia (1%), cellulitis or abscess (1%), and gastroenteritis or diarrhea (<1%). In a randomized study in 414 patients that compared consolidation with ^{90}Y-ibritumomab tiuxetan vs. no further treatment after first-line therapy, grade 3/4 infections were observed in 7.9% of patients in the consolidation arm, 7.4% of whom required hospitalization [121].

Second-Generation Anti-CD20 Antibodies

A number of second-generation anti-CD20 monoclonal antibodies are currently in development for the treatment of hematologic malignancies subdivided into those with engineered Fc portions and those with engineered Fab regions (Table 5.3). Research focuses on either making antibodies with a greater degree of humanization, more efficient binding, or antibodies that can target other CD20 epitopes, This may translate into improving infusion-related adverse effects, improving efficacy, overcoming rituximab resistance, and exploring the effects of combining anti-CD20 antibodies. Ofatumumab (HuMaxCD20) is in the most advanced stage of clinical development with phase III trials ongoing in several hematologic malignancies.

Anti-CD52 Antibodies

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody currently approved for the treatment of B-cell CLL [122]. Cellular immune reconstitution is significantly affected by

Table 5.3 Anti-CD20 monoclonal antibodies in development [37, 39]

Therapy	Stage of development	Details
Fc-engineered anti-CD20 monoclonal antibodies		
AME-133v	Phase I/II: follicular relapsed/ refractory B-cell NHL	• Novel engineered anti-CD20 antibody with increased affinity to the FcγRIIIa (CD16) vs. rituximab • Tenfold increase in cytotoxicity vs. rituximab in preclinical studies
PRO131921 (rhuMAb v114)	Phase I/II: indolent B-cell NHL relapsed/refractory to rituximab; relapsed/refractory CLL	• Fc-engineered humanized anti-CD20 monoclonal antibody • 30-fold greater binding to low-affinity variant of FcγRIIIa vs. rituximab
	Phase II: FL relapsed/refractory to rituximab	• ↑ADCC (two to tenfold in vitro) and ↑CDC
GA-101	Phase I/II: CD20+ malignancies (including DLBCL, CLL, B-cell NHL)	• Third generation, glycol-engineered type II humanized IgG1 anti-CD20 monoclonal antibody and a modified elbow hinge • 50-fold higher binding affinity to FcγRIIIa vs. rituximab • Engineered to ↑ADCC (10–100-fold in vitro), ↓CDC, and strongly induce apoptosis vs. rituximab
Fab-engineered anti-CD20 monoclonal antibodies		
Ofatumumab (HuMaxCD20)	Phase III: relapsed and untreated CLL; FL; rituximab-refractory FL	• Fully human IgG1$_K$ monoclonal antibody targeting a novel epitope of CD20
	Phase II: relapsed/progressive DLBCL	• Activity in cells with low CD20 expression (CLL) • Slower rate of disassociation from antigen and therefore higher potency for CDC vs. rituximab
Veltuzumab (IMMU-106/hA20)	Phase I/II: untreated or relapsed B-cell NHL and CLL	• Humanized anti-CD20 monoclonal antibody with CDRs of murine origin and 90% of human framework regions identical to epratuzumab (anti-CD22 IgG1 antibody) • Induces apoptosis of B cells and mediates ADCC and CDC
Ocrelizumab (PRO70769)	Phase II: B-cell NHL	• Fully humanized IgG1 anti-CD20 monoclonal antibody • ↑ADCC vs. rituximab

CDR complementarity-determining regions; *CLL* chronic lymphocytic lymphoma; *DLBCL* diffuse large B-cell lymphoma; *FL* follicular lymphoma; *NHL* non-Hodgkin's lymphoma

alemtuzumab treatment, with prolonged depletion of major blood lymphocyte subsets (including NK, T-, and B-cells), which may be sustained for over 9 months after the last treatment dose [123]. While it is effective for the treatment of CLL [4], alemtuzumab has been shown to be associated with diverse infectious complications [11]. Infections are also reported when alemtuzumab is used off-label for the treatment of acute rejection in organ transplant patients [124].

Alemtuzumab-Associated Infection

To date, two randomized controlled trials have investigated the efficacy and safety of alemtuzumab in patients with CLL [125, 126]. As with rituximab, alemtuzumab treatment appears to be associated with CMV reactivation. Both randomized trials reported a higher rate of CMV reactivation in patients treated with alemtuzumab compared with patients in the other arm of the trial (Table 5.4). In the trial comparing alemtuzumab and chlorambucil as first-line treatment for CLL [125], asymptomatic CMV (confirmed by polymerase chain reaction [PCR] testing) was confirmed in 52% of alemtuzumab-treated patients and 7.5% of those treated with chlorambucil, with symptomatic CMV reactivation occurring in 16 and 0% of patients, respectively. Symptomatic infections and asymptomatic CMV PCR positivity were managed successfully with standard therapies. In a consolidation study by the German CLL Study Group in which patients who had responded to treatment with fludarabine alone or in combination with cyclophosphamide subsequently received a standard dose of alemtuzumab or observation, alemtuzumab was associated with a higher rate of infectious complications [126]. Indeed, the trial was closed early after 7 of 11 patients in the active-treatment group discontinued treatment as a result of serious infections. These included one life-threatening pulmonary aspergillosis infection, three cases of CMV reactivation, two cases of CMV pneumonia, one herpes zoster infection, and one reactivation of pulmonary tuberculous. Only two episodes of infection were observed in the control group.

CMV reactivation rates in Phase II studies of single-agent alemtuzumab in patients with pretreated CLL have varied from 1 to 22% [122, 127–132]. In these studies, grade 3/4 infections included disseminated viral infection, systemic *Candida* spp. infection, mycobacterial reactivation, invasive fungal infection, *Listeria* meningitis, and PCP, the latter occurring primarily in patients not receiving antiviral prophylaxis. Alemtuzumab has also been used in combination

Table 5.4 Alemtuzumab infections in phase III clinical trials in patients with CLL

	Hillmen et al. [125]		Wendtner et al. [126]	
Setting	First-line CLL		CLL in first remission	
Treatment	Alemtuzumab	Chlorambucil	Alemtuzumab (30 mg IV TIW for 12 weeks)	Observation
No. of patients	149	148	11	10
Grade 3/4 neutropenia, %	41	25	64	0
Viral infection	CMV (symptomatic 16%; asymptomatic 52%)	CMV (asymptomatic 7.5%)	Bronchitis (9%), CMV reactivation (27%), CMV infection (18%), herpes zoster (9%), gastroenteritis (9%), HHV/HSV-6 (9%), sinusitis (9%)	Herpes zoster (10%), sinusitis (10%)
Bacterial infection	Bacteremia (3%), sepsis (1%), bronchopneumonia (0.7%), tuberculous (0.7%)	*Listeria monocytogenes* (0.7%), pneumonia (0.7%)	Tuberculous (9%)	–
Other infections	*Candida albicans* (0.7%)	NR	Aspergillosis (9%)	–

CLL B-cell chronic lymphocytic leukemia; *CMV* cytomegalovirus; *HHS* human herpes virus; *HSV* herpes simplex virus; *NR* not reported

with rituximab in patients with CLL. In a pilot study, Nabhan and colleagues [133] reported no treatment-related mortality and no CMV reactivation in 12 patients treated with escalating doses of alemtuzumab. Others, however, have reported serious toxicity with this combination [103, 134]. Faderl and colleagues [103] reported that 52% of patients ($n=25$) experienced one or more infection, including pneumonia ($n=5$) and sinusitis ($n=3$), while seven patients in the Minnie Pearl study experienced opportunistic infection, including five patients with CMV, one of whom died [134].

Alemtuzumab has been shown to have limited efficacy and considerable toxicity in NHL, as demonstrated by the results of a multicenter Phase II trial in 50 patients with advanced low-grade NHL who had previously been treated with chemotherapy [135]. Opportunistic infections occurred in seven patients, nine patients had bacterial septicemia, and three patients died as a result of infectious complications. CMV reactivation was also reported in one of ten patients with pretreated peripheral T-cell lymphoma following treatment with low-dose alemtuzumab [136]. The response rate reported in this study was similar to that previously reported with higher, more toxic doses [137, 138].

Gallamini and colleagues [139] observed a CMV reactivation rate of 9% in 24 patients with peripheral T-cell lymphoma who were treated with first-line alemtuzumab combined with CHOP; invasive aspergillosis was diagnosed in further two patients and bacterial infectious complications in three patients. Similar results were observed in the study by Lundin and colleagues [140], in which 4 of 41 patients with CLL experienced CMV reactivation. One patient who was allergic to cotrimoxazole and therefore did not receive prophylaxis developed PCP. However, a much higher CMV reactivation rate (31%) was observed in a phase II study of 16 patients with relapsed peripheral T-cell lymphoma treated with alemtuzumab plus dexamethasone, cisplatin, and cytarabine (A-DHAP) [141].

Although mycobacteria are rarely reported to cause infection after alemtuzumab treatment, infection with *Mycobacterium haemophilum*, a fastidious tuberculous mycobacterium, has been reported in two patients who experienced cutaneous lesions during alemtuzumab treatment [142]. Both infections were successfully treated using standard regimens. Viral infections have been anecdotally associated with alemtuzumab, including polyoma viruria in 21 of 58 T cell-depleted HSCT patients [143] and polyoma viremia in 6 of 54 highly HLA-sensitized renal transplant recipients [144]. HBV reactivation has been observed in two subjects with CLL and occult HBV infection who developed a virologic and biochemical flare of HBV following immunotherapy with alemtuzumab [145]. Pure red cell aplasia secondary to parvovirus B19 infection has also occurred in a number of patients undergoing alemtuzumab treatment [146, 147].

Alemtuzumab-Associated Infection: Prophylaxis

With a significant incidence of bacterial, fungal, and viral infectious complications expected as a result of the significant lymphopenia seen with alemtuzumab treatment, prophylactic PCP antibiotics (e.g., cotrimoxazole) and antiherpes viral therapies (e.g., valacyclovir) are mandated. In addition, antifungal prophylaxis is often administered. As CMV reactivation is commonly reported during treatment with alemtuzumab, a recent randomized study investigated the efficacy of valganciclovir compared with valacyclovir prophylaxis in patients receiving any alemtuzumab-based regimen for the treatment of hematological malignancies [148]. None of the 20 patients receiving valganciclovir developed CMV reactivation compared with 7 of 20 patients receiving valacyclovir ($p=0.004$). Hence, using valganciclovir prophylaxis appears to prevent CMV reactivation during treatment with alemtuzumab.

Anti-CD33 Antibodies

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) consisting of a semisynthetic derivative of calicheamicin, a potent cytotoxic antibiotic, linked to a humanized anti-CD33 monoclonal antibody. Gemtuzumab ozogamicin is internalized by target cells that express the CD33 surface antigen, and hydrolysis results in intracellular release of the cytotoxin [10]. This agent was first approved by the US Food and Drug Administration in 2000 for recurrence of acute myeloid leukemia (AML) in patients aged ≥60 years. Toxicities associated with gemtuzumab ozogamicin are primarily related to its myelosuppressive effects; in particular, neutropenia occurs in almost all patients undergoing this treatment [149] and hepatic veno-occlusive disease (VOD) (also known as sinusoidal obstructive syndrome [SOS]) has been reported at a rate up to 14% in patients undergoing allogeneic bone marrow transplant [150].

In a pooled analysis of three studies, the rate of neutropenia was high following gemtuzumab ozogamicin monotherapy for patients with AML who had failed prior treatment [16]. The vast majority of patients in this study had grade 3/4 neutropenia (97%) and thrombocytopenia (99%), although neutropenia would also be a characteristic of AML. Grade 3/4 infection occurred in 40 of the 142 patients (28%) and included sepsis in 16% and pneumonia in a further 7% of patients. A higher rate of sepsis was observed in a pilot study of combined gemtuzumab ozogamicin, idarubicin, and cytarabine in patients with refractory AML [151]. In this study, grade 3/4 sepsis occurred in 10 of 14 patients (71%), similar to the 63% grade 3/4 sepsis reported in the study of cytarabine, gemtuzumab ozogamicin, cyclosporine, and liposome-encapsulated daunorubicin in patients with refractory AML [152].

In a study in which 53 treatment-naïve or primary refractory/relapsed, poor-prognosis elderly patients with AML were treated with gemtuzumab ozogamicin, cytarabine, and granulocyte colony-stimulating factor, all 53 patients experienced grade 3/4 neutropenia [153]. In total, 19 patients (36%) had grade 3/4 infections, including bacterial sepsis ($n=13$) and pulmonary aspergillosis ($n=6$); the treatment-related mortality rate was 13%, with four patients dying as a result of infection. Similarly, in a study of 277 patients with CD33-positive AML who were treated with first-line gemtuzumab ozogamicin, sepsis and pneumonia occurred in 17 and 8% of patients, respectively [154]. In this study, 44 patients (16%) died within 28 days of the last dose of gemtuzumab ozogamicin, with infection being cited as the cause of death in 13 of these patients.

Anti-CD23 Antibodies

Lumiliximab

Lumiliximab is a chimeric macaque-human anti-CD23 monoclonal antibody that appears to induce apoptosis of CLL cells and CD23-expressing B cells [155]. In a phase I study of patients with CLL, lumiliximab was associated with a grade 3/4 infection rate of 15%, but the incidence and severity of infections were not related to the lumiliximab dose and there was no evidence of significant myelosuppression or cellular immune suppression [156].

Anti-CD22 Antibodies

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (CMC-544) is an ADC combining a humanized anti-CD22 monoclonal antibody (IgG4 type) with the potent cytotoxic antibiotic, calicheamicin [157]. CD22 was chosen as a rational target for ADC therapy as the receptor is internalized following antibody binding facilitating the intracellular delivery of the cytotoxic. There have been no reports of infectious complications with inotuzumab ozogamicin treatment when administered as a single agent or in combination with rituximab in early phase I and II clinical trials [158–161]. However, grade 3–4 neutropenia has been reported in 12–31% of these patients, so further clinical development will elucidate whether the myelosuppressive effects associated with this agent will translate into an increased risk of infection.

Anti-CD4 Antibodies

Zanolimumab

Zanolimumab, a fully human monoclonal cytotoxic IgG1$_\kappa$ antibody targeting the CD4 molecule on T cells, is currently being investigated for the treatment of CD4+ malignancies such as cutaneous T-cell lymphomas (CTCL) and noncutaneous peripheral T-cell lymphomas (PTCL) [5, 162, 163]. In two phase II studies, 49% of patients with CTCL treated with zanolimumab developed infections (mainly skin or upper respiratory tract infections), although the majority were considered to be mild and unrelated to treatment [164]. A phase III efficacy trial of IV zanolimumab administered once weekly for 12 weeks is ongoing in patients with mycosis

fungoides (MF)-type CTCL or Sezary Syndrome who are intolerant to or do not respond to treatment with bexarotene and one other standard therapy [162]. Data from this trial may provide more information on the toxicity, and specifically the risk of infection, associated with this agent.

Anti-CD3 Antibodies

Muromonab

Muromonab-CD3 (OKT3) is a murine IgG2a immunoglobulin used in transplant rejection that has also been used to treat steroid-resistant GVHD [165]. Muromonab-CD3 binds the CD3 molecule adjacent to the T-cell receptor, leading to nonspecific T-cell activation with cytokine release followed by transient but marked lymphocyte depletion and reemergence of CD3-negative T cells [166]. This lymphocyte depletion and T-cell receptor modulation result in immunosuppression and an increased risk of infection. High rates of opportunistic bacterial infection (21–50%) have been reported with muromonab in clinical trials of patients with transplant rejection [167–169].

Anti-CD2 Antibodies

Siplizumab

Siplizumab is a humanized anti-CD2 monoclonal antibody currently in phase I clinical development for the treatment of patients with relapsed/refractory CD2-positive T-cell lymphoma/leukemia, including T cell large granular lymphocyte (LGL) leukemia [170]. However, a phase I dose-escalation study had to be prematurely terminated after 14% of patients developed EBV-induced B-cell lymphoproliferative disease (LPD) [171]. Although T-cell counts were depleted in all patients, those who developed EBV-LPD had a significantly greater reduction in NK cells and CD2 expression on T cells.

Anti-Interleukin-2 Receptor Antibodies

Denileukin Diftitox

Denileukin diftitox (DAB389IL-2), a recombinant fusion protein consisting of IL-2 combined with the enzymatically active domain of diptheria toxin, is approved for the treatment of CTCL in patients with the CD25 component of the IL-2 receptor [172]. Denileukin difitox has also demonstrated efficacy in PTCL, B-cell NHL, CLL, and GVHD. After binding to the IL-2 receptor, denileukin diftitox is internalized via endocytosis and acts by inhibiting protein synthesis resulting in cell death. Results from three large phase III, randomized, double-blind, placebo-controlled trials conducted in patients with CTCL indicated that treatment with denileukin diftitox did not increase infection complications compared with placebo [173, 174]. In addition, when patients with relapsed/refractory B-cell NHL were treated with a combination of denileukin diftitox and rituximab in a phase II trial, myelotoxicity was reported to be uncommon [175]. However, in phase II studies of denileukin diftitox in patients with CLL, grade 3/4 neutropenia and infections (mainly bacterial, e.g., pneumonia) were reported in approximately 30% of patients [176, 177].
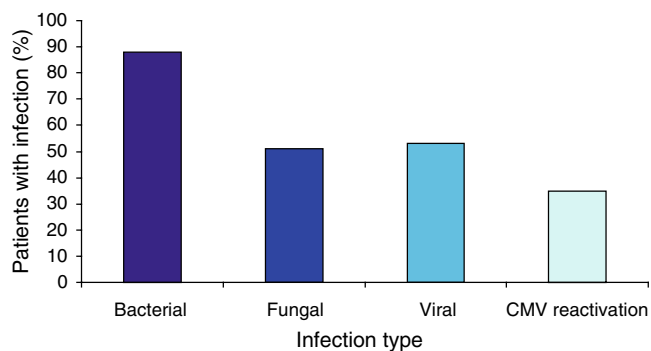
Daclizumab

Daclizumab and basiliximab are chimeric anti-IL-2Rα monoclonal antibodies approved for the prevention of renal allograft rejection, which act by blunting the antigenic challenge response. Both have also been used for the treatment of steroid-refractory graft versus host disease (GVHD).

Although the use of daclizumab in the treatment of leukemia and lymphoma has been limited to date, it has been used for the treatment of GVHD. Treatment of GVHD with daclizumab has been associated with high rates of infectious mortality, although this may, in part, be attributed to the underlying disease and prior therapies received by the patients. This theory is supported by the results of a randomized comparison of standard corticosteroids vs. corticosteroids plus daclizumab for the upfront treatment of acute GVHD, in which similar rates of grade 4/5 infections were seen in both arms (16% with corticosteroids alone vs. 25% with combination therapy; $p = 0.34$) [6]. The study was, however, halted after a planned interim analysis showed significantly worse 100-day survival in the group receiving corticosteroids plus daclizumab compared with those receiving standard corticosteroids alone (77 vs. 94%; $p = 0.02$). The higher mortality rate in the combination arm was attributed by the authors to both GVHD- and relapse-related deaths.

Perales and colleagues [178] reported a high rate of opportunistic infections in a retrospective review of 57 patients who underwent allogeneic HSCT and treatment with daclizumab for steroid-refractory acute GVHD. Opportunistic infections occurred in 95% of patients; 75% of patients died following treatment with daclizumab. Causes of death

Fig. 5.3 Infection rates in a retrospective review of 57 patients who underwent an allogeneic hematopoetic stem cell transplant and treatment with daclizumab for steroid-refractory acute graft versus host disease (GVHD) [178]. *CMV* cytomegalovirus

included active GVHD and infection (79%), active GVHD (5%), chronic GVHD (2%), and relapse (14%). Bacterial, fungal, and viral infections occurred in 50 (88%), 29 (51%), and 30 (53%) patients, respectively, with CMV reactivation occurring in 35% of patients (Fig. 5.3). In another study of 12 patients undergoing nonmyeloablative allogeneic hematopoietic cell transplantation, daclizumab was associated with a rate of CMV reactivation of 87% and respiratory viral infections occurred in 42% of patients, including one fatal case of parainfluenza-3 infection and 1 case of Epstein–Barr virus-associated posttransplant lymphoproliferative disorder [179]. Willenbacher and colleagues [180] also reported a high infection rate in patients with corticosteroid-refractory GVHD undergoing daclizumab therapy. Fourteen out of 16 patients acquired infections during daclizumab treatment and three infection-related deaths were recorded.

Daclizumab has also been used to treat GVHD in children, but no treatment-related infections were reported [181, 182].

Basiliximab

Evidence for infection among patients with GVHD who were treated with basiliximab is limited, but appears to show a comparable rate and range of infectious complications to that seen with daclizumab. In a retrospective evaluation of 34 patients with refractory grade III/IV GVHD who received basiliximab, 19 infectious deaths were reported, 8 of which resulted from bacterial sepsis, 4 from CMV, and 6 from invasive fungal infection [183]. A high rate of infection was also seen in a prospective Phase II study of basiliximab in patients with steroid-refractory acute GVHD [184]. Ten of 23 patients developed bacterial infections, 4 of which led to deaths from sepsis. In addition, CMV reactivation was reported in five patients, two patients had invasive fungal infections, and 1 developed cerebral toxoplasmosis.

## Anti-Interleukin-6-Receptor Antibodies

Tocilizumab

Tocilizumab is a humanized antihuman IL-6 receptor antibody that specifically blocks IL-6 cell-to-cell signaling. Tozilizumab was developed and is pending FDA approval for the treatment of patients with moderate-to-severe RA. In addition to being a key proinflammatory cytokine in the pathogenesis of RA, IL-6 is involved in cell proliferation and survival [185, 186]. Hence, tocilizumab may be useful in the treatment of IL-6-related malignancies. Initial research has shown that IL-6 is involved in angiogenesis in several cancers, including multiple myeloma [187], and IL-6 expression is often elevated in patients with glioma [188]. Indeed, a recent study has shown tocilizumab to have an antitumor effect in glioma cells in vitro [186]. Clinical phase II/III and long-term trials in patients with RA have shown that neutropenia and infections (bacterial and viral) are commonly reported to occur with tocilizumab, with serious infections including pneumonia, gastroenteritis, upper respiratory tract infection, herpes zoster, and sepsis [189–191].

Anti-TNFα Monoclonal Antibodies

Infliximab

Infliximab was approved in November 1999 for the treatment of RA, but has also shown a therapeutic benefit in steroid-refractory GVHD. However, in this setting infliximab appears to increase the risk of infection compared with standard therapy. In a prospective trial of infliximab for the prophylaxis of acute GVHD in 19 patients undergoing myeloablative allogeneic stem cell transplantation for hematologic malignancies, significantly more bacterial and invasive fungal infections were observed compared with a matched control group of 30 patients contemporaneously undergoing treatment ($p = 0.01$ and $p = 0.02$, respectively) [192]. In a retrospective analysis of patients with severe steroid-refractory acute GVHD undergoing treatment with infliximab, 23 of the 32 patients (72%) developed one or more infectious episodes [193]. In total, seven patients developed septicemia (5 Gram-positive and 2 Gram-negative infections), two patients had septic shock, and seven patients had pneumonia. In addition, there were 13 cases of CMV reactivation, 4 cases of infectious enteritis, 2 invasive mycoses (candidemia and pulmonary aspergillosis), and one patient developed encephalitis. Marty and colleagues [194] undertook

Fig. 5.4 Infections in patients treated with infliximab: retrospective analysis of 134 patients with acute GVHD [195]
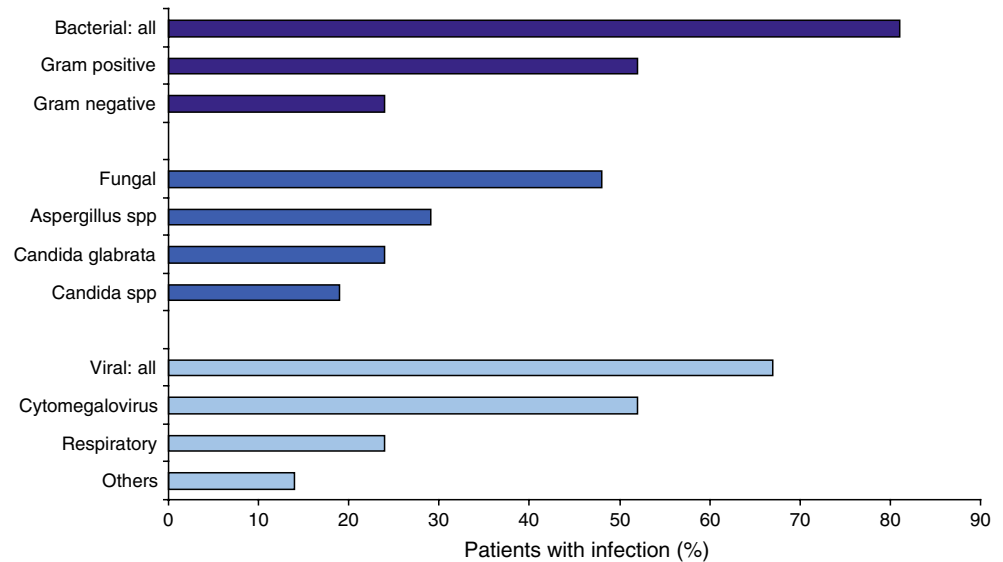
a retrospective analysis of 264 patients with severe GVHD, in order to determine if this population was at an increased risk of non-*Candida* spp. invasive fungal infections. Of 11 infliximab recipients, 5 (45%) developed an invasive fungal infection compared with 5 such fungal infections among 42 patients (12%) who did not receive infliximab (adjusted hazard ratio 13.6; $p = 0.004$). These data led the authors to conclude that infliximab administration was associated with a significantly increased risk of non-*Candida* spp. invasive fungal infections in patients with severe GVHD disease.

Couriel and colleagues [195] performed a retrospective evaluation of 134 patients with steroid-refractory GVHD, 21 of whom received infliximab therapy. Ten patients (48%) had 18 fungal infections, including *Aspergillus* spp. in 7 and *Candida* spp. in 10; 17 patients (81%) had bacterial infections, including 32 Gram-positive and 8 Gram-negative infections; and 14 patients (67%) had viral infections, primarily CMV reactivation (Fig. 5.4).

HLA-DR Antibody

Apolizumab (Hu1D10)

Apolizumab, a humanized monoclonal antibody against a polymorphic epitope on HLA-DRβ, has demonstrated evidence for therapeutic activity in 1D10-positive NHL when administered in combination with granulocyte colony-stimulating factor (G-CSF) [196]. The combination was well tolerated in this small pilot study, but further research is needed to clarify its effects.

Summary

Monoclonal antibodies have had an enormous impact on the treatment of patients with hematologic malignancies, improving response rates and survival for many. As with any oncology treatment, however, the benefits of therapy must be balanced against the risks. The ability of monoclonal antibodies to bind to specific antigens on malignant hematologic cells may provide a targeted therapy, but also leads to depletion of non-malignant immune cells, which in turn may increase the risk of infectious complications. The different targets of each of the monoclonal antibodies described in this chapter result in differences in the risks of infection, but the reactivation of latent infections such as HBV and CMV is a particular problem for many. The infectious complications associated with the most commonly used antibodies are now better understood, allowing physicians to anticipate these events, to monitor patients for early signs of infection, and to give prophylaxis where possible or treat when necessary, further improving outcomes for this patient population.

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Chapter 6
Postsurgery Infections in Cancer Patients

Emilio Bouza, Almudena Burillo, Juan Carlos Lopez-Gutierrez, and José F. Tomás-Martinez

Abstract Many different infections may occur after surgical events in patients with solid tumors, though infections of the operative site are the most common nosocomial infections in any surgical patient. Also frequent are infections of the lower respiratory tract, related or not to endotracheal intubation; of the urinary tract, usually related to the need for bladder or other urinary catheters; and bloodstream infections, mainly related to the use of intravascular catheters. This chapter reviews and discusses surgical site infections (SSI) produced after surgery for the most common tumors paying special attention to incidence, common clinical presentations and risk factors, diagnostic alertness, therapeutic principles, and particular aspects of prophylaxis if pertinent. Due to the existing variety of tumors and surgical procedures, we first address – from head to limbs – the most common tumors requiring surgery in adults and end the chapter with a section in which SSI are described in child cancer and compared to the situation in adults.

Keywords Neoplasms • Postoperative complications • Infection

Introduction

Many different infections may occur after surgical events in patients with solid tumors, though infections of the operative site are the most common nosocomial infections in any surgical patient [1]. Also frequent are infections of the lower respiratory tract, related or not to endotracheal intubation; of the urinary tract, usually related to the need for bladder or other urinary catheters; and bloodstream infections, mainly related to the use of intravascular catheters. These and other infections distant to the surgical site will be discussed in several other chapters of this book.

The general pathogenic mechanisms, therapeutic principles, and preventive measures for surgical site infections (SSIs) accepted for noncancer patients also generally apply to patients with solid tumors. This chapter reviews and discusses SSI produced after surgery for the most common tumors paying special attention to incidence, common clinical presentations and risk factors, diagnostic alertness, therapeutic principles, and particular aspects of prophylaxis if pertinent. Due to the existing variety of tumors and surgical procedures, we first address – from head to limbs – the most common tumors requiring surgery in adults and end the chapter with a section in which SSIs are described in child cancer and compared to the situation in adults.

Brain Cancer

Complications of cerebral spinal fluid (CSF) leakage and infections usually account for over half of all neurosurgery complications. Infections following brain cancer resection include superficial wound infection, subgaleal fluid collection infection, meningitis, and brain abscess. Other infections, such as postoperative pulmonary infections, may present in up to 25% of patients [2].

As with any other type of brain surgery, postoperative fever in patients with brain cancer may be caused by local inflammation induced by the surgical insult, tumor-associated fever, brain hemorrhage, central fever, or postoperative meningeal syndrome and is not always attributable to infection. In cases of SSI, fever onset usually occurs later than 72 h postsurgery.

Incidence

After a craniotomy, without the implant of a biomaterial, the incidence of infection is estimated at 0.3–5% depending on

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the type of surgery, the presence of risk factors, the surgeon's skills, or the use of antibiotic prophylaxis, etc. [3–6]. In a recent study addressing this issue, McClelland and Hall examined the incidence of postoperative central nervous system infection after 2,111 neurosurgical procedures at their institution during a 15-year period [7], but the proportion of infections occurring in patients with cancer was not specified.

The incidence of infection among patients with a ventricular shunt [8] has steadily fallen with estimates in recent series running at 1.6–2.6% [7, 9].

Risk Factors

In the previously mentioned study by McClelland and Hall [7], the neurosurgical procedures associated with the highest rates of postoperative infection were CSF shunting (1.6%), followed by Ommaya reservoir placement (1.4%) and craniotomy for a mass, tumor, and/or lesion (1.1%). The risk factors for SSI following neurosurgery in cancer patients are prior neurosurgery, chemotherapy, radiotherapy, prolonged use of corticosteroids, a history of prior wound infection, prolonged intraoperative time, and the placement of a gliadel (BCNU) chemotherapy wafer into the brain tumor cavity [10, 11].

Risk factors for meningitis include CSF leak, concomitant incision infection, male sex, and duration of surgery [4].

The age groups most susceptible to ventricular shunt infection are infants under 1 year of age and elderly patients. Infections of a ventriculoatrial shunt are also more frequent than those of a ventriculoperitoneal shunt. The reimplantation of a shunt in the presence of an active infection at another anatomical site has also been linked to a greater infection risk.

Risk factors for postoperative pulmonary infection include type of surgery performed, prolonged mechanical ventilation over 48 h, time spent in the intensive care unit over 3 days, reduced level of consciousness, duration of surgery over 6 h, and previous chronic lung disease [2].

Etiology

The most common causative agents of superficial and deep-seated postneurosurgery infections are *Staphylococcus aureus* and Gram-negative bacilli, especially *Pseudomonas aeruginosa* and *Enterobacter* species [3, 4, 7]. *Propionibacterium acnes* is a rare but life-threatening cause of brain abscess or meningitis following neurosurgery [12]. If a foreign body is in place, such as a bone plate or a ventriculoperitoneal shunt, then coagulase-negative staphylococci are the most common cause of neurosurgical infection. Rarely, anaerobes such as anaerobic streptococci can provoke a deep-seated infection if the sinuses are entered during surgery.

Diagnosis

Craniotomy infection is frequently accompanied by osteomyelitis of the skull plate and manifests as a painful tumefaction with a purulent wound secretion, generally appearing within the first week of surgery.

Meningitis usually appears 7–10 days after surgery. It is more common after surgery performed at the suboccipital level and may occur in the absence of fever [4, 13]. Headache is the most constant clinical factor. CSF examination is of limited diagnostic value because cyto-biochemical variables may be normal or difficult to interpret. A positive Gram stain is obtained in a low proportion of cases (30–50%), and thus culture results need to be awaited. Prolonged incubation is recommended so that slow-growing microorganisms are not missed. Blood cultures may prove positive in a high proportion of patients, especially if the causal agent is *S. aureus* (64–100%).

Treatment

The drugs of choice for empirical therapy of deep-seated brain infection include intravenous vancomycin or linezolid for Gram-positive bacteria and meropenem or cefepime for Gram negatives. Osteomyelitis of the skull plate may require removal of the bone plate followed by placement of a titanium prosthesis. Radionecrosis of surrounding bone may lead to recurrent infection and chronic osteomyelitis despite the best of resection procedures.

Prevention

Antibiotic prophylaxis in craniotomy has proven effective in preventing SSI even in low-risk patients [3]. However prophylaxis does not clearly prevent meningitis and tends to select out antibiotic-resistant microorganisms [4]. The pathogenesis of postoperative meningitis is different from that of SSI in that the causative microorganisms are not acquired during the intraoperative period, but rather, later on as a consequence of a CSF leak.

Postoperative Infections Following Non-Neurosurgical Head and Neck Cancer Interventions

Patients undergoing head and neck oncologic surgery carry a high risk of complications [14]. These patients often have significant comorbidities and show a high anesthesia and surgery risk. An SSI in these patients can have devastating effects [15] leading to wound breakdown, mucocutaneous fistulae, esthetic and functional sequelae, and often severe sepsis and death. It can also prolong hospital stay and increase costs [16] and may delay the administration of radiotherapy or chemotherapy following surgery, which will increase the risk of tumor recurrence [17].

Incidence

Rates of SSI reported after clean-contaminated head and neck surgery range from 11 to 87% [16–22], and there is little doubt that bacterial contamination following the opening of the mucosal barriers increases the risk of SSI due mainly to the high bacterial load in saliva and mucosal surfaces [23].

Risk Factors

The main preoperative risk factors for SSI after head and neck surgery are age, previous radiotherapy, underlying diseases such as diabetes mellitus, an advanced tumor clinical stage, previous surgery, cigarette smoking, and alcohol consumption [22, 24–28]. Poor oral hygiene increases the risk of bacterial contamination of the surgical field [29].

Patients with laryngeal and hypopharyngeal tumors show a higher incidence of SSI [19].

Operative factors include technical skills of the surgeons, the extent of resection, methods of reconstruction, duration of surgery, and volume of blood transfused.

The following situations place patients with head or neck tumors at a higher risk of postoperative infection: total laryngectomy [24], stage III and IV tumors, composite resections, and flap reconstruction [22].

Performing a neck dissection appears to contribute to a higher incidence of infection [24], and skull base tumors present numerous surgery-related problems because of the involvement of functional structures, difficult access, and the creation of large defects after removal [20, 30, 31].

Postoperative factors include chemotherapy and exposure of tissues and prosthetic material to saliva and tracheal secretions. The impact of tracheotomy either before or after surgery

on the incidence of SSI is still under debate [19, 24, 32, 33], but extending prophylaxis to exceed 48 h is also associated with an increased risk of infection [18, 19, 22, 32, 34].

In a retrospective review of 1,693 patients with cancer of the oral cavity, SSI occurred in 19.8% [35]. Wound infection also affected 69 out of 111 patients (62.1%) after oral and oropharynx cancer surgery with an immediate reconstruction [36].

Etiology

SSI in patients with head and neck tumors is commonly polymicrobial, and the role of individual microorganisms in its pathogenesis is difficult to assess. Etiologic agents frequently involved include microorganisms commonly found in oral flora such as staphylococci, streptococci, and anaerobic bacteria. However, when infections occur in patients already receiving antibiotics, resistant pathogens tend to predominate. These organisms include methicillin-resistant *S. aureus* (MRSA), Gram-negative rods, mainly *Enterobacteriaceae* and *P. aeruginosa*, and *Candida* species [23, 37].

Radionecrosis of the mandible may result in osteomyelitis, usually of polymicrobial cause.

Diagnosis

Diagnosis of infection is usually made on a clinical basis and a practical approach is to consider as infected any wound graded 4+ or above in the following scale: 0: no erythema, 1+: less than 1 cm of erythema, 2+: less than 5 cm of erythema and induration, 3+: greater than 5 cm of erythema and induration, 4+: purulent drainage, and 5+: wound breakdown with mucocutaneous fistula [29].

For a microbiological diagnosis, only specimens obtained during surgical examination of the wound or via radiology-guided puncture are considered valid since samples of wound secretions or from drainage tubes are often contaminated and results are not predictive of the bacteriologic findings in surgical samples [38].

Treatment

As in any SSI, surgical debridement is key in the treatment of these patients.

Empirical antibiotic treatment should be started in patients with cellulitis or systemic inflammatory response syndrome. There is no scientific evidence supporting one over another

regimen recommended for empirical treatment. The antimicrobial selected should be active against commensal aerobes and anaerobes of the upper airways and against *P. aeruginosa* (meropenem or imipenem, piperacillin-tazobactam). In the context of a high incidence of MRSA, a glucopeptide or linezolid should be added.

Prevention

There is general agreement that perioperative antimicrobial prophylaxis should be given to patients undergoing clean-contaminated surgery for head and neck cancer. Rates of infection before prophylaxis could be as high as 87%, and after antimicrobial prophylaxis it may be reduced to below 10% [17, 29, 33, 39, 40]. There is still controversy regarding the drug of choice and the length of prophylaxis, but common recommendations include cephazolin or the combination of clindamycin with gentamicin [41]. Alternatives include amoxicillin-clavulanate [40], ampicillin/sulbactam [37, 42], and piperacillin-tazobactam [43].

In a prospective and comparative study involving 53 consecutive patients scheduled to receive either 1 or 3 day of antibiotic prophylaxis for major head or neck surgery, incidence of infection was not related to the duration of antibiotic prophylaxis [44].

Topical antibiotics have been advocated either alone or in combination with systemic therapy, but there is no clear evidence of their clinical benefits and the ecological implications of their use are a cause of serious concern [45–49].

A microorganism of particular importance is MRSA, which may colonize patients before surgery or be acquired in the postoperative period. A systematic search for MRSA colonization is mandatory in countries in which MRSA is a significant pathogen and for all major head and neck surgery procedures. Screening must be performed 7–10 days before surgery because if present, the time needed for MRSA decolonization before surgery is around 5 days [50]. In such a situation, the patient should be decolonized with topical mupirocin or other agents and with daily use of antiseptic soap while isolated in an individual room. In this case, surgical prophylaxis must include an antimicrobial agent active against MRSA such as vancomycin or teicoplanin [51].

In patients who acquire MRSA infection after surgery, contact isolation is also mandatory and antimicrobial therapy must include an agent active against MRSA such as the glycolipopeptides (vancomycin, teicoplanin, and daptomycin), linezolid, or other agents.

MRSA-infected patients require prolonged ICU stay and overall intrahospital stay, extra intensive care and medical care as well as additional costly antibiotics [51].

In a recent report from a maxillofacial unit in the United Kingdom, 14% of patients admitted for definitive treatment for previously untreated oral and oropharyngeal squamous cell carcinoma showed MRSA colonization and the two main risk factors were stage of cancer and free flap [52]. Compared to patients infected with methicillin-sensitive *S. aureus*, the MRSA group was associated with significantly longer hospitalization periods and intervals between admission and MRSA detection, as well as a significantly greater likelihood of a need for intravenous hyperalimentation, prior antibiotic use, and co-isolation of other pathogens [53].

Surgical Site Infections Following Breast Cancer Interventions

Infections following surgery for breast cancer include SSI from lumpectomy, mastectomy, and axillary lymph and node dissection. Breast expanders or implants can likewise become infected with pathogens commonly associated with a foreign device. Myocutaneous flaps can develop necrosis, fail to engraft or become infected. Rarely, chest wall infection (ribs and cartilage) can develop, especially if a mesh is present. Infection may lead to significant morbidity for the patient, delay in adjuvant treatments such as radiotherapy, and increased costs of care if the patient requires supplementary treatment due to infection [54–56].

In patients with postsurgical lymphedema, lymphangitis and erysipelas may develop, although these are not very frequent.

Incidence

The incidence of SSI after breast cancer surgery ranges from 0.8 to 30% [57–61] depending on the duration of surgery, underlying patient comorbidities, definitions used for infection, and other perioperative therapy. SSI has been reported in approximately 2.8% of mastectomy patients according to the most recent report by the National Healthcare Safety Network (NHSN) issued in 2008.

Risk Factors

The risk factors for SSI following breast cancer surgery are the same as for other body sites, including hematoma or seroma formation, prolonged surgical drains, lymphedema, prior chemotherapy or radiation therapy, reoperation for recurrence or to achieve better tumor-free margins, reconstructive surgery with implants, suboptimal prophylactic antibiotic dosing, smoking, a history of a previous SSI or postmastectomy wound infection, and skin flap necrosis

[56–59, 62–66]. The subset of patients undergoing immediate breast reconstruction is at a higher risk of infection [67, 68]. Knowledge of specific risk factors for SSI is essential to create a SSI risk stratification index specifically for breast operations.

Etiology

S. aureus is the most common pathogen followed by betahemolytic streptococci, enteric Gram-negative bacilli and, occasionally, rapidly growing mycobacteria [69]. *Pseudomonas* spp. may be found when infection of the cartilage of the costochondral junction is involved.

Diagnosis

According to the Centers for Disease Control (CDC), an SSI is diagnosed in the following situations: purulent drainage from the incision with or without laboratory confirmation; at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and incision deliberately opened by a surgeon; or an abscess or other evidence of infection involving the deep incision found on direct examination, during reoperation or by histopathologic or radiologic examination. A microbiological examination is only one of the criteria used for a diagnosis of SSI and is neither indispensable nor sufficient for a valid diagnosis.

Sometimes, patients who have undergone partial mastectomy, breast biopsy, or axillary lymph node excision shortly thereafter present with clinical signs (most notably erythema and edema) suggestive of infectious mastitis or inflammatory breast cancer. Representative histologic sections of involved skin usually reveal dilated dermal vessels with no specific evidence of infection or cancer. The hypothesis is that this might be due to interruption of lymph vessels. Although antibiotic therapy is generally ineffective, clinical findings resolve with time (from 2 months to 1 year). This condition should be considered in the differential diagnosis when this circumscribed patient population has such intervention-related symptoms [70].

Treatment

Mild incisional cellulitis can be treated with oral antibiotics, but nonresponding or extensive soft-tissue infection requires intravenous therapy. A minority of breast wound infections progress to a fully developed abscess. The pointing, fluctuant, and exquisitely tender mass of a breast abscess usually becomes apparent 1–2 weeks postoperatively and occurs at a lumpectomy, mastectomy, or axillary incision site. When there is uncertainty regarding the diagnosis (as may be the case with deep-seated abscesses after lumpectomy), ultrasound imaging may be helpful, but the complex mass that is visualized can appear identical to a consolidated seroma or hematoma. Aspiration may also confirm the diagnosis, but sampling error can mislead the clinician. Definitive management of an abscess requires incision and drainage; curative aspiration of purulent material is rarely successful, and the abscess generally reemerges. Usually incision and drainage can be accomplished by reopening the original surgical wound; the resulting cavity must be left open to heal by secondary intention. When recurrent cancer is a concern, it is prudent to perform a biopsy of the abscess cavity wall.

Prevention

In a review of antibiotic prophylaxis to prevent SSI after breast cancer surgery, it was shown that the infection risk is effectively reduced [68]. In this review, seven randomized controlled trials of pre- and perioperative antibiotics for patients undergoing surgery for breast cancer were included, with a total of 1,924 patients. Although there is no consensus as to the antibiotic of choice, additional postoperative doses are not recommended [61].

Suboptimal prophylactic antibiotic dosing is a potentially modifiable risk factor for SSI after breast operation [65]. Local infiltration of an anesthetic agent has been found to be associated with substantially reduced odds of SSI (odds ratio, OR 0.4; 95% confidence interval [CI] 0.1–0.9) [65].

Prevention of arm lymphedema and avoidance of any trauma to the arm are important prophylactic measures. Sentinel lymph node biopsy reduces the rate of axillary lymph node dissection and should thus reduce the incidence of lymphedema and erysipelas.

Infections Following Lung Cancer Interventions

The great majority of patients presenting with lung cancer are inoperable, and this disease is therefore very largely incurable [71].

Surgery-related infections following lung cancer resection include pneumonia, empyema, SSI, and bronchopleural fistula (BPF) formation. Extensive chest wall resections (defined as resection of at least one rib, and/or part of the sternum) can provoke a wide variety of complications, particularly, complicated wound healing [72].

Incidence

Pneumonia and acute respiratory distress syndrome (ARDS) are responsible for most postoperative deaths, accounting for 22–67% of all deaths following surgery [73, 74].

The incidence of postoperative pneumonia remains at 2–30% [72, 73, 75–78] and empyema complicates 6–10% of interventions [79].

BPF remains one of the most feared complications following surgery and affects between 2–12% of cases [77, 79, 80], usually as a late complication (10–45 days after surgery). Its associated mortality is around 60%.

SSI occurs less frequently (1–5%) [72, 75–78, 81].

Risk Factors

Risk factors for postoperative pneumonia include moderate to severe chronic obstructive pulmonary disease (COPD), perioperative/intraoperative airway colonization with a potential pathogen, age over 70 years, a high body mass index, the type and extent of resection, a high postoperative pain score, and type of prophylaxis [71, 73, 77, 78, 82].

BPF is most common following a right-sided pneumonectomy [71]. It is likelier if the residual bronchial stump is of larger diameter and if its blood supply has been reduced by surgical dissection. It is also more common with pleural space infection and empyema, which need prompt drainage to prevent the development of a stump infection [71, 73].

Etiology

Microorganisms causing postoperative pneumonia are Gram-negative bacteria and *Candida albicans* in 75% of patients [83], being acquired postoperatively from the patient's oral cavity and upper respiratory tract [83]. Most common causative pathogens include *Haemophilus influenzae*, *S. aureus*, *Enterobacteriaceae*, *Streptococcus pneumoniae*, *Aspergillus fumigatus*, MRSA, and *P. aeruginosa* [73].

Empyema due to chest tube placement is usually due to *S. aureus* (including MRSA) originating from skin colonization. Occasionally, enteric Gram-negative bacilli, alpha-hemolytic streptococci and *Candida* species cause empyema, especially if a BPF or esophageal anastomosis leak is present.

Diagnosis

The usefulness of procalcitonin (PCT) in the early detection of infection after thoracic surgery was evaluated by Falcoz et al. [84]. These authors found that the best cutoff value for detection of infection was 1 ng/mL, with an area under the ROC curve of 92% (95% CI 0.87–0.96). Thus, in patients with no postoperative infection, a steadily decreasing PCT level or a level <1 ng/mL is reassuring and may be helpful in deciding upon a safe early discharge.

In patients with suspected posterior mediastinitis, transesophageal endosonography with fine-needle aspiration of posterior mediastinal lesions is an effective and relatively noninvasive way to detect mediastinitis and provides material for culture to identify the etiologic agent [85].

Treatment

The mainstay of treatment is surgical drainage of pockets of fluid collection and appropriate antimicrobial therapy for 3–6 weeks. BPF may close spontaneously in time, but subsequent reoperation is frequently required. Chronic drainage of pleural fluid collections is necessary to prevent recurrent empyema and pneumonia.

Prevention

Antibiotic prophylaxis during surgery is effective at reducing the incidence of SSI and of postoperative pneumonia in these patients [82]. The antibiotics recommended for cardiothoracic procedures are cefazolin or cefuroxime, and alternatives are vancomycin or clindamycin [86].

Infections Following Surgery for Esophageal Cancer

Incidence

Major infections, including pneumonia, intra-abdominal or intrathoracic abscesses, sepsis or SSI requiring intervention, have been estimated to affect around 15–20% of patients undergoing esophageal surgery for cancer [87, 88]. Mediastinitis caused by anastomotic leaks is the most severe complication after esophagectomy and the major source of morbidity and mortality. It is characterized by local intrathoracic reactions (mediastinitis) and sepsis, and its incidence has been estimated at around 10% [81, 88].

Risk Factors

To determine risk factors for complications after esophageal resection for cancer, a prospective, nationwide, population-based

study was conducted in Sweden in 2001–2003. Among 275 patients undergoing surgical resection for esophageal or cardiac cancer, 122 (44%) had at least one predefined complication. Thus, operations by low-volume surgeons (<5 operations annually) were followed by more anastomotic leakages than those conducted by higher-volume surgeons (OR 7.86; 95% CI 2.13–29.00). Hand-sewn and stapled anastomoses were associated with a similar risk of anastomotic leakage. Among the patients with cardiac cancer, a transthoracic approach resulted in more respiratory complications compared to a transhiatal (abdominal only) approach (OR 4.78; 95% CI 1.66–13.76). Older age, adjuvant oncologic therapy, and higher preoperative bleeding volume were related to a non-significantly greater risk of complications, while no influence of sex or tumor stage was found [88]. Other risk factors for complications include liver cirrhosis and cervical anastomosis [87].

Diagnosis

For successful management, early diagnostic workup is mandatory in every disturbance of the normal postoperative course. This includes direct endoscopic inspection of the anastomosis to evaluate the viability of the anastomosed organs and the size of leaks.

Treatment

According to the site and clinical classifications of the leak, the spectrum of therapeutic options ranges from simple drainage procedures, endoscopic interventions, and stent implantation to reoperation or discontinuity resection. In any case, the treatment goal must be immediate and should achieve sufficient drainage of the leakage and hindrance of further contamination across the leakage caused by gut contents. Also mandatory, is the early initiation of supportive systemic strategies according to pathophysiologic principles of sepsis [89]. The use of broad-spectrum antibiotics, such as piperacillin-tazobactam or a carbapenem, is recommended in these patients.

Turkyilmaz et al. recently presented a treatment algorithm for esophagogastric anastomotic leaks in their excellent review of this topic [90].

Prevention

The CDC's Guideline for Prevention of Surgical Site Infection, 1999 recommends several measures to reduce the SSI risk [91]. In patients with esophageal cancer and esophageal stenosis, the esophageal floral often switches to the fecal type. Thus, antimicrobial prophylaxis with the drugs used in colorectal surgery is recommended [92] such as a single dose of a third generation cephalosporin (ceftriaxone 2 g) and a nitroimidazole (metronidazole 1 g).

Intra-Abdominal Infections and Surgical Site Infections in Patients Undergoing GI Tract Interventions for Malignant Diseases

The main infections following gastrointestinal cancer surgery besides SSI are peritonitis, intra-abdominal abscess, and sepsis. Abdominal wall mesh infection may occur in patients requiring hernia repair following abdominal surgery for colorectal cancer. Enterocutaneous fistulas require prolonged bowel rest, and frequently, future bowel repair. Perineum infections can occur after abdominal perineal resection, as well as a presacral abscess, and much less frequently sacral osteomyelitis [93–95].

Postoperative infection in intra-abdominal cancer patients is clearly linked to a poorer prognosis and a higher mortality [96–100].

Incidence

The overall incidence of superficial or deep SSI after surgery for gastrointestinal cancers is 4.1% in patients receiving antimicrobial prophylaxis [101]. Figures in gastric cancer (2.8–18.7%), colon cancer (5.2–14.5%), and hepatic/biliary/pancreatic cancers (4.9%) are variable.

The incidence of space/organ SSI after surgery is higher in hepatic/biliary/pancreatic cancer (14.7%) than esophageal cancer (8.4%; $p = 0.02$), gastric cancer (1.5–7.9%), or colon cancer (1.4–11.1%) [101–110].

Risk Factors

Risk factors for infection after surgery for intestinal cancer include advanced age, overweight, patient comorbidities, preoperative radiotherapy, emergency surgery, extended operation time, and combined organ resection [93, 95, 102–104, 109, 111–116]. Laparoscopic surgery for colorectal cancer is associated with a lower incidence of SSI than open colectomy [106, 117–119].

Table 6.1 Microorganisms isolated after laparotomy

Organism	Solomkin [127][a]	Mosdell [128][b]	Organism	Solomkin [127][a]	Mosdell [128][b]
Aerobic and facultative Gram positives			Aerobic and facultative Gram positives		
Escherichia coli	56.8	68.4	Streptococci	35.8	25.9
Enterobacter spp.	13.5	6.1	Enterococci	23.5	10.5
Klebsiella spp.	15.4	17	*Staphylococcus aureus* or *S. epidermidis*	10.5	10.5
Pseudomonas aeruginosa	14.8	19.1	Anaerobes		
Proteus spp.	6.2	2.7	*Bacteroides fragilis*	22.8	44.5
Serratia marcescens	1.2	4.1	*Bacteroides* spp.	21	–
Morganella spp.	1.2	–	*Clostridium* spp.	17.9	5.8
Citrobacter spp.	3.1	3.4	Peptococci/streptococci	7.4	16
Other	3.7	7.5	*Fusobacterium* spp.	6.2	5.1

Adapted from refs. [127, 128]
[a]Percentage of patients
[b]Percentage of abscesses

Risk factors for infection after resection of hepatic/biliary/pancreatic tumors include age older than 65 years, preoperative chemotherapy, type of surgery, the use of drainage tubes, the use of nonabsorbable silk sutures and bile leak, intraoperative bowel injury, blood loss >2,000 mL, and poor postoperative blood glucose control [120–126].

Etiology

Predominant pathogens include enteric Gram-negative bacilli, enteric anaerobes, enterococci, *S. aureus* (including MRSA), and *Candida* species, usually as part of a polymicrobial infection. The microorganisms isolated in patients with postsurgical peritonitis are shown in Table 6.1.

Diagnosis

Early focus identification by clinical, laboratory, and radiologic examination is of major importance. Sonography plays a minor role in the detection of intra-abdominal abscesses in patients undergoing colorectal surgery; computerized tomography (CT) and gallium scans are more helpful [129].

Treatment

Broad-spectrum antibiotics and sometimes also antifungals, occasionally for prolonged periods of time, along with surgical debridement and drainage, are needed for successful management. Postoperative infections are caused by more-resistant flora, which may include *P. aeruginosa*, *Enterobacter* spp., *Proteus* spp., MRSA,

enterococci, and *Candida* spp. For these infections, complex multidrug regimens are recommended [130] since adequate empirical therapy is important to reduce mortality. Local nosocomial resistance patterns should guide empirical treatment, and treatment should be thereafter altered on the basis of the results of a thorough microbiologic workup of infected fluid.

These regimens include piperacillin/tazobactam; broad-spectrum carbapenems, including imipenem/cilastatin, meropenem, and doripenem; third- or fourth-generation cephalosporins plus metronidazole; and ciprofloxacin plus metronidazole. The regimen may be further broadened in selected patients to provide coverage of *Enterococcus*, yeast, and resistant gram-positive cocci.

In the case of progressive cancer, when the patient is no longer a surgery candidate, lifelong antimicrobial therapy may be needed to prevent further spread of infection. Aggressive radiation therapy may induce radiation colitis with perforation and fistula formation, which may require resection and a colostomy.

For severe intra-abdominal infection complicating colorectal disease, laparostomy may be useful in extreme circumstances [131].

Prevention

Antibiotic prophylaxis is effective to prevent postoperative SSI in patients with a gastrointestinal tumor [101, 132]. Prolonged antibiotic prophylaxis longer than 24 h does not reduce the SSI risk after elective gastric and colorectal surgery [133].

In a recently published meta-analysis, the oral and intravenous use of antibiotics covering aerobic and anaerobic bacteria is recommended prior to colorectal surgery, as

antibiotics delivered within this framework reduced the risk of SSI by at least 75% [134]. In this meta-analysis, no statistically significant differences were detected when comparing short-and long-term duration of prophylaxis, or single dose vs. multiple dose antibiotics.

Supplemental perioperative oxygenation is beneficial in preventing SSI in patients undergoing colorectal surgery [135].

The administration of an immunonutrition diet preoperatively supplemented with two or more nutrients including glutamine, arginine, omega-3 polyunsaturated fatty acids, and ribonucleic acids has been identified as protective against the development of SSI (OR=0.41, $p < 0.001$) [136, 137].

Infections Following Surgery for Genital and Urinary Tract Neoplasms

Genital and urinary tract neoplasms include a variety of tumors that are treated using different techniques and approaches.

In the case of gynecologic procedures, the risk of infection is directly related to the contaminating load of genital flora during surgery. Surgical procedures in the gynecologic oncology patient frequently leave behind large raw surfaces, such as in pelvic node dissection, extrafascial radical hysterectomy, pelvic exenteration, and debulking operations. The resulting rough areas, despite meticulous hemostasis, may lead to fluid collections and hematomas deep in the pelvis. Further, when bowel resection with or without primary anastomosis is part of the procedure, despite bowel preparation and a careful aseptic technique, fecal contamination frequently occurs. It is not surprising that the incidence of infected pelvic collections is higher in patients with gynecologic malignancies than in any other group of cancer patients, with the exception of patients with colorectal cancer.

The most serious type of infection after a hysterectomy is vaginal cuff infection. The cuff, created from the vaginal vault when the uterus is removed, is virtually always contaminated with vaginal flora and highly susceptible to postoperative infections. Vaginal cuff infections are more frequent after vaginal hysterectomy, but can also occur after abdominal hysterectomy. Cuff infections may be complicated by pelvic cellulitis and abscess formation [138]. In patients with pelvic exenteration, intestinal fistula formation is an uncommon but very serious complication [139].

Prostate cancer is the most common noncutaneous malignancy diagnosed in men older than 60 years. Advances in techniques, instrumentation, and surgical and perioperative management have made resection of the prostate a relatively safe procedure. Endoscopic extraperitoneal radical prostatectomy (EERPE) is a further advance in minimal invasive surgery as it overcomes the limitations of laparoscopic (transperitoneal) radical prostatectomy by the strictly extraperitoneal route of access, combining the advantages of minimal invasive surgery with those of an extraperitoneal procedure. The incidence of most complications directly correlates with the surgeon's experience.

Incidence

Brooker et al. [140] reported on 496 gynecologic oncology patients detecting an overall infection rate of 11%, excluding uncomplicated urinary tract infections (UTIs). The surgical infectious morbidity rate was 15%. By cancer site, rates of postoperative infection were 22% for cervical cancer, 12% for vulvar cancer, 12% for uterine cancer, and 11% for ovarian cancer. More recently, Iatrakis et al. [141] reported similar surgical infectious morbidities in a series of 1,180 gynecologic oncology patients.

After radical hysterectomy in patients with cervical or endometrial cancer, the incidence of SSI ranges from 3 to 20% [142, 143] and of vaginal cuff infection from 0.5 to 10% [142, 144]. SSI is more common in laparotomy patients while vaginal cuff infection occurs more frequently in patients undergoing a laparoscopic procedure. However, some studies have shown no differences in outcomes and costs of endometrial cancer treatment via traditional laparotomy, standard laparoscopy, and robotic techniques [145].

In urologic surgery (including radical or partial nephrectomy, nephroureterectomy, radical prostatectomy, and radical cystectomy), the incidence of postoperative infectious complications (SSI and UTI) ranges from <1–7% [146–149]. The incidence of postoperative UTI after transurethral resection of the prostate is around 5% [150].

Risk Factors

The patient's ultimate susceptibility to infection is influenced by factors inherent to the host, factors related to treatment, and factors associated with the malignant process [151]. Host factors include altered vaginal flora and microbial virulence, poor nutritional status, advanced age, comorbidities, and immunosuppression. Treatment-related factors include previous invasive diagnostic tests, adjuvant therapy with chemotherapy, radiotherapy or steroids, and complex surgical procedures (type of surgery, duration of the intervention) [143]. Tumor related-factors include malignancy-associated immunosuppression, microvascular alterations, necrotic tumor, and obstructive lesions.

The gamut of invasive diagnostic and therapeutic procedures that patients undergo increases the likelihood of infectious

complications [151]. These procedures include cystoscopy, sigmoidoscopy, needle or incisional biopsy or both, conization, laparoscopy, dilatation and curettage, and invasive radiography. Any tumor that obstructs natural elimination pathways, such as the pulmonary, gastrointestinal, or urologic tracts, can also induce infection. Following urologic surgery, the most important risk factor for SSI is preoperative colonization of the urinary tract with bacteria (i.e., significant bacteriuria) [152]. Other risk factors are age [153] and patient comorbidities [148].

Etiology

The indigenous flora of the genital tract has long been considered a determining factor for postoperative infection [154]. However, though most infections in patients with gynecologic malignancies arise from the endogenous flora of the lower genital tract, especially anaerobic bacteria such as *Prevotella* spp., *Bacteroides* spp., and peptostreptococci, a significant percentage of infectious organisms are acquired during hospitalization. The most common isolates in such cases include *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *C. albicans*, and several *Enterobacteriaceae* [140].

Antibiotic prophylaxis in urologic patients with preoperative urinary tract bacterial colonization selects for more resistant pathogens that postoperatively cause UTI [152].

Diagnosis

Most wound infections become apparent 4–6 days postoperatively.

Posthysterectomy pelvic cellulitis presents with fever and lower pelvis pain, with an indurated and often exquisitely painful vaginal cuff 2–5 days after surgery. Postoperative pelvic abscesses of the vaginal cuff, pelvic floor, and sidewalls, or at the site of intra-abdominal blood or fluid collections, tend to present more than 5 days after the surgical procedure and may not manifest until after the patient has been discharged from the hospital. The clinical presentation of the patient with a pelvic abscess includes low-grade fever with mild-to-moderate abdominal pain and a pelvic mass.

Treatment

The preferred treatment for wound infections, whether superficial or deep, is still adequate drainage. No systemic antibiotics

are usually administered, except to immunosuppressed patients, patients with an implanted prosthetic device (e.g., a mesh, infusion pumps), or patients with extensive cellulitis. Once the wound is clean, usually within 4–5 days, the wound edges can be reapproximated using skin tape (modified delayed secondary closure). Continued wet-to-dry dressing changes may result in adequate healing by secondary intention [155].

Management of postoperative pelvic abscess includes optimizing the patient's general status, antibiotic administration, and abscess drainage. Empiric antibiotic therapy should be directed against the microorganisms most likely to be recovered from the abscess. Surgical drainage is indicated for the treatment of postsurgical pelvic abscesses that fail to respond to maximal antibiotic therapy [151]. Percutaneous drainage of pelvic collections under ultrasound or CT guidance has proven to be a safe and effective alternative to open surgical drainage. A simple, well-defined abscess can be treated successfully by percutaneous drainage in more than 90% of cases. Even in patients in whom abscess elimination is not accomplished by percutaneous drainage, this maneuver facilitates subsequent surgery by diminishing the local inflammatory response.

Prevention

Today, the incidence of postoperative pelvic abscess with the use of prophylactic antibiotics is 1–4% for vaginal hysterectomy and 0.1% for abdominal hysterectomy. The American College of Obstetricians and Gynecologists has just issued its updated antibiotic prophylaxis guidelines for gynecologic procedures [156].

In these guidelines, level A recommendations (based on consistent scientific evidence) are single-dose antimicrobial prophylaxis given preoperatively to patients undergoing hysterectomy or elective suction curettage abortion, and *no* such prophylaxis in patients undergoing diagnostic laparoscopy. Level B recommendations (based on limited or inconsistent scientific evidence) include no antibiotic prophylaxis for hysteroscopic surgery.

The American Urological Association (AUA) recently published their guidelines for antimicrobial prophylaxis in urologic surgery [157]. These guidelines provide information on antimicrobial agents used for specific procedures, the duration of antimicrobial therapy, and doses. Antimicrobial prophylaxis is recommended for most urologic operations, including transurethral endoscopic, open or laparoscopic procedures, as well as extracorporeal shock wave lithotripsy. For some procedures, such as those not accessing the urinary tract, these guidelines endorse antimicrobial prophylaxis only in patients with a high risk of

infection. Several issues remain to be addressed, especially operations in which bowel segments are grafted. These are classified as clean-contaminated operations in the CDC guidelines for the prevention of SSI [91] but as contaminated in the Japanese Urological Association (JUA) guidelines. In addition, the choice of antibiotics and optimal duration of antimicrobial prophylaxis for bowel segment procedures have yet to be determined. Another unresolved issue is whether laparoscopic operations require the same antimicrobial prophylaxis regimens as open surgery procedures [158].

Infections Following Limb Interventions in Cancer Patients

Bone and soft-tissue sarcomas account for only about 2% of all malignancies. Their treatment aims to both cure the patient and preserve the functionality of the affected body part. Several techniques of reconstruction have been advocated and have gained popularity following malignant tumor resection due to the introduction of allografts, tumor prostheses, composite allograft prostheses, or the technique of arthrodesis.

Endoprostheses are of established use to reconstruct defects following bone tumor resection. The long-term durability of reconstruction is excellent, with long-term limbsalvage achieved in 91% of patients at 20 years postsurgery. The main reasons for secondary amputation are locally recurrent disease and deep periprosthetic infection. Infection remains one of the greatest threats for early failure of a reconstruction using an endoprosthesis [159]. Most series of patients undergoing reconstructions show a periprosthetic infection rate of approximately 10% [160, 161]. Infection most frequently occurs within 12 months of the last surgical procedure. However, the risk of infection is life-long [162]. Risk factors for infection are preoperative radiotherapy and a tumor size over 5 cm [163]. The most common pathogenic organism is coagulase-negative *Staphylococcus*. The most effective treatment for deep infection is two-stage revision, with local treatments being of little use to cure a deep infection. Research is on-going into surface treatments with silver and other materials to help reduce infection rates. Jeys and Grimer have recently published an excellent review on the outcome of the use of endoprostheses in limb salvage surgery for the treatment of bone tumors [161].

Antibiotic prophylaxis is warranted in all patients undergoing surgery for limb cancer. When the patient requires major limb amputation, antibiotic prophylaxis has been shown to significantly reduce the rate of stump infection [164].

Emerging Prevention and Management Trends for Cancer Surgery Infections

In the near future, it is anticipated that we will continue to see developments in minimally invasive procedures. Laparoscopic surgery and video-assisted thoracoscopy have rapidly expanded in a number of applications. The net effect of the minimally invasive surgical strategy is that the surgical wound, as the origin of so many infectious complications in the past, will be far smaller and that the frequency and severity of SSI will most likely be reduced. Minimally invasive techniques should reduce the risks of bacterial contamination of the abdominal cavity, the pleural space, and the joint spaces manipulated in the operative procedure. Following surgery, workup of infection is most commonly prompted by fever. However, the presence of fever as a predictive factor for postoperative infections has been examined many times in the literature, and almost all studies have demonstrated its lack of sensitivity (14–60%) and specificity (69–80%), both in adult and pediatric patients [165–168]. Unnecessary workups initiated because of fever increase hospital costs, unnecessarily worry patients, and prolong hospital stay. Notwithstanding, the timing of postoperative fever is significant. Hence, fever that begins beyond the fifth postoperative day is much more likely to indicate a clinically significant infection [169].

In a growing number of reports, a relationship between intraoperative body temperature and the risk of postoperative SSI is starting to emerge. Thus, close attention paid to normothermia in the operating room, routine body temperature measurements during surgery, and correction of low body temperatures could reduce the number of SSI.

Evolving issues in the prevention of SSI also include tight adherence to prophylactic antibiotic guidelines, and good glycemic control and supplemental oxygenation during surgery [135, 170–173].

General risk factors for surgery and preventive measures apply to all types of procedure [91].

Postoperative Infections in Children with Cancer

Survival rates in children with cancer have improved dramatically over the past 30 years. Identifying biological and genetic characteristics as risk factors for the various tumors has led to changes in treatment using risk-based management as the template for care. Refinements in surgery, chemotherapy, and radiation therapy have been particularly helpful [174]. Surgery plays a pivotal role in treating most childhood cancers. Whether surgically removing a tumor,

supporting nonsurgical treatment such as chemotherapy, or performing reconstructive surgery, the pediatric surgeon contributes to the comprehensive care of each child.

Despite significant advances in supportive care during the last years, infection remains a major cause of therapy-associated morbidity and death. Pediatric cancer patients have an increased risk of potentially life-threatening infectious complications due to their underlying illnesses and aggressive anticancer treatment. Rates of septicemia and its mortality are significantly higher in malignant hematologic disease than in solid tumors [175]. Major factors associated with the occurrence of postoperative infections in children with cancer include length of the surgical procedure and surgical procedure category (class I-clean, class II clean-contaminated, class III-contaminated, and class IV dirty-infected). Minor factors include age, myelosuppressive therapy with preoperative anemia, neutropenia or lymphopenia, bone marrow transplant, remote infection, obesity, malnutrition, central venous access devices, chemotherapy and radiotherapy [176], type of tumor [168], disease state (primary active, recurrent active, primary remission, or secondary remission) [10, 177, 178], operation room (intensive care unit vs. operating room), emergency operation, extensive surgery [178], length of intervention [168], surgical bleeding, external drains [121], and reoperation.

Risk Factors

Age

Infections in a pediatric oncologic surgery unit show a very different pattern to infections in adults. In children, it is widely accepted that surgery-related risk factors are more important than those related to the physiologic status of the patient. In general, children show a better overall success rate of surgery and lower mortality than adults. Death from infection is only 1% in children. Both neonates and children with cancer show a lower incidence of postsurgical infection (2–4%) and a lower surgery-related mortality [179–182].

Malignant neonatal tumors are rare and comprise 2% of childhood malignancies. This is an interesting group of tumors because their natural history and response to treatment differ from those seen in older children. Histologic type distributions (neuroblastoma 60%, mesenchymal tumors 15%, and brain tumors 10%) also differ considerably to those seen in older children such that oncologists are often faced with diagnostic, therapeutic and ethical challenges. A given neoplasm can be extremely malignant in an older child, while the same tumor type in a newborn may be generally well circumscribed and show benign biological behavior. Most patients undergo surgical resection and approximately 50%

of neonates receive chemotherapy administered at a 30–50% reduced dose. Hematologic toxicities and infections are the main therapeutic complications. Nosocomial infection in newborns with solid tumors is significantly related to gender, birth weight, and the use of a central venous catheter (CVC) [183, 184]. Other devices including artificial ventilation, an umbilical artery catheter, umbilical venous catheter, and urinary catheter are not significant risk factors [185, 186].

Type of Tumor

Brain tumors are sometimes associated with abscess formation. Intrasellar or parasellar tumors are among the brain tumors that most frequently develop bacterial abscesses as the result of direct migration of flora from the paranasal sinuses. Intraparenchymal posterior fossa neoplasms harboring intratumoral abscesses are rare and, in such cases, a bloodstream route of spread has to be considered. All meningiomas with this complication reported have been parasagittally located.

SSI is not uncommon following abdominal cancer surgery and can be associated with serious morbidity, mortality, and increased resource utilization [187]. Our experience suggests that laparotomy infections in children are related more to factors inherent to the surgical procedure than to the overall physiologic status of the patient.

Surgery for colorectal tumors has returned some of the highest rates of infectious complications, but fortunately these tumors rarely appear in children.

The prognosis for children with bone sarcoma treated with limb-sparing surgery has improved considerably over the past 20 years, but this has also meant an increase in the number of complications requiring treatment. Limb-sparing wide excision is now as effective as amputation for treating limb sarcoma. Limb reconstruction traditionally involved allografting, but current reconstructive procedures include the use of a microvascular-free fibula flap, associated with a lower infection rate (around 15%) than traditional allograft reconstruction (even considering that vancomycin-supplemented allografts restore bone stock and provide sound fixation with a low incidence of further infection) [188]. If an endoprosthesis is used, it should be a "growing endoprosthesis" that requires revision to an adult prosthesis around the time of skeletal maturity. Gaur et al. report a SSI incidence of 16.5% and orthopedic device infection incidence of 21.3% in children and young adults with bone malignancies undergoing limb-sparing surgery [189]. Nonunion of the allograft-host junction after bone transplantation is not uncommon, and its treatment is frequently problematic. The greater the number of surgical procedures, the worse is the outcome. The rate of nonunions significantly increases in patients who receive chemotherapy as compared to patients not given

chemotherapy. In order, the allograft types associated with the highest rates of infection and nonunion to the lowest rates are alloarthrodesis, intercalary, osteoarticular, and alloprostheses. The fracture rate is also higher in children with infection and nonunions than in those without infection or nonunions [189, 190].

Other Risk Factors

Minimally invasive surgery (MIS). Thoracoscopic and laparoscopic techniques play a major role in pediatric surgery. MIS is already established in pediatric oncology surgical treatment. So far in our experience, MIS is performed in every fourth patient and has proved to be an excellent approach in diagnostic interventions and tumor biopsies, whereas its efficacy is more limited in tumor resections [191]. Further factors (tumor recurrence, trocar site recurrence, tumor growth, and dissemination after CO_2 insufflation) still need to be assessed. Despite several reports on MIS procedures at several institutions, no significant differences have been found in the incidence of superficial or deep SSI, and at present surgeons are attempting to perform more oncological procedures as minimally invasive procedures.

Robot-assisted surgery represents an improvement over MIS that will most likely be increasingly utilized. Children as young as 5 months and as small as 20 lb have successfully undergone robotic surgery. Initial experience indicates that the robotic system is associated with an acceptable risk for SSI. Technologic advances in surgery will continue to be evaluated from an infection control viewpoint as the operating room remains a dynamic environment undergoing rapid change and innovation.

Neutropenia. Severe neutropenia is defined as an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L or a decreasing leukocyte count $<1.0 \times 10^9$/L with no differential count available. In pediatric patients with SSI, the proportion of patients with neutropenia at the onset of infection is around 25%.

Therapy-induced neutropenia is the most important risk factor for infection in pediatric patients with hematologic cancer, but other factors, such as alterations in skin/mucosal barriers, and defects in cell-mediated or humoral immunity, also contribute to the risk of infection [192, 193]. The management of pediatric oncology patients with fever and neutropenia assumes that all patients are at risk of bacteremia, and therefore generally involves hospitalization and broad-spectrum parenteral antibiotics.

The incidence of postoperative SSI has been estimated at 3% in nonimmunocompromised children with a preoperative ANC under 1,000/mL, similar to the overall SSI rate in children with normal ANC. Thus, the cancelation of an elective surgery procedure in children with an ANC under 1,000/mL is not warranted on the grounds of concern about postoperative infection.

CVCs. Neutropenia is recognized as a risk factor for infection and compromised wound healing. The placement of a CVC in neutropenic children is associated with substantial infectious morbidity [179, 194]. In our recent experience (5 years), among children diagnosed with acute lymphocytic leukemia or aplastic anemia and a low ANC who receive a CVC, the removal of a port is more likely than the removal of a Hickman catheter for any reason including infection [195, 196]. When possible, CVC, particularly ports, should be avoided in the presence of neutropenia. Other authors have reported no differences in the risk of infection between tunneled catheters and implanted ports [194] or attributed a significantly higher rate of bloodstream infection to the use of Hickman catheters compared to implantable ports (4.6 vs. 1.45 episodes per 1,000 catheter-days) [197].

Despite the management benefits offered by permanent CVC, it is clear that children with a CVC show an increased rate of infection and their use should be carefully contemplated. The most important consideration is that fever >39.5°C in a child with a CVC is likely to be associated with a documented infection irrespective of the neutrophil count [194].

Nutrition. The frequencies of superficial, deep, and organ/space SSI in children with cancer who fail to thrive have been well documented. Preoperative enteral immunonutrition appears to be effective for preventing SSI in children with cancer and malnutrition [198]. Nutrition via a nasogastric tube or by means of a gastrostomy in children with cancer has several advantages. Gastrostomy is rarely associated with more than minor complications (the most frequent complication is inflammation during periods of neutropenia), it is cosmetically more acceptable than the nasogastric tube and it improves nutrition at a far lower cost than parenteral nutrition. In selected cases in which bone marrow transplantation or intensive treatment protocols are planned, gastrostomy should be considered before malnutrition develops to avoid surgical infection complications.

Blood transfusion. Perioperative blood transfusion carries numerous potential risks for the transmission of infective diseases, and immunosuppression will promote the occurrence of postoperative infectious complications. The link between perioperative blood transfusion and postoperative septic complications worldwide has not been well documented.

In conclusion, the accurate identification of risk factors is essential to design strategies aimed at preventing potentially devastating postsurgery infections in children [199]. In every pediatric oncology center, a team comprising surgeons, anesthesiologists, operating room nurses, oncologists, microbiologists, pharmacists, postoperative inpatient and clinical nurses, infection control professionals, and healthcare epidemiologists, among others is directly responsible for the

prevention of nosocomial infections. Hospital guidelines for postoperative infection control in pediatric cancer patients have to be defined, personnel roles and processes should be standardized, and we should also try to encourage communication/education among health care professionals.

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Chapter 7
Management of Infections in Critically Ill Cancer Patients

Henry Masur

Abstract Advances in critical care medicine have enabled cancer patients to survive aggressive medical and surgical therapies that they could not have tolerated a decade ago. For patients whose goals can be met by ICU support, the diagnostic and empiric therapeutic approach will be far different than when patients are more stable in other hospital areas: evaluations must be completed rapidly while patients are able to tolerate such testing, and empiric therapy must be broad and promptly administered. Oncologists and infectious disease specialists need to be actively involved in evaluating cancer patients in the ICU and in developing their management plans due to the enhanced knowledge they are likely to have of the patient's history prior to the ICU, their knowledge of the underlying disease and life-threatening process, and their expertise in drug selection and monitoring.

Keywords Critical Care • ICU • Infection

Introduction

The past decade has witnessed dramatic improvement in prognosis for patients with many types of cancer. This improvement is due to aggressive management of medical and surgical approaches that can induce remissions and cures if patients can be kept alive despite the complications of their neoplastic process and if they can be kept alive despite the organ dysfunction brought about by their therapies. Critical care services clearly provide benefit to cancer patients with life-threatening complications [1–10].

A substantial fraction of cancer patients spend time in intensive care units due to complications arising from their disease or the antineoplastic therapy. Infections are responsible for a high percentage of such admissions and are a common complication of patients admitted to the ICU for noninfectious processes.

Cancer patients are admitted to the ICU for neutropenic fever with hypotension, catheter-related infections, pneumonia, gastrointestinal infections, urinary tract infections, and central nervous system infections, all of which are discussed in detail in Chaps. 1–6. The treatment of specific pathogens follows the recommendations detailed in Sects. 3 and 4. Patients in the ICU, however, require some special considerations.

Role of Oncologist and Infectious Disease Specialist in ICU

ICUs can be intimidating environments due to the complexity of equipment and the frenetic pace of staff activity. Some ICU staff take special pride in their ability to manage patients using the resources available to them in the ICU. Oncologists and infectious disease specialists must recognize, however, that they are likely to know the underlying disease, the patient's prior history, and the subtleties of infection management better than the ICU staff in some situations.

In some hospitals, oncologists and infectious disease specialists cease to follow patients regularly in the ICU. While there is no study proving the utility of having oncologists and infectious disease providers carefully evaluating patients in the ICU and taking an active role in management, it is likely that the specialized knowledge and continuity of care will result in improved outcome.

Oncologists and infectious disease experts must learn how to read the flow sheets and charts in the ICU and should communicate in person at least daily to the ICU physicians and nurses. An area of special attention should be drug selection, drug doses, drug interactions, and drug toxicities. Given the complex management required in the ICU, the oncology and infectious disease providers need to review drugs daily, assuring that the right drug, the right dose, the right time, and

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the right monitoring are documented in the record, i.e., have in fact been selected and administered, rather than relying on verbal reports on rounds that may or may not be accurate. They also need to assist the ICU staff in assuring that the correct tests are ordered, are received by the laboratory, and are acted upon as soon as results are available. The infectious disease specialist interacting with the microbiology laboratory can often provide accurate information well before the intensivist might have received the helpful test results.

For prevention of complications, oncology and infectious disease teams can also assist ICU providers to be certain that the invasive equipments, such as intravenous catheters, are inspected daily and removed promptly when no longer needed, and that drugs are discontinued when the situation no longer warrants the use of these agents.

Critical Care Utilization: Does ICU Care Meet the Patient's Goals?

Before any patient is brought to the ICU, especially a patient with cancer, realistic planning should have taken place about the role of the ICU in achieving the patient's goals. Some patients have such a dismal prognosis from their underlying disease that intensive interventions in the ICU have virtually no likelihood in achieving the patient's goals. Some patients are willing to tolerate certain intervention, but are unwilling to undergo intubation and mechanical ventilation.

Too often, patients are brought to the ICU without a clear understanding of what can realistically be achieved, and what should be done that will meet the patient's wishes. Such planning is important before the need for critical care interventions occurs [11–13].

Critical Care Utilization: Does Critical Care Benefit Cancer Patients with Life-Threatening Complications?

As the therapeutic options for patients with cancer have expanded, and as critical care services have improved, it is clear that many patients with cancer survive their ICU admission to be discharged from the hospital for meaningful periods of time [1–8]. This is more likely to occur in ICUs that have extensive experience dealing with cancer patients. While there are some specific syndromes that continue to have very poor prognoses, such as diffuse alveolar hemorrhage, studies have shown that it is difficult in this rapidly evolving area to make meaningful generalizations that do not take into account many individual specifics [14–20].

Thus, the literature to date supports using ICUs to support patients through life-threatening complications despite their underlying disease and making individual decisions to limit care based on specific scenarios related to the underlying disease, the life-threatening complication, relevant comorbidities, and patient goals. Specifically, an underlying cancer should be considered no differently in deciding whether to use critical care services than other underlying diseases: each patient must be evaluated using the same general types of parameters.

A variety of scoring systems, including Simplified Acute Physiology Score (SAPS) II and APACHE II, have been assessed for patients with various types of cancer [21–24]. These scoring systems have yielded conflicting results about their ability to predict outcome in patients with various forms of cancer. There have also been conflicting results related to the impact of parameters of immunity/inflammation, such as neutropenia, and the impact of bacterial or fungal processes, which is not unexpected given the complex nature of variables related to the specific pathogen, the specific host defense defect, and the era when the study was performed.

There is extensive literature documenting improved prognosis for cancer patients in ICUs over the past decade [5, 15, 25]. This is undoubtedly due to a wide variety of issues related to improved patient selection, improved anticancer therapy, and improved critical care capabilities.

Providers need to keep in mind that these systems are intended to assess patient groups, and not individual patients. Moreover, with the development of new antimicrobial agents, new immunosuppressive drugs, and new critical care support modalities, many studies using various scoring systems are not contemporaneous enough to be relevant.

Diagnostic Approach

Cancer patients, especially those with substantial immunosuppression, require aggressive attempts to establish the precise cause of any infectious process that is severe enough to bring them to the ICU. While patients who are immunosuppressed are well recognized to require prompt and aggressive diagnostic approaches, those in the ICU deserve special attention.

By definition, such patients are unlikely to have a favorable prognosis if the correct diagnosis is not established promptly. It is well known that failure to institute appropriate therapy promptly reduces the likelihood for a successful outcome with bacterial, fungal, and viral processes.

It is also important to recognize that the window of opportunity to perform certain diagnostic testing may be very limited. Patients may quickly become too hypotensive to be safely moved for imaging studies. Patients with respiratory

compromise may become so hypoxic that it is unsafe to perform bronchoscopic or surgical procedures to obtain pulmonary secretions or lung tissue. Thus, aggressive attempts to obtain appropriate studies and appropriate specimens take on an added sense of urgency.

Also important is for clinicians to take a broad approach to the differential diagnosis. When patients appear with febrile syndromes, healthcare providers dealing with cancer patients often leap to the assumption that infection is the only likely cause of the life-threatening disorder. Neutropenic patients or patients receiving high-dose corticosteroids who develop fever and diffuse pulmonary infiltrates may have pulmonary edema due to myocardial dysfunction (related to atherosclerotic disease or chemotherapeutic toxicities), drug toxicity, cryptogenic organizing pneumonia, radiation pneumonitis, or transfusion-associated lung injury. Patients with fever and hypotension may have bacterial or fungal sepsis, but they may also have febrile neutropenia of unknown cause in addition to adrenal insufficiency, myocardial ischemia, hyperthyroidism, or pericardial tamponade.

Thus, when cancer patients are admitted to the ICU, there is an urgency to consider a broad range of potential causes for their syndrome and to rapidly obtain the tests that are most likely to be diagnostic.

Given the narrow window of opportunity, diagnostic samples must be processed for the full range of potential pathogens. While with more stable patients there may be some valid reasons to be more cost conscious in ordering diagnostic tests, in most situations in the ICU, diagnostic and therapeutic approaches need to be comprehensive since the margin for error is so small.

Therapy

For patients in ICUs who appear to have microbial cause for their ICU admission or for a complication of their ICU stay that was initiated due to a noninfectious process, empiric therapy must be broad and must be delivered promptly.

Many consultants fail to grasp the difference between treating immunologically normal patients who are stable, as opposed to unstable patients, especially those with significant immunosuppression. First, the empiric regimen must be broad and must be active against all causes that are logically plausible. Many providers are reluctant to start "too many" antimicrobials for fear of creating resistance or drug-related toxicities. However, the primary goal in the ICU is to save the patient's life from the imminent threat rather than potential or hypothetical threats. Thus, several antibacterial and antifungal agents may be appropriate to start. As soon as the diagnosis is established, some of the multiple drugs can be discontinued or modified. Thus, "polypharmacy" may be

dismissed by some providers as dangerous, when in fact the danger is failing to institute effective therapy promptly.

In choosing therapeutic regimens, clinicians often focus primarily on bacteria; however, especially for immunosuppressed patients, fungi and viruses need to be important considerations. Clinicians should keep in mind that for ICU-related blood stream infections, Candida is the fourth most common pathogen. Thus, for sepsis, antifungal therapy should be a prime consideration for initial therapy and should likely be a consideration for certain intraabdominal and genitourinary infections. Therapy for molds may also be appropriate initially in certain patient populations presenting with certain syndromes. Also, as CMV, VZV, HSV, Influenza, RSV, Adenovirus, and other viruses are more commonly documented as causing life-threatening disease, initial empiric therapy with antiviral agents needs to be a consideration.

Once a regimen is chosen, all providers must participate in assuring that the right drug at the right dose is administered promptly. Every member of the ICU staff should be well acquainted with the correlation between time to administration of antibiotic or antifungal and survival [26–32].

ICUs are complex organizations: many have difficulty assuring that the important antimicrobials are administered within the first hour after a regimen is ordered. Some physicians appear to believe that once they enter an order into the computer, their responsibility ends. The entire ICU team and consultants must make certain that the correct orders are entered and that the chain of responsibility from the pharmacy to the bedside nurse to the patient functions such that the patient receives the drug promptly.

Pharmacokinetics in the ICU must also be attended to. Critically ill patients are different from many other kinds of patients. Their volumes of distribution may be acutely altered due to aggressive fluid resuscitation, heart failure, or renal failure. Their renal or hepatic function may be compromised. They may have complex drug interactions. These issues must be carefully followed by subject-matter experts. Measurement of serum drug levels is especially important in the ICU where pharmacokinetics may not be as predictable as in more stable patients.

For cancer patients who are receiving chemotherapy or immunosuppressive therapies, critical illness may be a reason to reduce the doses of drugs or to temporarily or permanently discontinue the cancer therapies. Critically ill patients may not absorb oral agents if drugs are not available by parenteral route. Critically ill patients may not be able to survive the toxicities of these drugs. Such decisions must be carefully made. Orders for such agents are probably best entered not by the intensivists, who are usually unfamiliar with the doses and agents, but by the primary team managing the cancer.

Prevention of Infectious Complications

When patients enter ICUs for any reasons, there is an appropriate concern that infectious complications will occur involving invasive devices, surgical wounds, loss of ability to protect the airway, superinfection with virulent organisms, and multiple other factors. While patients often will survive only if they are monitored invasively, intubated and placed on mechanical ventilation, or administered very broad-spectrum antimicrobial therapy, there are many interventions that can reduce the likelihood of infectious complications.

Section 5 reviews some interventions that are likely to be useful. However, as stated above, removing invasive devices and antimicrobial therapies promptly when they are not needed will go a long way towards improving patient outcome.

Critical care units generally maintain a high degree of focus and adherence to infection control practices related to proper isolation, hand hygiene, staff immunization, and careful epidemiological monitoring to look for outbreaks and trends. When the patients involved are immunocompromised, such focus is especially important. Adherence to infection control practices is important by not only for the ICU staff, but for consultants and families as well.

Summary

Cancer patients can clearly benefit from critical care services, although decisions to admit them to ICUs or to continue to offer supportive care need to be individualized based on patient wishes, the prognosis for the underlying disease, and the prognosis for the life-threatening complication that makes them ICU candidates. Infections are well known to be frequent causes for ICU admission and to be frequent complications in patients admitted to ICUs for noninfectious complications. Oncologists and infectious disease specialists must be active members of the ICU team if patient outcome is to be optimized.

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Part II
Clinical Syndromes

Chapter 8
Management of the Neutropenic Patient with Fever

Kenneth V.I. Rolston and Gerald P. Bodey

Abstract Neutrophils provide protection against a wide variety of common and opportunistic bacterial and fungal pathogens. Consequently, the frequency and severity of infections caused by these organisms is increased in patients with neutropenia. At most cancer treatment centers, Gram-positive organisms are isolated more frequently from neutropenic patients with documented bacterial infections than Gram-negative bacilli, although institutional and regional differences occur as do periodic shifts in the spectrum of bacterial infections. *Candida* spp. and *Aspergillus* spp. remain the most common fungal pathogens in this setting, although a number of opportunistic fungal pathogens have emerged. The prompt administration of empiric, broad-spectrum, parenteral antibiotics in the hospital when a neutropenic patient becomes febrile is the standard of care. Over the past decade, it has become possible to reliably identify "low-risk" neutropenic patients both in adult and pediatric patient populations. Infection prevention (prophylaxis), infection control, and antimicrobial stewardship are important aspects in the overall management of the febrile neutropenic patient.

Keywords Neutropenia • Antimicrobial therapy • Low-risk • Febrile neutropenia • Fungal infection • Bacterial infection

Introduction

Neutrophils provide protection against a wide variety of common and opportunistic bacterial and fungal pathogens (Fig. 8.1). Consequently, the frequency and severity of infections caused by these organisms is increased in patients with neutropenia. The currently accepted definition of neutropenia

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is an absolute neutrophil count (ANC) of ≤500/mm^3 [1]. At most cancer treatment centers, Gram-positive organisms (coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus* spp., *viridans* group streptococci) are isolated more frequently from neutropenic patients with documented bacterial infections than Gram-negative bacilli (*Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*), although institutional and regional differences occur as do periodic shifts in the spectrum of bacterial infections [2–4] (Fig. 8.2). *Candida* spp. and *Aspergillus* spp. remain the most common fungal pathogens in this setting, although a number of opportunistic fungal pathogens have emerged [5]. The prompt administration of empiric, broad-spectrum, parenteral antibiotics in the hospital when a neutropenic patient becomes febrile is the standard of care [1]. Over the past decade, it has become possible to reliably identify "low-risk" neutropenic patients both in adult and pediatric patient populations [6–8]. Carefully selected low-risk patients can be safely treated with oral or parenteral antibiotics without hospitalization or after a short period (~48 h) of hospitalization [9–12]. Patients failing to respond to appropriate antibacterial therapy frequently harbor fungal infections and should receive empiric or preemptive antifungal therapy while a diagnosis of a fungal infection is being pursued [13]. The overall duration of therapy will depend on several factors including the nature, anatomical site, and severity of infection, and recovery of the neutrophil count to normal levels [1]. Infection prevention (prophylaxis), infection control, and antimicrobial stewardship are important aspects in the overall management of the febrile neutropenic patient.

Epidemiology of Infections in Neutropenic Patients

Bacterial infections generally occur during the initial phases of neutropenic fever, whereas fungal infections are more common in patients with prolonged neutropenia. Table 8.1 provides a list of bacterial and fungal pathogens that cause infections in neutropenic patients. Recent epidemiologic surveys have
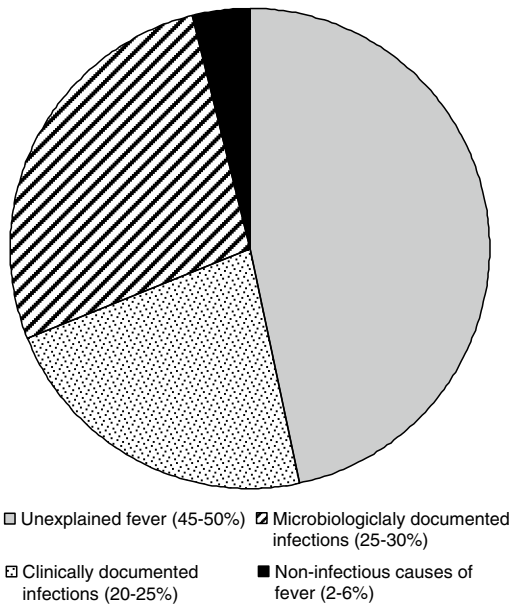
Fig. 8.1 Nature of febrile episodes in neutropenic patients. Data from recent surveys at The University of Texas M. D. Anderson Cancer Center, 2007–2008
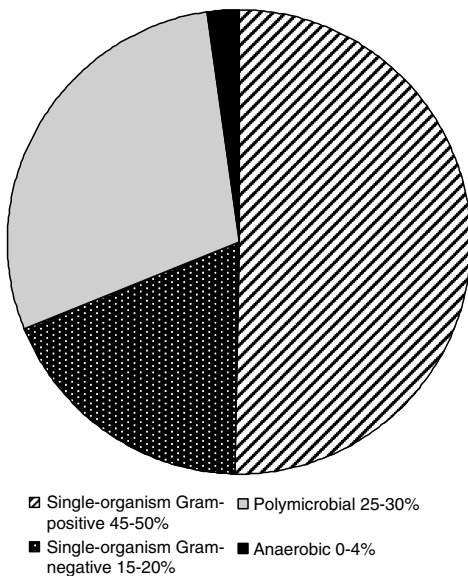
Fig. 8.2 Distribution of bacterial infections in neutropenic cancer patients. Data from recent surveys at The University of Texas M. D. Anderson Cancer Center, 2007–2008

Table 8.1 Common bacterial pathogens in neutropenic patients

Organism	Comment
Gram-positive	
Coagulase-negative staphylococci	>90% Methicillin resistant
Staphylococcus aureus	>50% Methicillin resistant
viridans group streptococci	~60% Penicillin non-susceptible
Enterococcus species	15–25% Vancomycin resistant
Bacillus species	10% Vancomycin resistant
Streptococcus Groups A, B, C, G, F	Penicillin/vancomycin tolerance
Streptococcus pneumoniae	~60% Penicillin non-susceptible
Corynebacterium species	Beta-lactam resistant
Stomatococcus mucilaginosus	Frequently causes meningitis
Gram-negative	
Escherichia coli	ESBL, increasing quinolone resistance
Klebsiella species	ESBL, carbapenamase (KPC)
Other *Enterobacteriace*	ESBL, multiple resistance mechanisms
Pseudomonas aeruginosa	Multidrug-resistant strains
Stenotrophomonas aeruginosa	Multidrug-resistant strains
Pseudomonas non-*aeruginosa* species	
Acinetobacter species	Multidrug-resistant strains
Anaerobes	
Bacteroides species	
Clostridium species	

demonstrated predominance of Gram-positive organisms over Gram-negative bacteria [2, 3]. The proportion of infections cause by Gram-positive organisms has been reported to be as high as 75–80% at some cancer treatment centers. However, both the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) and the European Organization for Research and Treatment of Cancer (EORTC) studies focus only on single-organism (monomicrobial) bacteremias. These data paint an incomplete picture because bacteremias cause only 20–30% of infection in cancer patients and other sites of infection, such as the lung, urinary tract, gastrointestinal tract, and skin/skin structure sites are not uncommon [4]. Although Gram-positive bacteria are the predominant organisms isolated from blood, Gram-negative organisms predominate at most other sites (e.g., pneumonia, neutropenic enterocolitis, perirectal infections, UTI's). Another critical piece of information missing from the SCOPE and EORTC studies is the proportion of infections that are polymicrobial. Data from our institution document that polymicrobial infections have more than doubled in frequency since the early 1980s and currently account for 25–30% of all bacterial infections [4, 14–16]. Additionally, approximately 80% of polymicrobial infections have a Gram-negative component and approximately 33% are caused exclusively by multiple species of Gram-negative bacilli [15]. When all sites of infection are taken into account and monomicrobial as well as polymicrobial infections are included in the overall spectrum, a substantially different epidemiologic picture emerges in which the proportion of monomicrobial Gram-positive infections falls sharply from approximately 80 to <50%. This can have a significant impact on the choice of

agents used for antimicrobial prophylaxis and for empiric therapy in such patients.

Gram-positive organisms colonizing the skin are isolated frequently. These include coagulase-negative staphylococci, *Staphylococcus aureus*, *Bacillus* spp., and *Corynebacterium* spp. Gram-positive organisms arising from the oro-pharynx and upper airways include *viridans* group streptococci (VGE), *Streptococcus pneumoniae*, and *Stomatococcus mucilaginosus*, whereas *Enterococcus* spp. arise primarily from the intestinal tract. Gram-negative organisms are represented frequently by the Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp.) and *Pseudomonas aeruginosa*, with *Acinetobacter* spp. and *Stenotrophomonas maltophilia* being reported with increasing frequency at some institutions [17, 18]. Strict anaerobes are seldom isolated from neutropenic patients. Rapidly growing mycobacteria are also uncommon but occasionally cause catheter-related infections in neutropenic patients [19].

Candida spp. are still the most common fungi isolated from neutropenic patients and cause infections ranging from superficial lesions (e.g., thrush and esophagitis) to deep, systemic candidiasis [20]. Most cancer treatment centers have reported a decline in the proportion of infections caused by *Candida albicans* and an increase in the proportion caused by other *Candida* species (*C. tropicalis*, *C. glabrata*, *C. parapsilosis*, etc.) [21, 22]. *Aspergillus* spp. are second in frequency among fungal pathogens in neutropenic patients [5]. They also cause a range of infections, including localized infections such as sinusitis, cutaneous aspergillosis, and aspergilloma (fungus ball), and invasive pulmonary or disseminated diseases frequently involving the central nervous system [23].

Many centers have reported an increase in the frequency of fungal infections caused by Zygomycetes, in part related to the use of agents such as voriconazole [24, 25]. These infections are often indistinguishable from aspergillosis, with the rhino-central form being particularly devastating. A large number of other opportunistic fungal pathogens have emerged in this patient population. They include *Fusarium* spp., *Trichosporon beigelii*, *Blastoschizomyces capitatus*, and *Scedosporium* spp. [5].

Viral infections are not common as a result of neutropenia, but are seen more often in patients with impaired cellular immunity. It is important to remember that such patients do develop neutropenia, and viral infections may then need to be considered [1, 13].

Initial Assessment of the Neutropenic Patient

A complete history and physical examination are essential. Historical information of interest should include details about antineoplastic therapy, the use of antimicrobial prophylaxis, travel history and potential exposure to sick contacts, and previous episodes of infection and their treatment. Underlying comorbid conditions such as diabetes, chronic lung disease, cardiac and hepatic problems, and recent surgeries should also be noted as they might have an impact on the nature and severity of infection and the risk of complications developing during a febrile episode.

The inflammatory response is often blunted in neutropenic patients resulting in a paucity of signs and symptoms usually associated with infections. Consequently, the physical examination should focus on the detection of subtle signs, particularly at frequently infected sites including the skin, oro-pharynx, gastro-intestinal tract, perineum, and larynx. Although fever is the most common manifestation of infection in neutropenic patients, some patients may harbor a serious infection without mounting a febrile response, especially if they are receiving corticosteroids or other immunosuppressive agents.

Standard laboratory investigations include blood and urine cultures and cultures of other sites (e.g., respiratory specimens, CSF, wounds, etc.) when indicated. Obtaining blood for culture simultaneously from a peripheral vein and from each lumen of a catheter, if a multilumen catheter is in place, is recommended. In patients with diarrhea, two stool specimens for the detection of *C. difficile* toxins should be obtained. Stool cultures for bacterial pathogens are of limited value. Patients with a pulmonary infiltrate might require a bronchoscopy to obtain adequate specimens for microbiologic evaluation as very few will have a productive cough. Nasal specimens are adequate for detecting the presence of community respiratory viruses, especially in the winter season.

Routine chest radiography is not recommended and should be done only in patients with respiratory signs and symptoms. CT scans of the chest and other areas (sinuses, abdomen, pelvis) should be performed as clinically indicated, and are generally more informative than routine radiographic imaging. Other laboratory tests include complete blood cell and differential counts, a serum electrolyte panel, levels of blood urea nitrogen, and serum creatinine and hepatic panel – serum bilirubin and liver enzymes. These investigations should be repeated as indicated clinically.

Risk Assessment and Risk-Based Therapy

It has long been recognized that not all neutropenic patients have the same risk of developing serious infections and/or complications. However, our ability to identify low-risk patients reliably was quite limited until recently, leading to the practice of administering hospital-based empiric antibiotic therapy to all febrile neutropenic patients [26]. With a greater

Table 8.2 The MASCC risk-index for low-risk neutropenic patients[*]

Clinical characteristic	Score
Burden of illness – no symptoms or mild symptoms	5
Burden of illness – moderate symptoms	3
Absence of hypotension	5
Absence of chronic lung disease	4
Solid tumor/no previous fungal infection	4
Absence of dehydration	3
Outpatient status at onset of fever	3
Age <60 years	2

MASCC Multinational Association for Supportive Care in Cancer
[*]Highest possible score = 26. A score of 21 or more indicates low-risk status [6]

Table 8.3 Treatment options for low-risk febrile neutropenic patients

- Hospital-based parenteral or oral antibiotics
- Initial stabilization in hospital (24–48 h) followed by early discharge on outpatient parenteral or oral antibiotic regimen
- Outpatient antibiotics (parenteral → oral, or oral, if tolerated) for the entire febrile episode

Table 8.4 Frequently used antibiotic regimens in low-risk febrile neutropenic patients

Parenteral regimens
  Aztreonam + clindamycin
  Ciprofloxacin + clindamycin
  Ceftriaxone ± amikacin
  Ertapenem ± amikacin
  Ceftazidime or cefepime
Oral regimens
  Ciprofloxacin + amoxicillin/clavulanate, or azithromycin, or clindamycin, or linezolid
  Moxifloxacin ± agents listed above

understanding of the syndrome of "febrile neutropenia," several investigators have developed reliable risk-prediction rules in recent years. The most widely accepted of these is the risk-index developed by the Multinational Association for Supportive Care in Cancer (MASCC) [6]. This risk-index was developed by assigning integer weights to seven characteristics to develop an index score (Table 8.2). A score of 21 or greater identified low-risk patients with a positive predictive value of 91%. This index now forms the basis for most clinical trials in low-risk neutropenic adult patients. Separate, but similar risk-prediction rules have been developed for pediatric oncology patients [27]. Many institutions have developed simple clinical criteria to identify low-risk patients without having to calculate a risk-index score. This might be a more practical method in busy clinical settings. There is uniform agreement that patients who are not classified to be low-risk should be hospitalized for the administration of prompt, empiric, parenteral, broad-spectrum antibiotic therapy [1].

Several different approaches have recently been evaluated in low-risk, febrile neutropenic patients, including early discharge after a short period of hospitalization, and treatment of the entire febrile episode without hospitalization. All these options are discussed in detail below.

Empiric Antibiotic Therapy in Low-Risk Patients

The various treatment options for low-risk febrile neutropenic patients are listed in Tables 8.3 and 8.4. Despite the development of accurate risk-prediction rules, the availability of suitable oral antimicrobial agents and the emergence of home health care agencies capable of delivering outpatient antibiotic therapy, many clinicians are still not comfortable with this approach (KR – personal observations).

Many clinicians prefer to admit low-risk febrile neutropenic patients to the hospital for an initial 24–48 h "stabilization period" followed by early discharge on oral or parenteral regimens. This approach has been demonstrated to be successful in various clinical trials both in adult and pediatric patients [9, 10, 28]. Table 8.5 summarizes the results achieved in some of these trials. The results of the pilot study conducted by Talcott et al. were disappointing since 9 of 30 patients (30%) required readmission to the hospital and 4 (13.3%) developed serious medical complications [29]. These results brought into question the criteria used to identify low-risk patients, particularly the inclusion of patients with leukemia with the potential to develop prolonged neutropenia [30, 31]. Better results were achieved by investigators from the United Kingdom who only enrolled patients with solid tumors and lymphoma with an anticipated duration of neutropenia of 7 days or less [10]. Early discharge on oral ciprofloxacin and amoxicillin/clavulanate was associated with a much lower readmission rate (7.6%), the regimen was well tolerated, and there were no deaths among patients enrolled on this trial. Investigators from the Institute Jules Bordet in Belgium also used this approach (i.e., early discharge on oral ciprofloxacin plus amoxicillin/clavulanate) in 79 patients, mainly with solid tumors [9]. No complications occurred, and the overall success rate was 96%, with only three patients needing to be readmitted. In a similar study, children presenting with fever and neutropenia were assigned to receive oral cefuroxime 24–36 h after hospitalization if categorized to be low-risk [28]. Seventy-four (95%) of 78 patients treated in this manner had a positive response.

Table 8.5 Outpatient management of low-risk febrile neutropenic patients after a short hospital stay

References	Type of study and patient population	Antibiotic regimens	% Response to initial regimen ± No readmission
Talcott et al. [28]	Open-label, pilot study of 30 low-risk patients	IV mezlocillin + gentamicin or IV ceftazidime	70
Innes et al. [10]	Randomized study comparing oral outpatient therapy ($n=66$) to parenteral inpatient therapy ($n=60$) after 24 h of hospitalization	IV gentamicin + piperacillin/tazobactam vs. PO ciprofloxacin + amoxicillin/clavulanate	90 84.8
Klastersky et al. [9]	Open-label study of oral, outpatient antibiotics in 79 low-risk patients	Ciprofloxacin + amoxicillin/clavulanate	96
Santolaya et al. [27]	Prospective, randomized comparisons of hospital-based ($n=71$) and ambulatory ($n=78$) antibiotic therapy in low-risk pediatric patients following 24–36 h of hospitalization	IV ceftriaxone + teicoplanin (hospital-based treatment)	94
		PO cefuroxime (ambulatory treatment)	95

Ambulatory Management of the Entire Febrile Episode

A significant proportion of patients cared for at cancer treatment centers, such as The University of Texas M. D. Anderson Cancer Center (MDACC), come from other countries, are uninsured, or pay out-of-pocket. Even a short hospital stay can have a significant financial impact for such patients. In the early 1980s, approximately 90 patients with solid tumors who developed fever while being neutropenic refused hospital admission. They were treated with oral antibiotics (TMP/SMX plus rifampin or clindamycin) as outpatients. Most responded to these regimens with no serious complications or deaths (K. Rolston – unpublished data). This experience served as background data for formal trials of outpatient antibiotic treatment of febrile neutropenic patients at this institution. To date, three randomized trials at MDACC have evaluated this approach (i.e., outpatient treatment of the entire febrile episode) along with a few trials conducted at other institutions [32–35]. Institutional pathways in place at MDACC and small pilot studies have added to this experience which is summarized in Table 8.6 [36–38]. These studies demonstrated that both parenteral and oral regimens are safe and effective with response rates ranging from 80 to 95%. Many patients not responding to the initial regimens responded to alternative outpatient regimens [Table 8.3]. Among the few patients requiring hospitalization, none had serious complications, none required care in the intensive care unit, and there were no infection-related deaths. A recently published meta-analysis concluded that "oral antibiotics may be safely offered to neutropenic patients with fever who are at low-risk for mortality" [39].

Empiric Antibiotic Therapy in Patients Not Classified as Low-Risk

Standard therapy for neutropenic patients not considered to be low-risk includes the prompt administration of parenteral, broad-spectrum antibiotic therapy with close monitoring in the hospital [1]. The various treatment options are listed in Table 8.6. Until the availability of broad spectrum beta-lactams (extended spectrum cephalosporins, carbapenems), the combination of an antipseudomonal beta-lactam and an aminoglycoside was the most frequently used regimen, resulting in response rates of ~70% [1]. The potential advantages of such combination regimens include broad coverage against most pathogens seen in this setting (including anaerobes), possible synergy resulting in rapid bactericidal activity, and the potential for reducing the emergence of resistant organisms. The major disadvantages are increased oto- and nephrotoxicity, and suboptimal activity against many Gram-positive organisms. With the emergence of resistant Gram-positive organisms (coagulase-negative staphylococci, MRSA, viridans group streptococci, *Corynebacterium jeikeium*) as frequent pathogens in neutropenic patients, the inclusion of vancomycin and later linezolid into the initial regimen became common place [1, 13, 40]. Several studies, however, have demonstrated that the initial use of an agent like vancomycin is not associated with superior outcomes when compared to the use of this agent after isolation of a resistant Gram-positive pathogen [41–43]. These data and the association of increased vancomycin usage with the selection of VRE and staphylococci with reduced susceptibility to vancomycin have led to the recommendation by many experts and societies that vancomycin

Table 8.6 Outpatient antibiotic therapy of low-risk, febrile neutropenic patients: The M. D. Anderson experience

References	Type of study and patient population	Antibiotic regimens	% Response to initial regimen
Rubenstein et al. [33]	Randomized trial of IV vs. PO outpatient regimen. 83 episodes, all adult	IV – aztreonam+clindamycin PO – ciprofloxacin+clindamycin	95 88
Rolston et al. [34]	Randomized trial of IV vs. PO outpatient regimens 179 episodes, all adults	IV aztreonam+clindamycin PO ciprofloxacin+amoxicillin/clavulanate	87 90
Mullen et al. [35]	Randomized trial of IV vs. PO regimens in pediatric patients, 75 episodes	IV ceftazidime PO ciprofloxacin	94 80
Rolston et al. [36]	Open label, pilot study of oral quinolone monotherapy in adult, 40 episodes	PO gatifloxacin	95
Rolston et al. [37]	Open label, pilot study of oral quinolone monotherapy in adults, 21 episodes	PO moxifloxacin	95
Escalante et al. [38]	257 episodes, adult patients enrolled on institutional outpatient pathways	IV ceftazidime+clindamycin PO ciprofloxacin+amoxicillin/clavulanate	80[a]
Elting et al. [11]	529 episodes, adult patients enrolled on institutional outpatient pathways	PO ciprofloxacin+amoxicillin/clavulanate	80

IV intravenous, *PO* oral

[a]Combined response rate for parenteral and oral regimens, as individual response rates were not mentioned

should only be included in the initial regimen at institutions that have a high rate of isolation of resistant Gram-positive pathogens [1, 44].

With the availability of truly broad-spectrum agents since the 1980s, empiric monotherapy became an option in this patient population. Many prospective randomized studies have demonstrated that monotherapy with agents such as ceftazidime, cefepime, imipenem, meropenem, and piperacillin/tazobactam are associated with response rates similar to those associated with various comparator combination regimens [1, 5, 45]. A recently published meta-analysis showed that monotherapy regimens are as effective as combination regimens with similar mortality rates, similar rates of bacterial and fungal superinfections, and are associated with lower rates of treatment failures and fewer adverse events [46].

The same group has published an analysis linking cefepime monotherapy with a higher all cause mortality than other agents [47]. Ceftazidime is associated with substantial resistance against most Gram-positive and many Gram-negative pathogens at many institutions and may not be suitable for empiric monotherapy. At least one meta-analysis has reported lower response rates with ceftazidime, and this agent has largely been replaced by cefepime in general practice. The weight of current data/opinion supports the use of empiric monotherapy for most neutropenic patients with fever, selecting suitable agents based on local epidemiology and susceptibility/resistance patterns. In today's economic environment, monotherapy may represent the most cost-effective option. Figure 8.3

provides an algorithm for the management of various subsets (risk-groups) of febrile neutropenic patients.

Evaluation of Response and Duration of Therapy

The median time to defervescence in low-risk patients is approximately 2 days, and it is approximately 5 days in patients not classified as low-risk [48–50]. Persistence of fever for 3–5 days in otherwise stable patients does not necessarily indicate failure of the initial regimen. However, persistence of fever beyond 3–5 days should lead to a full reevaluation of the patient including a search for drainable and/or removable focus of infection or the development of a superinfection. A change of the initial regimen is recommended at this stage, and this may consist of additional antibacterial agents depending on the gaps in the original regimens, or the administration of antifungal or antiviral agents, if indicated [51].

The duration of therapy continues to engender considerable debate with opinion almost evenly split between two different approaches. Some authors advocate continuation of antibiotic therapy in all patients until the resolution of neutropenia (ANC>500/mm^3) regardless of whether or not an infection was documented during the febrile episode [1, 13, 51]. Others recommend administration of therapy for 4 days after resolution of signs and symptoms (including microbiologic or radiographic evidence if present initially), with a
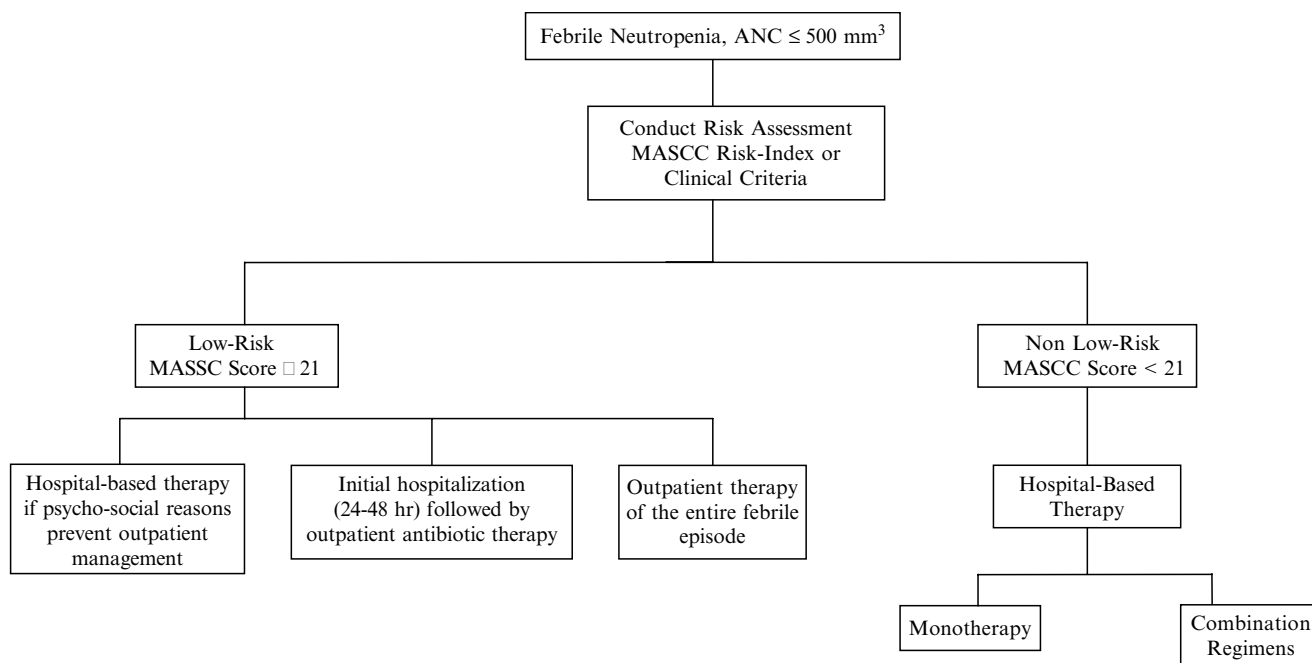
Fig. 8.3 Algorithm for the management of febrile neutropenic patients. Adapted from reference numbers [1, 6, 8–11, 13, 25, 26, 28, 29, 35]

minimum of 7 days treatment, regardless of whether or not the patient has persistent neutropenia. The former approach may result in needless administration of antibiotics to many patients potentially increasing costs, toxicity, and the development of bacterial or fungal superinfections. The latter approach requires careful observation of the patient after discontinuation of therapy. The ultimate decision of when to stop therapy often needs to be individualized and depends on several factors such as (1) the patient's risk group, (2) the presence of a documented infection, (3) the nature of the underlying malignancy (solid tumor or hematologic malignancy), (4) the need for additional chemotherapy or invasive procedures, and (5) the persistence of neutropenia. These and other controversial issues in the management of febrile neutropenic patients are discussed in detail in Chap. 9.

Antimicrobial Stewardship

Antimicrobial agents are used with greater frequency and for a larger number of indications (prophylaxis, empiric therapy, targeted therapy, maintenance therapy) in cancer patients than in most other patient populations [52]. This has led to an increase in the emergence of resistant pathogens [53]. Additionally, the development of novel agents is at an all time low, mandating the judicious use of currently available agents – termed antimicrobial stewardship. The various

components of an effective antimicrobial stewardship program are listed in Table 8.7 and include a multidisciplinary antibiotic stewardship team (MAST), institutional guidelines/pathways, formulary restrictions, clearance for the use of selected agents, and de-escalation or streamlining of therapy when appropriate [54]. Antibiotic stewardship programs have already been successful at several cancer treatment centers, and in the opinion of this investigator, will soon become mandatory at most institutions [55–57].

Summary

Neutropenic patients continue to develop infections despite improvements in supportive care of the cancer patient, and the implementation of preventive and infection control strategies. The spectrum of infection undergoes periodic changes with the emergence of newer opportunistic pathogens and/or the development of resistance among recognized pathogens. Empiric antibiotic therapy remains the standard of care. However, not all febrile neutropenic patients have the same risk of developing severe infections or serious medical complications. Low-risk patients can now be reliably identified early on in the febrile episode and can be treated with a short period of hospitalization, or entirely as outpatients. Very little change has occurred in the management of moderate to high-risk febrile neutropenic

Table 8.7 Antibiotic regimens commonly used in febrile neutropenic patients not classified as low-risk

Combination regimens with vancomycin[a]
Vancomycin+cefepime or ceftazidime[b]
Piperacillin/tazobactam
Imipenem or meropenem
Aztreonam[c]
Ciprofloxacin (or other quinolone)[d]
Combination regimens without vancomycin
Aminoglycoside+cefepime or ceftazidime[b]
Piperacillin/tazobactam
Imipenem or meropenem
Quinolone[d]
Monotherapy
Cefepime or ceftazidime[b]
Piperacillin/tazobactam
Imipenem or meropenem

[a]Vancomycin is occasionally replaced by linezolid

[b]Ceftazidime not useful at many institutions due to the emergence of resistant pathogens

[c]Aztreonam used primarily in patients with severe beta-lactam allergy

[d]Quinolones should not be used if patients have received prophylaxis with these agents

patients over the past decade. Antimicrobial stewardship has become an important strategy in the overall management of these patients since new drug development has declined appreciably. It is hoped that antimicrobial stewardship and strict adherence to infection control measures will reduce the selection and spread of multi-drug-resistant organisms, which are posing serious therapeutic challenges to clinicians caring for these high-risk patients.

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Chapter 9
Controversies in Empiric Therapy of Febrile Neutropenia

John R. Wingard

Abstract Antineoplastic chemotherapy regimens induced myelosuppression was quickly recognized as a major limitation to the full utility of cytotoxic drug regimens targeting cancer. Measures taken to mitigate harm from myelosuppression have led to a number of controversies over the years. The first controversy faced by clinicians was whether or not empiric antibiotic therapy for febrile neutropenia is appropriate. The concerns was that fever may be due to noninfectious causes, inappropriate antibiotic use might lead to emergence of resistance or superinfections by resistant organisms, the patient might experience toxicities (the antibiotics of those days had considerable toxicity), and the drugs were costly. This controversy was eventually resolved in favor of empiric antibiotics through a series of studies. Today, there are yet other controversies about empiric therapy of febrile neutropenia. These include questions as to whether there is an optimal antibiotic regimen, persistent concerns about resistance, questions as to what are the causes for fevers that have no apparent explanation, quandaries about the role for empiric antifungal therapy, and the unresolved issues as to why some patients become quite ill while others are less affected. Other controversies as to optimal management of venous catheters, etiology of neutropenic enterocolitis (typhlitis), the role for antimicrobial prophylaxis, and antibiotic resistance are addressed in other chapters and will not be covered here.

Keywords Febrile neutropenia • Empiric therapy • Optimal antibiotic regimen • Drug resistance • Empiric antifungal therapy

Introduction

In the 1950s, antineoplastic chemotherapy regimens were first introduced into clinical practice and myelosuppression was quickly recognized as a major limitation to the full utility of cytotoxic drug regimens targeting cancer. Measures taken to mitigate harm from myelosuppression have led to a number of controversies over the years.

The first controversy faced by clinicians was whether or not empiric antibiotic therapy for febrile neutropenia is appropriate. Basic infectious disease principles for management of fever of unknown origin at the time dictated that antibiotics should be administered only after evaluation documented an infection and the therapy should narrowly target a specific pathogen. The reasoning was that fever may be due to noninfectious causes, inappropriate antibiotic use might lead to emergence of resistance or superinfections by resistant organisms, the patient might experience toxicities (the antibiotics of those days had considerable toxicity), and the drugs used were costly. This controversy was eventually resolved in favor of empiric antibiotics through a series of studies. Careful study of the epidemiology (most fevers are due to bacterial infections which can be documented if sufficient time lapses), elucidation of the natural history of febrile neutropenia (bacterial infections, especially by Gram negative organisms, progress rapidly and are associated with high mortality and morbidity if treatment is delayed), and evaluation of the efficacy of interventions (empiric antibiotics result in reductions in infectious morbidity and mortality) provided the basis for current concepts of empiric therapy febrile neutropenia. That controversy was resolved.

Today, there are yet other controversies about empiric therapy of febrile neutropenia. These include questions as to whether there is an optimal antibiotic regimen, persistent concerns about resistance, questions as to what are the causes for fevers that have no apparent explanation, quandaries about the role for empiric antifungal therapy, and the unresolved issues as to why some patients become quite ill while others are less affected. Other controversies as to optimal management of venous catheters, etiology of

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neutropenic enterocolitis (typhlitis), the role for antimicrobial prophylaxis, and antibiotic resistance are addressed in other chapters and will not be covered here.

Is There One "Best" Antibiotic Regimen?

Randomized trials have demonstrated multiple effective antibiotic regimens. Guidelines have been formulated to codify best practices [1–5]. Several crucial principles have emerged over the years. Patients can be stratified into groups at "low" and "high" risk for serious complications and different evaluation and management approaches should be pursued. Even though Gram positive bacteria are the most common bloodstream isolates, the empiric regimen must principally target Gram negative bacteria since they remain the most virulent pathogens except in isolated settings with high rates of *Staphylococcus aureus* infections. Monotherapy options are as effective as combination regimens and may be associated with less serious toxicity. The empiric antibiotic choices should take into consideration the impact of whether or not antibiotic prophylaxis had been used. With all that is known about empiric therapy, there remain several unanswered questions.

Recently, concerns have been raised about dangers with cefepime. Two meta-analyses from one group have noted increased mortality with cefepime when compared to other β lactams [6, 7]. The meta-analyses showed cefepime to offer comparable response rates, infection-related mortality, and similar rates for other infection-related endpoints to other antibiotic regimens. Thus, the explanation for the apparent higher mortality rate is not clear. Several important points should be pointed out. The individual trials (in contrast to the meta-analyses) were not set up as primary tests of mortality differences. All-cause mortality was not uniformly reported in the various trials. Stratification of patients for neoplastic and comorbidity factors known to influence mortality was not done in the individual trials; thus, it is possible that inadvertent imbalance of risk factors (for mortality) may have been present and may explain this observation rather than some adverse event due to cefepime. This matter is being reviewed by the FDA. For now, many experts believe this to be a reliable and safe option for febrile neutropenia, pending more information.

Adjuvant use of growth factors to bolster neutrophil recovery, while appealing conceptually, has not been consistently shown to be helpful as an adjunct to antibiotic therapy for febrile neutropenia. In a meta-analysis, mortality was not affected [8], although there was a marginal benefit in infection-related mortality and shorter times to neutrophil recovery and hospital discharge. So, today, the adjuvant role of G-CSF remains uncertain and is generally not recommended.

So, is there truly one "best" antibiotic regimen? The answer is yes and no. Clearly, the choice should be governed by both patient factors and local antibiotic susceptibilities. The key is to choose a regimen that is active against the organisms that are the cause of infection, since 30-day mortality is much higher in patients with Gram negative bacteremia if the first choice is not active against the infecting organism. Thus, although there may be a "best" regimen for a given patient in a given setting, the best regimen may differ for a different patient (with different risk factors) in the same setting, or a patient with similar risk factors in a different setting.

If the Cultures Are Negative, What is the Cause of Febrile Neutropenia?

In many febrile neutropenic patients, infection is not clearly documented. The etiology of unexplained fever is poorly understood. Sometimes, it is merely a slow clinical response to an infection, and given sufficient time, defervescence will occur without change in the empiric antibiotic regimen. Pro-inflammatory cytokines released because of tissue damage from the cytotoxic antineoplastic therapy is the most likely noninfectious cause [9]. Other possible noninfectious causes include fever from certain drugs, transfusion of blood products, and the malignancy itself.

In some cases the fever is due to an infection, but the burden of organisms is below the threshold of detectability in current cultural systems. The routine use of empiric antibiotics has exacerbated the challenge of detection of pathogens, since intervention occurs much earlier in the course of infection preventing the number of organisms from reaching a peak that otherwise would occur if no intervention took place. Thus, many cases of culture negative fevers represent infections, yet they are in an early phase that cannot be documented by currently available diagnostic testing (and clinical evaluation).

It is known that if the volume of blood drawn for blood cultures is small, the likelihood of isolating an organism is less than with larger volumes [10, 11]. Studies have been performed to determine the optimal volume, balancing detection, and waste considerations. Retrospective studies found that two blood culture sets of 20 mL each inoculated into automated culture systems detect 80–90% of bloodstream pathogens; three or four sets during the first 24 h are necessary to detect more than 96% [10, 11]. Unfortunately, such studies have not examined separately the group of neutropenic patients to determine if bacterial load and optimal volumes are similar to the entire group of hospitalized patients. One important characteristic about neutropenic patients that may make them different is that institution of empiric antibiotics at first fever renders the usual recommendation for several

samplings during the first 24 h moot since the antibiotics alter the organism load. This matter is in need of more study in febrile neutropenia.

It is known that antibiotics interfere with the organism being isolated from blood cultures, suppressing viable organisms to below the threshold of positivity. Resins added to the culture media can inactivate antibiotics and may improve the sensitivity of cultures in patients receiving antibiotics [12, 13]. However, the added advantage of resin blood culture media systems over conventional blood culture systems has been questioned [14]. Cell wall deficient bacteria can be induced by antibiotics that act on the cell wall and because of fragility they may not be easily identified by commercial blood culture systems. They are also occasional causes of unexplained fevers and in one series of neutropenic BMT patients, accounted for 25% of culture negative fevers [15].

Bacteria have been detected in blood samples from febrile neutropenic patients with negative blood cultures in studies using a eubacterial approach with PCR technology to detect 16S rRNA gene amplification. Up to 10–25% of culture negative febrile neutropenia may be due to bacteria detected by such assays [16, 17]. Although PCR diagnostic assays are increasingly assuming important roles in clinical microbiology for detection of many infectious pathogens, unfortunately, issues about suboptimal sensitivity, automation of the technology, and interpretation make this technology not suitable for this clinical application at present [18–20].

Similar molecular detection assays for fungi indicate fungi to be uncommon causes of FUO early in febrile neutropenia [17], but fungal DNA [21–26] as well as fungal proteins such as β-glucan and galactomannan [27–31] have been found to be present in a higher proportion of persistently febrile patients later in neutropenia.

These various observations indicate that even in the face of negative cultures many episodes of febrile neutropenia are truly infectious. Future studies are needed to improve our ability to detect organisms in culture negative patients so that targeting of antibiotics can be achieved.

Can Acute Phase Protein Responses Distinguish Infected Patients from Noninfected Patients?

A variety of inflammatory proteins and cytokines increase during febrile episodes. Various studies have examined the utility of these to attempt to distinguish fever due to infection from noninfectious causes.

C reactive protein (CRP) has been examined in chemotherapy and BMT patients. In BMT patients, the heights of CRP and temperature elevation were higher in fevers due to infection compared to fever due to GVHD [32, 33]. However, low sensitivities have been noted and other studies have not found CRP levels to reliably predict infection [34, 35]. Levels of interleukins-6 (IL6) and IL8 have been found to be elevated and in some studies these are useful to distinguish infection from noninfection [34, 35]. Procalcitonin (PCT) also has been evaluated and found to distinguish infection from noninfection [35]. In a meta-analysis PCT levels were more sensitive (88% [95% confidence interval [CI], 80–93%] vs. 75% [95% CI, 62–84%]) for CRP levels in differentiating bacterial infections from other causes of fever [36]. PCT levels were also more specific (81% [95% CI, 67–90%] vs. 67% [95% CI, 56–77%]) than CRP levels. A more recent review of procalcitonin studies in neutropenic infections also found promise in procalcitonin levels to distinguish infection from noninfection [37], but not superior to IL6 or CRP [37]. Several studies also suggest promise of such markers to predict outcome of the infection [38, 39]. At present, a lack of standard definitions, heterogeneity of study populations studied, and small numbers of patients make the true utility of such markers of infection not well established.

Is There Still a Role for Empiric Antifungal Therapy?

"Maintaining guidelines that dictate treatment of a population in which >90% of patients do not have invasive fungal disease is not justifiable…." [40].

Although invasive fungal disease is not a problem in short-term neutropenia (<7 days), prolonged neutropenia is associated with a risk for both invasive *Candida* and *Aspergillus* infections. It is undeniable that empiric antifungal therapy has dramatically reduced morbidity and mortality from invasive *Candida* and *Aspergillus* infections in patients with prolonged neutropenia. Since persistent fever is often the only manifestation of Candidemia, coupled with improved outcomes when therapy is begun early in the course of infection [41, 42], early therapy is crucial in patients with invasive fungal disease to minimize fungal deaths. The routine initiation of empiric antifungal therapy after 3–7 days of persistent fever has become widely practiced and endorsed by multiple expert consensus panels [1–5].

Amphotericin B was initially used but subsequently lipid formulations of amphotericin B, itraconazole, and caspofungin have also been shown to be effective. Although voriconazole has been studied, the pivotal randomized trial failed to demonstrate noninferiority and it has not received FDA approval for this indication. Notwithstanding, many experts feel that it is an acceptable option for empiric antifungal therapy based on its safety and efficacy demonstrated in documented *Candida* and *Aspergillus* infections in randomized trials of first-line therapy.

Generally, clinicians choose the "best" antifungal based on patient characteristics, weighing issues of activity of the agent against the suspected pathogen, safety, and cost.

Yet, the randomized trials that established the benefits for empiric antifungal therapy had few patients, data for several of the important endpoints were not significantly different due to limited statistical power, there was considerable heterogeneity of patients and treatments, and the use of antifungal prophylactic agents in some of the patients meant its impact could not be adequately assessed (discussed in [43, 44]). Moreover the use of myeloid growth factors and in the HSCT setting, optimization of stem cell content in the hematopoietic graft have led to shorter neutropenic episodes, raising the concern that empiric antifungal therapy may not be needed in many settings in which it was evaluated before these advances. Moreover, the use of azole prophylaxis has been widely adopted in high-risk patients, and the need for empiric antifungal therapy in patients receiving antifungal prophylaxis has not been evaluated.

The problem with giving antifungal therapy empirically to all patients with persistent fever is that most patients with persistent fever do not have invasive fungal disease. Thus, de Pauw's complaint above [40] rings true. Persistent fever is not a reliable guide for whom antifungal therapy is needed. Too many patients needlessly are exposed to drugs that are toxic, may interact with other drugs in potentially deleterious ways, and are costly. Moreover, overuse of any antimicrobial agent increases the risk for resistance, and that development ultimately may thwart the effectiveness of the drug. Its use encourages the risk that an inadequate course of therapy may be given to those who are truly infected since a diagnosis is not made and therapy is typically stopped at neutrophil recovery, whereas a longer course of therapy is needed for real infections.

Several strategies have been explored to better target antifungal therapy to those with a higher likelihood of invasive fungal disease. The first is the appearance of clinical signs and symptoms other than the mere presence of fever. For *Candida*, occasionally polyarthralgias or polymyalgias, new onset of azotemia, or maculopapular erythematous skin lesions may herald fungemia; the onset of such clinical manifestations are strong clues to Candidemia. For *Aspergillus*, the onset of respiratory, sinus, or orbital symptoms or signs are manifestations of *Aspergillus* pneumonia or sinusitis, the most common presentations of Aspergillosis. Radiologically, the appearance of dense nodules, a halo sign, cavitary infiltrate, boney erosion of sinus walls all strongly suggest invasive mold infection [42]. Although such clinical and radiologic manifestations are quite useful when present, they are not universally present and often are not manifested early during the course of infection.

The use of fungal biomarkers has been evaluated. Two diagnostic assays detecting fungal cell wall proteins have been FDA licensed. The β-glucan assay detects several fungal genera that include the most likely fungal pathogens, *Candida* and *Aspergillus*, along with several others (*Trichosporon* and *Fusarium*), but does not detect *Zygomycetes* and *Cryptococcus*. Sensitivity and specificity were 70 and 87%, respectively [28, 29]. A second assay is the serum galactomannan assay, which detects *Aspergillus* (but not *Candida*, *Zygomycetes* and most other fungal pathogens) [30, 31, 45, 46]. Data submitted to the FDA indicated sensitivity and specificity to exceed 80 and 80%, respectively. In practice, the sensitivity has been variable in different patient populations and generally somewhat less, with a sensitivity of only 71% with specificity of 89% in a meta-analysis [47]. Moreover, clinicians often forget that patients must be serially tested (typically 2–3 times weekly) over the period of risk rather than at a single point in time to achieve such sensitivity. A variety of conditions have been identified that affect the performance of these two tests, including the use of antimold prophylaxis (false negative) and the use of certain antibiotics such as piperacillin-tazobactam (false positive).

The ideal biomarker would detect infection at its earliest manifestation, at time of incipient invasion or tissue damage, even before the occurrence of clinical signs and symptoms. The serologic and PCR fungal assays are generally positive early in the course of infection and test positivity often antedates positive blood cultures and clinical signs and symptoms.

Evaluation of using a combination of fever, screening for presence of more specific clinical symptoms and signs, and serial monitoring of the galactomannan biomarker was performed in a pilot study in patients with hematologic malignancies and patients undergoing hematopoietic stem cell transplant [48]. Patients all received fluconazole prophylaxis to eliminate *Candida* from consideration so that the focus could be on Aspergillosis. No empiric antifungal therapy could be instituted unless some proof of definitive invasive fungal disease was documented. A total of 136 neutropenic episodes were assessed. Patients who met any of several clinical or biomarker criteria were evaluated with a CT scans and bronchoscopy. This strategy was able to detect a number of cases quite early, even while the patient was afebrile, in some cases and this provided an opportunity for accurate diagnosis, early intervention, and spared many patients from receiving unneeded therapy that would have been treated using persistent fever as the trigger for empiric antifungal therapy.

PCR fungal assays are also under development. Several have been evaluated in clinical settings and they too hold promise for even more sensitive detection. In one pilot study [25], a nested PCR that detects *Candida, Aspergillus, Trichosporon,* and *Cryptococcus* species and culture was evaluated in 42 neutropenic patients with cancer. Sequential blood samples were tested and infection was confirmed by

culture. Infection was noted in 26 of the 31 PCR-positive samples and in none of the 52 PCR-negative ones. Among the PCR-positive samples, the second sample was PCR-positive 1–8 days before the culture results were available. In one trial, empirical antifungal therapy (with liposomal amphotericin B after 120 h of febrile neutropenia) was compared with either PCR-triggered or empirical antifungal therapy (after 120 h of febrile neutropenia) after allogeneic HSCT [49]. A total of 409 patients were studied in a randomized trial. A higher percentage of patients in the PCR screening arm received antifungal therapy (57 vs. 37%, $p<0.0001$). Slightly fewer patients in the PCR arm developed proven invasive fungal disease (12 vs. 16 cases). Mortality at 30 days was superior in the PCR arm at the end of the screening period of 30 days (1.5 vs. 6.3%, $p=0.015$), but the survival at 100 days was similar. Other studies have evaluated PCR assays for *Aspergillus* (reviewed in [50]).

Although molecular testing holds enormous promise, as yet there are formidable obstacles to its use in clinical practice that include variable sensitivity and specificity, limited per test positivity, lack of standardized reagents and targets, issues regarding false positives and negatives, and lack of validation in multiple centers. Moreover, there is no licensed PCR as yet.

Certainly the use of fungal diagnostics holds enormous appeal and may allow targeting of treatment to those truly in need while sparing others from therapy that may cause toxicity and is costly. Further, antibiotic stewardship would be expected to reduce the risk of emergence of drug resistance. The replacement of empiric therapy with targeted therapy is a high priority for clinical research.

Why Do some People Get Sicker than Others?

The age-old question as to why one patient gets infected while another with the same degree of immune compromise and same exposure to potential pathogens does not still puzzle us today. Unraveling some of the intricacies of the innate and acquired immunities in recent years has provided some clues. We now know that polymorphisms of immune response genes explain important differences in both likelihood of invasive infection and how serious an infection is once it occurs. Two examples have received considerable attention. Mannose binding lectin (MBL) is a molecule that is part of the innate immune response system that is responsible for recognizing a broad range of viral, bacterial, and fungal pathogens and is key in activating complement and facilitating phagocytosis. Mutations in the MBL gene occur in 10–30% of the general population and can lead to lower serum levels of MBL. Coupled with neutropenia, MBL deficiency has been associated with more severe and more prolonged febrile neutropenic episodes in several studies [51–56] and after HSCT [57–60]. Recently, low levels of MBL were associated with a risk for neutropenic *Aspergillus* infections in patients with multiple myeloma undergoing autologous HSCT [61]. Toll-like receptors are also important pattern recognition receptors for microbial pathogens. Polymorphisms in TLR molecules have also been implicated in the risk for infection in immunocompromised patients [62–64]. Lipopolysaccharide binding protein promoter variants have also been associated with the risk for Gram negative bacteremia after HSCT [65]. Cytokine polymorphisms also influence the risk of infection [66]. These various observations suggest that polymorphisms of various pro-inflammatory and anti-inflammatory molecules and cytokines may explain much of the variability in susceptibility to infection and severity of infection.

Identification of certain immune polymorphisms holds the promise that molecular profiles of patients could allow customization of an anti-infective strategy for each individual patient. Prophylaxis would be appropriate for some patients who could be identified in advance as at high risk for infection or serious sequelae of infection, while monitoring for infection and treating only should an infection occur would be best for others at lower risk.

What Does the Future Hold?

Historically, neutropenia and mucosal injury are the major factors that have influenced the risk for neutropenic infections and the epidemiology of febrile neutropenia. The increasing use of purine analogs and monoclonal antibodies in the therapy of lymphohematopoietic diseases impairs other arms of the host immunity and exposes the neutropenic patient to a wider array of potential opportunists not seen historically. In particular, various series are today reporting much higher risks for serious infections by the herpesviruses (especially cytomegalovirus and varicella zoster virus) and molds in less intensively treated patients than historically seen. As new antineoplastic therapies emerge with novel mechanisms of action, one can expect an evolving epidemiology of infectious complications.

Historically, we have used group characteristics to ascertain the likelihood of infection by various pathogens. We have tailored our antimicrobial strategies for groups of patients sharing common treatment and disease characteristics. We have made enormous strides in minimizing the threat of infectious complications using such group identifiers. The use of genetic testing to identify individual variability in immune response genes of individual patients in advance will allow us to develop customized approaches that may be even more effective.

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Chapter 10
Catheter-Related Infections in Cancer Patients

Iba Al Wohoush, Anne-Marie Chaftari, and Issam Raad

Abstract Central venous catheters (CVCs) play a major role in the management of high-risk patients, particularly cancer patients, and are mainly used for the administration of anti-cancer agents, antibiotics, and blood products. Catheter-related blood stream infection (CRBSI) rates are influenced by patient-related factors, such as type and severity of the illness, by catheter-related factors, and institutional factors (e.g., bed size and academic affiliation). Catheter-related infections could be local, such as exit site, tunnel, and pocket infections; or systemic such as catheter-related bloodstream infection. Many diagnostic methods have been developed, some of which require catheter removal, whereas others do not. Strategies for prevention and management of CRBSI are presented in this chapter.

Keywords Indwelling catheter-related blood stream infection • Infection prevention • Pathogenesis • Bacterial infection • Fungal infections • Biofilm

Introduction

Central venous catheters (CVCs) play a major role in the management of high-risk patients, particularly cancer patients, and are mainly used for the administration of anti-cancer agents, antibiotics, and blood products.

Before the introduction of CVCs into medical practice, patients with cancer received chemotherapeutic agents through a small, peripheral venous catheter. This practice resulted in several complications such as extravasation and thrombosis of the peripheral vein, which interfered with the administration of the anti-cancer agents. CVCs are considered to be a revolutionary step in the care of cancer and critically ill patients, since their use is not accompanied with such complications. However the infectious complications associated with the use of CVC

are a major concern. In critically ill patients, CVCs are the leading source of bloodstream infections and are associated with substantial morbidity, mortality, and economical burden.

More than 150 million catheters are purchased annually by hospitals and clinics in the United States [1]. The majority of these devices are peripheral venous catheters, but more than five million CVCs are inserted annually [1]. Each year in the United States, CVCs may cause an estimated 80,000 catheter-related bloodstream infections and, as a result, up to 28,000 deaths among patients in intensive care units [2]. The median rate of catheter-related bloodstream infection in intensive care units of all types ranges from 1.8 to 5.2 per 1,000 catheter-days [3]. Given that the average cost of care for a patient is $45,000, such infections could cost up to $2.3 billion annually [2]. Catheter-related blood stream infection (CRBSI) rates are influenced by patient-related factors, such as type and severity of the illness, by catheter-related factors, and institutional factors (e.g., bed size and academic affiliation).

Pathogenesis

In order to diagnose, prevent, and manage CRBSI appropriately, the physician must have a complete understanding of the pathogenesis of CRBSI. The most common causative pathogens for CRBSI are coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococci*, and *Candida* species; less commonly are gram negative bacilli and micrococcus. The microorganisms that colonize the catheter surfaces may follow any of the following routes. Firstly, the skin organisms may migrate from the insertion site to the surface of the catheter, particularly the external one [4–6]; short-term nontunneled noncuffed catheters are usually colonized through this route. The second route is direct contamination of the catheter hub by contact with hands or contaminated devices; this route is particularly important in the long-term catheters such as tunneled catheters and ports [7, 8]. The third path, which is a rare form of catheter colonization, is hematogenous spread of the microorganisms from another site of infection. Lastly and rarely is infusate contamination [9, 10].

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Clinical Manifestations and Definitions

Catheter-related infections could be local, such as exit site, tunnel, and pocket infections; or systemic such as catheter-related bloodstream infection [11].

Local Catheter-Related Infections

The presence of local inflammatory signs, such as erythema, warmth, tenderness, and purulent exudates, suggests a local catheter infection. However, neutropenic patients may not develop these symptoms when they have a catheter-related infection. Furthermore, the insertion of some catheters (e.g., PICC) may be associated with similar symptoms due to secondary mechanical irritation. As a conclusion, local inflammatory signs are unreliable for establishing the diagnosis of catheter-related infection because of their low specificity and sensitivity, and must be paired with microbiological confirmation to reach a final diagnosis. Finally, it is worth mentioning that all of the local catheter-related infections (i.e., exit site, tunnel, and pocket infections) could be associated with a CRBSI. In other words, their presence does not necessarily predict a CRBSI; and more tests are needed to establish a diagnosis of CRBSI. The following are the most commonly used definitions of local catheter-related infections.

Exit-Site Infection

Characterized by inflammatory changes within 2 cm of the catheter exit site.

Tunnel Infection

The afore-mentioned inflammatory signs, erythema >2 cm from the exit site and along the subcutaneous tract of a tunneled catheter.

Pocket Infection

The pocket of a totally implantable catheter is infected and filled with purulent exudates; possibly complicated by necrosis of the overlying skin or pocket rupture.

Systemic Catheter Infections (CRBSI)

Any patient with a CVC who has signs and symptoms of infection such as fever, chills, or hypotension and does not have any obvious source of infection (except for the catheter) should undergo microbiological testing to determine if CRBSI is the underlying cause of his symptoms. Probable CRBSI can be diagnosed by one or more positive blood cultures, along with the above signs and symptoms, and with no apparent source for the bacteremia (except for the catheter). The infectious diseases society of America IDSA has suggested one of the following methods to confirm the Diagnosis of CRBSI [11]: Positive quantitative or semiquantitative culture of the catheter; a ratio of 3:1 between quantitative blood cultures drawn simultaneously from a CVC and a peripheral vein; or differential time to positivity. All of the mentioned methods will be explained in detail later in this chapter.

Diagnosis of CRBSI

The clinical signs and symptoms of sepsis are unreliable in reaching a correct diagnosis of CRBSI. Safdar and Maki evaluated the role of inflammation as a diagnostic indicator of CRBSI with short-term catheters. Their study showed that inflammation at the insertion site was rarely present and had a very poor sensitivity ($\leq 3\%$) for predicting CRBSI [12]. Therefore microbiological confirmation is always required for the diagnosis of CRBSI.

Many diagnostic methods have been developed, some of which require catheter removal, whereas others do not. The latter types of these diagnostic tests are preferable since the catheter can remain in place.

Diagnostic Tests Without Catheter Removal

Comparative Quantitative Blood Culture

This method involves obtaining paired blood cultures drawn concomitantly from the CVC and the peripheral vein. A large ratio of CFU from the catheter blood culture to CFU from the peripheral culture is indicative of a CRBSI. Since the studies have reported different cut-off points for a positive diagnosis ranging from two to tenfold [13–15], the IDSA accepted a CFU that is threefold or higher from the CVC drawn blood culture vs. peripheral vein culture is indicative of CRBSI. In a recent study where fivefold was the cut-off point, sensitivity, specificity, and positive predictive value were found to be 62, 93, and 92% respectively [16]. In a meta-analysis of studies of diagnostic tests, this method was found to be the most accurate for the diagnosis of CRBSI; sensitivity and specificity for short-term catheter were 75 and 97% respectively and for long-term catheters, 93 and 100% respectively [17]. However, the use of this method is limited because it is labor intensive and expensive. Single quantitative or qualitative blood cultures, where the blood is drawn through the catheter alone, are unreliable for the diagnosis of CRBSI due to low positive predictive values [17].

Differential Time to Positivity

The differential time to positivity is defined as the difference between the times a blood culture drawn from the catheter and a simultaneous blood drawn from a peripheral vein become positive [18]. Through this simple technique, blood cultures are drawn simultaneously or within 15–20 min, from the CVC and the peripheral vein. They are then placed in an automatic positive detector that records culture positivity every 15 min according to changes in fluorescence related to microbial growth. Several studies indicated that definite diagnosis of CRBSI is established when the blood culture drawn from the CVC becomes positive at least 2 h earlier than blood culture drawn from the peripheral vein [18–20]. In a study of 235 neutropenic patients with febrile neutropenia, DTP had 82% sensitivity and 88% specificity in the diagnosis of CRBSI.

Raad et al. [21] evaluated the DTP in 191 cases of CRBSI. The sensitivity and specificity for this method in short-term catheters were 81 and 92% respectively. On the other hand, the sensitivity and specificity for DTP in long-term catheters were 93 and 75% respectively. In a recent study comparing quantitative blood cultures and differential time to positivity in pediatric patients, DTP was significantly more sensitive and mildly less specific, with a higher diagnostic accuracy compared to quantitative blood cultures [22]. The limitation of this study is that the cultures drawn from catheters may be falsely negative if antibiotics are given intraluminally and also does not evaluate patients with positive CVC cultures and negative peripheral blood cultures.

Diagnostic Tests with Catheter Removal

Many methods that require catheter removal have been improved to diagnose CRBSI (Table 10.1).

Semiquantitative Roll-Plate Catheter Culture

The semiquantitative catheter culture, which is also known as the roll-plate method, is one of the most studied diagnostic techniques. In this method, the distal segment of the catheter is cut and rolled against a blood agar plate at least four times before the plate is incubated overnight [23, 24]. Catheters are considered to be colonized if at least 15 CFU/catheter tip segments are grown [25], but the diagnosis of CRBSI is only established if a peripheral blood culture yields the same organism as in the catheter tip culture [26–33]. In a recent study, a sensitivity of 78% and a specificity of 88% have been reported using the roll-plate catheter culture as a diagnostic tool for CRBSI in short-term catheters [34]. Even more, the pooled sensitivity and specificity for roll-plate catheter cultures in 14 trials involving short-term catheters were found to be 84 and 85% respectively [23]. Bouza et al. reported a specificity and sensitivity of more than 90% for both short-term, and long-term catheters; the limitation for their study is that they defined the long-term catheters as those with only 7 days of dwell time or more [35]. However, the sensitivity from different studies using the roll plate as a diagnostic technique in long-term catheters (more than 30 days of dwell time) was found to be ranging from 45 to 75% [6, 26]. The difference between the sensitivity and specificity for roll plate between the short-term and long-term catheters is justified by the fact that the short-term catheters are mainly colonized on the external surface of the catheter, while the long-term catheters are predominantly colonized in the lumen of the catheter. Given the fact that this method retrieves free-floating (nonbiofilm) microorganisms only from the external surface of the catheter, therefore false negative results can be expected in long-term catheters where organisms mainly colonize the intraluminal surface of the catheters. Hence the roll-plate method is mainly useful in short term catheters.

Table 10.1 Comparison of diagnostic methods of catheter related blood stream infection

Diagnostic method	Diagnosis criteria	Disadvantages
Without catheter removal		
Simultaneous quantitative blood cultures	CFU blood culture drawn through CVC>3 times CFU drawn simultaneously from peripheral vein	Labor intensive and expensive
Differential time to positivity	Blood culture drawn through CVC turns positive at least 2 h before blood culture drawn simultaneously from peripheral vein	Cultures drawn from catheters may be falsely negative if the antibiotics are given intraluminally and also does not evaluate patients with positive CVC cultures and negative peripheral blood cultures
With catheter removal		
Semiquantitative CVC tip cultures	>15 CFU/mL from CVC tip	Cultures only the organisms on the external surface and does not culture organisms embedded in the biofilm
Quantitative CVC tip cultures	>100 CFU/mL from CVC tip	May over release the biofilm microorganisms that might not be clinically relevant; whereas, relevant planktonic organisms might be killed

Quantitative Catheter Segment Culture

To overcome the roll-plate limitation of missing the organisms colonizing the catheters' lumen, several methods such as centrifugation, vortexing, and sonication have been used [36–38]. The catheter segments are immersed in broth and flushed, followed by serial dilutions and surface plating on blood agar. A count of greater than or equal 100 CFU is considered to be associated with infection. The diagnosis of CRBSI is established if a peripheral blood culture yielded the same organism grown from the catheter tip culture [39]. Brun-Buisson et al. suggested a modified version of this method where the segments are vortexed rather than flushed. He reported a sensitivity of 97.5% and specificity of 88% [40]. Raad et al. compared the roll-plate culture with the catheter sonication method, and yielded sensitivities of 78 and 93% respectively and specificities of 88 and 94% respectively [34]. Widmer and Frei compared the sonication with the roll-plate method in short-term catheters and found similar sensitivities and specificities [41]. However, for long-term catheters, the sonication method was found to have higher sensitivity than the roll-plate method [6]. The pooled sensitivity and specificity of quantitative catheter segment culture for short-term catheters were 82 and 89% respectively, and 83 and 97% for long-term catheters [23]. The disadvantage of this method is that it releases the biofilm microorganisms that might not be clinically relevant; whereas, relevant planktonic organisms might be killed.

Prevention of Catheter-Related Infections

An ounce of prevention is worth a pound of cure, and this is completely true in medical practice. Not only CRBSIs may require the removal of the catheter consequently interfering with the treatment plan but also they are associated with high morbidity and mortality rates, as well increase cost of care. Therefore, the prevention of CRBSI is of paramount importance (Table 10.2). Successful preventive strategies should focus on controlling all factors that could lead to the colonization of CVC by microorganisms. Traditional measures for the prevention of catheter-related infections, recommended by the healthcare infection control practices advisory committee (HICPAC) guidelines, include education of health care workers on proper catheter insertion and maintenance, routine monitoring of institutional rates of CRBSI, hand hygiene, use of a dedicated infusion therapy team, use of sterile dressings, avoidance of femoral insertion, and removal of the vascular catheter as soon as possible [2]. In the next section, we will review major strategies for the prevention of catheter-related infections.

Maximal Sterile Barrier

The following five evidence-based procedures are recommended by the CDC and identified as having the greatest effect on the rate of CRBSI: hand washing, using full-barrier precautions during the insertion of CVC, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters. These five elements are particularly important in nontunneled catheters and PICCs, which are usually inserted out of the operating room; and hence, their insertion may not be subject to the strict sterile atmosphere of an operating room. Pronovost et al. [42] reported a decrease of median rate of catheter-related infections from 2.7/1,000 catheter-days at baseline to 0 within the first 3 months of applying the mentioned five elements, and a reduction in the rate of CRBSI of 66% at 16–18 months after implementation.

Other studies reported a decrease in the rate of CRBSI from 0.5/1,000 to 0.02/1,000 catheter-days after applying the maximal sterile barrier precautions consisting of wearing sterile gown, gloves and cap, and using a large drape during the insertion of catheters.

Tunneling

Tunneling the catheters creates a fibrous tissue around the dacron cuff (which is used to anchor the catheter in place), and this tissue will act as a barrier against the migration of microorganisms. A recent study comparing the tunneled and nontunneled catheters showed that the infection rate was 1.9 per catheter-days in the nontunneled group vs. 0.7 per catheter-days in the tunneled catheter group. Another study comparing these two groups failed to demonstrate a difference between them, and showed a rate of 0.22/1,000 catheter-days was reported in the nontunneled catheter group vs. 0.20/1,000 catheter-days in the tunneled group. More studies are needed to prove the efficacy of tunneled catheters in preventing catheter-related infections; especially since tunneling a catheter is a surgical procedure that may cost an additional $2,500.

Antimicrobial Coating of Catheters

Coating the catheters with antibiotics leads to a slow release of the antibiotics that prevent the adherence of the microorganisms to the catheter surfaces and preclude the initial formation of the biofilm [43]. Many generations and types of antibiotic-coated catheters were studied with different rates of success in preventing catheter-related infections.

Table 10.2 Prevention of catheter related blood stream infection

	Method	Advantages	Disadvantages
Maximal sterile barrier	Hand washing, using full-barrier precautions during the insertion of central venous catheter, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters	It lowers the rates of CRBSI	It requires continuous staff education and reinforcement Role of all components have not been determined
Catheter tunneling	It creates a fibrous tissue around the dacron cuff, which acts as a barrier against the migration of microorganisms	The tunneled catheters are long-term ones	Costly, requires surgical procedure or interventional radiology for insertion and efficacy still not proven completely
Antiseptic catheters. First and second generation	They are coated only on the external surface of the catheter using CHX-SSD in first generation External and luminal surfaces are impregnated in the second generation	Can lower the incidence of CRBSI in short-term catheters	Failed to show a decrease in CRBSI in long-term catheters Inferior efficacy to CVC impregnated with minocycline-rifampin
Antibiotics-impregnated catheters	It is a polyurethane and silicone catheter impregnated with minocycline and rifampin on both the external and luminal surfaces of the catheter	It decreases the incidence of CRBSI significantly It is not associated with increased resistance for minocycline or rifampin	It has no effect on catheter-related candidemia
Antimicrobial lock solution	The catheter lumen is filled with 2–3 mL of a combination of anticoagulant and an antimicrobial agent	Using EDTA with minocycline may have a synergistic activity against methicillin resistant staphylococci, gram negative bacilli, and *Candida albicans*	Use of vancomycin is associated with increased risk for resistance Vancomycin has no coverage against gram negative bacteria And limited activity against organisms embedded in the biofilm

Antiseptic Catheters

These catheters are impregnated with chlorhexidine and silver sulfadiazine. Two generations were developed in order to lower the rates of CRBSIs. The first generation of the chlorhexidine-silver sulfadiazine was coated only on the external surface of the catheter. Different prospective randomized clinical trials [2, 6, 27–38, 44–48] have evaluated this generation of chlorhexidine-sulfadiazine catheters, and most of them showed a reduction in the CRBSI but only two trials reported a significant reduction in CRBSI [49, 50]. It is estimated that the use of these catheters in patients at high risk for catheter-related infection can save $68–391 per insertion [51]. Several studies failed to show a decrease in catheter-related infections in long-term catheters. This lack of long-term efficacy is based on the limited antimicrobial durability of these catheters (around 7 days in serum) and the fact that only the outer surface of the catheter was impregnated, consequently providing no protection against luminal colonization [44]. As a conclusion, the first generation of the chlorhexidine-sulfadiazine impregnated catheters can reduce the risk of catheter-related infection in short-term catheters, but cannot reduce the risk of CRBSI in long-term catheters.

The second generation of these catheters was impregnated on the external and the luminal surfaces of the catheter. In one study, the use of these catheters decreased the catheter colonization from 11/1,000 to 3.6/1,000 catheter-days; but

failed to decrease the rate of CRBSI's [52]. Three subsequent studies also failed to prove a decrease in the rate of CRBSIs [53–55]. The use of these catheters might be cost effective in high-risk patients such as ICU patients, burn patients, and other patient populations in which the rate of infection exceeds 3.3/1,000 catheter-days [4].

Antibiotic-Coated Catheter

The only FDA approved antibiotic-coated catheter is a polyurethane catheter impregnated with minocycline and rifampin on both the external and luminal surfaces of the catheter. Two trials demonstrated that the use of minocycline-rifampin coated catheters is associated with lower rates of CRBSIs compared to the use of uncoated catheters [56, 57]. A prospective, randomized, double blinded study comparing the first generation of chlorhexidine-sulfadiazine coated catheters and minocycline-rifampin coated catheters showed that Minocycline-rifampin coated catheters were 12-fold less likely to be associated with CRBSI and threefold less likely to be colonized [56, 58]. In a recent study, Wright et al. showed a reduction in ICU stay and ICU mortality after the introduction of antibiotic-coated catheters, but reported an increase in rifampin resistance among Staphylococcus epidermis isolates [59]. However, data from MD Anderson cancer center concluded that after 4 years, and more than 24,000 catheter-days,

of using antibiotic-coated catheters in stem cell transplant patients, staphylococcus isolates remained highly susceptible to minocycline and rifampin [60]. Raad et al. reported in a 7-year study that the resistance to tetracycline and rifampin decreased 44 and 56% respectively among coagulase negative staphylococci; similarly, the resistance patterns to tetracycline and rifampin among MRSA clinical isolates had a significant decrease of 42 and 67% respectively. Several other studies have shown that the risk of minocycline and rifampin is very low [61, 62]. The risk to develop minocycline and rifampin resistance is low because both require different mutation mechanisms at a cumulative frequency of approximately $1:10^{12}$ bacteria. Such bacterial concentrations are only found in the gastrointestinal tract and are unlikely to be observed in the surrounding subcutaneous environment of the catheters. Moreover, antibiotics delivered by antibiotic-coated catheters are not detectable in the blood [63].

The authors recently suggested that it is mandatory to combine the maximal sterile barrier precautions and antimicrobial-impregnated catheters to achieve the desired goal of "zero tolerance" [64]. The use of the aseptic techniques bundle, including maximal sterile barrier precautions, prevents contamination of the CVC. However, the use of antimicrobial-coated CVC will prevent biofilm colonization of the external and the internal surfaces of the CVCs during the insertion and subsequently during the time it remains in place.

Antimicrobial Lock Solutions

Heparin has been used as an antithrombotic agent in catheters after several studies showed that heparin can reduce the catheter-related infections [65]. However, subsequent studies showed that heparin is as effective as saline in preventing phlebitis and enhances the staphylococcal biofilm formation [66]. Therefore, a novel technology was developed, in which the catheter lumen is flushed and filled with 2–3 mL of a solution that is usually a combination of an anticoagulant and an antimicrobial agent such as vancomycin. Few studies showed a decrease in the rate of CRBSI after using heparin-vancomycin as a lock solution [67, 68], other studies failed to show a significant benefit [69, 70]. However, using

Vancomycin prophylactically should be avoided to minimize the risk of emergence of vancomycin-resistant organisms, besides it does not cover for gram negative bacteria and *Candida* species. Chelators as EDTA have an anticoagulant activity similar to heparin and have been found to enhance the activity of antimicrobial drugs against organisms in the biofilm [71–74]. Raad et al. used EDTA with minocycline as prophylaxis in three patients [75], and showed a synergistic activity against methicillin-resistant staphylococci, gram negative bacilli, and *Candida albicans* and a cidal effect against bacteria in the biofilm.

Management of Catheter-Related Blood Stream Infections

Antibiotic therapy for CRBSIs should be initiated empirically. The decision to remove the catheter has to be made cautiously since it is often assumed to be the source of infection, and there is tendency to remove the catheter even before determining whether it is the source of infection or not. The above decisions depend mainly on the type of the organism causing the CRBSI (Table 10.3). Usually vancomycin is the recommended drug for the empirical treatment for CRBSI, with the exceptions of hospital with predominance of MRSA, or when vancomycin MIC >2, in which case other agents such as Daptomycin should be used [5, 6].

Coagulative Negative Staphylococci

Coagulative negative Staphylococci (CoNS) are the most common cause of CRBSI, but at the same time they are a common colonizer of the human skin. Most patients have a benign clinical course; however occasionally, patients may develop frank sepsis with poor outcome [76–78]. A definite diagnosis of CoNS bacteremia requires at least two positive blood cultures, one of them obtained from a peripheral vein. CoNS bacteremia is treated with antibiotics for 5–7 days if the catheter is removed, and for 10–14 days in combination with antibiotic lock therapy if the catheter is still in place.

Table 10.3 Management of catheter related blood stream infection according to the causative agent

	CoNS	*S. aureus*	Enterococci	Gram negative	Candida Spp.
Catheter removal	Occasionally	Yes	Yes	Yes	Yes
Alternative for catheter removal	Antibacterial lock solution				ETOH lock solution
	Exchange over a guide wire for a new antimicrobial-impregnated catheter				
Duration of treatment	5–7 days if catheter is removed	14 days	7–14 days	7–14 days	14 days
	10–14 days + antimicrobial lock if catheter is retained				

Staphylococcus aureus

S. aureus is associated with a high rate of complications [79], most commonly septic thrombosis of large veins [80] which mainly occurs among patients with solid tumors [81]. The most serious complication associated with *S. aureus* CRBSI is endocarditis, thus it is always necessary for every patient with *S. aureus* bacteremia and a persistent fever or bacteremia to undergo a transesophageal echocardiography to exclude endocarditis [11, 82].

Many prospective studies have shown that removal of the CVC in patients with *S. aureus* CRBSI is associated with a more rapid response to therapy and a lower relapse rate [79, 83, 84]. Therefore, it is essential to remove the catheter in every patient with *S. aureus* CRBSI unless there is a major contraindication (i.e., no another venous access) [85, 86]. The type of antibiotics used should be based on the susceptibility of *S. aureus*. Semisynthetic antistaphylococcal penicillin or first generation cephalosporins are the first choice for patients with methicillin sensitive *S. aureus*, while vancomycin and daptomycin are the drugs of choice in patients with methicillin resistant *S. aureus* CRBSI [83, 84].

The usual duration of treatment of *S. aureus* CRBSI is 4–6 weeks, but it can be shortened (>14 days) if the patient is not diabetic, not immunocompromised, has no prosthetic intravascular device, has no complications associated with *S. aureus* CRBSI, and the catheter is removed [85].

Gram Negative Bacilli

Gram negative bacilli are not the usual suspects in CRBSI. However, gram negative bacillary CRBSI caused by organisms such as *Klebsiella pneumoniae*, Enterobacter spp., Pseudomonas spp., Acinetobacter spp., and Stenotrophomonas species have been reported [87, 88]. The empiric gram negative coverage should only be considered in specific groups of patients such as, neutropenic patients, severely ill patients with sepsis, or patients known to be colonized with these pathogens [81, 89, 90]. Hanna et al. showed that CRBSI caused by gram negative bacilli was associated with high rate of relapse if the catheter was not removed, whereas CVC removal was associated with only 1% risk of relapse [88]. Management of gram negative CRBSI consists of removing the CVC and treating with active antibiotics against gram negative bacilli such as gentamicin, amikacin, or ceftazidime [89, 91].

Candida Species

Catheter-related candidemia may be associated with serious complications such as septic thrombosis and endocarditis [92, 93]; therefore, rapid diagnosis and treatment are essential in the management of catheter-related candidemia.

Candida empiric coverage should be used in septic patients with any of the following risk factors: total parenteral nutrition, prolonged broad spectrum antibiotics, hematological malignancy, bone marrow transplant, femoral catheterization, and Candida colonization at multiple sites.

Several studies evaluated the impact of catheter removal on the outcome of the candidemia, and showed that catheter removal is associated with a better outcome [94–97]. Another study showed that catheter retention was found to be an independent variable risk of death in multivariate analysis independent of persistent neutropenia [95].

Raad et al. showed that CVC retention more than 72 h after the onset of candidemia is associated with poor outcome in patients with catheter-related candidemia [98]. Therefore, the catheter should be removed within the first 72 h in case of CRBSI due to Candida, and antifungal agents should be administered for at least 14 days according to the IDSA guidelines [91]. A recent study showed that fluconazole was shown to be equal in efficacy to amphotericin B in the treatment of candidemia with a better safety profile [99]. More recent studies showed that Echinocandin such as caspofungin and anidulafungin are equivalent or superior to fluconazole for the treatment of CRBSI due to Candida [99]. Fluconazole or any Echinocandins are considered as a first line in the treatment of CRBSI due to Candida.

Micrococcus

Micrococcus species have the ability to adhere to medical devices and cause associated infections, particularly CRBSIS [100]. These infections are more likely to persist in patients with prior hemodialysis, the absence of prior GCSF therapy, longer catheter retention intervals, and longer catheter dwell time [101]. A recent study showed that 100% of Micrococcus isolates were susceptible to vancomycin, 95% to trimethoprim-sulfamethoxazole, 84% to rifampin, and 41% to oxacillin [102].

Exchange over a Guide Wire

Catheter removal is required in almost all cases of CRBSI. However, in some instances (e.g., no another vascular access) removing the catheter may jeopardize the patient safety. Thus exchanging the infected catheter over a guide wire was suggested as an alternative method in treatment.

A recent study showed that exchanging the infected catheter with an uncoated one may result in a cross infection in the new catheter. Hence, exchanging the infected catheter with a minocycline-rifampin (M/R) impregnated catheter seemed to

prevent the "cross infection." Authors have showed that exchanging the infected catheters with those M/R impregnated was associated with lower morbidity and mortality rates when compared to those of uncoated catheters. An improved overall response rate, risk of mechanical failure and infection recurrence were also noted [103].

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Chapter 11
Intravascular Device-Related Infections: Catheter Salvage Strategies and Prevention of Device-Related Infection

Nasia Safdar and Dennis G. Maki

Abstract The use of intravascular devices for administration of chemotherapeutic drugs, fluids, blood products, and nutritional support is essential to the care of patients with cancer. Unfortunately, intravascular devices have great potential to produce iatrogenic disease, especially bloodstream infection originating from colonization of the device used for access or from contamination of the infusate administered through the device. Over two thirds of all healthcare-associated bacteremias originate from devices for vascular access. Probably, more than any other healthcare-associated infection, IVDR BSI is eminently preventable. The first step to preserve vascular access is a highly effective institutional program for the prevention of IVDR BSI. In recent years, high-quality research studies have delineated key measures for prevention, such as chlorhexidine (CHG) for cutaneous antisepsis, maximal barrier precautions, antiinfective-impregnated catheters, and the use of a CVC insertion "bundle," and IVDR BSI rates in the ICU have declined markedly in most hospitals. However, despite adherence to best practices, IVDR BSI continues to pose formidable challenges, especially in patients with cancer. Catheter salvage in the context of established IVDR BSI is particularly challenging, but recent advances such as antibiotic lock technique are now providing previously unavailable options.

Keywords Catheter infection • Bloodstream infection • Prevention • Treatment

Introduction

The use of intravascular devices for administration of chemotherapeutic drugs, fluids, blood products, and nutritional support is essential to the care of patients with cancer.

Unfortunately, intravascular devices have great potential to produce iatrogenic disease, especially bloodstream infection (BSI) originating from colonization of the device used for access or from contamination of the infusate administered through the device [1–4]. Over two thirds of all healthcare-associated bacteremias originate from devices for vascular access [5].

Every year more than five million central venous catheters (CVC) are inserted in the United States [6]. More than 250,000 intravascular catheter-related blood stream infections (IVDR BSI) occur annually with an associated mortality of 12–25% [6]. A recent meta-analysis found mortality to be significantly increased in intensive care unit (ICU) patients who had IVDR BSI compared with those without IVDR BSI (OR, 1.96; 95% confidence interval [CI], 1.25–3.09) (Fig. 11.1) [7]. Each episode of IVDR BSI significantly increases hospital length of stay, and the added health-care costs range from $4,000 to $56,000 per episode [8–10].

Probably, more than any other healthcare-associated infection, IVDR BSI is eminently preventable [5, 11–14].

This chapter focuses on catheter salvage in IVDR BSI. The first step to preserve vascular access is a highly effective institutional program for the prevention of IVDR BSI. In recent years, high-quality research studies have delineated key measures for prevention, and IVDR BSI rates in the ICU have declined markedly in most hospitals [12, 15–26]. However, despite adherence to best practices, IVDR BSI continues to pose formidable challenges, especially in patients with cancer. Catheter salvage in the context of established IVDR BSI is particularly challenging, but recent advances are now providing previously unavailable options.

Pathogenesis of IVDR BSI

There are two major sources of IVD-related BSI: (1) colonization of the IVD, *device-related infection*, and (2) contamination of the fluid administered through the device, *infusate-related infection* [27]. Contaminated infusate is the cause of most *epidemic* intravascular device-related BSIs

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Review:	Impact of catheter-related bloodstream infections on the mortality of critically ill patients: a meta analysis					
Comparison:	01 Mortality					
Outcome:	01 In-hospital mortality (all studies)					

Study or sub-category	CR-BSI n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Higuera	23/55	12/55		12.04	2.58 [1.12, 5.99]
Warren	21/41	301/1091		14.64	2.76 [1.47, 5.16]
Blot	49/176	82/315		17.37	1.10 [0.72, 1.66]
Rosenthal	77/142	42/142		16.44	2.82 [1.73, 4.60]
Renaud	10/26	7/26		8.62	1.70 [0.53, 5.48]
Dimick	5/9	53/251		7.27	4.67 [1.21, 18.00]
Rello	11/49	17/49		11.38	0.54 [0.22, 1.33]
Soufir	20/38	20/75		12.25	3.06 [1.35, 6.92]
Total (95% CI)	536	2004		100.00	1.96 [1.25, 3.09]

Total events: 216 (CR-BSI), 534 (Control)
Test for heterogeneity: CHI² = 21.63, df = 7 (P = 0.003), I² = 67.6%
Test for overall effect: Z = 2.91 (P=0.004)

0.01　0.1　1　10　100
Favours CR-BSI　Favours control

Fig. 11.1 Attributable mortality of IVDR BSI in critically ill patients. From Siempos et al. [7] with permission
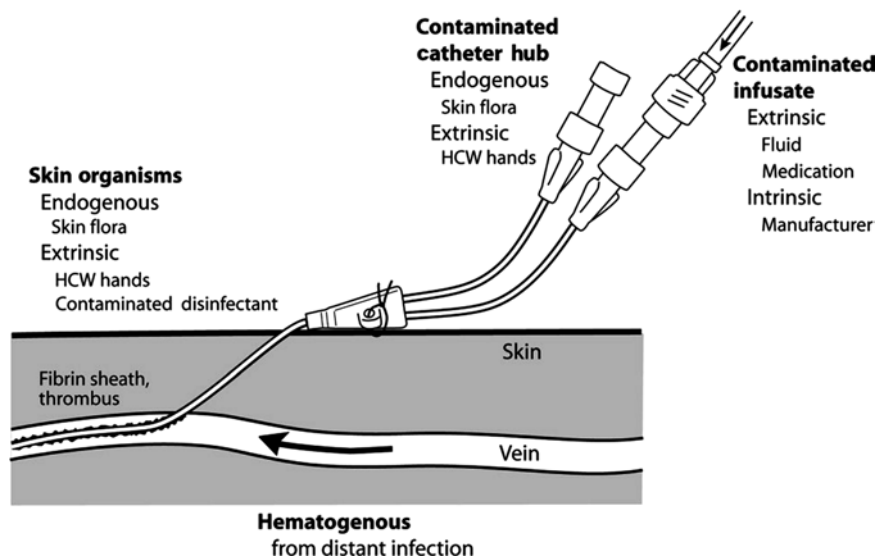
Fig. 11.2 Potential sources of infection of a percutaneous IVD: the contiguous skin flora, contamination of the catheter hub and lumen, contamination of infusate, and hematogenous colonization of the IVD from distant, unrelated sites of infection [174]

[4, 28]; by contrast, catheter-related infections are responsible for most *endemic* device-related BSIs. Understanding the pathogenesis of IVD-related BSIs is fundamental to devising effective strategies for the prevention and treatment of these infections; however, relatively few published studies have determined the mechanism of IVD-related colonization and infection using sophisticated molecular techniques to prove or disprove potential routes of infection [29–35].

In order for microorganisms to cause catheter-related infection, they must first gain access to the extraluminal or intraluminal surface of the device where they can adhere to and become incorporated into a biofilm that allows sustained colonization and ultimately hematogenous dissemination [36]. Microorganisms gain access to the implanted IVD by one of three mechanisms: skin organisms invade the percutaneous

tract, probably facilitated by capillary action [37], at the time of insertion or in the days following; microorganisms contaminate the catheter hub (and lumen) when the catheter is inserted over a percutaneous guidewire or later manipulated [38]; or organisms are carried hematogenously to the implanted IVD from remote sources of local infection, such as a pneumonia [39] (Fig. 11.2).

With *short-term* IVDs (in place <14 days) – peripheral IV catheters, arterial catheters and noncuffed, nontunneled CVCs – most catheter-related BSIs are of cutaneous origin, from the insertion site, and gain access extraluminally or occasionally intraluminally [35, 40, 41]. For long-term catheters – tunneled, cuffed CVCs, totally implantable ports and PICCs – luminal colonization has been shown to be the major route of access leading to BSI [42, 43]. A characteristic

pulsed-field gel electrophoresis image obtained from a short-term noncuffed CVC causing BSI is shown in Fig. 11.3 and a long-term catheter (PICC) in Fig. 11.4.

Microbiology

Antimicrobial resistance, now considered to be at global crisis levels, continues to loom large, and the organisms implicated in IVDR BSIs are no exception. In the past 2 decades, the proportion of IVDR BSIs caused by multidrug-resistant (MDR) organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and fluconazole-resistant *Candida* species, has risen inexorably [6, 44–46]. Overall, the organisms encountered most frequently in IVDR BSI are coagulase-negative staphylococci (CoNS) (31%), *S. aureus* (20%), Enterococci (9%), and *Candida* species (9%) [24–26, 44, 47].

In one large prospective surveillance study using data from SCOPE (Surveillance and Control of Pathogens of Epidemiological Importance), comprising 24,179 cases of nosocomial BSI reported over a 7-year period from 49 hospitals, rates of MRSA infection increased from 22% of all *S. aureus* BSIs in 1995 to 75% in 2001 ($P < 0.001$), and resistance to vancomycin was found in 60% of *Enterococcus faecium* isolates [44].

Fig. 11.3 Pulsed-field gel electrophoresis image showing the probable pathogenesis of a central venous catheter-related bacteremia with coagulase-negative Staphylococcus. The isolates from the catheter tip, blood, and skin of the insertion site were all concordant, indicating an extraluminal route of infection [35]

Catheter Salvage in the Context of Prevention

In 2002, The Healthcare Infection Control Practices Advisory Committee (HICPAC) of the CDC published a comprehensive Guideline for the prevention of IVDR BSI, which is summarized in Table 11.1 [6]. This Guideline focuses on educating all healthcare workers on best practices for catheter insertion and care; choosing the optimal insertion site; practicing maximal antisepsis, including hand hygiene and barrier precautions; removing the device as soon as it is deemed unnecessary; and surveillance of catheter infection rates [5, 6]. Reviewed below are topics of importance in prevention as well as novel strategies not addressed in the guidelines (Table 11.2) [48–55]. The recommendations are rated based on the strength of evidence supporting them as follows. IA: strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies; IB: strongly recommended for implementation and supported by some experimental, clinical or epidemiologic studies, and a strong theoretical rationale; IC: required by state or federal regulations, rules, or standards; II: suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale [6].

Fig. 11.4 Pulsed-field gel electrophoresis image showing the probable pathogenesis of a PICC-related bacteremia with *Serratia marcescens*. The isolates from the catheter tip, blood, hub, and fluid were all concordant, indicating an intraluminal route of infection

Table 11.1 Recommendations for prevention of IVDR BSI, 2002 CDC-HICPAC guideline [175]

Recommendation	Rating[a]
Education	
• Educate all relevant healthcare personnel regarding indications for IVC use, proper procedures for insertion and maintenance, and infection-control measures	IA
Surveillance	
• Conduct institutional surveillance for rates of IVDR BSI, monitor trends, identifying lapses in infection-control practices	IA
• Express ICU data as number of IVDR BSIs per 1,000 catheter days	IB
Antisepsis	
• Maximal sterile barrier precautions during catheter insertion: cap, mask, sterile gown, sterile gloves, and large sterile sheet	IA
• Hand hygiene: wash hands with antiseptic-containing soap and water or waterless alcohol-based product: before insertion or any manipulation of any IVC	IA
• Gloves: required for any manipulation of any IVC	IA
• Sterile gloves required for arterial and central catheters	
• Clean gloves acceptable for peripheral IVCs if site not touched after application of skin antiseptics	
• Cutaneous antisepsis: use before insertion and during dressing changes: 2% chlorhexidine is preferred, an iodophor or 70% alcohol are acceptable	IA
Insertion	
• When possible, use subclavian site when using a nontunneled CVC	IA
• Use designated personnel for insertion and maintenance of IVCs	IA
• Use sterile gauze or sterile, transparent semipermeable dressing	IA
• Do not give prophylactic antibiotics to prevent catheter colonization or BSI	IA
Maintenance	
• Change dressing at least weekly	II
• Monitor site visually or by palpation through intact dressing on regular basis and remove dressing for full exam if tender, fever without obvious source or other manifestations suggesting local or BSI	IB
• Do not routinely culture catheter tips	IB
• Do not use topical antibiotic ointments or creams (except with dialysis catheters)	IA
• Remove IVCs as soon as not necessary	IA
• Do not routinely replace CVCs, PICCs, HD catheters, or pulmonary artery catheters to prevent IVDR BSIs	IB
• Replace peripheral venous catheters at least every 72–96 h in adults	IB
• Replace administration sets no more frequently than at 72 h unless infection or unless infusing blood produces, or lipid emulsions	IB
• If after implementing a comprehensive strategy to reduce rates of IVDR BSIs and rates remain high, use antimicrobial or antiseptic-impregnated CVC in adults if CVC is expected to remain >5 days	IB
Novel strategies not addressed in current guidelines	
• Consider antimicrobial lock solutions for use in all long-term devices	IB
• Chlorhexidine-impregnated dressings (Biopatch®) should be used with all short-term catheters	IA
• A sutureless catheter securement device (StatLock®) is preferred to sutures	IB
• Adhere to the IHI bundle for CVCs	IA
• Chlorhexidine bathing in the ICU	IA

IVDR BSI catheter-related blood stream infection; *CVC* central venous catheter; *HD* hemodialysis; *IVC* intravenous catheter; *PICC* peripherally inserted central venous catheter

[a]CDC categories of evidence: *IA* strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies; *IB* strongly recommended for implementation and supported by some experimental, clinical or epidemiologic studies, and a strong theoretical rationale; *IC* required by state or federal regulations, rules, or standards; *II* suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale [6]

Cutaneous Antisepsis

Iodophors, such as 10% povidine-iodine, or 70% alcohol were the most widely used agents for cutaneous antisepsis of the insertion site in US centers [56, 57]. However, several studies, including a meta-analysis, have shown that 2% CHG is unequivocally superior for preventing IVDR BSI [54, 58] and is now recommended by the HICPAC Guideline as the agent of first choice (rating IA) [6, 56, 58].

Topical Antimicrobials

The HICPAC Guideline specifically recommends against the application of topical antimicrobial ointments or creams to the IVD insertion site, except in the case of hemodialysis catheters [6], to avoid promotion of fungal infection and antimicrobial resistance (rating IA). The Guideline also discourages the use of intranasal mupirocin for staphylococcal decolonization before IVD insertion or during the use of an IVD as a means to prevent colonization or IVDR BSI (rating IA) [6].

Table 11.2 Novel strategies for the prevention of intravascular device-related bloodstream infection

Strategy	References	Design	Technology	Outcome
Antimicrobial lock solutions	Safdar and Maki [48]	Meta-analysis	Vancomycin-containing locks vs. heparin	50% risk reduction (RR, 0.49; 95% CI, 0.26–0.95)
	Yahav et al. [52]	Systematic review and meta-analysis	Various antibiotics[a]	Antibiotic solutions: RR, 0.44 (95% CI, 0.38–0.5)
			Antibiotic plus antiseptic[b]	
			Antiseptic[c]	Nonantibiotic antiseptic solutions alone: RR, 0.9 (95% CI, 0.48–1.69)
				Nonantibiotic antiseptic solutions + other prevention methods[d]: RR, 0.25 (95% CI, 0.13–0.5)
	Sanders et al. [92]	Double-blind randomized trial	Ethanol-containing locks vs. heparin	OR, 0.18 (95% CI, 0.05–0.65)
Antimicrobial catheters	Veenstra et al. [51]	Meta-analysis	Antiseptic-impregnated CVCs[e]	OR, 0.56 (95% CI, 0.37–0.84)
	Ramritu et al. [50]	Systematic review	Antibiotic-impregnated CVCs[f]	RR, 0.39 (95% CI, 0.17–0.92)
	Crnich and Maki [174]	Meta-analysis	Silver-impregnated CVCs	RR, 0.40 (95% CI, 0.24–0.68)
	Ramritu et al. [50]	Systematic review	Antibiotic vs. first-generation antiseptic-impregnated CVCs	RR, 0.12 (95% CI 0.02–0.67)[g]
	Hockenhull et al. [176]	Meta-analysis	Antiinfective CVCs (all types)	OR, 0.49 (95% CI 0.37–0.64)[h]
Chlorhexidine dressings	Maki et al. [79]	RCT	Chlorhexidine-impregnated sponge dressing	IVDR BSI: RR 0.37 (0.17–0.80)
	Ho and Litton [49]	Meta-analysis	Chlorhexidine-impregnated dressing vs. placebo or povidone-iodine dressing	Catheter or exit site colonization: 14.3 vs. 27.2%; OR, 0.4 (95% CI, 0.26–0.61)
				IVDR BSIs: 2.2 vs. 3.8%; OR, 0.58 (95% CI, 0.29–1.14, $P=0.11$)
	Timsit et al. [80]	Randomized, controlled trial	Chlorhexidine-impregnated dressing vs. standard dressing	IVDR BSI: 0.4 vs. 1.3/1,000 catheter days; HR, 0.024 (95% CI, 0.09–0.65; $P=0.005$)
Cutaneous antisepsis	Chaiyakunapruk et al. [54]	Meta-analysis	Chlorhexidine vs. povidone-iodine	RR, 0.49 (95% CI, 0.28–0.88)[i]
	Maki et al. [58]	RCT	Chlorhexidine vs. alcohol vs. povidone-iodine	IVDR BSI RR 0.16, $P=0.04$
Mupirocin prophylaxis	Tacconelli et al. [55]	Meta-analysis	Mupirocin prophylaxis in dialysis patients[j]	Decrease in *S. aureus* bacteremia in hemodialysis patients by 78%; RR 0.22 (95% CI, 0.11–0.42)

CI confidence interval; *EDTA* ethylenediamine tetraacetic acid; *OR* odds ratio; *RR* relative risk

[a]Gentamicin; gentamicin+citrate; gentamicin+vancomycin; gentamicin+cefazolin; cefotaxime

[b]Minocycline with EDTA

[c]Citrate; citrate with taurolidine

[d]Nasal mupirocin and exit-site iodine dressing

[e]Chlorhexidine-silver sulfadiazine

[f]Minocycline and rifampin

[g]Reduced risk with antibiotic catheters

[h]Reduced risk with antiinfective catheters: all types combined, see text for subgroup analysis

[i]Reduced with chlorhexidine

[j]Six studies used intranasal mupirocin 2–3 times daily for 5–14 days with various maintenance schedules; 4 studies used mupirocin applied to catheter exit site

A meta-analysis of mupirocin prophylaxis to prevent *S. aureus* infections in patients undergoing dialysis showed a 63% reduction (95% CI), (50–73%) in the rate of overall *S. aureus* infections [55]. The study population included both hemodialysis and peritoneal dialysis patients. Of the ten studies, six used intranasal mupirocin 2–3 times daily for 5–14 days, with various maintenance schedules, and four used mupirocin applied to the catheter exit site. In patients undergoing hemodialysis, *S. aureus* bacteremias were reduced by 78% (relative risk [RR], 0.22; 95% CI, 0.11–0.42). However,

the differences in site, frequency, and duration of mupirocin treatment in these studies and the resulting clinical heterogeneity make it difficult to offer robust recommendations [55].

A randomized, double-blind, placebo controlled trial evaluating mupirocin prophylaxis for nosocomial *S. aureus* infections in nonsurgical patients found that restricting the use of intranasal mupirocin to patients shown to be carriers on admission did not prevent nosocomial *S. aureus* infections [59]. Increasing reports of mupirocin resistance [60–65], call decolonization with mupirocin into question as a strategy

to prevent IVDR BSI, even in hemodialysis centers, and we do not recommend topical or intranasal mupirocin for prevention of IVDR BSIs.

The early promise of mupirocin has suggested that other topical approaches to preventing IVDR BSIs bear study. One such agent is honey, which has long been known to have antibacterial properties. In a randomized, controlled trial (RCT) to compare the effect of thrice-weekly application of Medihoney (commercially available; pooled antibacterial honeys including *Leptospermum* species honey; Medihoney Pty Ltd, Brisbane, Australia) or mupirocin to the IVD exit site in 101 patients who were receiving hemodialysis through tunneled and cuffed CVCs, catheter-associated bacteremia rates in the two arms were similar (0.97 vs. 0.85 episodes per 1,000 catheter days; $P > 0.05$) [66]. Although these results are promising, a larger trial powered to show equivalence or superiority and provide information on tolerance and effect of the topical agent on resistance patterns of infecting microorganisms is needed to establish the utility of Medihoney for the prevention of IVDR BSIs in patients receiving hemodialysis through cuffed and tunneled CVCs.

Maximal Barrier Precautions

The use of maximal barrier precautions, including cap, sterile gown, mask, large sterile drape, and sterile gloves, significantly reduce the rate of IVDR BSIs when used during catheter insertion [6, 67, 68]. In a RCT, Raad et al. compared maximal barrier precautions with limited precautions (e.g., sterile gloves and a small fenestrated drape) and found the CVC-related BSI rate to be 6.3 times higher in the control group ($P = 0.06$) [67]. The HICPAC Guideline recommends that maximal barrier precautions be used for all central IVD insertions, including PICCs (rating IA) [6].

Insertion Site

According to the HICPAC Guideline, the preferred site for insertion of nontunneled CVCs in adult patients is the subclavian vein (rating 1A) [6]. The femoral site has been reported to be associated with higher rates of catheter colonization as well as increased risk of deep vein thrombosis compared to cephalad sites in adults [6, 40, 69–71]. In an RCT with uncuffed CVCs, comparing femoral and subclavian sites, catheters inserted in a femoral site were associated with a higher incidence of infectious complications (19.8 vs. 4.5%; $P < 0.001$) [71].

The internal jugular vein site has also been associated with higher rates of IVDR BSI than the femoral or subclavian sites in several studies [6, 40, 72]. However, a recent RCT comparing the jugular and femoral sites found no difference in the risk for infection between the two sites (2.3 vs. 1.5, $P = 0.42$) [73]. A prospective, observational study comparing the subclavian, internal jugular, and femoral insertion sites found colonization lowest at the subclavian site but no difference in rates of BSI between sites [74, 75].

Using real-time ultrasound guidance for catheter insertion significantly reduces mechanical complications deriving from catheter insertion and catheter infection [6, 76, 77]. In a recent randomized study, real-time ultrasound guidance vs. the landmark technique for catheter placement in the internal jugular vein resulted in significantly fewer complications, including fewer IVDR BSIs ($P < 0.001$) [77]. A recent meta-analysis found that the use of ultrasound for insertion at internal jugular and subclavian vein sites reduced cannulation failure (RR, 0.32; 95% CI, 0.18–0.55), the need for multiple placement attempts (RR, 0.60; 95% CI, 0.45–0.79) and complications during catheter placement (RR, 0.22; 95% CI, 0.10–0.45), in comparison with insertions using anatomic landmarks [76].

Although no RCT to date has compared the three insertion sites, based on the available data, we recommend the subclavian site as the first preferred site for CVC insertion routinely employing real-time ultrasound to minimize mechanical complications.

Simulation-Based Training

A recent observational study, completed in an urban teaching hospital, evaluated the impact of a simulation-based educational intervention on the rates of IVDR BSI in a medical ICU [78]; third-year internal medicine and emergency medicine residents completed the educational program, which included a pretest, an informational video demonstrating proper CVC insertion technique, training with ultra-sound and hands-on practice using a simulator device, and a post-test with a required minimum score [78]. There were 3.2 infections per 1,000 catheter days in the 16 months prior to the educational intervention in this medical ICU and 4.9 infections per 1,000 catheter days in a comparator unit in the same hospital, the surgical ICU, during the preintervention period. The rate of IVDR BSIs in the medical ICU during the 16-month intervention period, when all of the second- and third-year residents had completed the training, decreased to 0.5/1,000 catheter days. The rate in the surgical ICU, where no rotating residents completed the simulation training, remained stable at 5.3/1,000 catheter days during the same 16-month time period [78]. This study affirms the value of cutting-edge programs for training healthcare personnel in proper CVC insertion techniques, addressing a priority recommendation in the CDC HICPAC Guideline for the Prevention of IVDR BSI [6].

Chlorhexidine-Impregnated Insertion Site Dressings

The application of a CHG-impregnated sponge dressing (BioPatch®, Johnson & Johnson Gateway) over the CVC insertion site has been shown to greatly reduce the incidence of IVDR BSI in several randomized trials [5, 56, 79–81]. A large, randomized, open, controlled trial compared this dressing to standard sterile dressings in 601 chemotherapy patients, with 9,731 catheterization days, recently showed a significant reduction in IVDR BSIs in the intervention group (6.4%, 19 of 300) compared to the control group (11.3%, 34 of 301; $P = 0.016$, RR, 0.54; 95% CI, 0.31–0.94) [81]. In ICU patients, the use of CHG-impregnated dressings led to significantly fewer IVDR BSIs when compared with standard sterile dressings, in a large, multicenter RCT ($P = 0.005$, HR 0.024, 95% CI, 0.09–0.65) [80].

The latest 2002 CDC Guideline makes no recommendations regarding the use of CHG-impregnated dressings. However, considerable emerging data indicate that CHG-impregnated dressings are effective in reducing IVDR BSIs, and we recommend their use (rating IA) [56, 79–81].

Chlorhexidine Bathing

Several before-after time-sequence trials have been undertaken to ascertain the impact of daily 4% CHG bathing to prevent healthcare-associated BSIs in critically ill ICU patients. Overall, CHG bathing, using either CHG-impregnated wipes or adding CHG to the bathwater, has been shown to have a positive outcome on CRBSIs [82–90]. However, patients with cancer who are not critically ill have not been studied. Daily CHG bathing is recommended if other, simpler measures for reducing CRBSI have been implemented, but rates of CRBSI continue to be high.

Antiinfective-Impregnated Catheters

The HIPAC Guideline recommends the use of antiinfective-coated CVCs if the catheter is expected to remain longer than 5 days and is used in combination with a comprehensive IVDR BSI reduction strategy (rating IB) [6]. However, the majority of the studies have focused on the use of antimicrobial-coated CVCs used as short-term devices, and few data have been published on their use as long-term devices [50, 56]. Several types of catheters are available: catheters coated either externally (first generation) or externally and internally (second generation) with chlorhexidine and sulfadiazine silver (CH-SS), catheters coated with minocycline or rifampin, and silver-impregnated catheters [5]. Silver-coated catheters include silver, platinum and carbon-coated catheters, and silver ion/alloy catheters [56].

A recent comprehensive meta-analysis of antiinfective-coated catheters included clinical trials comparing antimicrobial-coated CVCs with either a standard CVC or another antimicrobial-coated CVC [91]. The main outcomes were catheter colonization and catheter-related BSI. The first-generation chlorhexidine-silver sulfadiazine (CSS) CVCs were shown to reduce colonization (OR 0.51, 95% CI 0.42–0.60) and catheter-related BSI (OR 0.68, 95% CI 0.47–0.98). Minocycline-rifampin-coated CVCs also reduced catheter colonization (OR 0.39, 9%% CI 0.27–0.55) and catheter-related BSI (OR 0.29, 95% CI 0.16–0.52), and performed better than the CSS CVCs for reducing catheter colonization and BSI (OR 0.18, 95% CI 0.07–0.51).

The choice of which catheter to use is governed by many factors including efficacy, cost, cost-effectiveness, and risk of promoting drug resistance. A recent analysis (2008) found an estimated cost savings of £138.20 (approximately $227) for every antiinfective catheter inserted [10]. Antibiotic-resistance is a particular concern with antibiotic-impregnated catheters, although trials assessing the efficacy of minocycline-rifampin-coated catheters have not found evidence of emergence of drug resistance to date [50].

Antiinfective Lock Solutions

The major mechanism of IVDR BSI in long-term IVDs is intraluminal colonization. For this reason, antimicrobial lock solutions have been a logical step to prevent colonization of the intraluminal surfaces of long-term IVDs to prevent IVDR BSIs. A small volume of the antimicrobial solution is instilled into the lumen of the IVD and allowed to dwell for a proscribed period, after which it is either removed or flushed into the patient's bloodstream.

A meta-analysis of seven RCTs, involving mostly cancer patients, comparing a vancomycin-containing lock solution with sterile saline showed a significantly reduced risk of IVDR BSI (RR 0.49, 95% CI, 0.26–0.95) [48]. A recent systematic review and meta-analysis of RCTs in patients receiving maintenance hemodialysis of a variety of antiinfective lock solutions, including various antibiotic combinations, minocycline with ethylenediamine tetraacetic acid and nonantibiotic antiseptic solutions including citrate and citrate with taurolidine was recently reported [52]. All of the lock solutions reviewed showed significant benefit for prevention of IVDR BSI [52]. Ethanol has also recently been shown to be safe and effective as an antimicrobial lock solution [53, 56, 92]. A recently published prospective, double-blind, RCT comparing ethanol with heparinized saline in granulocytopenic hematology patients showed a fourfold

reduction in the number of IVDR BSIs in the ethanol group compared to controls (OR 0.18, 95% CI, 0.05–0.65) [92]. While a number of new antibiotics show promise as lock solutions based on in vitro studies [93], further research of their efficacy in clinical trials is mandatory.

We recommend the use of antiinfective lock solutions for prevention of IVDR BSIs with long-term IVDs in patients at high risk for IVDR BSIs such as those receiving hemodialysis. In general, antiseptic lock solutions are preferable to antibiotic lock solutions because of their greater spectrum of activity and lesser risk of promoting antibiotic resistance.

Antiinfective Luer-Activated Devices

In addition to the above novel technology-based strategies for the prevention of IVDR BSI, an emerging role of needleless connectors in the pathogenesis of IVDR BSIs must be mentioned, with conjecture of possible preventive strategies.

Needleless connectors were developed in response to demands for enhanced safety for healthcare workers, to prevent needle-stick injuries, and are currently an integral component of infusion systems across North America. Although needleless connectors, when properly used, clearly reduce the risk for needle-stick injuries during access of an IVD or injection port [18, 94–97], a growing number of reports published over the past decade have raised concerns about the potential for an increased risk of iatrogenic IVDR-BSI associated with the use of luer-activated, valved connectors [40, 73, 98–101]. Most of these studies have been retrospective and uncontrolled, and suboptimal manipulation of the device, rather than the device itself, may have been responsible for some of the increased incidence of BSIs in some settings, however, many hospitals experienced sharp increases in primary BSI following introduction of a new luer-activated, valved connector and intensified infection control practices had no impact; only after removing the new connector from the hospital did the rates of CVC-associated BSI return to baseline levels [102]. Most notably, multiple commercial valved connectors have been implicated, indicating that these devices appear to have a generic risk of becoming contaminated during use and producing iatrogenic BSI.

Typically, healthcare personnel disinfect connectors with 70% (v/v) isopropyl alcohol before accessing them. Although needleless connectors appeared to reduce contamination in comparison with standard caps [103], a recent study by Menyhay and Maki found that conventional methods of disinfection of the membranous septum may not prevent microbial entry if the membrane of the luer-activated device (LAD) is heavily contaminated, which may account for the increased risk for CVC-associated BSIs seen in some centers [104].

The V-Link with VitalShield (Baxter Healthcare) is an LAD protected with an interior and exterior antimicrobial coating and was recently approved by the FDA. The V-Link with VitalShield is effective against 99.9% of pathogens known to cause IVDR BSIs in in vitro testing and was recently shown in a simulation study to prevent internal contamination, even with heavy contamination of the membranous septum [105].

Saralex-cl (Menyhay Healthcare Systems), another promising device, is an antimicrobial-barrier cap that threads onto the end of a needleless LAD system. A recent prospective in vitro study compared standard disinfection of common LADs using 70% isopropyl alcohol with the new antiseptic-barrier cap [106]. This new antiseptic cap, which bathes the connector septum with 0.25 mL of 2% CHG in 70% isopropyl alcohol, was almost totally effective in preventing transmission of pathogens across the membranes of precontaminated LADs when compared to standard disinfection with 70% alcohol (positive control, 100% transmission, standard disinfection with 70% alcohol, 20 transmissions in 30 trials, 67% transmission, Saralex-cl = 1 transmission in 60 trials, 1.6% transmission; $P < 0.001$) [106]. Data on the clinical efficacy of antimicrobial-coated LADs and antimicrobial-barrier caps, based on an RCT, is needed.

Catheter Securement

Choices for securement of a percutaneous uncuffed CVC or PICC include sutures, tape, or novel catheter securement devices, such as StatLock® (Venetec International, CR Bard). Sutures are often painful for the patient, pose the risk of needle-stick injury to the provider placing them, and foster infection of the suture sites, potentially increasing the risk of catheter-related BSI. StatLock®, a sutureless catheter securement device, reduces catheter-related complications including IVDR BSIs [107–109]. A randomized trial comparing suture securement to the StatLock® with peripherally inserted central catheters, showed a significant reduction in the number of catheter-related BSIs in the StatLock® group (2 vs. 10; $P = 0.032$) [108]. We recommend the use of a sutureless securement device for peripheral I.V. and extended-dwell catheters, such as noncuffed CVCs and PICCs.

Intensive Insulin Therapy

Glycemic control in critically ill ICU patients is essential for the prevention of IVDR BSI. However, the optimum level of glycemic control has been controversial. A large, RCT in 1,548 critically ill patients in a surgical ICU, the majority of

whom were postsurgical patients, compared intensive insulin therapy – maintenance of blood glucose level between 80 and 110 mg/dL by using continuous infusions of insulin (insulin drips) with conventional insulin therapy – subcutaneous insulin given only if blood glucose levels exceeded 215 mg/dL, striving to maintain levels between 180 and 200 mg/dL [110]. The study found a markedly reduced ICU and hospital mortality with intensive glycemic control (8.0% with conventional treatment vs. 4.6% with intensive treatment; $P < 0.04$); the greatest reduction in mortality was seen in patients with multi-organ failure due to a septic focus [110]. Most noteworthy, the incidence of nosocomial BSI was cut in half (8 vs. 4%). A similar study in medical ICU patients found no reduction in mortality or difference in bacteremia rates with intensive glycemic control [111].

A meta-analysis of 29 RCTs encompassing 8,432 patients found no difference in hospital mortality with tight glucose control vs. moderate control, glucose levels <150 mg/dL (21.6 vs. 23.3%; RR, 0.93; 95% CI, 0.85–1.03), and the results did not change when patients were stratified by type of ICU: surgical, medical, or medical-surgical. However, tight glucose control was associated with a reduced risk of septicemia (10.9 vs. 13.4%; RR, 0.76; 95% CI, 0.59–0.97) [112].

In the NICE SUGAR study, a large, randomized multi-center trial in 6,104 adult ICU patients, intensive glycemic control (goal 81–108 mg/dL) was associated with increased mortality compared to conventional control (goal ≤180 mg/dL) (OR, 1.14; 95% CI, 1.02–1.28; $P = 0.02$) [113]. The study population included more medical than surgical ICU patients (intensive group: 36.9% surgical, 63.1% medical; conventional group: 37.2% surgical, 62.8% medical). Severe hypoglycemia (≤40 mg/dL) was significantly more common in the intensive control group (6.8 vs. 0.5%, $P < 0.001$) [113].

A recent meta-analysis of 26 trials involving a total of 13,567 patients, including the data from the NICE SUGAR trial, found no mortality benefit to intensive insulin therapy in critically ill patients (pooled RR of death with intensive therapy using insulin drip as compared with moderate control using subcutaneous insulin (RR 0.93; 95% CI, 0.83–1.04)) [114]. However, when analyzed separately, surgical ICU patients experienced significant benefit (RR 0.63, 95% CI 0.44–0.91) while patients in nonsurgical ICUs did not.

Based on these studies, all hospitalized patients are likely to benefit from moderate glycemic control, and we recommend the use of intensive glycemic control with an insulin drip in surgical ICU patients to reduce the risk of healthcare-associated infections, particularly BSIs. However, stringent monitoring to avoid severe hypoglycemia is essential, and a glycemic target that can be achieved safely should be chosen, generally 120–150 mg/dL.

Achieving High-Level Compliance with Essential Control Measures Through Institutional Systems

A multifaceted approach with near-100% compliance is essential to consistently and maximally reduce the risk of IVDR BSI. The Institute for Healthcare Improvement (IHI) has promoted the concept of "bundles" to aid in risk reduction. A bundle, according to the IHI, is a structured way of improving the processes of care and patient outcomes using a set of practices, generally three to five, that when performed collectively and reliably, have been shown to improve patient outcomes [115]. The IHI-recommended evidence-based bundle for CVC care includes the following: (1) hand hygiene before IVD insertion; (2) maximal barrier precautions during the insertion procedure; (3) cutaneous antisepsis with CHG; (4) optimal catheter insertion site selection, with the subclavian vein the preferred site for CVCs, and (5) daily review of continued need for the, with immediate removal when no longer needed [115]. In an elegant time-sequence trial in 100 Michigan hospitals, Pronovost et al. showed that development of effective systems within the hospitals which assured a very high level of compliance with the bundle for every CVC insertion resulted in a striking reduction in IVDR BSI in the individual hospitals over 18 months, with a reduction from prestudy baseline of 0.62 (95% CI, 0.47–0.81) at 0–3 months and 0.34 (95% CI, 0.23–0.5) at 16–18 months [12]. These numbers represented an overall 66% reduction in rates of IVDR BSIs, which has now been maintained for 36 months [14].

Bhutta et al. undertook a prospective quasi-experimental study in a children's hospital, which included the stepwise introduction of interventions over a 5-year period [116]. The interventions included maximal barrier precautions, a transition to antibiotic-impregnated CVCs, annual hand washing campaigns, and the use of CHG in place of povidone-iodine. Significant decreases in rates of infection occurred over the intervention period and were sustained over a 3-year follow-up. Annual rates of CVC-associated BSI decreased from 9.7/1,000 days in 1997 to 3.0/1,000 days in 2005 (RR reduction, 0.75; 95% CI, 0.35–1.26). The investigators found that multifaceted interventions and development of systems to achieve uniformly high compliance reduce IVDR BSIs but require strong institutional support.

The recent implementation of a multifaceted approach in a pediatric cardiac intensive-care unit, which included CVC insertion and maintenance bundles, CHG-impregnated dressings, nurse and physician education, and the addition of a unit-based infection control nurse, resulted in a reduction in their rate of IVDR BSIs from 7.8 to 2.3 infections per 1,000 catheter days over a period of less than 2 years [117].

Pronovost et al. have outlined the essential steps to establishing an effective institutional system to achieve these recommended results [13].

Catheter Salvage in the Context of Treatment

The optimal management of IVDR BSI requires two basic clinical decisions: (1) the appropriate and timely administration of intravenous antiinfective therapy and (2) removal of the IVD or an attempt at catheter salvage (Fig. 11.5). A recent evidence-based Guideline from the Infectious Diseases Society of America is now available [118].

Systemic antiinfective therapy given intravenously should be selected based on the suspected or proven bloodstream pathogen(s) in accordance with published guidelines and resources [118]. It is extremely important to begin the therapy within 1 h of the encounter with clinical suspicion of IVDR BSI cite, as delays of 2 or more hours increase mortality by 30–40% [119].

The decision whether to remove the IVD is based on the clinical picture, the type of IVD being used and the organism in question. This decision becomes more complex when specific patient characteristics are considered, such as the type of device required (e.g., tunneled CVC or implanted port) and the ease of venous access.

First of all, we believe IVDs of all types should be promptly removed if the patient presents with septic shock and there is strong suspicion that IVDR BSI is the cause. The recent IDSA Guideline recommends removal of nontunneled catheters in all complicated infections (e.g., thrombosis, endocarditis, osteomyelitis) and in all infections caused by *S. aureus*, gram negative bacilli, Enterococcus, and *Candida* species [118]. In IVDR BSIs associated with tunneled or implantable devices, the catheters also require removal for all complicated infections (thrombosis, endocarditis, osteomyelitis), tunnel or pocket infections, and port abscesses, and for all infections caused by *S. aureus* and *Candida* spp.
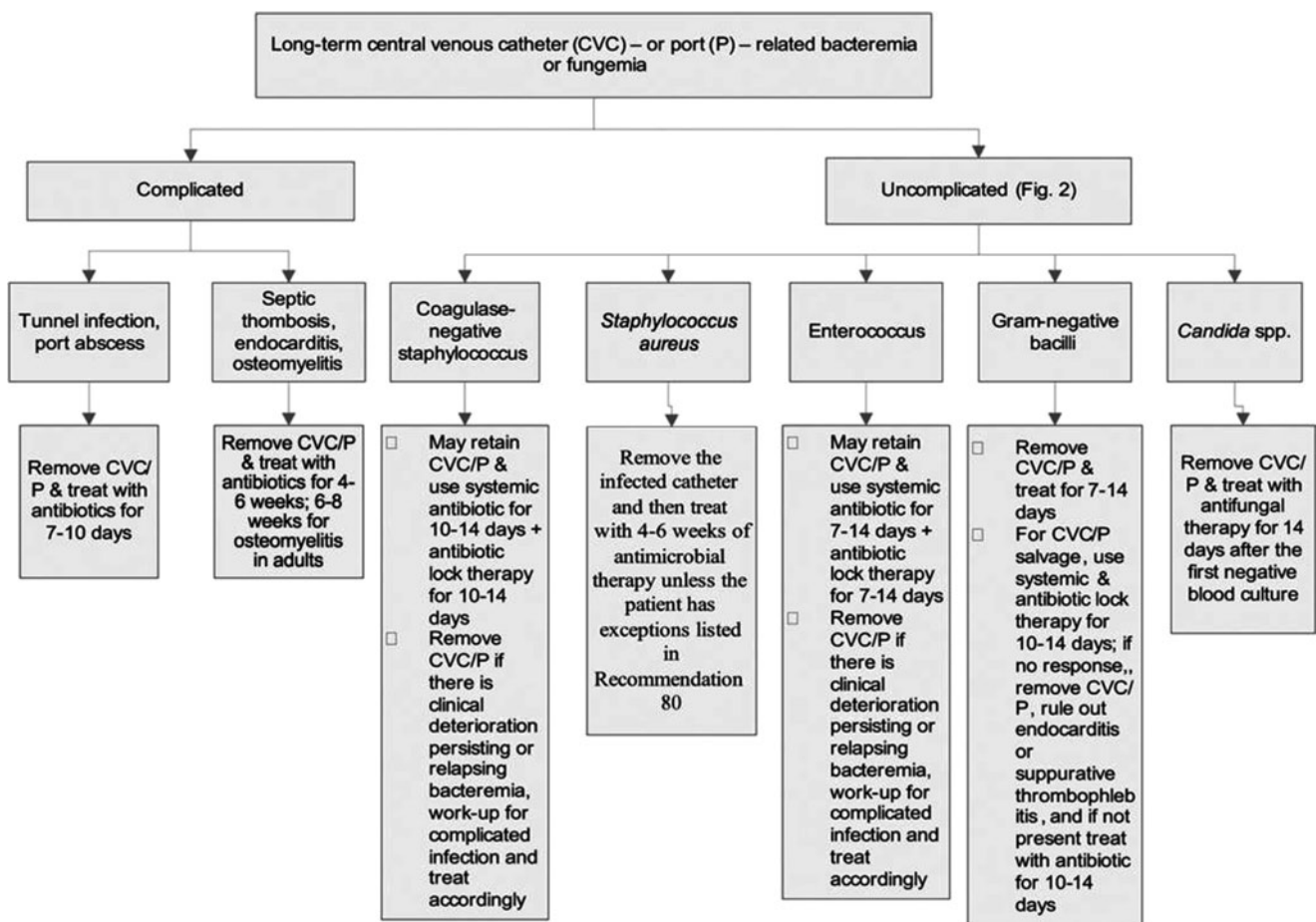
Fig. 11.5 Approach to the treatment of a patient with a long-term cuffed and tunneled central venous catheter (CVC) or a subcutaneous totally implanted port (P)-related bloodstream infection. From the IDSA guideline on management of IVDR BSI [168]

By the Guideline, catheter salvage regimens including the use of antibiotic lock therapy may be attempted, when necessary, for infections due to organisms *other* than *S. aureus*, fungi, *Pseudomonas aeruginosa*, *Bacillus* species, *Micrococcus* species, Propionibacteria, or mycobacteria [40, 118, 120].

Antiinfective Lock Therapy

The most frequently used implanted IVDs in patients with cancer are long-term cuffed and tunneled catheters, such as Hickman or Broviac catheters, and totally implanted subcutaneous central ports. Given that the major route of infection for these catheters is intraluminal contamination, a promising approach to the prevention of these infections has involved instilling an antiinfective solution into the device lumen or lumens to prevent colonization of the intraluminal surface by suspended planktonic-phase contaminants [121–123]. Antiinfective lock therapy (ALT) has also been applied, but much less rigorously studied for the *treatment* of IVDR BSI.

ALT for the treatment of IVDR BSI should always be used in conjunction with systemic antiinfective therapy when the goal is to successfully eradicate the BSI while retaining the device (Table 11.4). The likelihood of success of ALT varies with the infecting microorganism and the extent of infection. Recurrent bacteremia after parenteral therapy is more likely to occur if that therapy is administered through a retained catheter than if the catheter is removed. Several small cases series have shown ALT to be promising as adjunctive treatment when the original, presumably infected IVD is retained [121, 124–148]. In 21 open trials of ALT for IVDR BSI involving long-term catheters, with or without concomitant parenteral therapy, catheter salvage without relapse was achieved in 77% of episodes [135]. Table 11.3 summarizes the major studies that have examined lock therapy for adjunctive treatment of IVDR BSI with the goal of IVD salvage.

The only randomized trial of ALT to date compared a vancomycin or ceftazidime lock in addition to parenteral antibiotic therapy with parenteral antibiotic therapy plus a placebo lock [149]. The investigators found that in the analysis population of 44 patients (21 antibiotic lock arm and 23 in the placebo arm), by day 180, 33% of BSI in the antibiotic lock group had not been eradicated compared with 57% in the placebo arm (HR 0.55, $P=0.10$). Of note, only half of potentially eligible patients with an IVDR BSI met IDSA Guideline criteria for eligibility for this study. Frequent reasons for exclusion were the IVD was not available for >8–12 h/day for the antiinfective lock ($n=10$); yeast infection or mixed Gram-positive/negative infections ($n=13$); catheter removal preferred by the treating physician ($n=7$); and CRBSI <14 days after insertion, or pocket or/tunnel infection ($n=10$). Thus, barriers to the use of ALT are common and must be acknowledged when considering ALT as an option for adjunctive therapy of IVDR BSI.

To be practical in the acute care setting, the antiinfective lock regimen should exhibit efficacy over a sufficiently short dwell time to be practical in hospitalized patients with the need for extended "line time," for clinical use of the line. The minimum time recommended for exposure to the concentrated antiinfective lock solution is 60 min, if there is not a critical need for access, the dwell times should extend as long as possible [10]. Longer dwell times are possible in patients with hemodialysis catheters or implantable ports that are not routinely accessed on a daily basis.

The formation of a biofilm within the catheter lumen limits penetration of anti-infective solution and sterilization of the heavily colonized catheter. Bacteria within a biofilm require 100–1,000 times greater antiinfective concentrations to achieve killing as compared with the same organisms in the planktonic state [9]. Standard intravenous antimicrobial therapy does not reach sufficiently high concentrations to materially reduce the bacterial burden within a biofilm in the catheter lumen.

Stability and compatibility of the antiinfective lock solution with an accompanying anticoagulant must also be considered when ordering an antiinfective lock solution. Temperature, dwell time, addition of anticoagulant or other antiinfectives all

Table 11.3 Studies of antiinfective lock therapy as adjunctive treatment of intravascular device-related bloodstream infection

References	Type of lock therapy	Number of BSI receiving lock therapy	Salvage rate in lock group (%)	Relapses in lock group (%)	Catheter removals for failure in treatment group (%)
Messing et al. [145]	Antibiotic	22	20/22 (90)	NR	2/22 (9)
Dannenberg et al. [134]	Ethanol	24	23/24 (95)	0/24 (0)	1
Williams et al. [167]	Antibiotic	7	4/7 (57)	NR	2/7 (28)
Poole et al. [147]	Antibiotic	47	33/47 (70)	7/47 (15)	14/47 (30)
Rijnders et al. [149]	Antibiotic	22	14/21 (66)	3/21 (14)	3/21 (14)
Fortun et al. [139]	Antibiotic	19	16/19 (84)	2/19 (10)	1/19 (5)
Onder et al. [177]	Antibiotic	264	170/264 (64)	67/170 (39)	94/264 (36)
Aslam et al. [125]	N-acetylcysteine and tigecycline	18	15/18 (83)	NR	NR
Broom et al. [129]	Antibiotic and ethanol	17	15/17 (88)	0	2

NR not reported

Table 11.4 Final concentrations of antibiotic lock solution used for the treatment of intravascular device-related bloodstream infection

Antibiotic and dosage	Heparin or saline (IU/mL)
Vancomycin, 2.5 mg/mL	2,500 or 5,000
Vancomycin, 2.0 mg/mL	10
Vancomycin, 5.0 mg/mL	0 or 5,000
Ceftazidime, 0.5 mg/mL	100
Cefazolin, 5.0 mg/mL	2,500 or 5,000
Ciprofloxacin, 0.2 mg/mL	5,000
Gentamicin, 1.0 mg/mL	2,500
Ampicillin, 10.0 mg/mL	10 or 5,000
Ethanol, 70%	0

Adapted from the 2009 IDSA guidelines for management of IVDR BSI [168]

influence stability. In the case of ethanol lock solutions, the effect of ethanol on the mechanical and structural integrity of the catheter has been studied. These studies showed no change in the integrity of the catheter when exposed [27].

Although the duration of ALT has varied substantially among different studies (3–30 days), most studies have used a 2-week duration. Vancomycin, cefazolin, and ceftazidime remain stable in heparin solutions at 25 and 37°C for several days [178]. Not all antibiotic-heparin combinations can be used because precipitation can occur when some antibiotics are mixed with heparin, especially with high antibiotic concentrations [51, 150]. Ethanol is not compatible with heparin [151]. An ethanol lock should dwell for at least 60 min, then be removed and the VD flushed with *0.9% sodium chloride*. Heparin can then be instilled into the CVC/ID. Ethanol 50% is not a commercially available product. The compounded ethanol 50% (v/v) product is stable in syringes at room temperature for up to 28 days (unprotected from light) [35].

Table 11.4 lists antibiotic lock solutions that can be used without the risk of precipitation.

Exchange over a Guidewire

In patients with cancer who have long-term catheters and limited alternative sites for vascular access, catheter salvage is desirable, and another approach to salvage is to "exchange" the catheter (replace the infected catheter by a new uninfected catheter) over a guidewire. Current recommendations suggest that guidewire catheter exchange is acceptable in the management of suspected CVC-related BSI, although the catheter should be relocated to a new site if culture of the removed catheter confirms the diagnosis of CVC-related BSI. The evidence for this recommendation is, however, scant, and most studies have been undertaken in patients on hemodialysis [152, 153]. In patients with malignancy and thrombocytopenia,

this procedure may be associated with an increased risk of bleeding.

The safety and efficacy of CVC exchange by guidewire after unsuccessful antimicrobial therapy were recently evaluated in a prospective quasi-experimental study of patients undergoing BMT or intensive chemotherapy [154]. CVC exchange was considered when fever and positive blood cultures persisted after 2 days of adequate antimicrobial therapy and no potential source of bacteremia other than CVC could be identified. The guidewire exchange was preceded and followed by a slow infusion of antimicrobial therapy. In 19 episodes of cryptogenic bacteremia during a 1-year period, 14 episodes (74%) were catheter-related and 71% of these were with CoNS. Guidewire replacement was accomplished uneventfully 4 (range 3–6) days after the development of bacteremia. In all cases, clinical signs of infection disappeared within 24 h after the exchange. Definitive catheter withdrawal was carried out a median of 16 days (range 3–42) after guidewire exchange; in all cases, the catheter culture was negative. The findings from this nonrandomized small study with no comparison group are intriguing, and this approach should be studied further, but at the present time, there is insufficient evidence to recommend its routine use.

Urokinase as Adjunctive Treatment for IVDR BSI

Catheter occlusion and thrombus formation can occur as part of an IVDR BSI. Dissolution of the infected thrombus using a thrombolytic agent such as urokinase may be a potential strategy to treat IVDR BSI in conjunction with antibiotics; however, this approach has not been adequately studied. In a prospective randomized trial in 63 children, 33 of whom received urokinase and antibiotics and 30 received antibiotics alone, the investigators found that treatment failures leading to catheter removal occurred in 9 of 33 in the experimental group and 9 of 30 in the control population (*P*=NS). Of note, all catheters in the study were shown to be free of thrombus by radiographic imaging prior to enrollment in the study. The role of urokinase as an adjuvant to antibiotics for the treatment of IVDR BSI is uncertain and is not recommended at the present time, but deserves further study.

IVDR BSI Pathogen-Specific Recommendations

Pathogen-specific recommendations are summarized in Tables 11.5 and 11.6 and described in more detail below.

Table 11.5 Recommendations for the use of antiinfective lock therapy for treatment of IVDR BSI

Recommendation	Strength of recommendation
Antibiotic lock is indicated for patients with IVDR BSI involving long-term catheters with no signs of exit site or tunnel infection for whom catheter salvage is the goal	B-II
For IVDR BSI, antibiotic lock should not be used alone; instead, it should be used in conjunction with systemic antimicrobial therapy, with both regimens administered for 7–14 days	B-II
Dwell times for antibiotic lock solutions should generally not exceed 48 h before reinstallation of lock solution; preferably, reinstallation should take place every 24 h for ambulatory patients with femoral catheters (B-II). However, for patients who are undergoing hemodialysis, the lock can be renewed after every dialysis session	B-II
Catheter removal is recommended for IVDR BSI due to *S. aureus* and *Candida* species, instead of treatment with antibiotic lock and catheter retention, unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site)	A-II
For patients with multiple positive catheter-drawn blood cultures that grow coagulase-negative staphylococci or gram-negative bacilli and concurrent negative peripheral blood cultures, antibiotic lock therapy can be given without systemic therapy for 10–14 days	B-III
For vancomycin, the concentration should be at least 1,000 times higher than the MIC (e.g., 5 mg/mL) of the microorganism involved	B-II
At this time, there are insufficient data to recommend an ethanol lock for the treatment of IVDR BSI	C-III

Adapted from the Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America [168]

Table 11.6 Pathogen-specific recommendations regarding catheter salvage

Organism	Decision to remove CV or ID?	Decision to retain CVC/ID?	Salvage regimen	Salvage regimen failure?
S. aureus	Yes – always remove CVC/ID and treat with systemic antimicrobials	No – low success rate		
Coagulase-negative Staphylococcus	May retain – see salvage therapy	Yes – use salvage therapy	Systemic treatment plus ALT (antiinfectives and duration per infectious disease)	Remove CVC/ID if persistent or relapsing bacteremia or clinical deterioration
Gram-negative bacilli	If yes – remove CVC/ID and treat with systemic antiinfectives	If yes – use salvage therapy, only if not MDR GNB	Systemic treatment plus ALT (antiinfectives and duration per infectious disease)	If no response, remove CVC/ID and treat with systemic antiinfectives
Candida spp	Yes – remove CVC/ID and treat with systemic antifungal therapy	No – low success rate		

Candida spp.

The two major sources of candidemia are the CVC and translocation from the gastrointestinal tract in immunocompromised patients [155].

Candidemia deriving from IVDs is challenging to treat because of heavy biofilm formation on the surface of the catheter. In general, IVD removal is recommended for IVDR candidemia because of the risk of endophthalmitis, septic thrombophlebitis, and endocarditis if the candidemia is not quickly controlled, as conventional antifungal therapy will not effectively eradicate Candida organisms embedded in biofilm [156]. Preliminary studies, mainly in vitro, suggest that ethylene diamine tetra-acetic acid (EDTA) (an anticoagulant-chelating agent with antifungal as well as antibiofilm activity) might be useful as a lock agent. The utility of amphotericin B lipid complex (ABLC), with and without EDTA, was studied in an in vitro model of Candida biofilm. Clinical blood isolates from cancer patients infected with

Candida albicans or *Candida parapsilosis* were used. ABLC+EDTA (30 mg/mL) was significantly more effective than ABLC alone, EDTA alone against *C. parapsilosis* at 6 h ($P \leq 0.01$) and against *C. albicans* at 8 h ($P \leq 0.04$) [157].

Staphylococcus aureus

The optimal duration of treatment for *S. aureus* bacteremia is unclear because of ever-present concern regarding complications such as endocarditis and hematogenous osteomyelitis. As many as a third of patients with *S. aureus* bacteremia will have metastatic infection [158]. In the past, prolonged treatment for 4–6 weeks for *S. aureus* bacteremia has been recommended.

Predictors of hematogenous metastatic infection include persistent bacteremia on therapy, evidence of cutaneous septic emboli, and community-acquired bacteremia [159].

In recent years, short-course therapy for *S. aureus* IVDR BSI has been extensively evaluated relying upon a transesophageal echocardiogram to rule out endocarditis cites. If the IVD is removed and there is no clinical evidence of metastatic infection, and the TEE shows no evidence of endocarditis, short-course parenteral antimicrobial therapy for 2 weeks in immunocompetent nonneutropenic patients is considered acceptable [62, 160, 179]. Of note, TEE is most sensitive for detecting endocarditis when performed 5–7 days after the onset of bacteremia [161].

Catheter salvage for S. aureus bacteremia is not recommended. Studies have shown that removal of vascular catheters infected with *S. aureus* is associated with more rapid clearance of the bacteremia and symptomatic improvement, with a higher cure rate, compared with catheter retention. Small series of patients in whom the catheter was retained and parenteral and ALT was employed have shown mixed results [147, 148, 162–167]. These studies suggest an unacceptably high failure rate for catheter salvage when *S. aureus* is the infecting pathogen. In extenuating circumstances, if the catheter is retained, the patient should receive systemic and ALT for at least 4 weeks (B-II). Catheter guide wire exchange should be done, if possible, and if done, an antimicrobial-impregnated catheter with an antiinfective intraluminal surface should be considered for the new catheter exchange (B-II).

For patients with catheters found to be colonized with *S. aureus* at removal who are not bacteremic, the recent IDSA management Guideline recommends a 5–7-day course of parenteral antibiotic therapy and close monitoring for signs of ongoing infection, with additional blood cultures, as indicated.

Coagulase-Negative Staphylococci

CoNS are the most frequent causative microorganisms in IVDR BSI. In the majority of patients, the clinical course is benign and complications are infrequent, with the exception of *Staphylococcus lugdenensis*, which produces invasive infection very similar to *S. aureus*. No randomized trials have been conducted on the optimal type and duration of antimicrobial treatment for IVDR BSI with CoNS. For uncomplicated infection by CoNS, treatment with ALT is considered acceptable if given in conjunction with systemic antimicrobial therapy for 10–14 days [168]. In an observational study of 188 patients with CoNS, Raad et al. found that patients in which the IVD was retained had a 6.6-fold (95% CI, 1.8–23.9) higher likelihood of having a recurrence than those patients whose IVD was removed or exchanged [169].

If the IVD is removed, antimicrobial treatment may be given for 5–7 days following device removal.

Gram-Negative Bacilli

Multiresistant (MDR) gram-negative bacilli are major pathogens in patients with cancer and the incidence of IVDR BSI caused by MDR gram-negative bacilli appears to be increasing [44]. Of particular concern is extended spectrum beta-lactamase producing gram-negative bacilli and the recent emergence of carbapenemase-producing *Klebsiella pneumoniae* [170]. Infections caused by these MDR bacteria are often associated with adverse clinical outcomes [171–173], in part because of a delay in initiating appropriate antimicrobial therapy. No randomized trials have been conducted to address optimal management of IVDR BSI with gram-negative bacilli. The IDSA Guideline recommends a 7–14-day course of antibiotic therapy tailored to the susceptibility of the infecting organism. ALT for catheter salvage may be considered for occasional patients with susceptible organisms and uncomplicated infection, but we do not recommend attempting catheter salvage for MDR gram-negative bacteremia deriving from an IVD.

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Chapter 12
Pneumonia in the Cancer Patient

Scott E. Evans and Amar Safdar

Abstract Lower respiratory tract infections result in unacceptably high mortality among cancer patients. Pneumonias cause death in this population both directly through impairment of gas exchange and progression to system infection/sepsis, as well as indirectly by precluding delivery of necessary, antineoplastic therapies. Malignancy and treatment-related impairments of host immune responses and the emergence of multidrug-resistant organisms associated with recurrent exposures to hospital environments may not only enhance the risks of mortality, but also exacerbate the difficulty of diagnosing pneumonia in the cancer setting. As a consequence of disordered inflammatory responses, the typical clinical observations of pneumonia, including purulent respiratory secretions and early radiographic findings, may be inapparent or absent. A comprehensive review of etiology, clinical presentation, diagnosis, and management of pulmonary infections is presented in this chapter.

Keywords Pneumonia • MRSA • Fungal disease • CMV • Pneumococcus • Drug resistance • Immune defects

Lower respiratory tract infections result in unacceptably high mortality among cancer patients. Pneumonias cause death in this population both directly through impairment of gas exchange and progression to system infection/sepsis, as well as indirectly by precluding delivery of necessary, antineoplastic therapies [1–3]. Malignancy and treatment-related impairments of host immune responses and the emergence of multidrug-resistant (MDR) organisms associated with recurrent exposures to hospital environments may not only enhance the risks of mortality, but also exacerbate the difficulty of diagnosing pneumonia in the cancer setting. As a consequence

of disordered inflammatory responses, the typical clinical observations of pneumonia, including purulent respiratory secretions and early radiographic findings, may be inapparent or absent. Adding to this diagnostic challenge is the frequent colonization of the upper airway with microorganisms that do not contribute to disease, rendering the diagnosis of pneumonia by conventional culture techniques difficult. Conversely, sterile respiratory tract cultures do not exclude an infectious etiology, particularly in the setting of recent exposure to broad-spectrum antibiotics.

Susceptibility to pneumonia in the cancer patient is not only conditioned by the type and degree of immune suppression, but also by its duration. Multiple immune defects may coexist among patients with cancer, which adds to the conundrum and spectrum of opportunistic infections. Immune defects, including compromised acellular and cellular (alveolar macrophages, mast cells, neutrophils) innate and/or altered adaptive immune function, leading to either inadequate immmunoglobulin or defective T-cell mediate defenses may promote the development of specific types of pneumonia. In addition, treatment-induced disruption of the respiratory mucosa and ciliary dysfunction may result in inadequate clearance of airway secretions, enhancing the likelihood of pneumonia. Hence, the individual patient's predilection for pneumonia in the cancer setting is best understood by examining the effect of malignancy and its treatment on specific host immune defenses (Table 12.1). Because the immune defect is often mixed, careful attention to clinical and radiographic features and recognition of nosocomial versus community-acquired sources of the infection are critical to making the diagnosis and guiding empiric antimicrobial therapy [4]. Delays in appropriate antimicrobial therapy increase the risk of secondary complications and infection-associated deaths, especially in severely immunosuppressed individuals. Therefore, it is common practice to initiate empiric and/or preemptive antimicrobial therapy in patients in whom the suspicion of infection is high. An approach to the diagnosis and treatment of cancer-related pneumonias based on the specific defects in the major arms of host immunity and broad categories of infection source is emphasized in

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Table 12.1 Infections causing pneumonia in cancer patients based on the underlying immune defect

Immune defect	Bacteria	Fungi	Parasites	Viruses
Granulocytopenia	*Staphylococcus aureus*	*Aspergillus fumigatus;* non-*fumigatus Aspergillus*		Herpes simplex virus I and II
	Streptococcus pneumoniae	Non-*Aspergillus* hyalohyphomycosis such as *Pseudallescheria boydii, Fusarium solani*		Varicella-zoster virus
	Streptococcus species			
	Pseudomonas aeruginosa	*Mucorales* (zygomycoses)		
	Enterobacteriaceae	Dematiaceous (Black) fungi such as *Alternaria, Bipolaris, Curvularia, Scedosporium apiospermum, S. prolificans*		
	Escherichia coli			
	Klebsiella species			
	Stenotrophomonas maltophilia			
	Acinetobacter species			
Cell-mediated immune system	*Nocardia asteroides* complex	*Aspergillus* and non-*Aspergillus* filamentous molds	*Toxoplasma gondii*	Cytomegalovirus
Dysfunction	*Salmonella* species	*Pneumocystis jiroveci* (*P. carini*)	*Microsporidium* spp.	Respiratory viruses
	Rhodococcus equi	*Cryptococcus neoformans*	*Strongyloides stercoralis*	Influenza A and Influenza B
	R. bronchialis	Endemic mycoses due to *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis*		Parainfluenza type-3
	Listeria monocytogenes			Respiratory syncytial virus
	Mycobacterium tuberculous			Adenovirus
	Nontuberculous mycobacteria			Varicella-zoster virus
				HHV-6
				SARS-associated coronavirus
				Paramyxovirus
				Hantavirus
Humoral immune	*S. pneumoniae*			VZV
Dysfunction	*Haemophilus influenzae*			Echovirus
Splenctomy	*Neisseria meningitidis*			Enterovirus
	Capnocytophaga canimorsus			
	Campylobacter			
Mixed defects	*S. pneumoniae*	*P. jiroveci* (*P. carini*)	*T. gondii*	Respiratory viruses
	S. aureus	*Aspergillus* spp.	*S. stercoralis*	Influenza
	H. influenzae	*Candida* spp.		Parainfluenza
	K. pneumoniae	*C. neoformans*		Respiratory syncytial virus
	P. aeruginosa	*Mucorales* (zygomycoses)		Adenovirus
	Acinetobacter spp.	Endemic mycoses (severe systemic dissemination)		VZV
	Enterobacter spp.			
	S. maltophilia			
	N. asteroides complex			
	L. monocytogenes			
	Legionella spp.			

Note. Patients with mixed immune defects includes, recipients of allogeneic hematopoietic stem cell transplant; acute or chronic GVHD; myelodysplastic syndrome; adult T-cell leukemia lymphoma; antineoplastic agents like cyclophosphamide and fludarabine

VZV is rarely associated with systemic dissemination in patients with humoral immune defects, or even those with mixed immune dysfunctions

S. stercoralis may lead to serious, life-threatening hyperinfection syndrome in patients with marked cellular immune defects

HHV-6 Human herpesvirus-6

the early part of this section, followed by a more detailed discussion of selected pathogens that may cause fulminant infection in the cancer patient.

Specific Immune Defects

Disruption of local airway defense mechanisms often increases vulnerability to pneumonia among cancer patients. Breach of the respiratory epithelial barrier function and altered mucociliary clearance of secretions may occur as a result of cancer therapy, both through cell-specific injury and through generalized mucositis. Medical devices, such as nasogastric and endotracheal tubes, hinder coordinated glottic activities and mucociliary function and act as conduits for chronic colonization of pathogenic organisms [5]. Numerous defects of local innate defenses are also described following chemotherapy, including derangements of chemotaxis, phagocytosis, and killing by alveolar macrophages and resident mast cells. Respiratory epithelial cells tend to maintain their capacity for elaboration of inflammatory mediators following exposure to pathogens, despite cytotoxic chemotherapy [6, 7]. Yet, they are the primary interface with lower respiratory tract pathogens and are often susceptible to direct injury by MDR pathogens, due to the unique exposures of the cancer patients, as described further below. Further, concurrent alterations in systemic defense mechanisms, such as impairment of the circulating leukocytes of the innate immune system, are exceedingly common.

Neutrophils are exquisitely sensitive to the cytotoxic effects of chemotherapy, which may induce an agranulocytosis by direct myelotoxicity, as well as functional neutropenia by interfering with the phagocytic and chemotactic activity of these cells [8]. In addition, neutrophil dysfunction resulting from radiation therapy, corticosteroid administration and common cancer-related disorders, such as hypovolemia, prolonged hypoxemia, acidosis, and poorly controlled hyperglycemia, is a frequent problem. Severe neutropenia, defined as an absolute neutrophil count of ≤500 cells/μL, is associated with refractory lung infections caused by bacterial and fungal organisms [9]. In addition, the rapidity of onset of neutropenia and delay in neutrophil recovery play a role in the infection severity. More than 10% of patients with febrile neutropenia present with pulmonary infiltrates and infection remains the most frequent cause of radiographic abnormalities in these patients. The absence of consolidated infiltrates on chest radiographs does not exclude an evolving occult pneumonia, particularly in the setting of profound neutropenia (<100 cells/μL).

Severe pneumonias, including *de novo* infections and exacerbation of chronic lung infections, also arise in the

setting of neutropenia. Gram-negative bacilli (GNB) including Enterobacteriaceae (*Klebsiella, Escherichia coli, Enterobacter, Citrobacter, Serretia*) and *Proteus* spp., [10] are the predominant source of pneumonias associated with neutropenic fever. MDR Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta-lactamase-producing Enterobacteriaceae are also frequently cultured in the setting of neutropenic pneumonia. The incidence of pulmonary infections caused by Gram-positive bacteria (*S. aureus, Streptococcus* spp., including *Streptococcus pneumoniae*) has decreased over the past three decades, while Gram-negative pneumonias, particularly those caused by *Pseudomonas* spp., have become an increasing source of life-threatening, necrotizing lung infection (Fig. 12.1) [11]. Other nonfermentative Gram-negative bacteria (NF-GNB) such as *Stenotrophomonas maltophilia* [12–15], *Achromobacter,* and *Alcaligenes* species have also increased in the recent years and often lead to difficult-to-treat infections [14, 16]. As is the case in almost all other populations, aspiration of infected material remains the predominant mechanism of entry for lower respiratory tract infection among cancer patients. However, hematogenous dissemination represents a uniquely common source of pneumonia among cancer patients, and bacteremia in febrile neutropenic patients may not present with an obvious primary site of origin. Initial antimicrobial therapy for febrile neutropenia in patients with pulmonary infiltrates should be broad in spectrum and provide antimicrobial activity against drug-resistant strains of *S. aureus* and *Pseudomonas aeruginosa*. Early deescalation therapy may be attempted in patients who have demonstrated prompt clinical response and in whom granulocyte recovery has occurred or is expected to occur in the near future, especially if a pathogen has been identified. Deescalation should be undertaken with caution in high-risk patients with poor clinical response to antimicrobial therapy;

Fig. 12.1 *Pseudomonas* lung abscess in a patient with acute myelogenous leukemia awaiting bone marrow transplantation

persistent, severe, and/or long-standing granulocytopenia; or patients continuing on systemic immunosuppressive therapy.

In addition to neutropenia, cytotoxic antineoplastic therapies and hematologic malignancies may cause severe depression of humoral and cell-mediated adaptive immunity, resulting in inadequate immunoglobulin production and/or a variety of defective T and B cell-mediated defects. For example, immunoglobulin dyscrasias associated with hypogammaglobulinemia and defects in opsonization owing to asplenia are frequent among patients with certain types of lymphoreticular malignancies, such as multiple myeloma, chronic lymphocytic leukemia, and Waldenstom's macroglobulinemia. Hypocomplementemia associated with asplenia may lead to unchecked proliferation of encapsulated organisms that require opsonization with complement (C_3, C_5) for elimination. Furthermore, defects in antibody-dependent lymphocyte cytolytic activity may allow fulminant parasitic infections. Reduced T cell numbers and activity is a frequent finding among patients with Hodgkin's disease, hairy cell leukemia, adult T-cell leukemia, lymphocytic leukemia, and graft-versus-host disease (GVHD). In addition, viral illnesses, antineoplastic agents, and other immunosuppressive drugs (e.g., fludarabine, IL-2 inhibitors, antithymocyte globulins, calcinneurin inhibitors, tacrolimus, or glucocorticosteroids) may depress cellular immunity by inducing profound lymphopenia and/or interrupting activated T-cell inflammatory signal transduction pathways. Patients with cellular immune dysfunction are at increased risk of infection due to intracellular organisms such as *Listeria monocytogenes, Salmonella* spp., *Legionella* spp., *Pneumocystis jiroveci, and Toxoplasma gondii*, invasive pulmonary mycoses, and opportunistic viruses due to human cytomegalovirus, human herpesvirus-6 (HHV-6), and varicella-zoster virus. Thus, virtually every component of normal host immunity may be affected in an untoward manner by cancer or its treatment. The severe and oftentimes protracted immune suppression that follows encourages the development of unusual and intractable infections. Specific pathogens causing pneumonia that are commonly associated with depression of particular immune defects are listed in Table 12.1.

Community-Acquired Pneumonia (CAP). CAP, as defined by the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS), refers to the radiographic and clinical development of pneumonia in patients who have not been hospitalized or resided in a nursing home for 14 or more days prior to the onset of symptoms and who do not meet criteria for HCAP [4]. The distinction of CAP from nosocomial pneumonia remains important, as it allows prediction of likely pathogens and permits prognostic estimations based on epidemiologic descriptions of the underlying cause. Consequently, this distinction provides a framework for decisions regarding the diagnostic evaluation and empiric

antimicrobial therapy. Cancer patients are frequently exposed to the healthcare setting, both as inpatients and outpatients. Thus, pneumonia in the cancer patient is most often defined as hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP), rather than CAP.

The etiologic spectrum of bacterial pathogens causing CAP among those cancer patients with mild-to-moderate immunosuppression is similar to that of patients with no cancer history. However, a clinically insignificant microbial inoculum in the general population may cause severe infection among patients with underlying malignancy. *S. pneumoniae* remains the most commonly identified pathogen and the most frequent cause of lethal CAP [4]. Superinfection with MDR organisms is an emerging problem that complicates the management of CAP. *S. aureus*, nontypeable *Haemophilus influenzae*, *Pseudomonas* spp., and other GNB may also cause life-threatening CAP. Recently, other NF-GNB such as *Stenotrophomonas*, *Burkholderia*, *Chryseobacterium*, *Achromobacter*, and *Alcaligenes* species have been increasingly recognized as etiologic agents in both CAP and nosocomial infections [16, 17]. *S. pyogenes, Neisseria meningitidis*, and *Moraxella catarrhalis* also cause CAP less frequently. The incidence of CAP associated with the atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp. varies widely with patient age and geographic location. Viral pneumonias, most commonly influenza, parainfluenza, and adenoviral infections, are sources of CAP, which may cause severe pneumonias in the cancer setting.

The diagnosis of CAP is based on recovery of the likely pathogen from an otherwise sterile source (blood, urine, pleural fluid), isolation of a noncommensal organism in respiratory secretions, or positive results of selected serologic tests. Although the utility of Gram staining and culture of expectorated sputum in the diagnosis of pneumonia has been debated for years, carefully procured sputum specimens with cytologic confirmation of a lower respiratory source appear to be diagnostically useful, particularly if obtained before the initiation of antimicrobial therapy. Early and accurate diagnoses are critical to a successful outcome, although treatment should not be withheld while diagnostic interventions are undertaken. Antimicrobial selections are best based on knowledge of the infecting pathogen, if available, pneumonia severity, underlying immune status, and the presence of comorbid conditions [18, 19].

Hospital-Acquired Pneumonia. Lung infections that occur more than 48 h after hospital admission in patients without antecedent clinical symptoms or radiographic findings suggestive of pneumonia are referred to as HAP. HAP is a common complication in patients receiving treatment for cancer. Recently, the ATS and IDSA recognized HCAP as a distinct entity within the spectrum of HAP and ventilator-associated pneumonia (VAP) [20]. HCAP includes patients hospitalized in an acute care hospital for 2 or more days

within 90 days of the current infection, patients treated in a hospital or hemodialysis clinic within 30 days of the pneumonia diagnosis, nursing home, or long-term care facility residents, and recipients of intravenous antibiotics, chemotherapy, or wound care within 30 days of the current infection. HAP, HCAP, and VAP comprise the majority of pneumonias in the cancer setting. The spectrum of pathogens in HCAP closely resembles late-onset HAP and VAP, particularly among elderly patients [21]. Thus, guidelines for the management of HCAP generally overlap with HAP and VAP. In the nonimmunosuppressed solid-organ cancer patient, HAP is most often seen in the intensive care units (ICUs). In fact, admission to the ICU increases the risk of pneumonia in these patients by nearly 20-fold. As many as 80% of ICU-related HAPs occur among patients receiving ventilatory support and the effect of VAP in ICU length of stay, ventilator days, and hospital length of stay is well documented [22].

The etiologic spectrum of microbial pathogens causing HAP among low-risk solid-organ cancer patients with no recent antibiotic exposure is similar as that seen in the general population. *H. influenzae, S. pneumoniae, S. aureus*, and Enterobacteriacea are frequently encountered. MRSA may cause refractory HAP, especially among patients with prior community-acquired MRSA colonization, antibiotic exposure, advanced age, and/or prolonged ventilatory support. Protracted mechanical ventilation and recent antibiotic administration are also associated with increased rates of HAP caused by *P. aeruginosa, Acinetobacter baumannii*-complex, *Enterobacter* spp., and emerging strains of MDR NF-GNB such as *S. maltophilia, Burkholderia cepacia complex, and Alcaligenes (Achromobacter)* species, which may be difficult to treat. Mortality rates associated with HAP due to MRSA or *P. aeruginosa* are disproportionately higher than those caused by other nosocomial bacterial pathogens [22].

Severe neutropenia remains an independent predictor of HAP due to NF-GNB. Invasive fungal disease in the severely neutropenic patients with absolute neutrophil counts of <150 cells/L are difficult to treat with antimicrobial therapy alone. Aerosolized antifungals and immune stimulants may also be considered in this context.

Polymicrobial isolates and MDR pathogens are more common among patients with HAP, particularly when it occurs as a late complication during hospitalization. Because of the frequency with which multiple organisms are identified on a single respiratory sample, recent evidence-based guidelines advocate the use of quantitative or semiquantitative lower respiratory tract cultures obtained either bronchoscopically or noninvasively as part of the initial evaluation of the patients with suspected HAP, VAP, or HCAP [20].

Empiric antibiotic selections for HAP that develop within 7 days of admission should target *S. pneumoniae, S. aureus (including MRSA), Streptococcus* spp.*, H. influenzae,* and Enterobacteriaceae. Patients with late HAP (occurring >1 week

after hospitalization) should receive empiric antimicrobial therapy that includes coverage for MDR-GNB. The scope of alternative antimicrobial choices in patients with refractory or slow-to-respond hospital- and/or ventilator-acquired pneumonia (VAP) should be based on institution-dependent susceptibility profiles.

Pneumonias Caused by Aspiration and Bronchial Obstruction. Aspiration of orogastric contents and mechanical obstruction of the airways may create a favorable milieu for pneumonia caused by microaerophilic or anaerobic bacteria (e.g., *Peptostreptococcus* spp.). A variety of factors, such as abnormal swallow function, altered cough reflex, impaired mucociliary clearance, altered mental status, use of sedating medications, chemotherapy-induced mucositis, supine positioning, gastroparesis, mechanical ventilation, and nasogastric tube feeding all contribute to the increased predilection for aspiration in the cancer setting. Pneumonia associated with large-volume aspiration of gastric contents typically occurs as a late finding. The acidic gastric contents act as a poor medium for bacterial growth. Thus, the initial clinical syndrome following aspiration of gastric contents arises from the direct caustic effect of the acidic aspirate on the cells of the alveolar-capillary interface (i.e., chemical pneumonitis). Pneumonia due to superimposed bacterial infection, if it occurs, presents as a later finding. ARDS, respiratory failure, and death may rapidly follow. Aspiration of oral contents, by contrast, results from inhalation of nonsterile oropharyngeal material. The clinical presentation is often insidious and the diagnosis is commonly inferred based on a compatible patient risk profile coupled with radiographic evidence of pneumonia. Chest radiographs may show areas of geographic abnormalities that correlate with the patient's position at the time of aspiration. For example, aspiration that occurs while the patient is in the upright position typically localizes to the basilar segments of the lower lobes, whereas the superior segments of the lower lobes and posterior segments of the upper lobes are more frequently affected following aspiration that occurs in the supine position. The major pathogens underlying nosocomial versus community-acquired aspiration pneumonias differ, and in a substantial portion of patients, a microbiologic diagnosis may not be established due to the limited yield of conventional anaerobic cultures. If necessary, such cultures may be best obtained bronchoscopically using a protected specimen brush or other protected strategy.

The management of patients with significant lung injury associated with the aspiration of gastric contents includes aggressive supportive care. Upper airway suctioning, pulmonary toilet, and if necessary, positive pressure ventilation comprise the mainstays of therapy. There is no clearly established role for corticosteroids in this setting, though the practice of prescribing moderate- to high-dose prednisolone is not uncommon. Early and aggressive antimicrobial therapy

is recommended for patients with pneumonia secondary to aspiration of oropharyngeal contents. Antimicrobial selections should be tailored to the immune status of the patient and setting in which the aspiration occurred (community vs. nosocomial), but in general should be broad in spectrum and target Gram-negative organisms with or without anaerobic coverage. Anaerobic coverage should be considered for patients with periodontal disease, putrid sputum, or evidence of necrotizing pneumonia [23].

Solid tumors involving the lung may cause obstruction of the airways, atelectasis, and postobstructive pneumonia. Airway obstruction in this setting may be due to endobronchial tumor or an extraluminal mass that results in extrinsic compression of conducting airways. The associated pneumonias tend to be polymicrobial in nature (GNB, staphylococci, anaerobes) and may require relief of the obstruction to achieve adequate antimicrobial effects, even if appropriate antibiotics are selected. This is often most rapidly achieved through interventional bronchoscopic techniques such as tumor debulking by laser, electrocautery, or argon plasma coagulation with or without stent placement. Endobronchial brachytherapy or cryotherapy can be applied bronchoscopically as well, often with excellent results, but the time to effect is generally longer than with the formed strategies. Chemoradiation therapy can be similarly effective in relieving some obstructions, but the effect of these therapies is also delayed relative to bronchoscopic debulking.

Other Sources of Pneumonia. The lungs may also become infected via septic emboli arising from suppurative endovascular bacterial, and rarely, fungal infections. Infected intravascular septic deep venous thrombi are increasingly recognized as a potential source of infection in patients with cancer. The radiographic pattern in these patients is distinctive and includes multicentric, pleomorphic lung nodules, with asymmetric, relatively small, thick-walled cavities. In general, this appearance is distinct from the nonspecific infiltrates associated with hematogenous dissemination of distant site infections, as discussed previously.

Specific Pathogens

Nocardiosis. Nocardia asteroides complex, including *N. asteroids sensu stricto* and *N. farcinica*, accounts for nearly 90% of *Nocardia* infections, both in cancer patients and the general population. Risk factors for *Nocardia* pneumonia include profound deficiencies of cellular immunity, prolonged use of high-dose systemic corticosteroids, especially in the treatment of chronic lung diseases, [24] and the presence of GVHD. Although the latter two risk factors are often seen together (i.e., steroid treatment for GVHD), each appears to independently increase risk. Nodular pulmonary

infiltrates are common radiographic findings, although reticulonodular or diffuse infiltrates are occasionally described. Solitary nodules associated with irregular, thick-walled cavities that mimic invasive pulmonary aspergillosis, histoplasmosis, necrotizing cancer, or chronic bacterial lung abscess have also been reported (Figs. 12.2 and 12.3). Indolent *Nocardia* pneumonia is clinically indistinguishable from other actinomycetes infections and from pneumonias caused by pulmonary eumycetes infections. Severely immunosuppressed cancer patients with refractory leukemia or allogenenic hematopoetic stem cell transplant (HSCT) may

Fig. 12.2 Histoplasmosis in a patient with lung cancer
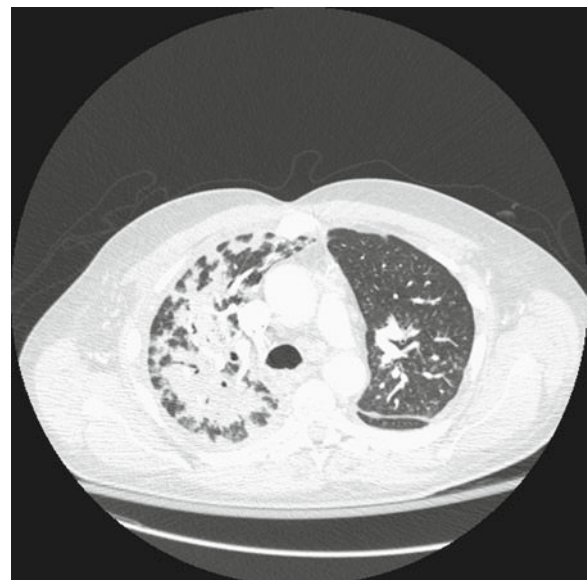
Fig. 12.3 *Nocardia abscessus* right lung infection in patient with lung cancer

present with pulmonary nocardiosis, a rapidly progressive, often multifocal form of *Norcardia*. Spontaneous pneumothorax and hemoptysis are widely reported presentations among immunocompromised patients (Fig. 12.3). Concomitant brain involvement is common, and preemptive evaluation is recommended to diagnose asymptomatic brain abscess in the setting of pulmonary disease. Trimethoprim-sulfamethoxazole (10–12 mg/kg daily) is effective against many *Nocardia* spp. Retrospective studies suggest improved outcomes when appropriate therapy is given for an extended period of time (6–12 months) [25]. Yet, despite antimicrobial therapy, pulmonary nocardiosis carries a high mortality in high-risk cancer patients [24]. Pulmonary actinomycosis typically presents in a very similar manner to nocardiasis, though sulfur granules are described more typically in samples from the former and infections classically cross tissue plans; pulmonary infection oftentimes involves the adjoining pleura and may erode through the chest wall. However, isolation of Actinomycetes from the respiratory tract should be evaluated critically, as in most patients their presence represents oropharyngeal contamination.

Tuberculous. *Mycobacterium tuberculous* is a rare cause of pulmonary infection in the developed world, but is still occasionally found in severely immunosuppressed cancer patients and in foreign-born individuals receiving cancer care in nonendemic regions of the world [26]. Patients with Hodgkin's disease and cancers of the head and neck, lung, and breast are considered at highest risk. Most pulmonary tuberculous infections in oncology centers in the United States are caused by reactivation of a remotely acquired latent infection. Pulmonary tuberculous may present as an insidious pneumonia that is difficult to distinguish from actinomycetes and eumycetes infection. Patients with impaired T-cell response may develop rapidly progressive tuberculous that follows a virulent bacterial infection. Systemic corticosteroid therapy is an independent predictor both of tuberculous reactivation and of a suboptimal response to combination antimicrobial therapy. Hence, once the diagnosis of tuberculous is established, every effort should be made to discontinue steroid therapy [26]. Just as observed in HIV-infected patients who initiate therapy with highly active antiretroviral therapy and demonstrate clinical worsening of their tuberculous pneumonia (i.e., immune reconstitution syndrome), tuberculous-related lung disease in cancer or stem cell transplant patients may infrequently worsen as patients' immune functions recover. Nonetheless, minimizing immune suppression is essential to clearing the mycobacteria.

Nontuberculous Mycobacteriosis (NTM). Pulmonary NTM is classically caused by *M. avium-intracellularae* complex and other slow-growing mycobacteria. These opportunistic pathogens can lead to chronic, indolent lung infections. In the United States, the rapidly growing mycobacteria (particularly *M. abscessus* and less frequently *M. fortuitum*, *M. smegmatis*,

and *M. goodii*) have emerged as less frequent causes of NTM infections. The diagnosis of pulmonary NTM remains a challenge as identification of these mycobacteria in respiratory culture samples may result from colonization of the respiratory tract or environmental contamination. Causality is suggested by identification of NTM in sterile lower respiratory tract samples coupled with nonspecific clinical features, such as chronic nonproductive cough and exertional dyspnea. The cough may occasionally become productive, indicating underlying bronchiectasis. Fever, night sweats, weight loss, pleuritic chest pain, and pleural effusions are seldom seen. Radiographic features include upper lobe predominant nonspecific nodular lesions and small, thin-walled cavities. Chest CT findings demonstrating the characteristic "tree-in-bud" appearance may also be seen in patients with chronic infection. The so-called Lady Windermere syndrome, characterized by relapsing or refractory pulmonary NTM due to slow-growing mycobacteria, may be seen in patients with defects in endogenous interferon-gamma activity [27]. NTM pulmonary infections are usually insidious, although rapidly progressive disease has been seen in patients with profound defects in helper T-cells. Treatment should include at least two antimicrobial agents to which the *Mycobacterium* is susceptible, including rifampin, and should be given for 12–24 months. *M. kansasii* is antigenically similar to *M. tuberculous* and causes lung disease that is clinically and radiographically indistinguishable from pulmonary tuberculous. Endemic areas for *M. kansasii* infections in the US include the urban Southeast and Midwestern States. Due to associated architectural derangements and possibly because of impaired phagocytosis by alveolar macrophages, pneumoconioses are well-established predisposing conditions for NTM infection. Prolonged therapy (12–24 months) with rifampin plus one or two other susceptible antimicrobials is recommended.

Pneumocystis. *P. jiroveci* infections are primarily seen in patients with marked CD4 lymphocytopenia [28]. In most cancer patients, *Pneumocystis* pneumonia presents as a slowly progressive infection accompanied by nonproductive cough, exertional dyspnea, and hypoxemia, although an acute, rapidly progressive form that rapidly progresses to respiratory failure has been reported. CT evidence of perihilar infiltrates may be mistaken for pneumonitis caused by common acquired viral infections (RSV, influenza, parainfluenza type 3) or CMV during the early phase of the infection. Bronchoalveolar lavage typically has a high diagnostic yield, though lung biopsy is occasionally needed, as cancer patients typically have lower fungal burden than do HIV-infected patients. High-dose trimethoprim-sulfamethoxazole given for 21 days is the treatment of choice. Adjuvant systemic corticosteroids should be administered to most patients with severe hypoxemia. Oral atovaquone and parenteral pentamidine may be given to patients who are intolerant to sulfa-containing regimens.

Invasive Pulmonary Mycosis. Invasive pulmonary aspergillosis is the most common fungal pneumonia in cancer patients. Risk factors for invasive pulmonary aspergillosis include prolonged (>1 week) and severe (<100 cells/µL) neutropenia, refractory leukemia, allogeneic HSCT, GVHD immunosuppressive therapy, and high-dose systemic corticosteroid therapy [29, 30]. *Aspergillus fumigatus* is most prominent in this group, although amphotericin B-resistant *A. terreus* has recently emerged as the second most frequent *Aspergillus* spp. in cancer patients [31]. The near-exponential rise in pulmonary invasive fungal infections due to non-*Aspergillus* molds such as *Fusarium, Pseudallescheria boydii, and Scedosporium* spp. and the dematiaceous (black) molds that are often not susceptible to conventional antifungal agents poses a serious challenge in the selection of effective empiric and preemptive therapy. Fever, cough, and dyspnea, when present, suggest lung infection. Hemoptysis is not uncommon chest imaging studies are frequently nonspecific, though CT scans may reveal a highly suggestive "halo sign" or "crescent sign." In most cases of pulmonary mycosis, the only radiographic findings at the time of presentation are peripheral, pleural-based lung nodules, sometimes with thick-walled regular or irregular cavities (Fig. 12.4) [32]. Alveolar hemorrhage may occasionally herald an invasive pulmonary fungal infection.

A decline in the incidence of endemic mycoses, such as pulmonary histoplasmosis, blastomycosis, and coccidioidomycosis, as well as *Cryptococcus neoformans* infections, has been reported. This has largely been attributed to effective prophylaxis with fluconazole in immunosuppressed cancer patients. The incidence of Zygomycosis, on the other hand, has increased in recent years. This is likely related to the increased utilization of the recently available antifungal agent, voriconazole, with a concomitant decline in the use of

amphotericin B. *Zygomycetes* organisms typically show a high level of susceptibility to amphotericin B. With the decreased utilization of this agent, rates of fungal infections at our institution caused by zygomycosis, invasive aspergillosis, and *Fusarium* species during the years 2002–2004 were 0.095/1,000, 0.302/1,000, and 0.073/1,000 patient-days, respectively [33].

The definitive diagnosis of pulmonary invasive fungal infection requires demonstration of fungal hyphae within the involved lung tissue. Therefore, the clinical diagnosis is often made by inference, as thrombocytopenia and coagulopathies often render biopsies unsafe. It is important to note that the isolation of molds in patients from peripheral or central venous blood samples may not indicate disseminated mycosis, even in severely immunosuppressed allogeneic HSCT recipients [34]. Similarly, isolation of fungi in respiratory samples may misrepresent the etiology of underlying pulmonary infiltrates. Therefore, the current consensus for invasive fungal infections diagnosis includes: (a) evaluation of host's predisposing factors such as prolonged granulocytopenia, high-risk HSCT, GVHD, immunosuppressive therapy; (b) clinical features (less often seen in cancer and stem cell transplant recipients); (c) radiographic features; and (d) isolation of pathogenic fungus from sterile respiratory sites. The measurement of fungal antigens such as serum galactomannan levels may be helpful in the detection of pulmonary mycosis. In a recent study of HSCT recipients, serum galactomannan levels were diagnostic in >85% of patients. The diagnostic utility of this test, however, was markedly compromised in the setting of antifungal therapy [35]. Newer diagnostic tests, including fungal DNA amplification in sterile samples, are currently under investigation and need clinical validation before routine use is recommended.
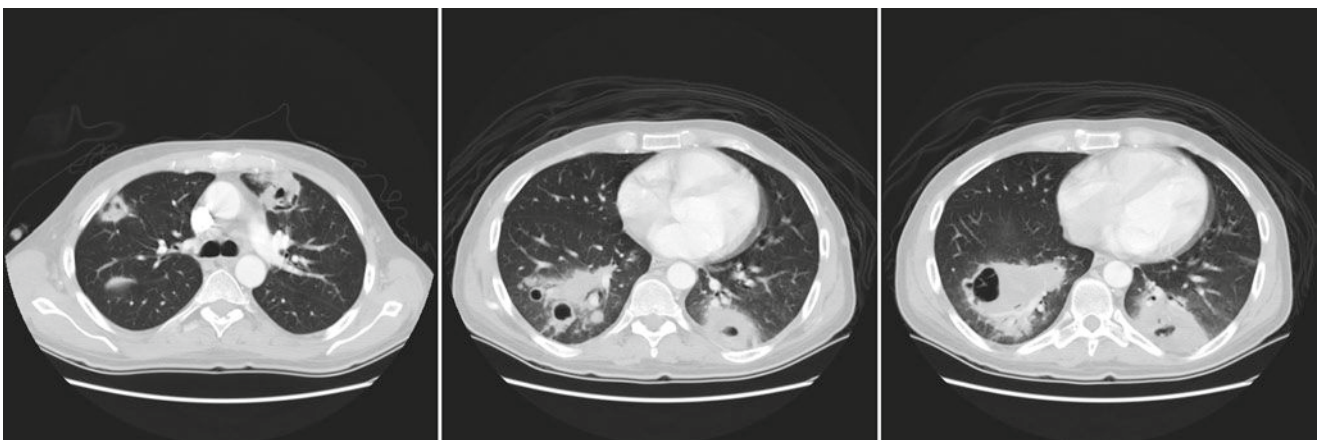
Fig. 12.4 Invasive *Aspergillus fumigatus* and *Rhizopus* multicentric cavitary pneumonia during graft-versus-host disease (GVHD) following donor lymphocyte infection in a patient with chronic lymphocytic leukemia and allogeneic hematopoietic stem cell transplantation; Postfungal pneumonia course was complicated by recurrent *Pseudomonas* and *Stenotrophomonas maltophilia* secondary lung infection

The treatment of pulmonary mycosis has improved considerably in the past ~10 years. The availability of voriconazole as primary therapy for invasive pulmonary aspergillosis [36] and caspofungin for salvage therapy of refractory invasive aspergillosis [37] is a promising addition to the antifungal armamentarium. Antifungal combinations may be prescribed for high-risk cancer patients and HSCT recipients with invasive mycosis. Due to the lack of prospective randomized trials, there is no consensus in recommending preferred antifungal combinations. A preliminary study using various antifungal combinations hinted modest superiority of caspofungin plus voriconazole in HSCT recipients with invasive fungal infections [38]. Reconstitution of the immune system, including recovery of severe granulocytopenia, remains the critical determinant in promoting resolution invasive fungal infections. Donor granulocyte transfusions and adjuvant recombinant T_H1 cytokines need prospective evaluation, although the results of preliminary observational studies among high-risk allogeneic HSCT recipients with disseminated mycosis appear promising [39].

Viruses. Human cytomegalovirus pneumonia is the most frequent cause of opportunistic viral complications in cancer patients with defective cellular immunity. Pulmonary Varicella-zoster virus and HHV-6 lung infections are difficult to distinguish from CMV pneumonitis. Seasonal respiratory viruses (RSV, Influenza A and B, Parainfluenza type 3, and Adenovirus) also cause serious lower respiratory tract infections in immunosuppressed cancer patients. Fever and nonproductive cough are prominent nonspecific features. In patients with extensive lung involvement, dyspnea may appear early in the course of infection. Viral antigen detection in nasal washes, tracheal aspirates, and bronchial specimens is most frequently used in determining active viral replication. Chest CT scans may show ground glass infiltrates, despite normal conventional chest radiographs. A normal chest CT scan in high-risk HSCT recipients with suspected viral pneumonitis excludes the possibility of infection in >95% of cases. The presence of CMV viremia is another helpful indicator in determining the etiology of a pulmonary process. The isolation of CMV antigen from lower respiratory tract secretions may not, however, necessarily indicate pulmonary infection, as patients with cellular immune defects may have intermittent low-level viral replication and shed virus without developing end-organ disease. Ganciclovir or foscarnet are commonly prescribed for systemic CMV and HHV-6 infections. Antiviral combinations with adjuvant immunoglobulin (IVIG) therapy are associated with variable results and presently not recommended for routine use. Human metapneumovirus (hMPV) has been recently recognized as a serious pulmonary pathogen. The spectrum of hMPV disease may range from mild upper respiratory tract infection to serious disseminated infection leading to respiratory failure and encephalitis. Ribavirin has been

used successfully and intravenous ribavirin may be considered for patients with life-threatening hMPV disease [40].

Miscellaneous. Pulmonary *T. gondii* and *L. monocytogenes* infections can lead to serious, often life-threatening, complications in patients with profound cellular immune dysfunction and disease characteristics are described in detail elsewhere [41, 42].

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Chapter 13
Noninfectious Lung Infiltrates That May Be Confused with Pneumonia in the Cancer Patient

Rana Kaplan, Lara Bashoura, Vickie R. Shannon, Burton F. Dickey, and Diane E. Stover

Abstract The clinical and radiographic presentation of noninfectious pulmonary disease can often mimic pneumonia in the cancer patient. This chapter provides an overview of some of the most commonly observed noninfectious entities which may be observed in the immunocompromised host with cancer. Hydrostatic and nonhydrostatic pulmonary edema, as well as transfusion-related acute lung injury, may cause bilateral airspace opacification that may be confused with an infectious process. Chemotherapy induced lung injury can occur with many classes of chemotherapeutic agents and requires a high index of clinical suspicion for diagnosis. It often results in distinct patterns of pathologic injury, which may present acutely, subacutely or chronically, and in some cases, up to years after initial administration of the chemotherapeutic agent. Radiation induced lung injury often causes a distinct pattern of radiographic abnormalities, which may occur many months after the initial radiation exposure. In hematopoietic stem cell transplant recipients, many pulmonary diagnoses, such as engraftment syndrome, idiopathic pneumonia syndrome and diffuse alveolar hemorrhage (occurring early) and cryptogenic organizing pneumonia (occurring late), can mimic infectious pneumonias. Small airway mucus impaction can present with tree-in-bud opacities on chest CT and mimics infectious bronchiolitis. It may resolve with only pulmonary hygiene maneuvers. A combined approach involving careful review of the patient's history, pattern of infiltrates on chest CT, and the use of bronchoscopy with bronchoalveolar lavage with or without transbronchial lung biopsy can often help provide clues to the noninfectious diagnosis.

Keywords Noninfectious • Lung infiltrates • Diffuse alveolar hemorrhage • Congestive heart failure • Drug toxicity • BOOP • Pulmonary alveolar proteinosis • Engraftment syndrome

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Introduction

Pneumonia is the leading cause of death from infection among cancer patients and second most common cause of death after uncontrolled cancer itself. Therefore, the prevention, diagnosis, and treatment of pneumonia are critical to outcomes among cancer patients. During the workup of a symptom or sign, such as cough, fever, or chills, abnormalities in imaging studies of the lungs are commonly detected. Consideration of the differential diagnosis of a lung infiltrate in a cancer patient includes both infectious and several common noninfectious causes. Failure to accurately diagnose noninfectious causes of lung infiltrates can lead to unnecessary treatment with antibiotics, and more importantly, failure to address the underlying pathophysiologic process. This chapter is focused on the many clinical presentations that mimic infectious pneumonia.

Hydrostatic Pulmonary Edema (Congestive Heart Failure)

Cardiogenic (hydrostatic) pulmonary edema is frequently observed in cancer patients, probably due to the high prevalence of cardiac disease in this relatively elderly population, the large volumes of fluid administered with chemotherapy and antibiotics, chemotherapy-induced cardiotoxicity, and comorbidities (e.g., renal insufficiency) [1]. The classic presentation of cardiogenic pulmonary edema, consisting of acute, bilateral, symmetrical, perihilar infiltrates, an enlarged heart, and pleural effusions (see Fig. 13.1) in a patient with peripheral edema and bibasilar rales is easy to recognize. However, cardiogenic pulmonary edema may also be the cause of asymmetrical infiltrates in a patient with underlying lung disease, such as bullous emphysema, which precludes alveolar filling in localized regions (see Fig. 13.2). An enlarged heart may not be present on the radiograph if cardiac dysfunction is not long-standing, so that the heart has not had time to remodel (e.g., acute volume overload, or diastolic dysfunction secondary to acute ischemia).
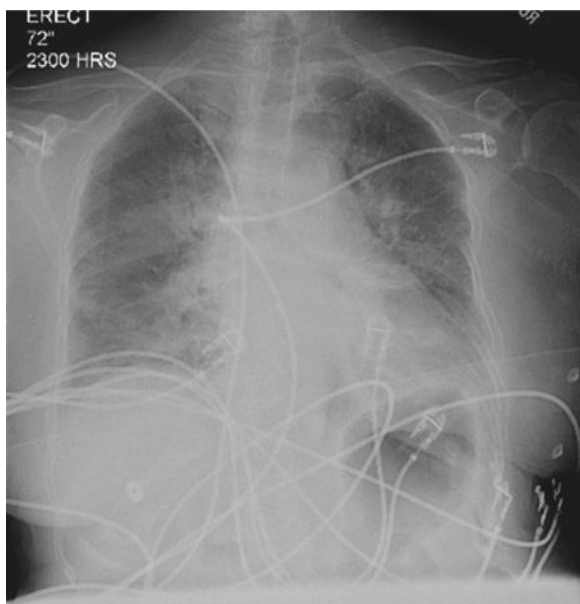
Fig. 13.1 Bilateral airspace opacities with a perihilar predominance and small bilateral pleural effusions are classic radiographic findings in *cardiogenic pulmonary edema*

Additional studies can be very helpful in establishing the diagnosis of cardiogenic pulmonary edema [2–4]. CT of the chest may show the diffuse nature of alveolar infiltrates and pleural effusions, less apparent on plain films, and may additionally reveal interstitial edema and cardiac chamber enlargement. Infiltrates may wax and wane in association with variations in patient weight, peripheral edema, or fluid administration. Echocardiography is very supportive when it reveals systolic dysfunction, but it is important to recognize that diastolic dysfunction is an equally prevalent cause of heart failure [5], potentially exacerbated by rhythm disturbances such as atrial fibrillation, valvular dysfunction, or transient ventricular wall stiffening due to ischemia. Brain natriuretic peptide (BNP) levels are quite specific and sensitive, but are less elevated in diastolic than in systolic dysfunction [5]. In the absence of heart failure, BNP levels can be elevated in patients with renal disease and obesity.

Nonhydrostatic Pulmonary Edema (Noncardiogenic Pulmonary Edema, Acute Lung Injury, and the Adult Respiratory Distress Syndrome)

Pulmonary edema due to increased permeability of the alveolo-capillary membrane can occur due to a wide variety of causes in cancer patients. Sepsis is the most common cause of permeability edema of the lungs in noncancer patients [6, 7] and can cause radiographic infiltrates in cancer patients. In addition, cancer patients are susceptible to lung injury

from causes unique to this population, such as from chemotherapy or the effects of hematopoietic stem cell transplantation. Cancer patients are also frequently exposed to treatments associated with lung injury in the general hospital population, such as transfusion. These causes of permeability edema are addressed individually within the following sections.

Chemotherapy-Induced Lung Injury

Chemotherapy-induced lung injury (CILI) has been documented following administration of all categories of chemotherapeutic agents, including the newer molecular-targeted therapies. Lung toxicity from cancer chemotherapy results in a limited number of stereotypic histopathologic lung injury patterns that may involve the lung parenchyma, conducting airways, pleura, or pulmonary circulation (see Table 13.1 for types of chemotherapy-induced lung injury and associated chemotherapeutic agents).

Diagnoses that mimic CILI, such as pneumonia and cancer relapse, pose challenges for both pulmonary and infectious disease practitioners. There are no pathognomonic abnormalities for the diagnosis of CILI. A high index of suspicion, coupled with knowledge of risk factors, clinical presentation, radiologic manifestations, and histologic patterns is critical for early diagnosis and successful outcomes. The diagnosis is largely based on the association between drug exposure and the development of pulmonary illness, although, in some cases, lung injury can occur many years after the drug is discontinued. Chemotherapeutic agents, such as the nitrosoureas, for example, can cause pulmonary fibrosis up to 20 years after completion of therapy [8]. Evidence of rapid clinical and radiologic improvement following drug withdrawal supports the diagnosis; however, lung injury can progress despite withdrawal of certain drugs, such as bleomycin, busulfan, and BCNU.

CILI can present acutely, subacutely, or chronically and can be idiosyncratic, i.e., unrelated to dose or duration of therapy. Of the types of injury which could mimic infection, noncardiogenic pulmonary edema (NCPE), hypersensitivity pneumonitis (HP), and organizing pneumonia (OP) generally represent subacute processes that can occur days to weeks following drug administration. Chronic manifestations of drug toxicity, such as interstitial pneumonitis (i.e., nonspecific interstitial pneumonitis, or NSIP) and fibrosis (i.e., usual interstitial pneumonitis, or UIP), evolve insidiously over weeks to months and up to years after exposure (see Figs. 13.3a, b and 13.4a, b). The clinician should also be aware of drug synergisms causing diffuse alveolar damage (DAD)/NCPE following bleomycin/oxygen, gemcitabine/taxane, and vinca alkaloid/mitomycin combinations [9–11].

Low-grade fever, dyspnea, and nonproductive cough are the usual symptoms of subacute and chronic forms of drug
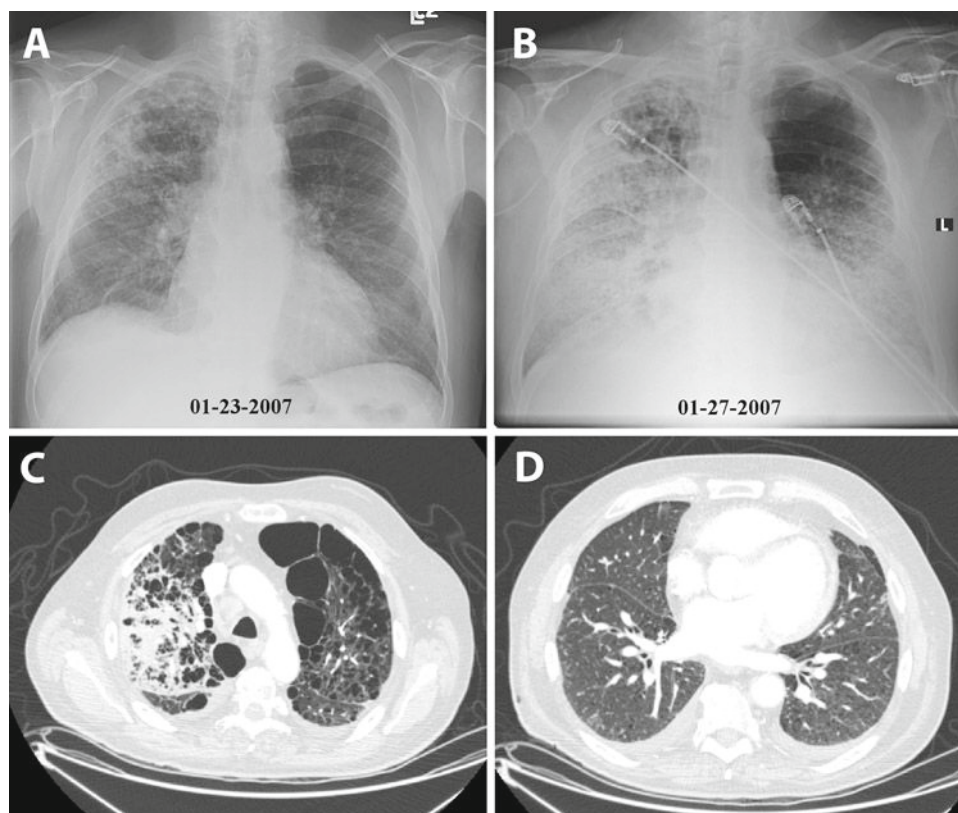
Fig. 13.2 *Atypical radiographic presentation of congestive heart failure.* A 68 year old male was receiving radiation therapy to a squamous cell carcinoma of the upper lobe of the right lung, because he was not felt to be a surgical candidate due to comorbidities, including coronary artery disease. He had received 19 of 37 planned fractions, when he was admitted because of increasing shortness of breath and cough thought to be due to pneumonia. (**A**) The PA radiograph on the upper left, taken one day prior to admission, shows the right upper lobe tumor with associated radiation pneumonitis. (**B**) The AP radiograph on the upper right, taken four days later, shows lung infiltrates that spare the left upper lobe. (**C**) However, CT angiogram on the lower panels, performed the day of admission, 01-24-2007, shows that the left upper chest is mostly occupied by emphysematous bullae, accounting for the sparing of the left upper lung field when pulmonary edema developed. (**D**) The remainder of the lung fields contain ground glass opacities, suggestive of *congestive heart failure*. The diagnosis of congestive heart failure was supported by the patient's history of prior episodes of pulmonary edema, bilateral 1+ ankle edema, a depressed left ventricular ejection fraction of 30–35%, moderate mitral regurgitation, elevated BNP of 1,043, transudative pleural effusion and improvement with diuresis

toxicity. Intractable respiratory impairment leading to respiratory failure and death may occur as the disease progresses.

Although radiographic changes in CILI are nonspecific, certain patterns are seen [12, 13]. Interstitial and mixed alveolar/interstitial abnormalities are commonly localized to the periphery of the lower lung zones and are the most frequent radiographic findings on chest CT in patients with chemotherapy-induced NSIP and UIP. DAD can present with pulmonary edema-like radiographs (see Fig. 13.5a), and OP often shows airspace consolidation mimicking bacterial pneumonia. Upper lobe predominate disease is characteristic of drug-induced hypersensitivity reactions (see Fig. 13.6a). CT scans and, occasionally, FDG-PET and gallium imaging may show abnormalities before chest radiographic changes and, in some cases, may precede clinical symptoms [14, 15].

Restrictive physiology and reduction in the diffusing capacity are commonly observed on lung function testing in CILI, with the latter often predating the onset of symptoms.

Histopathologic changes in CILI include endothelial swelling with exudation of fluid into the interstitium and intra-alveolar spaces. There is destruction of type I pneumocytes with proliferation of type II pneumocytes, which may appear large and "bizarre". Hyaline membranes may be seen in DAD (see Fig. 13.5b). Loosely formed granulomas are found in up to one third of lung biopsies in patients with methotrexate-induced lung injury, which is felt to represent a hypersensitivity reaction (see Fig. 13.6b).

Bronchoalveolar lavage (BAL) helps to exclude alternative pathologic processes, such as infection or malignancy [16]. A lymphocyte predominant alveolitis is most commonly observed in CILI. Transbronchial biopsy has limited utility in the diagnosis of CILI due to the inherent difficulty in extrapolating histopathologic patterns of lung involvement from small

Table 13.1 Types of chemotherapy-induced lung injury and some associated chemotherapeutic agents

LUNG INJURY	DRUG
UIP	bleomycin, busulfan, BCNU, melphalan, cyclophosphamide
NSIP	bleomycin, gemcitabine, mitomycin, docetaxel, dasatinib, nitrosureas
HP⁺	methotrexate, bleomycin, paclitaxel
OP⁺	bleomycin, interferon α or β*
DAD⁺	gefitinib, gemcitabine, cyclophosphamide
NCPE⁺	gemcitabine, cyclophosphamide, bleomycin, cytosine, arabinoside, docetaxel, fludarabine, mitomycin, vinca alkaloids, retinoic acid, methotrexate
LESS COMMON	
Diffuse alveolar hemorrhage	cytosine arabinoside, gemcitabine, mitomycin, retinoic acid, etoposide
Vascular changes	
Pulmonary hypertension	interferon α, mitomycin
Pulmonary veno-occlusive disease	bleomycin, busulfan, nitrosureas
Pleural effusion	dasatinib, docetaxel, methotrexate, busulfan
Pneumothorax	bleomycin, BCNU, retinoic acid
Mediastinal lymphadenopathy	methotrexate, bleomycin, interferon β
Bronchospasm	etoposide, interferon α and β, paclitaxel, vinca alkaloids

UIP = usual interstitial pneumonitis; **NSIP** = non-specific interstitial pneumonitis; **HP** = hypersensitivity pneumonitis; **OP** = organizing pneumonia; **DAD** = diffuse alveolar damage; **NCPE** = non-cardiogenic pulmonary edema

⁺In reporting histopathologic changes, there may be overlap between HP/EP, OP/EP and DAD/NCPE

*These cytokines have also been associated with granulomatous changes resembling sarcoidosis
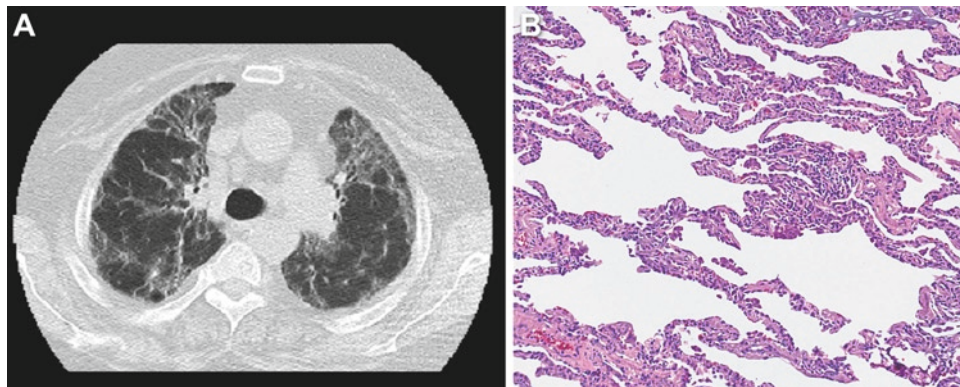
Fig. 13.3 *Pulmonary fibrosis* in a patient with a history of docetaxel use. (**A**) CT chest demonstrates a pattern of bilateral, symmetric, reticular infiltrates and ground glass opacities associated with traction bronchiectasis. (**B**) Histologic examination reveals *non-specific interstitial pneumonitis* (NSIP), characterized by uniform interstitial involvement of chronic inflammation, consisting mostly of lymphocytes and plasma cells, causing thickening of the alveolar walls

tissue samples and the lack of pathognomonic findings. Additionally, thrombocytopenia in the cancer treatment setting often precludes bronchoscopic biopsies. When safe, it should be performed along with BAL to help eliminate other diagnoses, such as infection or malignancy. Surgical lung biopsy should be considered, when fungal infection is an alternative diagnosis or when there is discordance between bronchoscopic biopsy and/or clinical or radiologic findings.

If pulmonary toxicity occurs, withdrawal of the offending agent is the mainstay of treatment. Although no controlled trials have explored the efficacy of corticosteroid therapy, a trial of systemic corticosteroid therapy is usually initiated in most cases. The optimal dose and duration of therapy are unknown; however, treatment with 1 mg/kg of prednisone daily is usually given, with a slow taper, as recurrence of symptoms has been reported in the setting of tapering. Given the increased incidence of *Pneumocystis jiroveci* pneumonia observed in non-HIV individuals with both hematologic malignancies and solid tumors on steroid therapy [17, 18], it is the authors' practice to routinely prescribe prophylactic trimethoprim–sulfamethoxazole
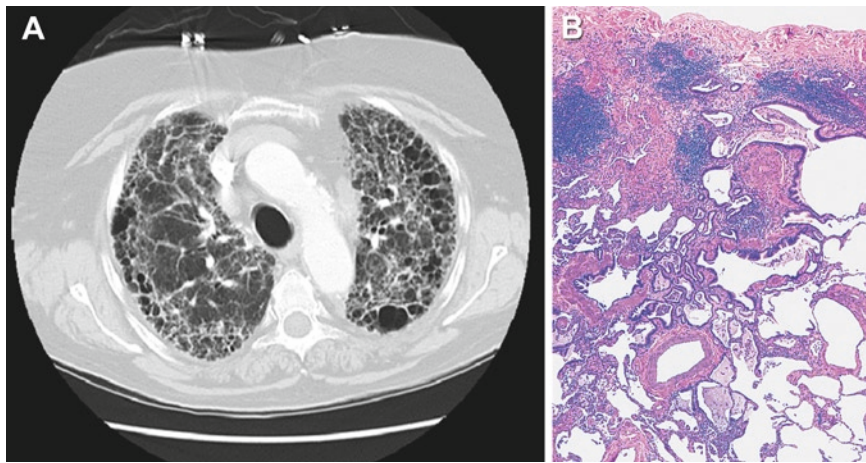
Fig. 13.4 *Idiopathic pulmonary fibrosis* (IPF). (**A**) Reticular infiltrates, associated with honeycombing and traction bronchiectasis in a basilar and peripheral predominance, are characteristic findings seen in CT imaging of IPF. (**B**) The histopathologic correlate of IPF is *usual interstitial pneumonia*, which is characterized by patchy, temporally heterogeneous subpleural fibrosis with honeycombing and the presence of fibroblastic foci
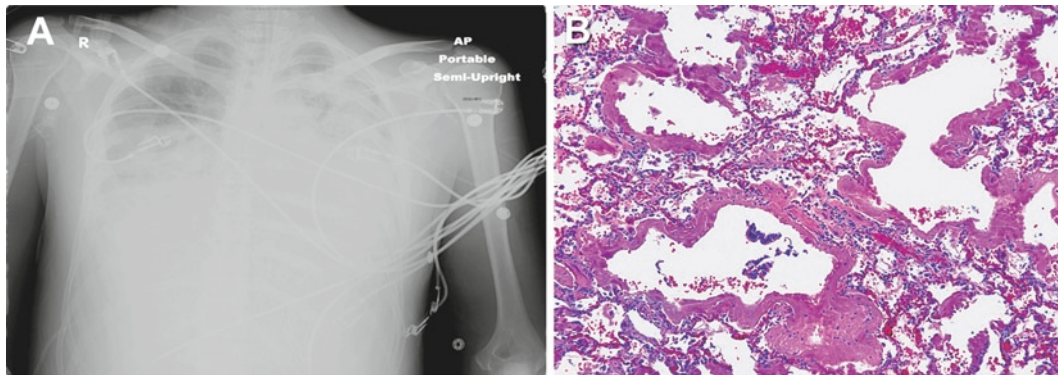
Fig. 13.5 *Diffuse alveolar damage*. (**A**) The chest radiograph demonstrates bilateral airspace opacities, characteristic of diffuse alveolar damage. (**B**) *Hyaline membranes* lining alveolar ducts are key features of acute diffuse alveolar damage on histopathologic examination; interstitial and alveolar edema may also be seen
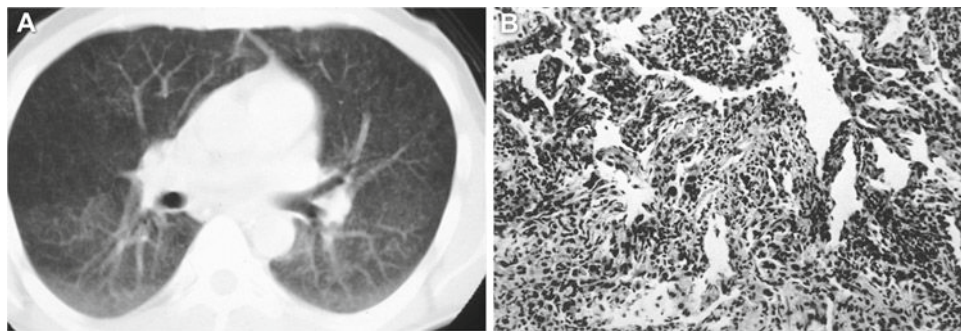
Fig. 13.6 (**A**) CT chest findings in a patient with methotrexate-induced *hypersensitivity pneumonitis*. High resolution CT chest reveals poorly defined centrilobular nodules and diffuse ground glass attenuation. (**B**) Methotrexate can cause loosely formed non-necrotizing granulomas in a background of cellular interstitial inflammation

in conjunction with the high-dose steroid therapy. Reports exist of a negative rechallenge (i.e., no subsequent recurrence of pulmonary toxicity) with some chemotherapeutic agents, such as cyclophosphamide and methotrexate; rechallenging patients with drugs previously implicated in CILI is not recommended.

Radiation-Induced Lung Injury

The incidence and severity of radiation damage to the lungs are related principally to the volume of lung tissue irradiated, the total dose of radiation, the fraction into which the total dose is divided, and the quality of the radiation. Damage to the lung increases as the volume of the irradiated lung increases, and there is a threshold effect, such that irradiation of at least 10% of the lung is required to produce significant pulmonary toxicity. Radiation pneumonitis seldom occurs with fractionated doses of <20 Gy, but it is likely when doses exceed 60 Gy. The greater the number of fractions in which the radiation is given, the lower the damaging effect from the radiation. Certain chemotherapeutic agents, such as bleomycin and doxorubicin, are known to potentiate the damaging effects of radiation to the lung, especially when they are administered concomitantly.

Symptoms of acute radiation pneumonitis usually are seen 1½–3 months after the completion of radiation therapy [19]. The early onset of symptoms portends a more serious and protracted clinical course. Dyspnea is the more common symptom, followed by cough, which may be either nonproductive or productive of small amounts of pink sputum. Frank hemoptysis is rare early in the clinical course, though massive hemoptysis has been noted to occur as a late complication of pulmonary irradiation. Fever, if present, is usually low grade and transient.

The diagnosis of radiation pneumonitis can be made clinically on the basis of the timing of the onset of symptoms with the irradiation and the detection of typical radiographic abnormalities [20]. Early abnormalities include ground glass infiltrates, diffuse haziness, or indistinct pulmonary markings over the irradiated area. In both radiation pneumonitis and fibrosis, the abnormalities usually conform to the outlines of the field of radiation and may not adhere to anatomic borders (see Fig. 13.7). In "out of field" radiation pneumonitis, a rare complication thought to represent a hypersensitivity response, extensive radiographic changes are seen outside the radiation field, including the contralateral lung. Radiation-related bronchiolitis obliterans organizing pneumonia (BOOP) is a recently reported complication, seen predominantly in breast cancer patients. The infiltrates generally appear within an 18-month period from the time of radiation treatment, are always seen outside the irradiated lung (see Fig. 13.8), and can be bilateral [21, 22].

Carbon monoxide diffusing capacity is the parameter most predictive of impaired pulmonary function following
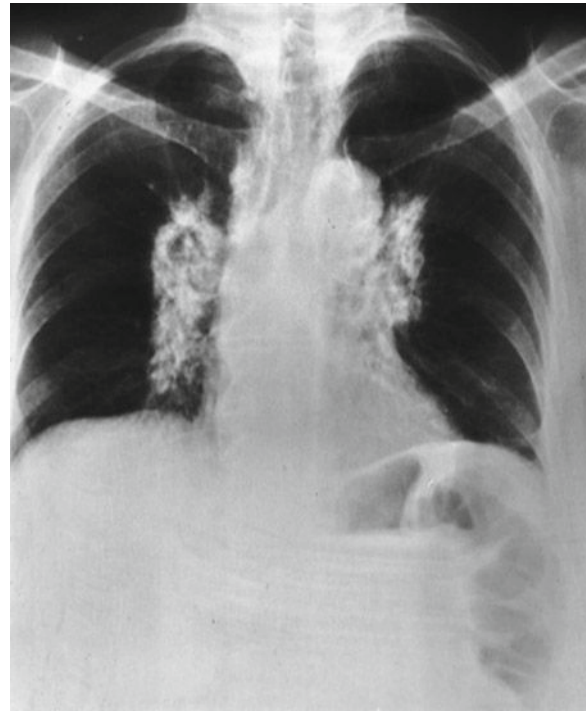
Fig. 13.7 Radiographic findings consistent with *radiation-induced pulmonary fibrosis* in a patient treated with mantle radiation for Hodgkin's lymphoma. Fibrosis and bronchiectasis are observed in a linear, geographic distribution corresponding to the field of radiation

Fig. 13.8 *Radiation-induced BOOP*. CT chest findings characteristically show the location of these infiltrates outside of the portal of radiation, which, in this patient, was on the right chest wall

radiation therapy and may prognosticate a higher risk of ongoing pulmonary damage [23].

The histopathologic changes of radiation-induced pulmonary injury are not specific; vascular congestion, fibrin-rich exudate within alveoli, hyaline membranes, and hyperplasia of type II pneumocytes, with infiltration of fibroblasts and mast cells may be seen [24].

Although no controlled human clinical trials exist on the efficacy of steroid therapy, corticosteroids have resulted in an improvement in symptoms [25]. Common practice is to begin prednisone 1 mg/kg daily, in conjunction with trimethoprim–sulfamethoxazole for *Pneumocystis* prophylaxis, as soon as the diagnosis of symptomatic radiation pneumonitis is reasonably certain. The initial dose is maintained for several weeks and then reduced cautiously, based on symptom control. If steroids are tapered too rapidly, symptoms can be exacerbated, necessitating higher doses for longer periods. Most authors agree that steroids do not have a role in treatment in radiation-induced pulmonary fibrosis.

The clinical, histologic characteristics and response to steroids in radiation-induced BOOP are similar to that of cryptogenic organizing pneumonia (COP). A high relapse rate is seen with steroid tapers, and macrolides have been used with success in patients who are either intolerant to steroid therapy or in whom relapse of BOOP occurs with steroid taper [26].

Noninfectious Complications of Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is widely used in cancer therapy and is the only curative option for many patients with relapsed and high-risk malignancies. Despite advances in treatment regimens and supportive care, pulmonary complications still occur in up to 60% of HSCT recipients, accounting for significant morbidity and mortality [27]. Pulmonary complications are conveniently divided into those that occur "early" (during the first 100 days after transplantation) and those that occur "late" (see Table 13.2). These complications are mostly due to direct toxicities from conditioning regimens, delayed bone marrow recovery, prolonged immunosuppressive therapy, and graft-versus-host disease (GVHD). As the incidence of infectious pulmonary complications diminishing, largely due to effective prophylactic therapy, noninfectious pulmonary complications are emerging as a major cause of post-HSCT morbidity and mortality [28]. This section focuses on these noninfectious pulmonary complications and the many clinical presentations that often mimic infections.

Early-Onset Noninfectious Complications of HSCT

Pulmonary edema. Cardiogenic pulmonary edema is one of the most common early complications after HSCT. Common etiologies include cardiac dysfunction and/or an increase in hydrostatic capillary pressure, often from administration of large volumes of fluid. The clinical and radiographic manifestations are similar to those outlined in the section on hydrostatic pulmonary edema.

Engraftment syndrome. Engraftment syndrome (ES) is characterized by a constellation of symptoms and signs including fever, erythrodermatous skin rash, diarrhea, and NCPE with bilateral pulmonary infiltrates, which generally occur within 5 days of neutrophil engraftment following HSCT. In more severe cases, systemic involvement, i.e., renal failure, hepatic failure, encephalopathy, or seizures, may be observed. Seen most often following autologous HSCT, ES has also been described in those individuals who have undergone allogeneic HSCT with a nonmyeloablative preparative therapy. The pathophysiology of ES is not well understood. It is thought to result from endothelial injury, the production of cytokines and neutrophil degranulation, leading to capillary leak [29]. BAL may show a neutrophilic alveolitis. Surgical lung biopsies, when obtained, often reveal DAD. Treatment entails observation and supportive care (i.e., antibiotics, intravenous fluids) in mild cases. High-dose corticosteroid therapy is very effective, often resulting in rapid clinical improvement in those with progressive or symptomatic ES. Respiratory failure requiring mechanical ventilation has been observed, in up to one third of patients [30].

Idiopathic pneumonia syndrome (*IPS*). In 1993, a panel convened by the NIH proposed a broad working definition of IPS as widespread nonlobar radiographic infiltrates in the absence of congestive heart failure or evidence of lower respiratory tract infection [31]. IPS occurs in 10% of HSCT recipients, usually 14–90 days following transplantation. Mortality rates range from 50–70% [32]. Possible etiologies of IPS include direct toxic effects of the chemoradiation conditioning regimen, occult infection, and/or the release of inflammatory cytokines, secondary to some as yet unknown inciting stimuli. The association of IPS with the presence of

Table 13.2 Pulmonary complications following hematopoietic stem cell transplantation

Early (<100 days)	Late (>100 days)
Infectious pneumonia (e.g., bacterial, fungal)	Infectious pneumonia (e.g., viral, fungal, mycobacterial, bacterial)
Pulmonary edema	
Engraftment syndrome	Cryptogenic organizing pneumonia
Idiopathic pneumonia syndrome/Diffuse alveolar hemorrhage	Post-transplant lymphoproliferative disorder
Pulmonary veno-occlusive disease	Delayed pulmonary toxicity syndrome
Pulmonary alveolar proteinosis	Post-transplantation constrictive bronchiolitis

acute GVHD after allogeneic HSCT suggests that alloreactive T cells may be at least one of these stimuli [32].

The clinical presentation is nonspecific, with symptoms of dyspnea, cough, and fever associated with diffuse infiltrates on chest radiograph. The diagnosis of IPS largely relies on the exclusion of infection on lower respiratory samples obtained from a diagnostic procedure, e.g., BAL or lung biopsy. Common pathologic findings of NSIP and/or DAD may be seen. Although no randomized controlled trials of treatment for IPS are available, current standards include high-dose intravenous corticosteroids and supportive care, such as supplemental oxygen and broad-spectrum antibiotics. Recent data suggest a potential role for tumor necrosis factor-α (TNF-α) in the pathogenesis of IPS and there are ongoing clinical studies involving etanercept [33–36].

Diffuse alveolar hemorrhage (*DAH*). Posttransplantation DAH was initially described in autologous HSCT recipients as widespread lung injury manifested by diffuse radiographic infiltrates that occurred in the absence of identifiable infection [37]. DAH is now known to occur in both allogeneic and autologous transplant recipients and is seen in approximately 5% of all HSCT [38]. The etiology is unclear, but is not related to any specific coagulopathy or to thrombocytopenia [39]. Pretransplant high-dose chemotherapy, thoracic and/or total body irradiation, and undocumented infections are putative factors which may cause the initial injury, priming the lung for subsequent development of DAH. It can coincide with stem cell engraftment, but late onset (after the first 30 days) has been observed and is associated with a worse prognosis.

Symptoms include dyspnea, cough, and fever, with hemoptysis occurring in less than 20% of patients. Chest radiographs usually show diffuse alveolar and interstitial infiltrates in a central distribution. Bronchoscopic diagnostic criteria include progressively bloodier returns on BAL or the presence of 20% or more hemosiderin-laden macrophages on cytologic inspection of BAL fluid. However, these bronchoscopic criteria may be seen in association with diffuse lung injury from a wide variety of causes, including infections, congestive heart failure, and malignancy, often making a definitive diagnosis problematic. There are no prospective randomized trials addressing the treatment of DAH. Earlier retrospective studies demonstrated reduced need for mechanical ventilation and mortality in a cohort of patients receiving high-dose methylprednisolone. Although more recent observational studies found no survival benefit to high-dose corticosteroids [40, 41], they are routinely used in HSCT recipients with DAH.

Pulmonary veno-occlusive disease (*PVOD*). PVOD is a very rare complication of HSCT in which progressive occlusion of pulmonary veins and venules caused by intimal proliferation and fibrosis leads to pulmonary arterial hypertension (PAH) [42]. High-dose chemotherapy and infections are implicated as causes of PVOD. The onset is typically insidious, with progressive dyspnea and fatigue occurring 6–8 weeks after transplant [43]. Radiographic manifestations of PVOD include Kerley B lines, septal thickening, and poorly defined centrilobular ground glass opacities on CT scans. Right heart catheterization will reveal an elevated mean pulmonary artery pressure, but normal or low pulmonary capillary wedge pressure. The diagnosis of PAH secondary to PVOD is primarily one of exclusion and should be suspected in the HSCT patient, once alternative etiologies for PAH have been excluded; a definitive diagnosis is rendered only by surgical lung biopsy. No definitive treatment aside from lung transplantation is available for this condition. Some patients do tolerate arterial vasodilators, but fatal pulmonary edema has been described with the use of arterial vasodilators [44]. Although data from randomized, controlled trials for pharmacologic treatment of PAH secondary to PVOD do not exist, there are case reports documenting improvement in exercise capacity, dyspnea score, and hemodynamics in patients receiving treatment with either sildenafil alone, or sildenafil in conjunction with high-dose intravenous epoprostenol [45, 46].

Pulmonary alveolar proteinosis (*PAP*). PAP is another rare complication that may occur within the first 3 months after HSCT [47, 48]. Patients typically present with slowly progressive dyspnea and a nonproductive cough. Bilateral diffuse alveolar densities and diffuse ground glass attenuation with superimposed interlobular septal thickening and intralobular lines suggesting a "crazy paving" pattern on chest CT are nonspecific, but supportive, radiographic findings (see Fig. 13.9a). Bronchoscopic examination demonstrates copious, milky BAL effluent, which on cytologic examination contains foamy macrophages engorged with periodic acid-Schiff-positive intracellular inclusions and granular, acellular eosinophilic proteinaceous material (see Fig. 13.9b). Concentrically laminated phospholipid lamellar bodies may be seen on electron microscopy, which is occasionally necessary to confirm the diagnosis. Spontaneous reversal of PAP has been described after the resolution of neutropenia or an associated infection, when present. In patients with severe dyspnea and/or significant hypoxemia, whole lung lavage has been an effective form of treatment [49]. Preliminary data suggest that GM-CSF administered either subcutaneously or via nebulization improves lung function in some patients [50]. There is no role for corticosteroids, since they may increase mortality.

Late-Onset Noninfectious Complications of HSCT

Cryptogenic organizing pneumonitis (*COP*) [formerly, bronchiolitis obliterans organizing pneumonia (BOOP)]. COP occurs mostly in allogeneic HSCT recipients with GVHD or following CMV pneumonitis [51], with an onset usually between 1 and 13 months after transplantation. It is less common
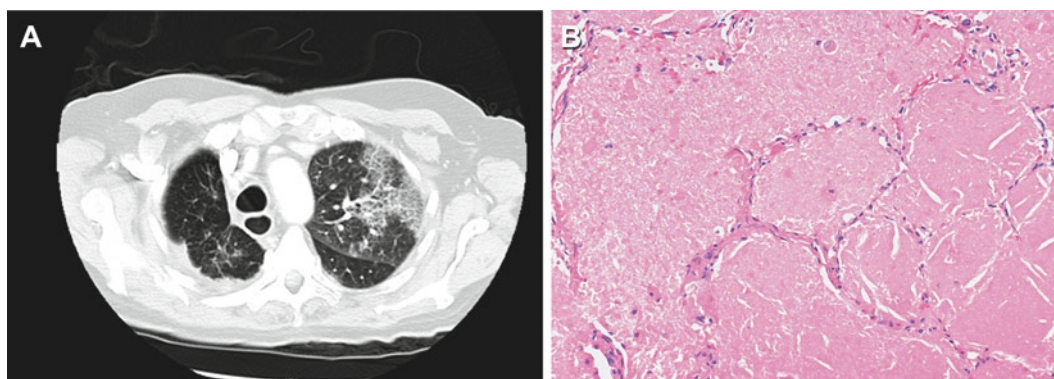
Fig. 13.9 *Pulmonary alveolar proteinosis* (PAP) in a patient with chronic myeloid leukemia. (**A**) CT chest demonstrates a "crazy paving" pattern, with a network of smoothly thickened reticular (i.e., septal) lines superimposed on ground glass opacities. (**B**) Histopathologic findings in PAP include the filling of alveolar spaces with eosinophilic proteinaceous material, which may stain periodic acid-Schiff-positive
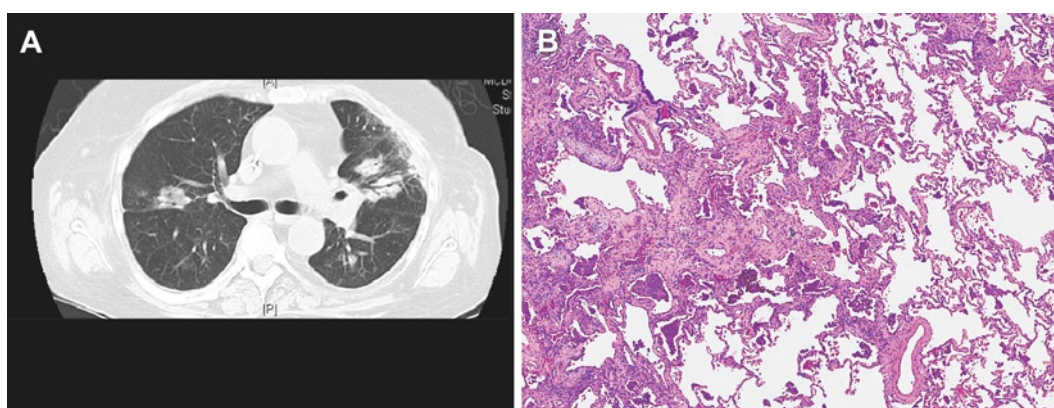
Fig. 13.10 *Organizing pneumonia* in a patient with a history of chronically waxing and waning pulmonary infiltrates. (**A**) Patchy airspace consolidation with air bronchograms, often in a subpleural location, is a characteristic radiographic presentation for organizing pneumonia. (**B**) On histopathologic examination, granulation tissue can be seen within the lumen of the distal air spaces, swirling into alveoli, associated with chronic inflammation in the surrounding alveoli

than posttransplantation constrictive bronchiolitis (PTCB) and should not be confused with it. Cough and fever are the most common symptoms on presentation; dyspnea, if present, is mild, and in some cases, patients are asymptomatic [52]. COP usually presents with patchy bilateral alveolar opacities which can be migratory on chest radiograph. The opacities have a lower lobe predominance and are peripheral in location. They may appear as ground glass opacities or consolidation with air bronchograms on high-resolution CT scans (see Fig. 13.10a). Occasionally, COP can present radiographically as a solitary nodule or mass mimicking a neoplasm or chronic nonresolving pneumonia. In one retrospective study of 43 cancer patients, 81% of patients with solid organ tumors had nodular or mass-like radiographic abnormalities and 19% presented with diffuse infiltrates [53]. In the same study, diffuse infiltrates were seen in the majority of patients with hematologic malignancies, including HSCT, and mimicked infection and drug-induced toxicity.

Pathologically, COP is characterized by the presence of granulation tissue within the lumen of the distal air spaces with or without bronchoalveolar involvement (see Fig. 13.10b).

This pathologic picture can be seen with multiple other accompanying diagnoses, such as congestive heart failure, infections, and drug-induced toxicity; hence, in the HSCT recipient, other diagnoses should be excluded before a diagnosis of COP is made.

COP is highly responsive to corticosteroids. The minimal effective dose and duration of therapy are unknown; however, a prolonged steroid course with a slow taper is usually necessary due to high relapse rates. Macrolides have been used with success in some cases and might be considered in those individuals who are intolerant to steroid therapy or in whom relapse occurs [54]. Although the specific mechanism of action is not known, macrolides are thought to exert their beneficial effects through anti-inflammatory rather than antimicrobial activities.

Posttransplantation constrictive bronchiolitis (*PTCB*). PTCB is the most common pulmonary complication among long-term survivors of HSCT and is considered a manifestation of chronic GVHD. Contrary to COP, PTCB patients present with dyspnea without significant infiltrates on chest radiograph. While chest

CT imaging may show a mosaic pattern, it is often unremarkable even with advanced disease, presumably due to the uniformity of small airway obstruction. Since this disorder is not likely to be confused with pneumonia, it is not further considered here.

Posttransplantation lymphoproliferative disorder (*PTLD*). PTLD is an uncontrolled expansion of donor-derived EBV-infected B lymphocytes which develops in response to inadequate cytotoxic T-cell function [27, 55]. It occurs in approximately 1% of HSCT patients, usually within the first 4–12 months after transplant. The clinical constellation may include fever, lymphadenopathy, pharyngitis, hepatosplenomegaly, and neurologic symptoms. There appears to be a greater incidence of fulminant, disseminated PTLD in HSCT recipients as compared to solid organ transplant recipients, possibly accounting for the increased mortality associated with PTLD in this population [56]. The lung is involved only 20% of the time, usually as a component of disseminated disease, most commonly with ill-defined nodular infiltrates. It can also present as well-defined nodules, surrounded by a rim of ground glass density (halo sign), mimicking the features of invasive aspergillosis. Hilar and mediastinal adenopathy, and pleural effusions may also be seen. PTLD may be treated with anti-B-cell antibody therapy; rituximab (human–mouse chimeric monoclonal anti-CD20 antibody) is used for this purpose, with favorable response profiles and acceptable toxicity rates [57]. It has also been successfully treated with chemotherapy, as well as donor leukocytes.

Delayed pulmonary toxicity syndrome. This syndrome has been described in breast cancer patients undergoing autologous HSCT. Patients usually present around 10 weeks following transplantation with dry cough, dyspnea, and fever [58]. It is characterized by interstitial pneumonitis and fibrosis and is thought to be due to the toxic effects of high-dose chemotherapy, including cyclophosphamide, cisplatin, and BCNU. Pulmonary function testing reveals restrictive lung disease and a reduction in diffusing capacity. These patients respond favorably to steroid therapy, and the mortality rate is low.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is defined as NCPE related to the transfusion of blood products. It is the leading cause of mortality from transfusions [59] and has been associated with all plasma-containing blood products, including immunoglobulins. The true incidence of TRALI is not known, but has been estimated at 0.02% per unit transfused and 0.16% per patient transfused [60]. Patients with TRALI commonly present with dyspnea, cough, fever, acute hypoxemia, and hypotension, generally within 1–6 h after the transfusion. Bilateral pulmonary infiltrates develop on chest radiograph.

Transient leukopenia, due to pulmonary sequestration of the circulating pool of leukocytes, may be observed.

The mainstay of treatment for TRALI is to discontinue the transfusion, followed by supportive care, which includes administration of supplemental oxygen, resuscitation with intravenous fluids, and implementation of mechanical ventilatory support, when indicated. Although there has never been a randomized, controlled trial of glucocorticoid therapy, they have no demonstrated role in the treatment of TRALI and no effect on the 5–8% mortality. With supportive treatment, infiltrates resolve, usually within 96 h, and survivors have no long-term sequelae [61].

Small Airway Mucus Impaction

Peripheral lung linear and/or tree-in-bud opacities can be seen on chest CT in cancer patients due to impaction of small airways (bronchioles and distal bronchi) with mucus, accompanied to a variable extent by airway inflammation (see Fig. 13.11). These opacities often involve the right middle lobe and lingula, but can be seen in other lung regions. The differential diagnosis includes asthma, noninvasive fungal infection of the airway in a patient with or without a known asthmatic diathesis, recent viral infection, atypical mycobacterial infection, or impaired pathogen clearance due to immunosuppression. The importance of seeking a pathogen and the role of antibiotic treatment is not clear. We have found that physical measures directed at clearing impacted mucus from distal airways can be helpful. Aerosolization of 4 ml of 7% hypertonic saline solution twice daily has resulted in reduced cough, reduced sputum, and clearance of radiographic opacities in
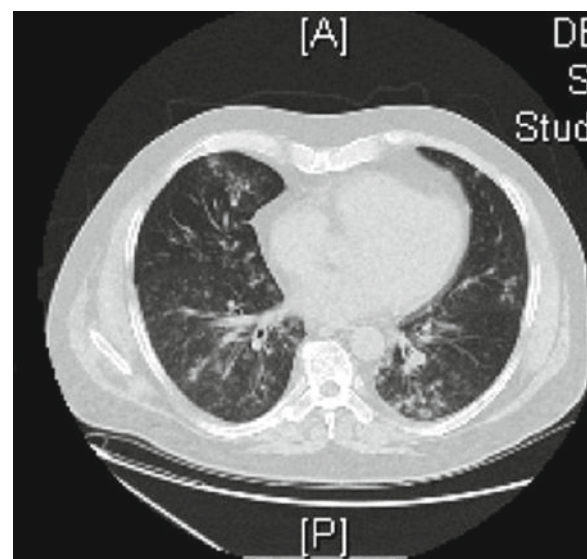
Fig. 13.11 Tree-in-bud infiltrates suggestive of *mucus impaction* in the small airways

some patients [62, 63]. An expiratory flutter valve may also be used to improve mucus clearance. In the case of mucus impaction following a viral respiratory infection, the virus has generally been cleared by the time radiographic abnormalities become evident. If an *Aspergillus* sp. is found in the airway lumen, antifungal agents are usually prescribed. It is debatable whether the morbidity imposed by use of multiple antibiotics to attempt to clear an atypical mycobacterial infection of the airways, in particular due to *M. avium* complex (MAC), is warranted, especially if minimal or no symptoms are present and radiographic and lung function changes are not progressive. In summary, there are no good studies to delineate the best treatment of this syndrome with or without MAC isolation.

Miscellaneous

Additional noninfectious causes of pulmonary infiltrates include pulmonary infarction from thromboembolic disease and metastatic or primary cancer. Venous thromboembolism is common in cancer patients [64] and may progress to lung infarction with radiographic infiltrates. If this diagnosis is suspected, a CT angiogram can be helpful in the differential diagnosis between pulmonary infarction and pneumonia. Infiltration of the lungs by cancer can also be mistaken for pneumonia. Rounded metastases to the lungs may resemble fungal or *Nocardia* infection, and localized lymphangitic spread can resemble viral or bacterial infection (see Fig. 13.12a, b). While
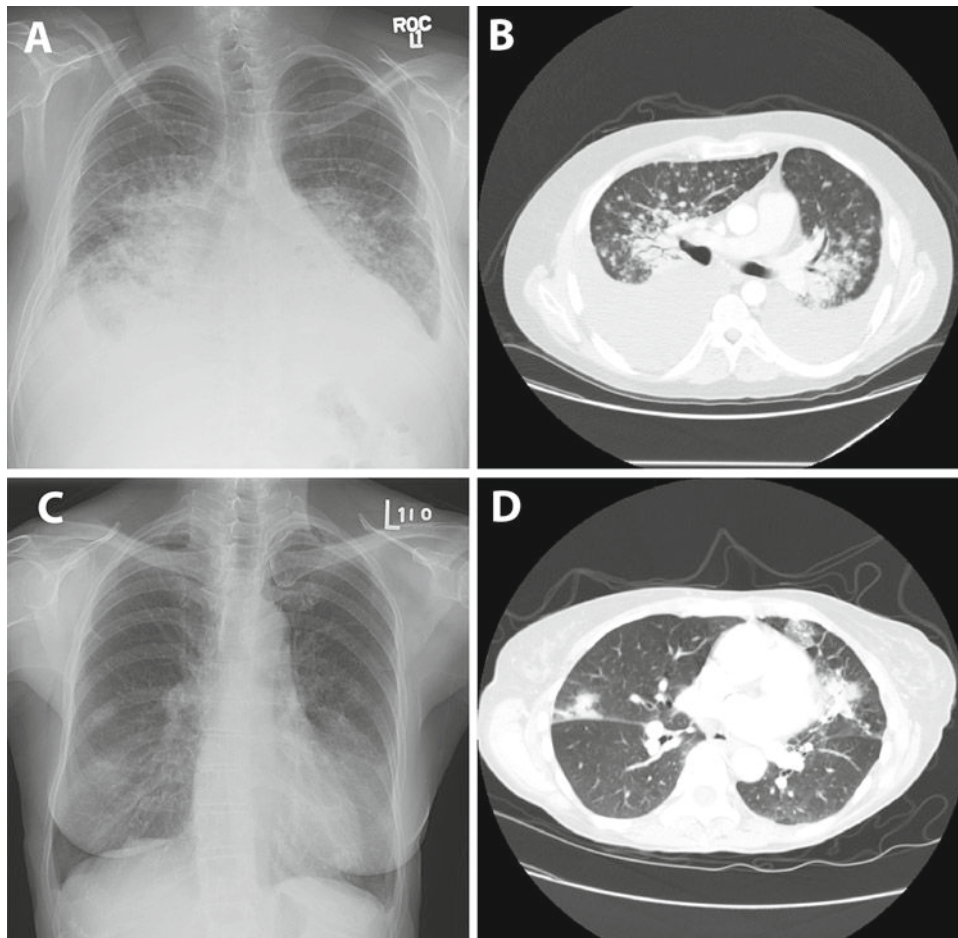
Fig. 13.12 *Tumor infiltration of lung tissue that can be confused with pneumonia. Top panel.* (**A**) On the left is an admission PA radiograph, of a 36 year old male with Hodgkin lymphoma diagnosed four years earlier. (**B**) On the right is a chest CT image the same day showing bilateral pleural effusions, hilar adenopathy, and perihilar consolidation, with multiple small nodules that are not contiguous with the consolidations. Despite extensive treatment with chemotherapy, there was progression of lung infiltrates. These were treated with multiple courses of antibiotics, despite the fact that video-assisted thoracoscopic biopsies of both lungs one year earlier, had all shown Hodgkin lymphoma. *Bottom panel.* The patient is a 68 year old female with chronic lymphocytic leukemia for seven years. On no treatment and routine follow-up, her white count had risen to 86,800 with an absolute lymphocyte count of 66,800, and she had developed a cough. (**C**) On the left, is an outpatient PA radiograph showing faint scattered lung infiltrates. (**D**) On the right, is a CT of the chest the same day showing new areas of consolidation. Transbronchial lung biopsy of the left lingula showed small lymphocytes with hyperchromatic nuclei, with the majority positive for both PAX-5 and CD5. The pathologic diagnosis was B-cell lymphocytic leukemia involving the lung parenchyma, with no evidence of acute pneumonia. Lymphoma and bronchoalveolar cancer are two malignancies that often mimic pneumonia, since they present with airspace consolidation, often with air bronchograms

infiltration of the lungs with malignant cells should be suspected in any patient with known cancer, atypical appearances due to prior treatment can complicate the presentation.

Summary

Multiple common noninfectious disorders in cancer patients are associated with radiographic lung infiltrates that can be confused with infectious pneumonia. Pneumonia is a serious complication in cancer patients and leads to an appropriately high index of suspicion, but accurate diagnosis of both infectious and noninfectious etiologies of lung infiltrates is essential to optimal treatment. The identification of noninfectious etiologies of lung infiltrates can sometimes be made on the basis of clinical findings and imaging studies, but invasive studies are sometimes necessary.

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Chapter 14
Mucosal Barrier Injury and Infections

Nicole M.A. Blijlevens and J. Peter Donnelly

Abstract Neutropenia is well known as a risk factor for infectious complications of patients treated for hematological malignancies. Less is known about the impact of intensive chemotherapy on the epithelial innate immunity that protects us from infections due to opportunistic pathogens that reside on the mucosal surfaces. Injury to the mucosal barrier leads to barrier dysfunction, perturbed microbial signaling and inadequate host responses all of which increase the risk for life-threatening clinically- and microbilogically-defined infections. Greater awareness of mucosal barrier injury should help the physician to know better when and how to act when fever occurs during neutropenia.

Keywords Mucositis • Neutropenia • Infection • Cancer

Introduction

The number and variety of patients who are being treated for cancer with chemo-, radio- or targeted therapy continue to grow and more aggressive treatment modalities have resulted in a better overall survival, albeit often at the price of inducing profound damage to the host defences. Administration of potentially curative chemotherapy is relatively straightforward since internationally accepted treatment protocols dictate the dosages. Once the treatment has started, it becomes essential to monitor the patient as his natural host defence systems gradually disintegrate. Virtually, all cytotoxic therapy regimens, particularly the myeloablative regimens, deplete the pool of polymorphonuclear leucocytes, monocytes and lymphocytes and also attenuate the killing capacity of macrophages. As a result, the patient becomes further dependent on the vestiges of his

innate immune system (e.g. complement, lysozyme, lectins), especially epithelial cells of the digestive tract and skin for protection against potentially lethal infectious complications. These epithelia form an anatomical and immunological barrier often referred to as the integument that serves as the front line against microbial invasion. Although these epithelia are highly organized and sophisticated structures, the barrier they create is not invincible to microorganisms, certainly not after it is damaged by anti-cancer therapy. Adequate supportive care is predicated by recognition of the disintegration of the primary host defence mechanisms aimed at early recognition and treatment of infection to improve survival.

Infections During Neutropenia

Over 50 years ago, Bodey et al. [1] showed a direct correlation between the severity and duration of neutropenia defined as an absolute neutrophil count of less than 0.5×10^9/L (500/mm^3) or a count less than 1.0×10^9/L (1,000/mm^3) expected to fall below 0.5×10^9/L (500/mm^3) and the risk of acquiring a life-threatening bacterial infection. Infections due to Gram-negative bacilli such as *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* and Gram-positive cocci such as *Staphylococcus aureus* were notoriously lethal to patients who were undergoing treatment for acute leukaemia or lymphoma as these diseases intrinsically interfere directly with vital components of the immune system. Indeed, fever was often the first and the only sign of infection of these patients and potentially heralded a life-threatening infection which, if left untreated, might result in fulminant sepsis and even death. This led to the practice of starting therapy promptly at the onset of fever with antimicrobial agents that covered the most likely potential pathogens without waiting for the results of the blood cultures [2]. This was probably the single most important factor in saving life and became widely accepted as empirical therapy. Broad-spectrum synthetic penicillins and third- and fourth-generation cephalosporins, and carbapenems alone, or in various combinations as the

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so-called double β-lactam combinations or together with an aminoglycoside were shown to be equally effective in large clinical trials that involved international cooperation [3]. However, in spite of changes in the spectrum of infectious agents, opportunistic pathogenic Gram-negative bacilli remain a threat because their virulence still accounts for serious morbidity and high early mortality rate [4]. Combination regimens of an anti-pseudomonal β-lactam, e.g. ceftazidime, and an aminoglycoside, e.g. amikacin covering *E. coli*, *P. aeruginosa*, *Klebsiella* species, other Enterobacteriaceae, and *S. aureus*, were not shown to be more effective than monotherapy [5]. These opportunistic pathogens are often part of the indigenous flora of the patient, but can be acquired during hospitalization. Whatever their origin, once they take up residence on the mucosal surfaces, they avail themselves of the opportunity to invade the body once the mucosal barrier is breached [6]. Modern anti-leukaemic therapy is inherently associated with breaches of the pulmonary and gastrointestinal mucosa, thereby allowing microorganisms originating from the damaged mucosal tracts ready access to the body [7]. Many centres therefore adopt prophylactic administration of anti-infective agents simultaneously with starting chemotherapy in an attempt to prevent these infections. A meta-analysis of 95 trials performed between 1973 and 2004 unequivocally showed a significant reduction in infection-related mortality, clinically defined and microbiologically defined infections (MDI) including bacteraemia, especially when fluoroquinolone was employed for patients treated for haematological malignancies [8]. Since these prophylactic agents were mainly targeted against the Enterobacteriaceae, a shift from Gram-negative to Gram-positive bacteria, including coagulase-negative staphylococci (CoNS) and the viridans streptococci, as the primary cause of bacteraemia in neutropenic patients was almost inevitable given their reduced susceptibility to the agents used for prophylaxis[9]. An epidemiological survey among hospitalized patients treated for haematological malignancies between 1995 and 2001 showed that approximately 70% (64% in 1995 and 76% in 2001) of all microbiologically confirmed febrile episodes were due to Gram-positive cocci and 18% (22% in 1995 and 14% in 2001) to Gram-negative bacilli [10]. Surprisingly, the use of vancomycin could be withheld empirically for treating persistent fever until the results of the cultures indicated otherwise [11]. Moreover, fever during neutropenia persisted in over 50% of 114 patients after treatment with broad-spectrum empirical therapy with or without teicoplanin [12]. A meta-analysis showed no negative impact of withholding glycopeptides on morbidity or mortality [13]. The use of leucocyte growth factors prevents febrile neutropenic episodes in patients treated for solid tumour or lymphoma only when the risk of febrile neutropenia is around 20%, but fails to do so in patients treated for leukaemia as most studies showed a shortening of duration of neutropenia, but no reduction in the incidence of febrile neutropenia or infections [14]. A recent meta-analysis could only show a slight reduction in MDI when growth factors were given to stem cell transplant (SCT) recipients after myeloablative conditioning [15]. The incidence of febrile neutropenia in those SCT recipients is almost 100%, but severe neutropenia is particularly short. These data indicate that duration of neutropenia is not necessarily the sole driver of the infection rate and many other factors play a role. Chemotherapeutic regimens designed to treat patients with acute lymphoblastic leukaemia incorporate high doses of corticosteroids rendering patients susceptible to infections typically related to impaired cellular immunity. The use of monoclonal antibodies further extends the suppression of B- and T-cell functions particularly when coinciding with prolonged, severe neutropenia.

Epithelial Innate Immunity

Only recently, it has become clear that the innate immune system not only specifically recognizes various classes of microorganisms, but also initiates and modulates the subsequent adaptive immune responses mediated by T cells and B cells through their interaction with antigen-presenting cells especially dendritic cells [16]. Epithelial cells as well as neutrophils and monocytes possess various pattern recognition receptors (PRRs) that sense conserved structures of the invading microorganisms, called pathogen-associated molecular patterns (PAMPs), and four major classes of PRRs have been identified; Toll-like receptors (TLR), C-type lectin receptors (LRs), NOD-like receptors (NLRs) and retinoic acid–inducible gene (RIG)-I-like receptors (RiG-I). The interaction of a PRR with a bacterial structure leads to activation of host response mechanisms, especially the release of cytokines and chemokines, responsible for elimination of the pathogen. For instance, human epithelial TLR4 directly protects the mucosa from *Candida* infection via a process involving cytokines and chemokines mediated by polymorphonuclear leukocytes. Infiltration of leukocytes of the mucosal tissues is not required [17]. Genetic variation, including single nucleotide polymorphisms (SNPs) in the non-HLA genes coding for PRRs, has been associated with increased susceptibility of SCT recipients to various bacterial and fungal infections [18]. For example, mannose-binding lectin (MBL2) is a PRR that activates complement independently of a specific antibody. MBL2 polymorphisms resulting in low MBL levels were associated with primary bacteraemia when there was mucosal damage following myeloablative TBI to prepare for an SCT [19].

A robust association between SNPs in NOD2/CARD15 and the outcome of allogeneic SCT has been reported by Holler et al. [20]. NOD2 is an intracytosolic PRR that senses

the cell-wall component muramyl dipeptide (MDP) of certain bacteria and is expressed in Paneth cells, dendritic cells, neutrophils and monocytes [21]. Altered function due to NOD2 polymorphisms can result in uncontrolled inflammation of the gut mucosa, which plays a pathogenic role in Crohn's disease and acute GvHD [22]. Interestingly, this SNP effect was strongly reduced among SCT patients receiving oral intestinal decontamination with agents active mainly against Gram-positive bacteria. Finally, a wide array of cytokine gene polymorphisms has been studied in the context of SCT, including polymorphisms in IL10, TNF, IFNγ, IL6, IL1 and TGFβ1 [23]. The variety of SNPs influences the balance between activation of pro-inflammatory cytokines and the down-regulation of inflammation in mucosal tissues damaged by conditioning regimens. This inflammatory response is the first step in the development of acute GvHD after exposure to bacterial products (e.g. LPS) that cross the perturbed gastrointestinal barrier. The intact gastrointestinal epithelial barrier is capable in withstanding microbial invasion by expressing and secreting antimicrobial products including defensins, lipopolysaccharide-binding protein (LBP), lysozyme and cathelicidins, without any accompanying pro-inflammatory responses [24]. The intestinal tract is actually unique in this respect as it is constantly exposed to rich and varied commensal flora and infrequently to pathogenic bacteria. Most commensal microorganisms colonize the mucosal surfaces without gaining direct access to the epithelial barrier which is restricted to the strictly residential flora. Once the mucous layer recedes, attachment to the epithelial barrier can occur as first step in the process of translocation. Treatment with cytotoxic drugs places the epithelial defences under severe stress resulting in a process called mucosal barrier injury (MBI) [7].

Mucosal Barrier Injury

The pathobiology of cytotoxic therapy-induced mucositis was first described in 2004 and details are still being unravelled [25]. Briefly, the process begins as an inflammatory complication of anti-cancer treatment and occurs in five biological phases: (1) the initiation phase of free radical generation and induction of apoptotic cell death induced by both DNA and non-DNA damage, (2) the up-regulation and message generation phase where the master transcription factor, nuclear factor-κB (NF-κB), leads to the up-regulation of many genes resulting in the production of pro-inflammatory cytokines, (3) the amplification and signalling phase of these pro-inflammatory cytokines (TNF-α, IL1 and IL6), (4) Ulcerations, crypt hypoplasia, villous atrophy and cleavage of extracellular-matrix substrates such as collagen and fibronectin by activated matrix metalloproteinases are the net

result. Microorganisms and their cell-wall products such as peptidoglycan and lipopolysacharide can breach the damaged physical barrier more easily and are able to activate tissue macrophages to produce more pro-inflammatory cytokines. The healing phase is the final stage in the process (5) when trefoil factors, secretory products of mucin-producing Goblet cells, in concert with matrix metalloproteinases down-regulate inflammation and restore the integrity of the mucosal barrier [26, 27]. Endogenous production of keratinocyte growth factor (KGF) is accelerated exclusively by mesenchymal cells, particularly fibroblasts. KGF is a paracrine mediator of mesenchymal-epithelial communication that plays a key role in maintaining the barrier function of epithelial tissues and the healing process after injury [28]. Mucositis of the entire alimentary tract is the clinical manifestation of the pathobiological process of MBI. Systemic drug exposure appears to be the key determinant of severe mucositis in a prospective audit of 197 patients with multiple myeloma (MM) or non-Hodgkin lymphoma (NHL) undergoing, respectively, high-dose melphalan (HDM) or BEAM chemotherapy and autologous stem cell transplantation [29]. Patients were 2.6 times more likely to develop severe mucositis when the dose of melphalan increased by 1 mg/kg of body weight. Dosing melphalan per kilogram bodyweight in either HDM or BEAM regimens tended to predict the risk of severe mucositis far better than dosing per body surface area [30, 31]. Furthermore, patients receiving a dose ≥70 mg/m^2 of melphalan had a 23-fold increased risk of developing mucositis (p <0.001) compared with those receiving lower doses irrespective of depth of neutropenia [32]. Patients developing severe mucositis had a higher incidence of fever (68% vs. 47%, p=0.004), more days of fever (4.2 vs. 3.0 days; p=0.033) as well as a higher incidence of MDI (27% vs. 12%; p=0.013) [33]. The length of hospital stay was increased by 2 days during chemotherapy cycles when both oral and gut mucositis were present [34]. The risk of mortality among SCT recipients suffering from severe oral mucositis was also increased [35]. Overall survival was significantly worse in patients with severe mucositis after high-dose chemotherapy regimen followed by autologous stem cell transplantation because of relapsed lymphoid malignancy [36].

Mucosal Barrier Injury and Infection

The median time to the onset of fever during neutropenia is around 12 days after starting myeloablative conditioning therapy when mucositis is at its worst and is independent of the nadir of neutropenia [37]. The inflammatory response measured by CRP and body temperature coincided with the occurrence of mucositis irrespective of the duration of neutropenia in 67 autologous SCT patients after HDM [38].

The systemic inflammatory response as measured by CRP, LPS-binding protein and IL8 of allogeneic SCT recipients after myeloablative conditioning was also predominantly related to the course of mucosal damage measured either by mucositis scoring scales, plasma citrulline levels or permeability tests [39]. The estimated surface area of the small intestine of adults is 200–300 m² and is roughly equivalent to the area of a soccer pitch. Damage of the epithelial lining of the small intestinal tract can be accurately documented by estimating the concentration of plasma citrulline which is almost exclusively produced by functional enterocytes [40]. The magnitude of the mucositis-related inflammatory response is not only boosted by bacteraemia, but often precedes it [41]. This is consistent with a study on rats exposed to chemotherapy in which the release of pro-inflammatory cytokines was associated with evolving mucositis and preceded microbial translocation [42]. Low citrulline levels reflecting intestinal MBI, rather than neutropenia per se, are associated with onset of bacteraemia [41]. In general, the risk of infection and use of antibiotics are significantly higher during chemotherapy cycles that are complicated by mucositis than during cycles without mucositis [34]. In particular, infections due to Gram-positive cocci tend to occur more frequently during cycles complicated by gut mucositis. Nowadays, Gram-positive cocci account for three of every four episodes of bacteraemia affecting patients treated for haematological malignancies (SCOPE project) [10]. CoNS are the most frequent isolates and, although CoNS bacteraemia is frequently associated with the use of central venous catheters, mucosal sites are also known to be an important portal of entry for these bacteria [43]. Indeed, plasmid pattern analysis of bacteraemic isolates of CoNS showed that the mucosa was the origin in 70% in haematology patients. CoNS bacteraemia mostly occurred within the first 2 weeks after transplant when gut integrity was markedly disturbed [44]. Bacteraemia due to oral viridans streptococci (OVS), mainly *Streptococcus mitis* and *S. oralis,* is clearly related to mucosal damage and can be associated with more serious complications such as sepsis and adult respiratory distress syndrome which carry a high mortality (80%) [45, 46]. Recipients of autologous SCT with oral ulcerative mucositis were found to be three times more likely to develop OVS bacteraemia than those without mucositis and the streptococci were isolated from blood cultures a median of 6 days (range 2–8 days) after transplant which is typically when the peak of mucositis occurs [47]. Drug-induced achlorhydria and the use of antimicrobial prophylaxis with fluoroquinolones contribute toward the development of OVS bacteraemia [48]. Significantly more patients develop infectious complications, including streptococcal bacteraemia, when the dose of cytarabine was increased from standard (200 mg/m²) to intermediate (1,000 mg/m²) [49]. Recently, a simple scoring system for predicting streptococcal infection was proposed,

but unfortunately did not include mucositis [50]. Adding mucositis to the MASCC risk-index score used to assess low-risk febrile neutropenia patients might also further improve the tool [51]. *Candida* species normally reside on the mucosal surfaces of the digestive tract of many adults. Adherence to these surfaces appears to be a prerequisite for local infection and subsequent invasive disease since regular surveillance cultures of haematological patients have shown that colonization invariably precedes infection [52]. Patients treated for AML who developed invasive candidiasis had significantly lower serum D-xylose levels indicating malabsorption with the maximum difference noted at week 2 after start than patients without invasive disease [53]. SCT recipients prepared with regimens composed of TBI and patients treated with remission-induction regimens containing either high-dose cytarabine or an anthracycline have an increased risk of developing invasive *Candida* disease. The risk of candidaemia is also increased when patients suffer from a clinical picture designated as neutropenic enterocolitis or typhlitis [53]. The current term NE is used to describe an inflammatory process involving the colon, mainly caecum and adjacent parts of the small bowel in the context of chemotherapy-induced neutropenia and mucosal damage. NE is the example of MBI-related infection (Fig. 14.1). NE can potentially result in life-threatening complications such as ischemia, necrosis, haemorrhage, bacteraemia and perforation. There have only been a few prospective surveys published, but the incidence of NE is estimated to be 6.5% [54]. Mortality rates vary between 50 and 100% [55]. A systematic review of 21 studies (mainly case reports and reviews) reported a pooled incidence rate of 5.6% (84/1,489; 95% CI: 4.6–6.9%) in a subgroup of patients exclusively treated with intensive chemotherapy [56]. A similar analysis showed that 80% of patients with NE had been treated for haematological
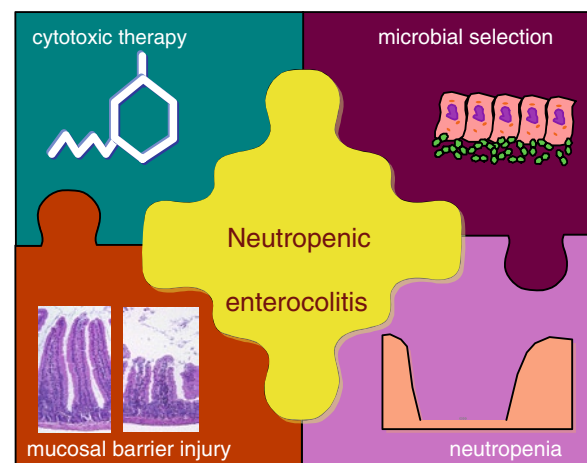
Fig. 14.1 Neutropenic enterocolitis – an example of mucosal barrier injury (MBI)-related infection

malignancies and that the overall mortality related to NE was 38% [57]. The common clinical manifestations of NE are fever, abdominal pain and diarrhoea [58]. These symptoms are not specific to NE and must be differentiated from other causes of abdominal complications such as appendicitis, pseudo-membranous colitis, ischemic colitis, obstruction and intussusceptions. NE occurs between 10 and 30 days after start of the cytotoxic treatment coinciding with MBI. Ultrasound sonography (US) or computer tomography (CT) proved to be more valuable in diagnosis and monitoring of clinical cases suspected of NE. The normal thickness of the bowel wall visualized by US is <2 mm and a thickening of >5 mm is considered abnormal and consistent with NE. Bowel wall thickening (BWT) between 2 and 5 mm is more difficult to interpret [59] and most reports adopt a threshold of >3 mm as being abnormal and supporting the diagnosis of NE. The typical five-layer morphology of ileum and colon seen by US and not CT scan is called the "gut-signature," suggesting that US is more accurate in measuring BWT [60]. However, the CT scan allows NE to be differentiated from other intestinal complications.

Summary

Recognizing MBI as an inflammatory complication of cytotoxic therapy should compel clinicians to change their approach in directing supportive therapy to those patients at greatest risk of developing infections during neutropenia (Table 14.1) Growth factors like recombinant human interleukin-11 which protect the integrity of the gut lowered the rate of bacteraemia in patients treated for acute leukaemia [61]. Moreover, the recombinant growth factor palifermin was able to significantly reduce the risk of febrile neutropenia and the rate of severe mucositis in patients undergoing SCT [62]. The possibility of treating or even preventing severe MBI will be an important step towards decreasing the infectious complications experienced by patients given intensive chemotherapy.

Table 14.1 MBI as a risk factor for infection

Why	The ulcerative phase of MBI allows translocation of residential microorganisms and their products from the alimentary tract into the bloodstream
Who	Intensive therapy for AML, MDS and HSCT recipients following myeloablative therapy
What	MBI as manifest by oral and gut mucositis
Where	Probably the gingival borders, soft tissues of the oral cavity, oesophagus, ileum, cecum and rectum
When	Second part of intensive chemotherapy, early (<14 days) after transplant, and during gut GVHD

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Chapter 15
Bacterial Colonization and Host Immunity

Coralia N. Mihu, Karen J. Vigil, and Javier A. Adachi

Abstract The gastrointestinal (GI) tract is a highly evolved anatomical and functional structure that encounters a vast array of antigens, food particles, and microorganisms on a daily basis. The intestine has to perform the daunting function of absorbing nutrients essential for human life, while keeping us protected from luminal antigens, particles, and pathogens. The adult human intestine is home to an enormous number of microorganisms that is extraordinarily complex, collectively known as intestinal microbiota. Understanding our relationship with commensal flora has gained more depth in recent years; new data demonstrate that gastrointestinal microbiota plays an important role in defense against pathogenic organisms. Since it is only a thin monolayer of epithelial cells that separates us from the intestinal flora and pathogens, the intestine has acquired specialized cells organized in complex structures that have to perform the function of defending us against pathogens by initiating innate and adaptive immune responses. By constant signaling and communication, intestinal immune cells are organized in a vast and complex network that contributes to the maintenance of homeostasis.

Keywords Gastrointestinal tract • Immunity • Bacteria • Fungus • Colonization • Disease pathogenesis

Introduction

The gastrointestinal (GI) tract is one of the most complex and important organ systems. It performs two main functions: uptake of nutrients and digestion and maintaining immune homeostasis (mounting host immunological responses). Its extensive surface area – composed of a great diversity of cell types – as well as the vast amount of immune cells (the largest in the human body) and its resident microbiota makes it possible to develop these functions. Functional or genetic alteration of any of its three main components will result in the development of GI or systemic diseases.

The objective of this chapter is to provide a comprehensive review of the GI system architecture, its microbiome, the GI innate host immunity, and the complex interaction among these components.

Bacterial Colonization: Microbiota

The GI tract is the most heavily populated system by microbiota. In general, human beings have 10^{14} (100 trillion) microbes inhabiting their bodies of which 10^{12} organisms/g of fecal material are in the colon [1]. Initial culture-based studies report 400–500 distinct species in the gut microbiota, and it was estimated that >90% of them could be cultivated [2]. However, more recent 16S rRNA-based studies have shown that the gut microbiota was underestimated. The gut microbiome is diverse and includes eight phyla, with members of the Gram-negative Bacteroidetes and Gram-positive Firmicutes constituting between 60 and 80% of the total fecal community [3]. Additionally, although there is individual to individual variation, the community within an individual appears to be constant over time [4].

The GI microbiota has a mutualistic relationship with the host. Although it benefits receiving nutrients, the host takes advantage from some of its metabolic products. As an example, some bacteria from the Firmicutes division ferment nondigestible starch into short-chain fatty acids like butyrate that is not only the preferred energy source for colonocytes but also plays an important role in the maintenance of tissue homoeostasis and disease prevention [5].

Additionally, the microbiota drives some aspects of postnatal intestinal maturation. Colonization of germ-free mice with *Bacteroides thetaiotaomicron* – a component of the intestinal microflora of mice and humans – has been shown to allow the restoration of the fucosylation program in the small-intestinal epithelium that occurs during the time of

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weaning [6] and also to modulate the expression of genes involved in several important intestinal functions, including nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, and angiogenesis [7].

Another microbiome–host interaction occurs in the host immune system. The microbiota provokes host immune responses. However it is still under investigation, the role of the host in the composition of the bacterial microbiota. Some studies have shown that secretory antibodies do not control its composition [8] while others have demonstrated that the host IgA is critical to its regulation of and the segmented filamentous bacteria antigens are strong stimuli of the mucosal immune system [9].

Therefore, we could say that the gut microbiota is part of a complex ecosystem along with the host mucosal epithelium and the host immunes system, and it plays a crucial role in homeostasis of the GI tract. Changes and disturbances in the GI microbiota play an important role in the pathogenesis of systemic and localized GI diseases either because of changes in the metabolic activity of an altered microbial community or because of the interaction between the microbiome and the host immune system. Perturbations of the normal microbiota have been linked to atopic dermatitis, eczema, food allergy, obesity, inflammatory bowel diseases, pouchitis, vaginitis, and infections such as antibiotic-associated diarrhea and *Clostridium difficile* infection.

In antibiotic-associated diarrhea, molecular phylogenetic analyses have shown temporal distinct changes in the diversity of fecal bacteria after antibiotic administration, including a marked decrease in the prevalence of butyrate-producing bacteria that resolved after the discontinuation of the antibiotic [10].

In *C. difficile* associated diarrhea, the fecal communities in patients with recurrent disease have been found to be highly variable in bacterial composition and characterized by markedly decreased diversity [11].

The microbial community in the human intestine may also play an important role in the pathogenesis of obesity. Collado et al. found that there is distinct composition of GI microbiota during pregnancy in overweight and normal-weight women. Bacteroides and *Staphylococcus* are significantly higher in the overweight state than in normal-weight women. Microbial counts have found to be higher in the third trimester of pregnancy, and high Bacteroides concentrations have been associated with excessive weight gain over pregnancy [12].

Finally, DNA-based techniques have demonstrated that patients with irritable bowel syndrome (IBS) have an increase number of total aerobes and great temporal instability of its microbiota [13]. Patients with different predominance of symptoms also have different microbiota. Diarrhea predominant IBS patients had lower numbers of *Lactobacilli* spp., while constipation predominant IBS patients had increased amounts of *Veillonella* spp [14].

Gastrointestinal Mucosa and Intestinal Immune Responses

The structure of GI mucosa varies from one site to another of the GI tract. It has three parts: a layer of specialized epithelial cells that line the lumen, the lamina propria (connective tissue with embedded vessels, nerves, and immune cells), and the muscularis mucosa. The GI tract surface has multiple invaginations called villi, which are lined with columnar epithelial cells. These cells have microvilli that help with the absorption of nutrients from digestion [15]. Interspersed in these structures are the gastrointestinal-associated lymphoid tissue (GALT) and the mesenteric lymph nodes (MLNs), which are the main tissues involved in GI immunity.

The intestinal immune system is the largest and most complex component of the immune system in general. In contrast to other parts of the body, it constantly encounters antigens and has to distinguish between harmful pathogens and commensal mucosal microbes that constitute microbiota. When pathogens are encountered, innate immune responses are generated immediately, producing a broad response directed mainly to decrease the pathogen load, while allowing for the highly specific adaptive immune response to succeed in clearing the pathogen.

The first line of defense between the external environment and the circulation is the intestinal epithelial cells themselves. Owing to their tight intercellular junctions, they provide a physical barrier that restricts access of pathogens to mucosal surfaces. Also, the brush border glycocalyx, the glycoproteins located in its border, prevents bacteria or large molecules to enter while allowing nutrients to cross [15]. Please review the previous Chap. 14 by Blijlvens and Donnelly for more information.

There are four different types of epithelial cells in the GI tract: columnar epithelial cells, goblet cells, enteroendocrine cells, and Paneth cells. Columnar epithelial cells can be found in the small intestine (enterocytes) or in the colon (colonocytes) and constitute 80% of the epithelial cell types. Goblet cells and enteroendocrine cells are located throughout the GI tract. Goblet cells are in charge of secreting mucin, while enteroendocrine cells integrate the GI system with the systemic nervous system. Paneth cells, initially described by Dr. Paneth in 1888, are found in the crypts of the small intestine and play an important role in innate immunity, mucosal inflammation, and absorption of fluids and nutrients [15, 16]. A more detailed review of the function of these cells is found later in this chapter.

In addition to being a mechanical barrier, intestinal epithelial cells are part of innate immune defense by secreting mucins, lysozymes, and defensins that prevent microbial adhesion and retain antimicrobial peptides and secretory antibodies inhibiting bacterial growth. Also, they transport luminal antigens for further presentation to underlying

immune cells and secrete cytokines, such as interleukin (IL) 1-α, IL-1β, IL-6, IL-8, IL-10, IL-17, monocyte chemoattractant protein 1, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor α (TNF-α) and transforming growth factor β (TGF-β), chemokines, and eicosanoids that help in innate and adaptive responses [15].

Closely interspersed in the intestine and associated lymphoid tissue, there is a widespread network of bone marrow-derived innate immune cells, such as macrophages, mast cells, neutrophils, eosinophils, dendritic cells (DCs), and natural killer cells that each secrete a repertoire of cytokines and chemokines with functional profiles that partially overlap.

Antigen-presenting cells (APCs), comprising macrophages, conventional DCs, and plasmacytoid DCs, play a central role in initiating immune responses. In recent years, DCs have emerged as major players in shaping the immune responses in the gastrointestinal tract, by both maintaining tolerance toward microbiota and generating protection toward pathogens. This dual role can be explained by their unique structural and functional properties. There are several subpopulations of DCs located in the lymphoid structures of the intestine, such as Peyer's patches, isolated lymphoid follicles (ILF), and MLNs as well as in the lamina propria. Furthermore, the DCs population can be subdivided by the receptors expressed on their surface, which dictates the pattern of cytokine production and T-cell activation. For example, in the Peyer's patches CD11b+ subset of DCs produces IL-10 and Th2 priming, whereas CD11b-CD8α- and CD8α+ DCs produce IL-12 and later interferon-gamma (IFN-γ) by T cells [17].

As APCs DCs require antigen uptake by engulfing antigens already transported through the epithelial barrier by the microfold (M) cells, located at the dome of Peyer's patch, but also by expressing transepithelial projections of dendrites directly into the lumen in response to stimulation of epithelial cells Toll-like receptors (TLRs) by bacterial products [18, 19]. By constantly sampling the luminal antigens and microbiota, DCs continuously obtain immunological information about luminal commensals and pathogens.

Lamina propria DCs that have taken luminal antigens migrate to the draining MLN where they present antigen to T cells. This migration is constitutive and can occur in the absence of an infectious or inflammatory stimulus, although it can intensify in the presence of inflammatory stimuli. Chemokine receptor 7 (CCR7) appears critical for this migration [20]. These DCs are phenotypically mature, able to prime T cells. CCR7 receptors may be involved in promoting tolerance to mucosal antigens. Mice lacking CCR7 receptors have impaired ability to acquire tolerance to oral antigens [21]. Recent studies have shown that DCs from the lamina propria can promote generation of forkhead box P3 regulatory T cells (FOXP3+Treg), a process dependent on TGF-β and retinoic

acid [22, 23]. Other mechanisms that can contribute to induction of tolerance are by induction of Th2 phenotype as well as promoting IgA secretion. It has been shown that DCs carrying commensal bacteria induce protective IgA [24].

In addition to promoting tolerance, DCs can induce adaptive immune responses that lead to generation of effector T cells directed toward clearance of intestinal pathogens. The mechanisms by which the DCs are able to promote tolerance vs. inflammation remain an area of active investigation. It has been suggested that the location and expression patterns of TLRs by intestinal epithelial cells may play a role. Alternatively, recruitment of DCs that have not been conditioned may be a factor. Another hypothesis that requires further investigation is uptake pathogenic species solely by DCs residing in MLNs [25].

Lastly, intestinal DCs play an important role in homing of recently activated T cells by promoting the expression of gut homing receptors (α4β7-integrin and CCR9) by both CD4+ and CD8+ T-cells subsets [26–28]. DCs are also involved in homing of IgA secreting B-cells [29].

Another important line of innate immune defense against pathogens is represented by antimicrobial peptides, a large group of peptides contained in the secretory granules of Paneth cells. Several members of this group have been the object of active investigation in the recent years, including α-defensins, angiogenins, and regIIIg.

Defensins are a family of evolutionary related peptides that have antimicrobial activity against bacteria and fungi. They are secreted by the Paneth cells into the crypt lumen by degranulation after stimulation by a variety of stimuli including gram positive, gram negative, and bacterial products such as lipopolysaccharide, lipoteichoic acid, lipid A, and muramyl dipeptide [30]. Recent studies performed in transgenic mice have shown that production of human defensin-5 protected mice against infection with *Salmonella typhimurium* [31]. It has been suggested that defensins may also play a role in antiparasitic immunity (*Giardia lamblia* and *Cryptosporidoim parvum*), but these findings need to be further confirmed [32, 33].

Angiogenin 4, produced by mouse Paneth cells, has antibacterial properties against *Enterococcus faecalis* and *Listeria monocytogenes*, two important gram positive pathogens, but does not affect other microorganisms such as *E. coli* or *Bacteroides thetaiotamicron*. Production of angiogenin 4 is stimulated by *B. thetaiotamicron*, suggesting that gut commensal microflora regulates the microbial environment and contributes to intestinal homeostasis through innate immune mechanisms [34].

More recently, a regenerating (Reg) family of proteins was described [35]. Structurally, C-type lectins, members of this family of proteins, are highly expressed at the level of the intestine. RegIIIg is found in mouse, with the counterpart in humans being HIP/PAP. RegIIIg binds to peptidoglycan

expressed on the surface of the Gram-positive bacteria [36]. They appear to play an important role in the innate defense against *L. monocytogenes* and vancomycin-resistant *Enterococcus* [37, 38].

It has been observed that the repertoire of antimicrobial peptides changes along the small intestine; a subset of these molecules is upregulated in response to commensal flora, but not to enteric pathogens. This observation suggests that antimicrobial peptides produced by Paneth cells play a role in regulating commensal microbial homeostasis, in addition to protecting against infection [39].

In addition to secreting antimicrobial peptides, Paneth cells can express several inflammatory molecules, such as TNF, GM-CSF, and inducible NO synthase (iNOS) [40, 41]. Moreover, Paneth cells have a clear capacity to respond to inflammatory cytokines as shown in the induction of iNOS by TNF [42]. By releasing TNF, they are thought to be essential both in mucosal immunity against pathogens and in the development of Crohn's disease. IL-17 expression seems to play a role in systemic inflammation and shock induced by TNF [41], and recent studies have been showing its significant role in innate and adaptive immunity.

Innate immune mechanisms maintain rapid responses to mucosal pathogens but can lead to harmful inflammatory mucosal injury. The intrinsic control of these responses is comprised by a variety of down-regulatory pathways that are initiated by activation of the innate immune cells. These mechanisms are complex and partially overlap. A central role is played by interleukin 10 (IL-10), a potent anti-inflammatory cytokine which exerts its action on both innate and adaptive immunity. IL-10 prevents intestinal inflammation not only through T cells but also by reducing the antigen-presenting capacity of monocytes and DCs; it also exerts an inhibitory effect on the production of cytokines and chemokines by monocytes and macrophages while also inducing production of soluble inhibitory factors of proinflammatory cytokines (i.e., TNF-alpha) [43].

Adaptive immunity is a highly evolved mechanism of defense against pathogens. The most important characteristic of adaptive immunity is the presence of highly specific T- and B-cell receptors (TCRs and BCRs), which allow for an antigen-specific response. Another key characteristic is the presence of antigen-specific memory cells, which allow for a rapid, specific response upon rechallenge with the same antigen. T cells are characterized by the presence of CD4+ or CD8+ molecules, which are associated with the TCR and by the components of TCR (TCR$\alpha\beta$ or $\gamma\delta$). CD4+ and CD8+ cells recognize antigens presented by MHC class II molecules and class I respectively.

Several structural and functional characteristics singularize intestinal lymphoid edifice. It can be simplistically divided in the initiation compartment and the effector compartment.

Initiation compartment includes Peyer's patches, MLNs, as well as numerous ILFs. Mature Peyer's patches are found abundantly in distal ileum, but more recently have been described throughout the GI tract [44]. Structurally, Peyer's patches are similar to lymph nodes, containing large B-cell follicles with interspersed T-cell area; they are separated from the intestinal lumen by a single layer of epithelial cells named follicle-associated epithelium (FAE) and an area located immediately bellow the epithelium named subepithelial dome. The FAE contains microfold (M) cells, which are implicated in binding invasive pathogens as well as sampling particulate antigens. FAE also contains DCs, B and T cells, and macrophages. At this level, the initiation of the immune response occurs. M cells assist in antigen transport from the intestinal lumen, which is then passed on to the APCs, DCs playing an important role in this process, as outlined earlier in this chapter. APCs will subsequently move to the B-cell follicles and/or T-cell areas where they can interact and prime lymphocytes. The lymphocytes that are primed in the Payer's patches will migrate to the MLNs where they reside for an undefined period before migrating into the circulation and subsequently into the effector compartment. As previously mentioned, homing of primed T cells into the intestinal mucosa is facilitated by upregulation of certain receptors: $\alpha4\beta7$-integrin and CCR9, which are not expressed by T cells that are primed in peripheral lymphoid organs.

Different from other GALT tissues, MLNs can develop in the absence of growth factors. Interestingly, in germ-free mice MLNs are smaller but still functional due to a lack of stimulation from microbiota [45]. By contrast, ILFs which are found along the whole intestinal tract seem to develop under the stimulation of intestinal flora [46].

The effector compartment consists of lamina propria T cells and T cells interspersed in the intestinal epithelium, among the epithelial cells called intraepithelial lymphocytes (IELs). The phenotype and function of mucosal T cells remain an area of active investigation. Some populations of IELs are conventional CD4+ or CD8$\alpha\beta$+ T cells. Other populations are distinctively different from other lymphoid organs, such as CD8$\alpha\alpha$+$\gamma\delta$ TCR. Subsets of CD8+ T cells have cytotoxic activity. Other subset of T cells has effector/memory/regulatory/tissue repair functions [47]. Many studies in recent years have focused on regulatory T-cell subsets, which maintain intestinal homeostasis. The mechanisms underlying promotion of tolerance are very complex and partially redundant. Several subsets of T cells have been shown to have regulatory properties, among which CD4+Foxp3+ have a central role, but other CD4+ and CD8+ subsets also participate through IL-10 and transforming growth factor $\beta1$ production and possibly other mechanisms [43].

B cells play an important role in intestinal immune responses by secreting IgA and cytokines. IgA production is a very important noninflammatory immune mechanism for

the maintenance of intestinal homeostasis. IgA, one of the most abundant immunoglobulin isotypes produced in our body, is secreted as a dimmer by the intestinal B cells. Once secreted, it binds to a polymeric Ig receptor (pIgR), an antibody transporter located on the basolateral surface of the intestinal epithelial cells. Subsequently, it is transported to the surface of epithelial cells generating secretory IgA complexes. It can be produced in both intrafollicular and extrafollicular sites, in T-cell dependent and T-cell independent manner [24, 48]. Intestinal IgA performs multiple functions, including entrapment of dietary antigens and bacteria, interaction with local microbiota, maintenance of commensal bacterial flora (communities), and facilitation of antigen sampling by binding to M cells. Additionally, secretory IgA (sIgA) produced on mucosal surfaces promotes an anti-inflammatory environment [15]. Several factors such as IL-10 that promote tolerance also promote intestinal IgA production [49]. The mutualistic relationship is once again noted: IgA production is dependent on intestinal colonization and in turn it participates in immune exclusion by preventing the commensal bacteria to enter the intestinal surfaces [50].

Summary

The GI tract is a multifaceted anatomical and functional structure. There are intricate interactions between the immensely complex microbial populations comprising microbiota with the components of innate and adaptive immune system at the thin, fragile interface that separates the two worlds. Incessant signaling and communication between components is necessary to maintain homeostasis. Cancer and its therapies including chemotherapeutic agents but also antibiotics may disrupt this homeostasis and lead to unintended consequences. Although much progress has been made in recent years, understanding the ability of the GI tract to protect against pathogens while avoiding destructive inflammatory responses toward microbiota remains an area of active investigation.

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Chapter 16
Neutropenic Enterocolitis and *Clostridium difficile* Infections

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Abstract Neutropenic enterocolitis is best defined as a clinical syndrome with features indistinguishable from other causes of bowel inflammation. Patients usually present with fever, abdominal pain, diarrhea, and have evidence of thickened bowel wall. This potentially fatal complication is not uncommon in neutropenic children, whereas in adults neutropenic enterocolitis is often seen in older patients with advanced cancer undergoing salvage chemotherapy for a hematologic malignancy. Patients with oro-intestinal mucosal damage following antineoplastic therapy are at an increased risk. The diagnosis is based on clinical features and evidence of diffuse or localized bowel wall thickening on CT scan; presence of air with in the bowel wall "pneumatosis intestinalis" indicates serious disease with an increased risk of perforation. Treatment is generally supportive with strict bowel rest, parenteral hydration, and nutritional support, along with broad spectrum antimicrobials. Myeloid growth factors promote early recovery form neutropenia. Surgery is reserved for patients with perforation of bowel with complicated peritonitis. In this chapter, a comprehensive discussion regarding *Clostridium difficile* (*C. diff*) is presented with emphasis on risk factors, clinical presentation, and antimicrobial therapy.

Keywords Neutropenia • Intestinal mucosal damage • Leukemia • Transplantation • Fever • Diarrhea • *Clostridium difficile*

Neutropenic Enterocolitis

Neutropenic enterocolitis (NEC) or typhlitis is a clinical syndrome characterized by fever, abdominal pain, and diarrhea [1–3]. Bowel wall thickening has been described, classically in the cecum; therefore, the term typhlitis from the Greek "typhlon" for cecum was used in earlier reports, this condition, however, involves all parts of postgastric intestinal tract [3, 4]. This potentially fatal complication of neutropenia is a form of colitis was originally described in patients undergoing chemotherapy for leukemia and solid organ cancer [1, 3–5]. The frequency may be as high as 26% based on autopsy findings in childhood leukemia cases [1, 4].

The diagnosis is difficult, most patients present with a nonspecific radiologic findings, and a differential diagnosis including appendicitis, ischemic colitis, pseudomembranous colitis, or antineoplastic drug or radiation toxicity [3, 5, 6]. Additionally, there is no internationally accepted standard for the diagnosis of NEC [3], with differences described between clinical presentation and diagnosis in children and adults [2, 3]. Given the challenge of accurate diagnosis, management becomes similarly difficult, involving supportive therapy with broad spectrum antimicrobials, strict bowel rest, and careful monitoring for complications that may require surgical intervention for perforated viscera [3, 5, 6].

In this chapter we present epidemiology, clinical presentation, and diagnosis and management of neutropenic colitis in adults and pediatric cancer patients.

Epidemiology

NEC has been described in association with chemotherapy, typically 10–14 days after cytotoxic chemotherapy, although cases have been described 30 days after chemotherapy [3, 5]. Patients with leukemia, aplastic anemia, and solid tumor undergoing high-dose chemotherapy are at an increased risk [3, 5]. Leukemia and other hematologic malignancies, as well as recipient of allogeneic stem cell transplantation with delayed engraftment or acute graft vs. host disease, account for approximately 75% of reported cases of NEC [2, 3].

Traditionally, cytotoxic drugs such as Ara-C and idarubicin are implicated [5]; whereas, recently a variety of other agents have been linked with NEC, including monoclonal antibody therapy with alemtuzumab [7], taxane-containing

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regimens [3, 8], cisplatin, and paclitaxel [3]. NEC may also be seen in noncancer population, recently a case was reported following unanticipated Chinese herbal drugs-induced neutropenia [9]. In children, similar agents have been associated with enterocolitis during neutropenia. A retrospective analysis from St. Jude's Children's hospital found a reduced risk of typhlitis in patients receiving Ara-C, methotrexate, and hydrocortisone along with trimethoprim-sulfamethoxazole [2]. By contrast, clinical trials with topotecan and irinotecan in children had to be terminated during the phase I due to high rates (45%) of typhlitis [10].

Neutropenia in patients with acute leukemia and those undergoing chemotherapy promotes translocation of microorganisms from host's intestinal lumen leading to tissue invasion and occasionally hematogenous dissemination. A retrospective study in pediatric cancer patients showed prolonged neutropenia and age >16 at cancer diagnosis were associated with a higher risk for typhlitis [2]. In a prospective study in adults, no specific risk factor for typhlitis was seen, and diagnosis was confirmed in 3.5% of cases [11]. An association with the presence of oropharyngeal mucositis and risk of NEC has been well described [4, 12].

NEC is a polymicrobial infection and organisms often associated with this disease entity include enteric Gram-negative bacteria (GNB) such as *Escherichia coli*, *Proteus* species, and nonfermentative gram-negatives in neutropenic patients like *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* are of concern; among the Gram-positive bacteria, streptococci, enterococci including vancomycin-resistant *Enterococcus* (VRE), and coagulase negative staphylococcus species may be accompanied with *Candida* species [1, 5, 13, 14]. Cytomegalovirus or adenovirus enterocolitis may act as a trigger for a secondary NEC in some cases [5, 15].

Pathogenesis

The pathogenesis of necrotizing enterocolitis remains uncertain. In the earlier studies, association with leukemia prompted theories of bowel wall infiltration of tumor cells as the initial insult for development of colitis during neutropenia [15]. It was later proposed that chemotherapy neutropenia on its own promoting colitis [3, 5, 12] especially, in patients with enterotoxic chemotherapy-related bowel wall injury. Interestingly, in a large series of children with cancer, typhlitis was noted in 12% of patients in the absence of neutropenia [2], suggesting an important role for a primary process, such as cancer infiltration, chemotherapy-mediated damage, undiagnosed viral, or toxin-mediated enterocolic damage. Although, occurrence of this disease in patients with aplastic anemia [12] and noncancer patient with Chinese herb-induced neutropenia [9] suggests

that severe neutropenic in certain individuals may lead to this clinical syndrome with no discernable prior damage to the intestinal tract.

Antimicrobial prophylaxis may influence the time of onset, etiology, and possibly incidence of NEC in patients undergoing cancer therapy. Antimicrobials are commonly used to prevent infections in high-risk patients with acute myelogenous leukemia, chronic lymphocytic leukemia, aplastic anemia, myelodysplastic syndrome, and those undergoing allogeneic stem cell transplantation. These antimicrobials have profound influence on microbial flora of the oro-intestinal tract, and may influence the potential organisms encountered with this syndrome [1, 5, 13, 14]. Increased use of high-dose chemotherapy and allogeneic stem cell transplantation in older patients may increase the rates of NEC. In a recent study, although in a small number of patients undergoing nonmyeloablative allogeneic stem cell transplant, the risk of typhlitis was only 6% [16].

Features on histopathologic examination of the involved bowel are diverse [3, 5]. These range from ischemic bowel in 12%, agranulocytic bowel in 19%, and pseudomembranous colitis in 69% [4]. Recent reports have shown findings indicative of mucosal damage and inflammation [4]. Some have reported leukemic infiltration of the bowel wall with no other significant findings [15, 17]. We suspect that NEC is a clinical syndrome of various primary causes, in most patients multiple factors appear to be responsible for this entity including severe neutropenia, young or advanced age, enteric insult due to cancer, drugs or bacterial toxins such as *Clostridium difficile*, subclinical viral disease, or unknown genetic polymorphisms that predispose some individuals to develop this disorder.

Diagnosis

In a retrospective study in adults, fever was present in 95%, 67% presented with abdominal pain which was often diffuse throughout the abdomen, and nearly all patients (95%) had diarrhea [5]. Presence of blood in the diarrheal stool indicated extensive intestinal wall damage and possibly herald bowel wall necrosis and perforation [5]. In a pediatric oncology study, 91% of patients exhibited abdominal pain, fever was present in 84%, and diarrhea in 72% of patients [2]. Distinguishing features for necrotizing enterocolitis in neutropenic patients are vague, and a high level of concern accompanied by frequent reevaluation remains central in the management for this potentially life-threatening complication in neutropenic cancer patients.

Fecal stool cultures provide limited information regarding the etiology of enterocolitis [18, 19]. Patients with concomitant bacteremia due to enteric organism(s) such as

Escherichia coli, enterococci, and streptococci give a partial spectrum of this polymicrobial disease, although sterile blood cultures do not exclude a low-grade, intermittent bacteremia and/or fungemia in the profoundly neutropenic susceptible patients [20]. Other common causes that may be mistaken for NEC include ischemic bowel injury, *C. difficile* colitis, appendicitis, or Ogilvie's syndrome [3]. To further complicate the diagnosis, there is a suggestion that the latter entities can coexist, with one small pediatric study suggesting that the combination of appendiceal thickening and enterocolitis may more likely to result in surgical intervention [21]. It was interesting to note that higher mortality was seen in children with NEC without evidence of appendicitis [21]. The frequency of NEC cases with concurrent or preceding *C. difficile* toxin-induced intestinal epithelia cell damage remains uncertain [22].

A comprehensive review of adult neutropenic patients with enterocolitis, appropriate diagnosis can be established by (1) >4 mm of bowel wall thickening on CT or ultrasonic abdominal scan combined with (2) clinical features such as fever, abdominal pain, and diarrhea (Fig. 16.1a) [3]. Several studies in pediatric and adults showed that a substantial proportion of neutropenic patients may not exhibit fever or abdominal pain during the early phase of the disease [2, 5, 11]. Therefore, a high level of suspicion in febrile neutropenic patients even in the absence of abdominal pain and/or distention with diarrhea or clinical or radiographic features of paralytic ileus should raise concerns for possible enterocolitis.

In older reports distal ileum and proximal colon were prominently involved in patients with this disease [23]. In recent reports, adult and pediatric neutropenic patients with clinical features of enterocolitis, mid and distal colon involvement is frequently appreciated and probably reflects frequently used sophisticated imaging scans [2, 3, 22]. As findings on abdominal ultrasounds and contrastenhanced CT scan are highly valuable [11], we recommend that bedside abdominal ultrasounds should be reserved for unstable patients in whom transport to the CT scan units is deferred, similarly, patients with other serious limitations for CT scan should than be evaluated with an abdominal X-rays and ultrasounds [2, 15].

The lack of an available gold standard for diagnosis of neutropenic colitis challenges the clinician to diagnose this syndrome. We suggest a combination of clinical symptoms such as abdominal pain, fever, or diarrhea in the setting of neutropenia and possibly cytotoxic chemotherapy combined with imaging studies (CT abdomen) that demonstrate bowel wall thickening (3–5 mm) and in severe case pneumatosis intestinalis may be used (Fig. 16.1b) [3, 11]. It is important to assess other potential treatable causes that may mimic these features such as ischemic colitis and *C. difficile* colitis. Some investigators have suggested that diagnosis of NEC
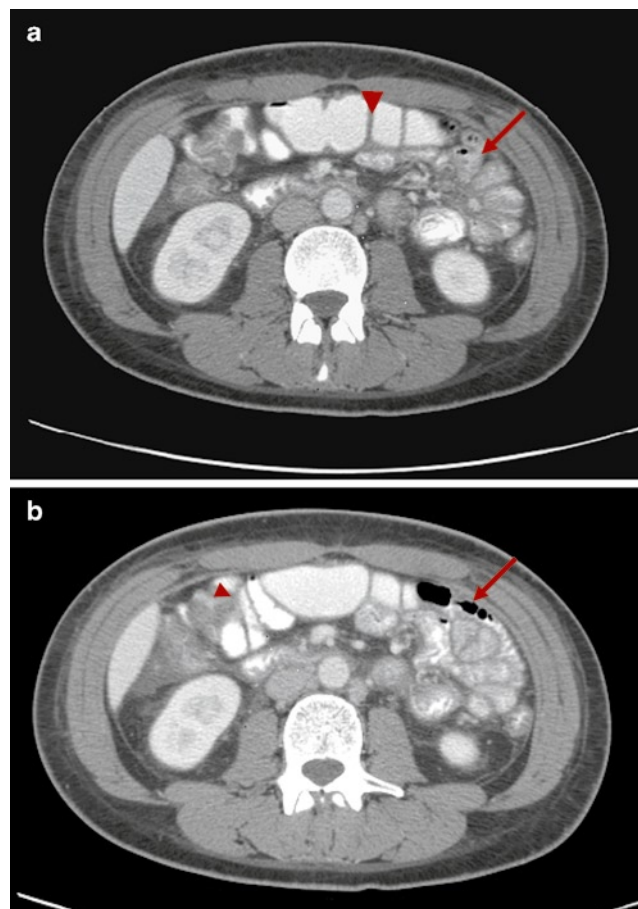
Fig. 16.1 CT scan findings show bowel wall thickening and areas of pneumatosis intestinalis in a patient with neutropenic enterocolitis. (**a**) Neutropenic colitis with thickening of the colon (*arrowhead*) and pneumatosis intestinalis (*arrow*), (**b**) Neutropenic colitis with thickening of the colon (*arrowhead*) and pneumatosis intestinalis (*arrow*)

should be reached after a thorough evaluation for other common etiologies [6].

Management

In patients with NEC, hastened recovery from neutropenia is important. Broad spectrum antimicrobial therapy is given for empiric coverage against enteric GNB, Gram-positive bacteria, and *Candida* species [3, 5, 13]. *Pseudomonas* species, other nonfermentative GNB, drug-resistant enteric GNB including extended spectrum beta-lactamases produces, and emergences of carbapenem-resistant enteric bacteria may further complicated empiric selection of appropriate antimicrobial choices. Similarly, vancomycin-resistant *Enterococcus*, multidrug-resistant staphylococci, and triazole-resistant yeast also play a role in the selection of appropriate therapy. In addition, there is a uniform recommendation to provide bowel rest, parenteral hydration,

electrolyte, and nutritional support. Bowel decompression in patients with ileus with nasogastric intermittent suction may also be warranted in select patients [3, 5, 13]. Cases of prolonged neutropenia may benefit from recombinant myeloid growth factors such as G-CSF or GM-CSF and in select patients with refractory neutropenia, healthy donor-derived granulocyte transfusions may be considered [5, 6, 17].

Surgery should be deferred in neutropenic patients when possible. Patients with complicated peritonitis, surgical intervention considerably improved outcomes and survival (100%) compared with patients who were given conservative supportive care alone (9%) [14]. Surgery may also be considered in children who have radiographic evidence of appendicitis, as rupture of inflamed appendix may significantly complicate management of NEC [21]. Minimally invasive surgical procedures such as laparoscopic repair and removal of devitalized tissue when possible are desirable, and laparotomy for a two-stage hemicolectomy has also been done for patients with disease confined to the right colon [6, 12]. The timely institution of therapy is the most important predictor of outcomes in patients with NEC. Delay in diagnosis and institution of appropriate therapy herald a poor prognosis [4, 6].

Clostridium difficile Infection

C. difficile infection (CDI) is a debilitating complication in cancer patients undergoing antineoplastic therapy and/or hematopoietic stem cell transplantation [24, 25]. The recent increase in the frequency of these infections in hospitalized patients, especially due to a hypervirulent strain, has further accentuated concerns for serious inpatient potentially life-threatening complications among immunosuppressed oncology patients [26, 27]. Antibiotic prophylaxis with trimethoprim-sulfamethoxazole and fluoroquinolones has been widely used in leukemic patients with chemotherapy-induced neutropenia to prevent bacterial infections. These patients have a higher risk for infections not only due to resistant Gram-negative bacteria and fluoroquinolone-insensitive viridans streptococci but also due to antibiotic-associated CDI [28].

In an epidemiologic study among 248 patients, diagnosis of acute leukemia was significantly associated with carrier state of *C. diff* during an outbreak of clinical disease [15].

In neutropenic patients who are undergoing treatment for hematologic malignancies, the frequency of CDI was 7% among 875 courses of myelosuppressive chemotherapy [29]. In another study of 557 stool samples from 156 hospitalized cancer patients, *C. diff* or its toxin was identified in 35% of patients on oral antimicrobial prophylaxis, whereas *C. diff* was isolated in only 12% of other patients [30]. Therefore,

CDI should be suspected in all hospitalized cancer patients with neutropenia who develop diarrheal illness, despite the fact that chemotherapy-induced oro-intestinal tract mucosal disruption may have indistinguishable clinical and radiologic features. Furthermore, in patients with leukemia, CDI has been associated with secondary systemic bacterial infections, such as vancomycin-resistant enterococcal intestinal colonization, and is at a significantly higher risk for VRE bacteremia following CDI [31].

Epidemiology and Risk Factors

The use of broad-spectrum antibiotics like fluoroquinolones has been identified as the most significant risk factor for CDI due to depletion of colonic aerobic flora. In addition, exposure to multiple antibiotics for the treatment of infections makes patients more vulnerable to this infection. Other precipitating factors that increase the risk for acquiring CDI include being elderly, immunosuppressed or with multiple comorbidities, receiving tube feedings, parenteral feedings, or undergoing gastrointestinal surgery, and cancer chemotherapy. Certain host-related factors like infection by human immunodeficiency virus, solid organ transplantation, or bone marrow transplantation render them particularly susceptible to CDI.

In a case-control study, treatment with low-dose chemotherapy, lack of parenteral use of vancomycin, and recent hospitalization were found to be independent predictors of CDI in oncology patients [32]. In an interesting study among children with cancer, no association was found between presence of toxigenic *C. diff* and receipt of antibiotics and/or administration of chemotherapy [33]. This absence of the classic risk factors seen in adults indicates that toxigenic strains of *C. diff* may in fact be part of the normal flora in young children [33]. However, outbreaks of CDI have been reported in pediatric oncology units [34]. On the other hand in adult oncology units, CDI outbreaks are more often seen in older individuals, those on antibiotics who are simultaneously treated with antineoplastic chemotherapy [35] or with chemotherapy alone [36]. Elderly patients are at a higher risk for developing serious CDI with an increased probability for recurrent CDI and secondary complications including prolonged bowel dysfunction, bowel perforation, and life-threatening toxic megacolon.

In another 2-year case-control study cancer patients compared with hospitalized patients without cancer were 22 times more likely to have received antibiotics during or 4 weeks prior to hospitalization. The trend for occurrence of CDI was higher in patients with exposure to an increased number of antibiotics [37]. Interestingly, the investigators noted a 7 times more likelihood of CDI in cancer patients treated with recombinant interleukine-2 [37]. In a case-control study in cancer

patients with diarrhea, it was observed that patients with CDAD were 22 times more likely to have received any antibiotics and 7 times more likely to have received interleukin-2 during hospitalization or in the preceding month [37]. In patients with multiple myeloma or lymphoma, the risk of CDI is low although this risk increases following autologous stem cell transplantation to 15% [38, 39]. Fifteen percent of the patients who underwent autologous peripheral blood stem cell transplant experience CDI [38, 39]. Two thirds of these patients had multiple myeloma while 1/3 had lymphoma. However, this difference was not statistically significant. The risk factors associated with CDI in these patients were prior therapy with cephalosporins and intravenous vancomycin, On the other hand, patients treated with paclitaxel had a lower incidence of CDI when compared to those who were treated with hematopoietic growth factor as part of mobilization regimen [39]. Whereas inpatients undergoing allogeneic hematopoietic stem cell transplantation, nearly 50% of diarrheal episodes is due to acute graft-versus-host disease, while 15% is due to intestinal infections, and <5% is due to nosocomial CDI [40]. In another case-control study among outpatients at a cancer center, CDI was associated with prior antibiotic exposure and not unexpectedly, patients receiving clindamycin were nearly fourfold more likely to develop CDI; and for each additional day of clindamycin and oral cephalosporins, the patients were nearly twofold more likely to develop CDI [38].

Acute leukemia patients are exposed to higher risk of CDI while on chemotherapy due to probable intestinal track colonization and diarrheal disease [41–44]. 5-fluorouracil has been implicated in increasing the risk of CDI in patients with solid-organ cancer [45]; 5-fluorouracil-associated CDI was not seen in the older studies [46]. Treatment with mitoxantrone and etoposide has also been associated with CDI in patients with no antibiotic exposure for over 6 months [47]. Similarly, in patients with gynecologic malignancies, treatment with paclitaxel, carboplatin combination, or cisplatin-based has been noted to increase the risk for CDI [48–50]. In breast cancer patients undergoing autologous stem cell transplantation, the risk of CDI is nearly 10% [51]; whereas 16% of those receiving salvage therapy with ifosfamide, carboplatin, and etoposide for metastatic and refractory breast cancer experience grade 3–4 gastrointestinal toxicity, although the risk of CDI is only about 1% [52]. Others have observed that 45% of diarrheal episodes were due to *C. diff* in patients receiving intensive chemotherapy for disseminated germ cell cancer [53].

Pathogenesis

The surface layer proteins (SLPs) of *C. diff* play a significant role in activating the host immune response in CDI. SLPs are the outermost surface components of the bacterium that are responsible for their colonization and adhesion to the intestinal mucosa [54]. It has been proposed that SLPs attach to both the intestinal epithelial cells and some components of their extracellular matrix fibers, resulting in epithelial damage. In addition, the pathogenicity of CDI is attributed to the loss of the delicate balance between regulatory and inflammatory cytokines in the immune regulatory cells like monocytes and dendritic cells [55].

Although strains of *C. diff* are noninvasive, their toxins penetrate the mucosal barrier and initiate an immune response in the host [56]. Depending on the immune status of the individual, the latency period also varies from few days to 8 weeks and they clinically manifest with varying degrees of severity, from episodes of diarrhea to fatal toxic megacolon [57]. The ability of the host to produce specific antibodies against toxins and/or cellular antigens [58, 59] and to initiate the most appropriate cellular response [60] is a key factor accounting for the wide spectrum of the disease [61]. Low serum and/or intestinal antibody response to *C. diff* toxin A is associated with severe, prolonged, and recurrent *C. difficile* diarrhea [62]. This was not due to widespread humoral immune deficiency or of IgG subclass deficiency but due to selective reduction in IgG2 and IgG3 subclass responses [63]. Adequate antibody response to toxin A is therefore an important element in asymptomatic carriage of *C. diff* and in clinical recovery from CDI [61, 62].

Diagnosis

The diagnosis of CDI is based on both clinical as well as laboratory findings. Early diagnosis of CDI helps to initiate aggressive treatment and prevents complications like dehydration, electrolyte imbalance or depletion, and even hemorrhage. In patients presenting with diarrhea, diagnosis of CDI can be established by any of the following standard stool investigations: stool culture for *C. diff*, stool enzyme immunoassay for enterotoxin A and cytotoxin B, and tissue culture stool cytotoxicity test for toxin B. Colonoscopy or sigmoidoscopy can reveal Pseudomembranes, which are diagnostic of advanced CDI. At times they help diagnose CDI even before the stool results are available [64]. It is also important to consider a concurrent opportunistic infection in severely immunosuppressed neutropenic patients with CDAD. In patients with acute leukemia and in whom symptoms persist despite appropriate CDAD therapy, diagnostic assays for CMV reactivation, such as CMV antigenemia, serum fungal antigen like galactomannan, and if possible histological evaluation of tissue samples for special viral and fungal stains, may provide life-saving information.

Management

The mainstay of treatment is withdrawal or substitution of the offending antimicrobial agent and initiating specific treatment for CDI. Oral vancomycin 125 mg is given 4 times a day for 10 days and metronidazole 250 mg 4 times a day for 10 days is considered standard treatment. Administration of intravenous metronidazole can be used in patients unable to take oral drug. Although majority of the patients show significant symptomatic improvement within 2 days, the mean time ranges from 2 to 5 days. Recurrent CDI as well as reinfection of *C. diff* strains can be successfully treated with the same specific treatment regime. More severe cases of CDI should receive oral vancomycin as has been established in noncancer patients [65].

Other pharmaceutical agents that can be as effective as the vancomycin regime against CDI are teicoplanin 100 mg administered twice a day. Treatment with bacitracin and colestipol, an ion exchange resin though effective, produces response rates that are lower than with vancomycin [64].

Prevention and Control

Prevention of CDI should be given priority. Adopting barrier precaution using gloves can significantly reduce the spread of infection from patient to patient as well as from medical personnel. Hand washing using soap and water can protect hospital personnel from acquiring this infection. Isolation of patients with CDI, cleaning and disinfecting the rooms occupied by CDI patients with dilute clorox, and use of disposable rectal thermometers can reduce the incidence of CDI [66]. Restricted use of broad spectrum antibiotics has proved to reduce the incidence of CDI in hospitals. Administration of the probiotic *Saccharomyces boulardii* may have prophylactic value in reducing CDI in the setting of a hospital outbreak [64].

Summary

Neutropenic colitis was first described in the 1970s [67] as a clinical syndrome characterized by fever, abdominal pain, and diarrhea in the setting of neutropenia with bowel wall thickening. In the absence of large multicenter prospective trials in adults with this gastrointestinal complication management is based on anecdotal evidence. Patients with acute leukemia, aplastic anemia, or advanced solid organ malignancies treated with salvage high-dose cytotoxic chemotherapy are at increased risk [2, 3, 5, 13]. A high level of suspicion

and evaluation for other frequently encountered conditions that mimic this syndrome is important. Most patients respond to a multifaceted approach including total bowel rest, parenteral hydration, electrolyte replacement, and nutritional support along with broad spectrum antimicrobial therapy [3, 5, 13]. Recombinant myeloid growth factors are important in the management of these patients and should be considered early in the course of therapy. Donor granulocyte transfusions are reserved for patients with refractory severe neutropenia and impending bowel perforation [5]. Finally, in patients with complicated peritonitis, surgical evaluation may be necessary [6, 14].

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Chapter 17
Management of Reactivation of Hepatitis B and Hepatitis C During Antineoplastic Therapy

Marta Davila and Harrys A. Torres

Abstract Hepatitis viruses can cause serious illness in patient with cancer and those who have undergone stem cell transplantation (SCT). Patients with hematological malignancies chronically infected with either Hepatitis B virus (HBV) or Hepatitis C virus (HCV) are at risk for viral reactivation following chemotherapy. HBV reactivation is a common and serious complication but preventable. HCV has a lower reactivation rate following chemotherapy than HBV, but its presentation can be severe and nonpreventable. In this chapter, we review the management of reactivation of viral hepatitis during antineoplastic therapy affecting patients with cancer or SCT.

Keywords Hepatitis B • Hepatitis C • Reactivation

Introduction

Viral infections are common complications among cancer patients associated with significant morbidity and mortality; especially those with hematologic malignancies and those who have undergone stem cell transplantation (SCT). Hepatitis viruses can cause serious illness in these patient populations.

Patients with hematological malignancies chronically infected with either Hepatitis B virus (HBV) or Hepatitis C virus (HCV) showed a significantly higher incidence of severe liver dysfunction, after chemotherapy, compared with noninfected patients [1, 2]. In this chapter, we review the management of reactivation of viral hepatitis during antineoplastic therapy affecting patients with cancer or SCT recipients.

Reactivation of Hepatitis B Virus

HBV reactivation is a well-recognized complication in cancer patients undergoing immunosuppressive therapy or hematopoietic SCT. Although it has been most reported in hepatitis B surface antigen (HBsAg) positive patients, it can also occur in those who are HBsAg negative but positive for the antibody to hepatitis B core antigen (anti-HBc) alone or with antibody to hepatitis B surface antigen (anti-HBs) [3, 4].

The reported frequency of HBV reactivation in HBV carriers undergoing chemotherapy ranges widely from 14 to 72% [3, 5]. The variation may be related to differences in patient populations, type of cancer (hematologic vs. solid), chemotherapy regimens, definition of HBV reactivation, and study designs.

Although there are no uniform diagnostic criteria available, most studies define HBV reactivation as an increase in serum HBV DNA level to more than 1 log higher than that of baseline, or an absolute increase exceeding 6 $\log_{10}$ copies/mL , or serum HBV DNA turning from negative to positive [6]. Hepatitis is commonly defined as a more than threefold increase of serum ALT on two consecutive determinations at least 5 days apart [6]. When evaluating patients with possible HBV reactivation, other causes of hepatitis should be excluded including superinfection with other viruses, drug toxicity, sino-occlusive disease, graft-versus-host disease, and liver involvement with tumor.

Pathogenesis and Clinical Manifestations

The typical course of reactivation starts with an increase in viral replication caused by the immune suppression of cytotoxic therapy [7, 8]. The degree of increase in viral replication can be demonstrated by a rise in HBV DNA in serum. During this time, there may be reappearance of HBeAg and HBsAg, with a decrease in anti-HBs titers. The second stage of reactivation occurs when chemotherapy is discontinued

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and the immune system is restored leading to the destruction of hepatocytes infected with HBV. Elevation in ALT levels and symptoms of hepatitis, including jaundice, may ensue. During this phase, HBV DNA levels may start to fall. The third phase of reactivation is recovery during which the clinical hepatitis resolves and HBV markers return to baseline levels [7]. Not all patients with HBV reactivation will go through all these phases. In some patients, HBV DNA remains high but there is no immune reconstitution; therefore, acute hepatitis does not develop. In others, the hepatitis phase is severe, leading to death. Yet, in other cases, the hepatitis phase persists and it may lead to the establishment of chronic hepatitis and deterioration of liver function [9].

HBV reactivation may be asymptomatic or may present with classic symptoms of hepatitis including fatigue, anorexia, jaundice, ascites, coagulopathy, and hepatic encephalopathy. Some patients may progress to liver failure and death. HBV reactivation may also result in significant delays or disruption in treatment and decreased overall survival [3, 10]. The mortality rate of HBV reactivation ranges from 5 to 40% [11, 12].

Risk Factors

Several risk factors are associated with an increased risk for HBV reactivation. Among them, a high serum HBV viral load has been consistently found to be one of the most important ones [13]. Other risk factors include a diagnosis of lymphoma or breast cancer, male gender, young age, use of steroids, and the use of certain chemotherapeutic agents (anthracyclines) [3, 14, 15]. Another viral factor that has been investigated is hepatitis B e antigen but the results are conflicting, and this is likely related to the presence of the precore/core promoter HBV mutants [3, 14, 16].

Monoclonal antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52), have also been linked to HBV reactivation. Rituximab is effective in treating B-cell tumors and is used for the treatment of both low-grade and high-grade non-Hodgkin's lymphomas. The most frequent viral infection complicating rituximab therapy is HBV reactivation, and it accounts for 39% of the reported cases, with a 52% mortality rate due to liver failure [17].

Management of HBV Reactivation

Multiple studies have shown that prevention is superior to intervention at the time of reactivation. Preventative measures should start with screening for HBV markers before initiation of chemotherapy. Patients should be tested for HBsAg and anti-HBc and anti-HBs antibodies. Those who are HBsAg positive should be further tested for HBeAg, anti-HBe, and HBV DNA.

For HBsAg positive patients, prophylactic therapy for HBV should be started as soon as possible before initiation of chemotherapy or other immunosuppressive therapy [8, 10, 12]. Lamivudine, a nucleoside analog, has been commonly used in this setting with minimal toxicity. In a randomized controlled study, 30 HBsAg-positive lymphoma patients were randomized to receive lamivudine 100 mg daily 1 week prior to initiating chemotherapy or to have this treatment deferred until was serologic evidence of HBV reactivation. None of the patients in the preemptive treatment group experienced reactivation, as opposed to eight patients (53%) in the deferred treatment group ($p = 0.002$) [18]. In another randomized trial of 73 patients with hepatocellular carcinoma undergoing transarterial chemo-lipiodolization (TACL), patients were randomized to preemptive lamivudine 100 mg daily at the start of TACL vs. deferred treatment (control) until there was confirmation of HBV reactivation. Patients in the preemptive group were continued on lamivudine for 12 months after completion of TACL. Eleven patients (30%) in the control group and one patient (3%) in the preemptive treatment group developed HBV reactivation ($p = 0.002$). In addition, there were significantly more episodes of overall hepatitis and severe grade of hepatitis in the control group [19]. A recent meta-analysis on the efficacy of preemptive lamivudine on HBV reactivation included 14 studies, with 275 patients in the treatment group and 475 control participants [20]. The relative risk (RR) in favor of preventive lamivudine vs. no prevention ranged from 0.00 to 0.21 for both HBV reactivation and HBV-related hepatitis. With one exception for an HBV-related death in one study, regardless of design, all studies reported beneficial effects of preventive lamivudine treatment [20].

The optimal time to start and discontinue anti-HBV treatment for the prevention of HBV reactivation remains uncertain. One concern is that the highest HBV reactivation rates have been observed in studies with the longest follow-ups after completion of chemotherapy [21]. Furthermore, reactivation rates after lamivudine withdrawal are significantly higher in patients with higher prechemotherapy HBV DNA levels and HepBeAg seropositivity [21]. For patients receiving conventional chemotherapy, lamivudine has been recommended for at least 6 months after discontinuation of all immunosuppression [7, 8, 12, 22]. Longer duration of treatment (12 months or more) may be necessary for patients receiving monoclonal antibody therapies or hematopoietic SCT [21, 23, 24]. Patients with high baseline HBV DNA (>2,000 IU/mL) should continue treatment until they reach treatment endpoints as in immunocompetent patients [22].

An area of concern with longer duration of lamivudine therapy is the development of resistant mutations [12].

There are newer nucleoside analogs approved for the treatment of patients with hepatitis B infection including adefovir, entecavir, telbivudine, and tenofovir. For those patients in need of prolonged anti-HBV therapy, it might be appropriate to use drugs with low-incidence of resistance (adefovir, entecavir, or tenofovir) as first-line preemptive therapy [22]. Interferons should not be used in patients undergoing cytotoxic therapy because of its bone marrow suppressive effects.

Patients who are HBsAg-negative and anti-HBc positive should be considered for antiviral prophylaxis, especially if prolonged immunosuppression or SCT is contemplated [7]. Prophylaxis should continue for at least 6 months after discontinuation of chemotherapy.

When managing a patient with the clinical diagnosis of HBV reactivation who has not received prophylactic anti-HBV therapy, all chemotherapy must be suspended and treatment with nucleoside analogs must be instituted. Experience with lamivudine indicates that this drug might be effective but mortality from hepatic failure may still be high [12, 23].

Reactivation of Hepatitis C Virus

The prevalence of HCV infection in cancer patients varies between 1.5 and 8.2% [1, 25, 26], and is more common than HBV infection even in endemic areas [1, 27]. On the other hand, although the prevalence of HCV infection in patients with cancer is high, patients with hematological malignancies and chronic HCV infection have a significantly lower incidence of severe liver dysfunction or viral reactivation following chemotherapy when compared to HBV-infected patients [1, 26]. The reason for this difference is unknown [1, 27]. Of interest, the mortality rate seems to be similar between HBV and HCV infected patients once severe hepatitis developed secondary to reactivation [28].

Currently, no uniform definition for HCV reactivation is available, but it has defined as a threefold or greater increase in serum alanine aminotransferase (ALT) level, in the absence of liver infiltration of cancer, hepatotoxic drugs, recent transfusion, and other systemic infections. Changes in liver enzymes should be accompanied by a sudden increase in serum HCV RNA level or reappearence of HCV RNA [27].

Pathogenesis and Clinical Manifestations

As reported for HBV infection [27, 29], reactivation of HCV occurs when chemotherapy depresses the immune system, leading to enhanced viral replication that exceeds largely the kinetics of the immune response and increased infected hepatocytes [30]. In addition, withdrawal of cytotoxic or immunosuppressive treatments may lead to an immunological rebound after a period of depressed cellular immunity with restoration of the host immune function and increase inflammatory activity in the liver, resulting in rapid destruction of the infected hepatocytes and liver injury [26, 30].

The possibility of HCV reactivation should be considered in patients with a history of chronic HCV infection developing liver dysfunction following chemotherapy. However, the timing of HCV reactivation may vary. It can occur during chemotherapy, but it is more frequently seen few weeks or months following withdrawal of chemotherapy and/or corticosteroids [26, 31–33]. In a series of 18 patients with hematologic malignancies who experienced acute exacerbation of chronic HCV infection, the increase in aminotransferase levels occurred at a mean of 19 days (range, 14–32 days) after withdrawal of chemotherapy, most commonly after the fourth or fifth cycle [32].

In the majority of cases, the acute elevation of ALT or HCV RNA is asymptomatic, with mild and transient elevation of the ALT levels. Some patients may have more severe flares with massive necrosis, liver failure, and death [34, 35]. In some of the fatal cases, HCV RNA levels increased dramatically during treatment, with a sharp decrease in HCV RNA and a marked increase in aminotransferase levels occurring on withdrawal of chemotherapy [35]. Of note, HCV viremia could be low in cases of severe hepatitis, probably because of massive liver cell necrosis and absence of suitable cells for viral replication [35]. Among patients who experienced severe hepatitis during chemotherapy, liver function tests return to normal within 2–3 weeks of discontinuation of the offending agent [32]. However, peak ALT levels above 6,000 IU/L with a delay recovery of about 7 weeks have been reported in cases of fulminant hepatitis [35].

In some cases of severe hepatitis due to HCV reactivation, chemotherapy needs to be discontinued [31, 32, 36]. Based on preliminary data from our institution, chemotherapy regimens in individuals with acute exacerbation of chronic HCV infection were discontinued in up to 22% of patients [25]. Chemotherapy can be restarted after the acute event when the liver function tests became normal.

In SCT recipients, severe hepatic dysfunction and fulminant hepatic failure can occur, with significantly increased HCV RNA levels during immunosuppressive therapy and fulminant hepatitis occurring after withdrawal of immunosuppressives, which most commonly included cyclosporine and/or prednisone [37–40].

HCV infection may be diagnosed using serological assays for antibodies and molecular tests for viral particles. Antibodies against HCV are detected by enzyme immunoassays that are very sensitive and very specific. However, cancer patients, especially those with hematologic malignancies,

can have false-negative results [31, 41–43]. Even more, during chemotherapy and immunosuppressive therapy, HCV serology may be negative, thus making HCV RNA monitoring by polymerase chain reaction useful. Patients who are chronically infected with HCV, and are suspected to be having an HCV reactivation, should have HCV RNA levels measured for virologic confirmation [33].

Risk Factors

HCV reactivation in cancer patients appears to be more common in males, with underlying lymphoma (mainly non-Hodgkin's lymphoma), and prior exposure to corticosteroids [25, 26, 35]. Reactivation has also been reported in patients receiving chemotherapy for solid tumors [44], or SCT recipients [37, 40].

The presence of corticosteroids in the chemotherapy regimens is considered one of the most important risk factors for chemotherapy-induced HCV reactivation. These agents can induce the replication of HCV in vivo and in vitro [45]. Other chemotherapy or immunosuppressive drugs that have been linked to the reactivation of HCV include cyclophosphamide, doxorubicin, vincristine, cytarabine, bleomycin, etoposide, vinblastine, dacarbazine, busulfan, methotrexate, and cyclosporine [25, 35, 37, 40, 46], and the newer chemotherapy drugs rituximab and alemtuzumab [34, 46, 47]. However, it should be noted that many of these patients were treated simultaneously with corticosteroids [25, 34, 37, 46, 47]. The association between HCV reactivation and specifics HCV genotypes has not been clearly established.

Management of HCV Reactivation

The combination of pegylated interferon alfa and ribavirin can eradicate the HCV in more than 50% of patients. Combination therapy is more effective than monotherapy with either agent and has a higher rate of sustained virological response [48].

Unfortunately, the best strategy of managing HCV reactivation is not clear. Unlike HBV, there are no approved drugs for primary prophylaxis of HCV reactivation in chronically infected patients undergoing chemotherapy.

In HCV-infected cancer patients, the hematologic side effects of HCV drugs can exacerbate the side effects of chemotherapy, and fear for complications such as severe cytopenias and invasive infections has excluded the use of HCV therapy in patients undergoing intensive chemotherapy [36]. However, there is emerging data to suggest that antiviral treatment could be considered when liver dysfunction prohibits the administration of life-saving chemotherapy. Based on a recent small case series, combination therapy of standard interferon-alfa and ribavirin was given simultaneously to chemotherapy in three children with hematologic malignancies who presented with severe HCV exacerbation during intensive chemotherapy. The decision to initiate concomitant therapy was made when hepatic dysfunction led to complete inability to use chemotherapy. Patients were continued on antiviral treatment while they received intensive chemotherapy. Two children tolerated interferon plus ribavirin well, while the remaining patient developed severe febrile episodes, with prolonged neutropenia and depression [49]. Unfortunately, HCV therapy could be poorly tolerated and had to be discontinued due to severe hematologic toxicity in some adults in whom simultaneous use of antivirals and chemotherapy has been attempted [34]. In other study, ribavirin monotherapy administered during conditioning regimen and after transplant in HCV-infected patients requiring SCT appeared to be safe and effective in clearance of HCV RNA [50]. Large scale studies are needed to better define the cancer population that will benefit from this simultaneous therapeutic intervention.

Potential strategies to reduce the risk of HCV reactivation in cancer patients with chronic infection undergoing cytotoxic chemotherapy include the use of less aggressive and less immunosuppressive chemotherapy protocols in HCV-infected patients, and close monitoring of ALT throughout the course of chemotherapy, especially after immunosuppressive therapy is reduced or withdrawn, with early measurement of HCV RNA levels during episodes of potential viral reactivation.

To date, there is not enough information to recommend secondary antiviral prophylaxis for the population that has been exposed to HCV but are HCV negative.

Summary

HBV reactivation is a serious but preventable complication of immunosuppressive therapy. All patients at risk should be screened for HBV markers. Prophylactic anti-HBV therapy is effective. Lamivudine has been found to reduce the risk for HBV reactivation and HBV-associated morbidity and mortality. The use of newer nucleoside analogs is recommended for those who will require prolonged (>12 months) therapy. It seems that HCV have a lower reactivation rate following chemotherapy than HBV, but its presentation can be fatal. The best strategy of managing HCV reactivation is not clear.

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Chapter 18
Management of Genitourinary Tract Infections

Amar Safdar and Maurie Markman

Abstract The risk of developing an infection in patients with genitourinary tract malignancy arise from a host of factors such as: (1) tumor encroachment and invasion of adjacent structures; (2) tumor necrosis; (3) complications arising from antineoplastic chemotherapy; (4) early and late effects of abdomiopelvic radiation therapy; (5) surgical tumor excision and removal of internal organs; (6) structural abnormalities resulting from surgical diversion procedures; and (7) other causes that disrupt protective barriers in urinary and female reproductive tract. The spectrum of causative organisms most frequently arise from patients' endogenous microflora. The vagina, lower urinary and intestinal tract colonization with bacteria and yeast serves as important sources for infection. The normal aerobic and anaerobic vaginal bacterial flora may be altered in patients undergoing antineoplastic therapy. Among factors that influence changes in colonization includes, hormonal dysfunction, frequent exposure to broad-spectrum antimicrobial agents, antineoplastic therapy, hospitalization, and instrumentization. Peritonitis, intraabdominal abscess, complicated urinary tract infection, surgical wound infection, skin and soft tissue infection such as cellulitis, necrotizing fasciitis, clostridial myonecrosis, and septic pelvic thrombophlebitis are important infectious complications encountered in patients with genitourinary tract malignancies.

Keywords Genitourinary tract • Cancer • Peritonitis • Intraabdominal abscess • Urinary tract infection • Surgical wound infection • Cellulitis • Necrotizing fasciitis • Clostridial myonecrosis • Septic pelvic thrombophlebitis

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Introduction

The risk of developing an infection in patients with genitourinary tract malignancy arise from a number of factors such as: (1) tumor encroachment and invasion of adjacent structures; (2) tumor necrosis; (3) complications arising from antineoplastic chemotherapy; (4) early and late effects of abdomiopelvic radiation therapy; (5) surgical tumor excision and removal of internal organs; (6) structural abnormalities resulting from surgical diversion procedures; and (7) other causes that disrupt protective barriers in urinary and female reproductive tract [1, 2].

The spectrum of causative organisms most frequently arise from patients' endogenous microflora. The vagina, lower urinary, and intestinal tract colonization with bacteria and yeast serves as important sources for infection. The normal aerobic and anaerobic vaginal bacterial flora may be altered in patients undergoing antineoplastic therapy. Among factors that influence changes in colonization includes, hormonal dysfunction, frequent exposure to broad-spectrum antimicrobial agents, antineoplastic therapy, hospitalization, and instrumentization.

The female genital tract is rich in anaerobic microflora. Bacteria belonging to *Peptococcaceae* are the most prominent organisms in the normal vaginal flora. Quantitative vaginal cultures in recent studies showed that anaerobic bacteria outnumbered aerobic bacteria by nearly 10:1; these include peptococci, *Lactobacillus*, *Corynebacterium*, *Eubacterium*, and *Bacteroides* species which are common organisms isolated [3]. *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species are the aerobic gram-negatives and streptococci, enterococci, and coagulase-negative staphylococcus are gram-positive bacteria isolated form of lower female genital tract. These organisms provide an important reference to local and invasive infections seen in patients undergoing treatment for gynecologic malignancy.

Patient with Fever

In Table 18.1 factors that increase the risk for infection are shown. Awareness of specific cancer-therapy associated risks and host's underlying immune dysfunction may allow proper selection of empiric antibiotic therapy in critically ill patients prior to the results of microbiologic culture and radiographic studies becomes available. It is important to note that patients with gynecologic cancer may have a high risk of polymicrobial infections due to anatomic proximity to lower intestinal and urinary tracts [4]. In certain infections such as deep tissue abscess, cellulitis in patients with chronic fistula tract, presence of large necrotic tumor, history of multiple instrumentization probability of polymicrobial infection remains high [4]. Obstruction to pelvic venous and lymphatic flow in patients with advanced cancer with history of radiation therapy increases the risk for skin and soft tissue infection, deep pelvic infection, abscess formation, and septic thrombophlebitis. These may be difficult to distinguish from noninfectious tumor-related complications.

Table 18.1 Predisposing risk factors and infections in patients with gynecologic tumor

Tumor-related

Obstruction of gastrointestinal or urinary tract

Erosion into bowel, urinary tract, peritoneum or retroperitoneal

Necrosis of rapidly growing cancer promote abscess formation

Lymphatic obstruction

Surgery

Aspiration pneumonia

Hospital-acquired pneumonia, including ventilator-associated pneumonia

Wound infection, skin and skin structure infection

Tissue necrosis due to disruption of blood supply

Infected hematoma

Fistula tract communication between intestinal and urinary tracts

Complicated peritonitis

Septic deep thrombophlebitis

Fasciitis, myositis, and gas gangrene are rare complications

Chemotherapy

Febrile neutropenia

Pneumonia

Neutropenic enterocolitis

Radiation therapy

Enteritis

Urinary tract infection

Poor wound healing

Catheter and implantable devices

Device infection

Peritonitis

Bloodstream infection

Urinary tract infection

Tumor-Related

The tumor associated infections are dependent on the site and extent of tumor involvement. In patients with early stage of locally involved cancer such as stage I cervical cancer, most infections remain localized to vagina. Whereas, in patients with advanced cervical cancer infections may involve fallopian tubes, ovaries leading to tubo-ovarian abscess, uterine involvement may cause less frequently seen pyometra. Extension of these infections to adjacent structures such as urinary tract presents as ascending pyelonephritis; rectal abscess, and complicated peritonitis are serious and difficult-to-treat infections [5, 6]. It is also important to note that an infection may be the primary presentation of an undiagnosed malignancy involving female reproductive tract. In a study of postmenopausal women who presented with tubo-ovarian abscess, nearly half of these patients were subsequently diagnosed with a gynecologic malignancy [7]. Therefore, we recommend a thorough investigation for possible underlying cancer that should be considered in postmenopausal women or those with no risk factors for sexually transmitted diseases who present with tubo-ovarian abscess or pyometra.

The advances in improved outcomes for serious systemic bacterial and yeast infections are in most part due to availability of well-tolerated broad-spectrum antimicrobial agents. The recent emergence and spread of multidrug-resistant organisms, however, may mitigate these gains and even patients with solid-organ cancer with limited immune suppression may develop life-threatening septicemia and peritonitis as noted during 1970s [8].

Surgery-Related

Patient undergoing surgery for cervical cancer have higher rate of infectious complications while patients with endometrial cancer tolerate surgery better and have less infections during early and late postoperative period [9]. Pelvic exenteration is performed in patients with advanced and/or treatment refractory cervical and upper reproductive tract malignancy. Infections remain as serious morbidity following pelvic exenteration; early postsurgical wound infection and wound dehiscence are not uncommon [10]. Urinary tract infections are also frequently seen in patients with urinary fistula, and/or those who develop urethral obstruction. Studies show, greater than 40% of patients undergoing pelvic exenteration for gynecological and rectal cancer had urinary tract infection and wound dehiscence [11]. Late infections such as ascending pyelonephritis may be serious, as these

infections are often recurrent and seen in patients with usually irreparable structural damage to the urinary reservoir, urethral stenosis, and anastomosis obstruction. Ureterointestinal fistula, stones in the urinary reservoir and stenosis all contribute to increase risk of infections and unless the anatomical abnormality are corrected, these patients remain at increased risk for recurrent urinary tract infections and complication arising from prolonged systemic antibiotic therapy and hospitalization.

Empiric therapy includes adequate coverage for possible polymicrobial infection, and choice should include drugs that provide adequate coverage for enteric coliforms, enterococci, including vancomycin-resistant *Enterococcus* species, especially in patient with known prior intestinal or genitourinary tract colonization due to these drug-resistant bacteria [12]. As most infections in this setting may also have an anaerobe as copathogen, even in patients with negative microbiologic evidence of anaerobic infection, antibiotic selection should entertain possibility of concurrent mixed anaerobic–aerobic infection. We recommend secondary suppressive antimicrobial therapy in patients with recurrent deep pelvic infection to reduced morbidity and subsequent hospitalization and surgeries. As it is critical to select high-risk patients judiciously, patients are not given prolonged courses of broad-spectrum antibiotics, inappropriately which is the single most important factor in promoting drug resistance in healthcare-associated infections.

Infections remain main concern in patients following radical vulvar resection and inguinal lymphadenectomy. Early postoperative cellulitis was noted in nearly one third of patients undergoing inguinal lymphadenectomy and in over 20%, early surgical wound breakdown also occurred [13]. Whereas, late cellulitis at surgical site was noted in patients with chronic lymphedema and in most patients surgical wound was not compromised [13].

Wound Infection

Infected surgical wound in patients following female genital tract surgery include *Staphylococcus aureus,* including multidrug-resistant strains (MRSA) obtained from healthcare microflora (healthcare-associated; HA) or community acquired (CA)-MRSA, which has now become the leading source of MRSA in the United States. *Streptococcus* species (group A, B, C and G) are also commonly pathogens in this population and nearly one third of infections, especially those with involvement of lower intestinal tract and urinary tract are less likely to be monomicrobial.

In patients treated with systemic corticosteroids for extended periods, patients with morbid obesity and those with diabetes mellitus have a higher risk of developing postoperative wound infections. Coagulase-negative staphylococcus, *Streptococcus* species, *S. aureus*, enteric gram-negative bacteria, and *Bacteroides* species are potential pathogens.

Patients who have a complicated hospital course following surgery may develop infections due to organisms acquired from the healthcare microenvironment. In critically ill patients, infections are treated empirically and spectrum of causative organism(s) may not be available at the time of medical decision making. Knowledge of regional and institutional prevalence of drug-resistant organisms is required in prescribing appropriate treatment regimen. The empiric therapy in patients with prolonged hospitalization, and anatomical abnormalities such as enterouretheral, entero-, rectovaginal or enterovesicular fistula increases probability of recurrent infection due to resistant HA-gram-negative bacteria such as *Pseudomonas* species, extended-spectrum beta-lactamases producing *Enterobacteriaceae*, including *E. coli*. Other nonfermentative gram-negative bacteria like *Acinetobacter* spp. and *Stenotrophomonas maltophilia* are often resistant to a wide spectrum of commonly used antibiotics and treatment for these multidrug-resistant (MDR) bacteria remains a daunting task [14, 15].

Intraabdominal and Pelvic Abscess

The secondary seeding of the intraperitoneal necrotic tumor mass in patients with bloodstream infection arising from a difference primary source such as urinary tract, or antineoplastic therapy-induced orointestinal mucositis may also occur. The spectrum of causative organism includes enteric bacteria such as *E. coli*, *Enterococcus*, *Staphylococcus* species, Bacteroides, and other anaerobes. *Candida* species infection is less frequent in nonneutropenic patients although patients with Candida species colonization at multiple sites in the body, exposure to prolonged broad-spectrum antibiotics, poorly controlled diabetes mellitus, systemic corticosteroid use, stay in critical care units, and presence of foreign devices may increase risk for invasive candidiasis.

Hematogenous or direct seeding of the retroperitoneal space may lead to paraspinal and psoas abscess, these infections escape early detection as patients may not have high-grade fever and de novo or sudden increase in chronic low back pain remain subject to interpretation. In the absence of a direct extension from intestinal or urinary tract, these retroperitoneal infections are usually monomicrobial, and diagnosis requires prompt aspiration of the infected collection. In tuberculous endemic regions, *Mycobacterium tuberculous* infection should be considered.

Pelvic abscesses that develop after instrumentization or following surgery are often polymicrobial and treatment is directed towards normal intestinal tract and cutaneous microflora.

Peritoneal infections following bowel perforation, anastomotic leaks, or fistula tracts may present with fever, abdominal pain and fistula drainage, and/or surgical wound dehiscence. Most infections, as expected are polymicrobial and *Enterobacteriaceae*, *S. aureus, Streptococcus* and *Enterococcus* species including vancomycin-resistant strains which are frequently encountered. *Bacteroides fragilis*, and *Clostridium* species are common anaerobes; *Fusobacterium*, *Peptostreptococcus,* and *Eubacterium* occur less frequently. Patients with peritoneal infections following surgery involving the nonsterile bowel and lower genitourinary tract may also have an increased risk for *Pseudomonas* species infection.

Chemotherapy and Radiation-Related

Patients with receiving chemotherapy may have increased risk of infection, neutropenia for less than a week increases risk for systemic bacterial infections due to *S. aureus* and *Pseudomonas* species. Patients who remain neutropenic for longer than 5 days are also at an increased risk for developing systemic *Candida* species infection [1, 2]. Disruption of orointestinal and genitourinary tract mucosa compromised an important barrier in prevention of bacterial and yeast invasion. In patients with severe treatment-induced mucositis, alpha hemolytic streptococcal and anaerobic septicemia may lead to devastating consequences [16].

Radiation therapy in patients with vulvar, vaginal, and cervical cancer causes microvascular damage to the tissue and may lead to difficult-to-treat intestinal, vaginal, and urologic complications.

Increased doses of radiation for gynecologic cancer have been associated with improved cancer-free survival [17]. Although with increase in radiation dose, the rate of complication has also risen [18]. Among noninfectious complications arising from high-dose radiotherapy include tissue and bone necrosis, fistula formation, enteritis, and fibrosis that may lead to vaginal, rectal, and ureteric stenosis and increased risk for secondary infection due to stagnation and inadequate tissue drainage [19]. Rarely, patients with radiation-induced necrosis of pelvic bones increase risk for secondary bone infection, these infection challenging and multifaceted treatment approach may be needed for implementing successful outcomes [20]. Patient with osteomyelitis in the setting of radiation-induced bone necrosis may need surgical debridement, appropriate selection of antibiotics given for a prolonged period. A high clinical suspicion

remains critical in timely diagnosis of radiation-related infectious and noninfectious complication.

Bacteremia

In patients with solid-organ cancer, *E. coli* and coagulase-negative staphylococcus account for nearly 40% of bacteremia; whereas, *Pseudomonas*, *S. aureus,* and enterococcal bloodstream infection are 10% or less, each [21]. *Klebsiella* species, other *Enterobacteriaceae* and *S. maltophilia* are a serious concern and may become prominent bloodstream infection in certain geographic regions.

In cancer patients with bacteremia, who present with extensive tissue involvement/infection are significantly less likely to respond to antimicrobial therapy [22]. Other factors associated with poor prognosis in bacteremic patients with an underlying malignancy include shock, infection due to MDR bacteria, *Pseudomonas* and *Clostridium* species infection [22].

Bacteroides and *Clostridium* species are most frequent cause of anaerobic bacteremia, which are most frequently seen in patients with abdominal and pelvic malignancy [23]. Polymicrobial infections are more frequent in patients with anaerobic bacteremia compared with aerobic bacterial infections. In patients with anaerobic bacteremia concurrent candidemia is seldom noted. Over 90% of patients with nonsporulating anaerobic bacteremia may also have a deep tissue abscess [24]. Authors suggest that all patients with gynecologic malignancy who present with anaerobic bacteremia require thorough evaluation for an occult abdomiopelvic infected collection.

Clostridial bacteremia is often seen in patients with gastrointestinal, genitourinary cancer, and acute leukemia [25]. Nearly one third of patients with bacteremia with *Clostridium* species alone and nearly half with polymicrobial infection present with septic shock. *Clostridium perfringens* is common species, and *Clostridium septicum* is rare albeit, serious infection, and mostly seen in patients with an intraabdominal cancer [25]. Diffuse, rapidly spreading cellulitis involving the abdominal wall groin, and upper thigh area, gas gangrene, and acute intravascular hemolysis indicates possibility of clostridial infection [25]. Early appropriate therapy remains critical in improved response and outcome for patients with systemic anaerobic infection.

Febrile Neutropenia

During the first week of neutropenia, bacterial infections are prominent; if neutropenia extends, invasive candidiasis

becomes a concern and in patients with greater than 2 weeks of profound neutropenia invasive mold infections such as aspergillosis may be occasionally encountered. [1, 2] However, in patients with gynecologic malignancy isolation of a mold even from a sterile body sites does not indicate invasive fungal disease; these patients with no predisposing factors [26], isolation of saprophytic molds represents colonization or a laboratory contamination.

Catheter-Related Bloodstream Infection

In patients with solid-organ cancer, nearly 70% of gram-positive bacteremia are associated with an infected catheter, similarly 60% of gram-negative bacteria are also related with an infected catheter whereas, only 19% of gram-negative bacteremia in patients with hematologic cancer are due to an infected catheter [27]. Coagulase-negative staphylococcus remains the most commonly isolated organisms in blood cultures drawn from an indwelling central venous catheter and frequently regarded as catheter-related infection. Similarly, *S. aureus*, including MRSA bacteremia may result from an infected indwelling catheter and successful therapy require selection of antimicrobial agents that penetrate the biofilm and are effective against the nonplanktonic, stationary phase of the bacteria [28].

Implantable Device Infections

Peritoneal, hepatic, and pleural implantable devices for delivering chemotherapy or drainage of recurring malignant effusions have successfully been used in the last decade. These devices are well tolerated, major complications including bowel perforation are uncommon and serious infections are seen in less than 5% of cases [29, 30]. Over all infections are seen in less than 20% of the cases, whereas serious infections including pocket infection are seldom noticed. When occur, pocket infection should be treated aggressively, requiring removal of the infected reservoir and appropriate systemic antimicrobial therapy [31]. Abdominal pain and chemotherapy-related discomfort remains the main problem with these chemotherapy infusion devices.

Urinary Tract Infection

Patients with gynecologic cancer have increased risk for urinary tract infection. The factors that promote infections are listed in (Table 18.2). Nearly one-third of patients while

Table 18.2 Factors promoting urinary tract infections

Tumor obstruction

Retrograde urine flow leading to ascending pyelonephritis

Stagnation in patients with outlet obstruction and abscess formation

Instrumentization

Cystoscopy-related introduction of pathogens

Dilatation of strictures

Foreign body

Urethral stent

Percutaneous nephrostomy tube placement/replacement[a]

Surgical drains for extended duration

Radiotherapy

Inflammation of bladder mucosa

Suppression of local innate cellular and acellular immune response

Surgery

Urinary diversions

Organ resection

lymph node dissection

Anastomotic leak

Chronic surgical wound breakdown

Chemotherapy

Neutropenia

Suppression of local immune surveillance and response to bacterial invasion

Mucosal damage and disruption

[a]Patients undergoing routine replacement of percutaneous nephrostomy tubes may develop transient into bacteremia in the event of prior colonization

undergoing pelvic radiotherapy for gynecologic cancer may have symptoms of urinary tract infection at the onset of therapy or develop infection during the course of radiation therapy [32]. Despite appropriate therapy, infections may recur and require several courses of antibiotic therapy [32]. Patients who have undergone pelvic exenteration remain at increased risk for ascending urinary tract infection; [10] recurrent pyelonephritis in these patients may lead to permanent renal damage. Older patients with advanced gynecological cancer are also being considered for pelvic exenteration surgery [33]. In these and other patients with lower renal reserves, a severe episode of pyelonephritis may further compromise renal function. We suggest in select group of high-risk patients preemptive antimicrobial therapy or even secondary antibiotic prophylaxis may be considered following recurrent episode of urinary tract infection.

Patients with urinary diversions including suprapubic cystostomy, neobladder/ileal pouch, and percutaneous nephrostomy tube placement increase the risk of recurrent and frequently difficult-to-treat infections. The management becomes further complicated due to presence of aberrant communications between the intestinal and urinary tract or genital and urinary tracts. Furthermore, patients given antimicrobial prophylaxis for prevention of secondary infections may develop breakthrough infections due to multidrug-resistant bacteria and yeasts.

Prevention of Surgical Infection

The overall postoperative infection rate has been as high as 46% and surgical site infection seen in nearly one fourth of patients [34]. The risk of postoperative infection is adversely effective by prolonged duration of surgery for >5 h, presence of remote infection at the time of surgery, and duration of hospitalization for longer than 3 weeks; in patients with all three risk factors the relative risk of infections increases to 7.3 compared to 3 in patients who have only one of these risk factors [34]. Risk factors that have been associated with an increased incidence of infection in patients undergoing surgery for reproductive tract carcinoma include lower socioeconomic status, preoperative colonization, failure to administer perioperative heparin, obesity, older patient age, a longer operative period, and a longer hospital stay before surgery. [35, 36] Extent of surgery plays a central role in predicting probability and severity of postoperative infections [9–11, 36]. However, these risk factors were not uniform among investigators' evaluations.

Guidelines for the administration of antibiotics to uninfected patients undergoing pelvic surgical procedures were first proposed by Ledger et al. [37]. There have been few studies evaluating prophylaxis for women undergoing radical pelvic surgery for gynecologic malignancies. Recently, cefazolin was showed to be inferior to cefotetan as a single-dose prophylaxis in women undergoing elective abdominal hysterectomy [38]. In a placebo-controlled trail using a broad-spectrum cephalosporin plus beta-lactamase inhibitor eliminated risk of major operation site infection up to 27% [39]. Interestingly, patients with preoperative cervical colonization did not increase postoperative complications including duration of hospitalization, operative time, or febrile episodes compared with patient in whom no cervical colonization was demonstrated [40]. Overall decrease in significant postoperative infections was reported in patients undergoing radical hysterectomy [41, 42]. The benefit however, was mostly reduced local surgical wound infection [43]. Prospective data have not resolved this issue. No significant difference in overall operative-site infection was observed after preoperative prophylaxis by research groups of Rosenshein et al. [44] or Marsden et al. [45], but significantly lower incidences of infection were reported by Sevin et al. [46] and Micha et al. [47]. Sevin et al. reported that a short course (three doses) of prophylaxis was as effective as a long course (12 doses) in preventing major infection after radical hysterectomy [48]. If separate operative-site data from prospective studies are combined, the overall incidence of pelvic infection and wound infection was significantly reduced by the administration of prophylactic antimicrobials.

A cost-benefit analysis of three doses of cefazolin antimicrobial prophylaxis showed 29% reduction in infectious morbidity following vaginal hysterectomy and an 18% reduction in postoperative infections in patients following abdominal hysterectomy [49].

One patient population that has a significant surgical incision breakdown is that of women undergoing radical vulvectomy. Anecdotal experience indicates the principle pathogens to be *S. aureus* and *S. epidermidis*. The administration of broad-spectrum medications, such as piperacillin or mezlocillin, did not significantly reduce the incidence of postoperative wound infection; 8 of 12 women undergoing radical vulvectomy for vulvar carcinoma who were given single-dose piperacillin or mezlocillin developed postoperative infections [50]. Drain sites fall into the same category. The foreign body undoubtedly contributes to the infections; local attention, rather than parenteral or oral antibiotics, is the appropriate preventive approach.

The first dose of an antibiotic should be given intravenously in the operating room. Combination regimens and prolonged administration did not appear to offer superior infection prevention when compared with that provided by a single agent given once. If the interval between the first dose and opening the vagina exceeds 2.5–3 h, a second intravenous dose should be given 15–30 min before the anticipated vaginal entry. This conclusion is based on data provided by Shapiro et al. [51]. This has not been clinically studied, but administration at longer fixed intervals has not enhanced protection at hysterectomy for benign indications. In patients who are expected to undergo prolonged surgical procedure (>4 h), and dose may be repeated after 4–6 h.

Bowel Preparation

Unobstructed Bowel

There are approximately 10^{11} bacteria in a gram of feces, making sepsis a major hazard if the colon is opened. It is desirable to reduce the patient's normal colonic microflora to diminish the postoperative infection rate in case it is necessary to perform colonic resection and reanastomosis. A recent multicenter, randomized trial has placed routine mechanical bowel preparation practice into serious question, as patients who underwent elective colorectal surgery, no difference in anastomotic leak, or other septic complications such as fascia dehiscence were noted in the group who had preoperative bowel preparation [52].

Clinical Syndromes

Peritonitis and Intraabdominal Abscess

The potential causes of infection include complications of the primary tumor, surgery, and radiation therapy. The tumor can compromise the integrity of the vaginal wall and allow seeding

of endogenous vaginal flora into the pelvic and peritoneal cavities. Previous antibiotics, radiation therapy, and the tumor itself may alter the normal genital flora. The tumor can also erode into the bowel and allow entry of fecal material into the peritoneal cavity. Rare cases of several other syndromes arising from untreated pelvic tumor, including spontaneous clostridial gas gangrene and pneumoperitoneum, have been reported [53, 54]. Peritonitis, with or without abscess formation, may occur postoperatively after hysterectomy or with bowel injury. Radiation therapy to the pelvis can cause radiation enteritis, leading to a chronic diarrhea syndrome, which may develop years after radiation therapy is completed. These patients are also at higher risk for bowel adhesions and subsequent obstruction and subclinical perforation may present as late insidious intraabdominal or deep pelvic abscess.

Peritonitis may develop at any time, including at initial diagnosis due to tumor infiltration of bowel, immediately postoperatively, or days or weeks after surgery resulting from tumor infiltration, vascular insufficiency, or tissue necrosis following radiation therapy. The signs are generally dramatic and familiar: abdominal pain, fever, and signs of peritoneal irritation. However, among postoperative patients or patients who have received radiation or corticosteroid therapy, the physical findings may resemble those of a routine postoperative patient, making the diagnosis more difficult. To assure proper diagnosis, frequent examinations and close observation are required.

Abscess formation can also occur in several settings. In some patients, a subclinical microperforation of bowel is successfully walled off by the body's immune system, forming a pericolic or intraperitoneal abscess. This has been shown to occur 7–10 days after microperforation [55]. Fever or mechanical obstruction may be the only presenting signs. Subphrenic, psoas, or liver abscesses may present as a fever of unknown origin and may require a methodical, diligent evaluation for diagnosis. A fistula, usually caused by tumor but also occurring postoperatively, may form between any two organ systems, including the bladder, vagina, bowel, or skin. Persistent suppuration despite therapy or the presence of a feculent discharge from skin, bladder, or vagina may suggest the development of a fistula.

In patients who have clinical evidence of peritonitis but are unable to undergo surgery because of bulky tumor, multiple prior surgeries, or general debility, paracentesis with appropriate cultures may be useful in guiding antibiotic therapy. Blood cultures are only rarely positive. Radiologic investigation is generally required to diagnose an abscess. Regular plain X-ray films of the abdomen are seldom revealing. A contrast enhanced computed tomographic scan of the abdomen may show the collection. In a particularly confusing case in which abnormalities of scans can represent an abscess, metastatic tumor, or postoperative changes, a labeled leukocyte scan may be required to diagnose the abscess.

The diagnosis of a fistula requires demonstration of abnormal drainage from one organ system to another. This can be shown by intravenous or intravesical injection of dye for fistulae arising from the bladder, oral or rectal instillation of dye for those arising from the gastrointestinal tract, or a fistulogram for a fistula involving the skin.

In patients with unexplained bacteremia due to enteric gram-negative rods or anaerobes, with pelvic tumor, a radiologic evaluation is warranted for possible subclinical (micro) perforation or and aberrant communication with intestinal or lower urinary tract(s).

Acute, generalized peritonitis where gastrointestinal perforation is suspected requires urgent surgery to irrigate the peritoneum and repair perforation. Broad-spectrum antibiotic coverage with agents such as anti-pseudomonal penicillin, aminoglycosides, carbapenems, and coverage for coagulase-negative staphylococci and Enterococci are recommended for polymicrobial infections. Patients are also given empiric coverage for a possible Candida species infection. Effective treatment of an abscess requires drainage. Percutaneous drainage is adequate in most cases, but laparotomy may be needed, especially in patients with bulky tumor, extensive adhesion from prior surgeries, and/or radiation therapy. Large or persistent abscesses may require placement of a suction drain. Patients with fistulae generally require resection of the involved tissue. Patients who are inoperable can be treated, as suggested, with chronic suppressive antimicrobial therapy.

Wound Infections

There are important variables that influence the development of wound infection after surgery. These include hospital flora, patient flora, operative technique and variables, patient nutrition, and immunocompetency. Women being treated for reproductive tract cancer may be at risk because of specific problems with immunocompetency, possible prior chemotherapy or radiotherapy, poor nutritional status, hypoproteinemia, or low socioeconomic status. Additional risk factors for incisional infection include obesity and diabetes.

Surgical variables include operative procedures in excess of 4 h, breaks in surgical technique, excessive inoculum at the operative-site, excessive cautery, passive drains, shaving of the area in which the incision is made immediately before surgery, and placement and types of sutures. Infections may range from a mild cellulitis to a devastating fasciitis, deep infection with myonecrosis and mixed anaerobic–aerobic synergistic abdomiopelvic gangrene [56].

Cellulitis

Cellulitis is a relatively frequent occurrence. The presence of a foreign body in a wound is an unavoidable risk factor in

many cases, but this variable should be removed or reduced as much as possible. Devitalized tissue, especially fat, can also act as a foreign body. Excess cautery causes thermal injury; the charred tissue may act as a foreign body. The presence of significant amounts of devitalized tissue usually produces a wound defect. A mechanical wound retractor placed for an extended duration can cause fat necrosis, and there appears to be only minimal ability to resorb these areas during wound healing. These areas should be carefully identified and excised before closing the wound. If drains are used, they should be closed, and drains should be vacuumed. Drains should not exit through the wound but rather through an adjacent puncture site, and they should be removed as early as possible. *S. aureus* is recovered from 50% or more of wound infections. If the operative procedure involves transection of the vagina, the infections may harbor other species of normal flora of the lower reproductive tract, such as gram-positive and gram-negative anaerobes and *Enterobacteriaceae*. Cellulitis of the leg occurs with increased frequency in patients after vulvectomy [57]. The affected leg is not always edematous. Group B beta-hemolytic streptococci are frequently recovered. Prophylactic therapy with oral penicillin may reduce recurrences in some patients [57].

The infected surgical incision should be explored. This can frequently be performed at the bedside. Opposing skin edges in such incisions are usually separated without difficulty and may expose underlying purulent material, seromas, hematomas, or any combination of these. The wound should be explored thoroughly, and, if the wound shows unusual features, aerobic and anaerobic cultures should be obtained. Foreign bodies such as sutures or drains should be removed, and obviously necrotic areas should be removed after the patient has been given parenteral pain medication. It is important to document deep fascial integrity. If this cannot be done at the bedside, it should be performed in the operating room.

The wound should be packed open with fine-mesh gauze approximated to the incisional margins. Gauze is used to fill the intervening spaces after each dressing change. The dressing is changed two to four times daily, with chemical and mechanical débridement of necrotic areas. In general, these débriding solutions should be removed from the wound with sterile normal saline before packing because they may impede healing. Except in unusual instances, it is unnecessary to administer parenteral antimicrobials. These incisions may be left open to heal by secondary intent, or they may be closed before discharge from the hospital after the margins are completely granulated. The optimal time for secondary closure is about the fourth day after institution of wound therapy. Studies have shown, normal wound healing was impaired in patients with anemia [58].

Necrotizing Fasciitis

Necrotizing fasciitis is a potentially life-threatening infection of the soft tissues above deep fascia that can involve the abdominal wall or vulva with extension to the proximal thighs and buttocks [59]. There are several descriptive names for this infection, such as beta-hemolytic streptococcal gangrene, hospital gangrene, gram-negative anaerobic cutaneous gangrene, nonclostridial gas gangrene, gangrenous erysipelas, or synergistic necrotizing cellulitis; but the name used by most is that coined by Wilson in 1952; that is, necrotizing fasciitis [60]. This significant infection has been reported in patients with endometrial cancer following irradiation and hysterectomy [61, 62]. It has also been found in endopelvic fascia, in a suprapubic catheter site during chemotherapy, in the vulva in diabetes, and after diagnostic laparoscopy [63].

Bacteria recovered from necrotizing fasciitis infectious sites include anaerobes, particularly *Peptostreptococcus*, *Prevotella*, and *Bacteroides* species, as well as *E. faecalis*, *S. aureus*, and *Enterobacteriaceae*. These bacteria produce large quantities of proteolytic and other enzymes and toxins that allow rapid spread to contiguous tissues. Superficial vessels are occluded, depriving the affected areas of oxygen, other nutrients, and antibiotics. This deprivation interferes with bacterial eradication. Patients at particularly high risk of developing this infection include women older than 50 years of age and those with arteriosclerotic heart disease, diabetes, or other chronic diseases.

The initial presentation of necrotizing fasciitis is of wound cellulitis, which fails to respond to standard antimicrobial therapy. The infection, however, seems to smolder, then rapidly progresses to involve the wound and to produce clinical sepsis. Mortality rates for this infection have been as high as 76%. The degree of disease evident on the skin is only a small fraction of the total amount of tissue that is involved because the skin is not the primary area of infection. Hallmarks of this infection include excessive pain, edema that is unusual for the apparently minimal degree of infection, and presence of superficial tissue crepitance. The skin overlying the affected area becomes blue or brown as the disease progresses, and there may be formation of bullae. Edema progresses, and there may be seepage of grayish fluid from the skin, which slips over underlying tissue and does not bleed if cut. Lack of familiarity with this infection and failure to recognize its signs may delay diagnosis. Even when recognized and treated early, there is a high mortality rate.

Diagnostic criteria as first outlined by Fisher et al. include [64]: (a) extensive necrosis of the superficial fascia with widespread undermining of surrounding tissue; (b) a moderate to severe systemic toxic reaction; (c) absence of muscle involvement; (d) failure to demonstrate *Clostridium* species in the wound or blood cultures; (e) absence of major vascular occlusion; and (f) histologic demonstration of intense

leukocytic infiltration, focal necrosis of the superficial fascia and surrounding tissues, and microvascular thrombosis characterize this infection. Early diagnosis followed as soon as possible by appropriate treatment produces the highest cure rate. Radiologic evaluation, particularly with MRI, may confirm the diagnosis rapidly, and should be ordered whenever the disease is suspected. The average interval between diagnosis and initiation of treatment is approximately 5 days. If the interval is 4 days or less, survival rates are high, but an interval of 7 days or more is more likely to result in patient death because even intense antimicrobial therapy is rarely successful at this late stage. Broad-spectrum antimicrobial therapy is important, wide and often disfiguring surgical débridement is the treatment required for preservation of life. The excision must extend to viable tissue that bleeds. The areas of débridement should be treated as areas of burns. Adjunctive therapy with whirlpool baths and perhaps hyperbaric oxygen may be of use.

Clostridial Myonecrosis

Clostridial myonecrosis (gas gangrene) was described by Altmeier and Furste [65]. It is an infection that occurs in muscle and adjacent tissues beneath the deep fascia and is seen most commonly after trauma. However, it can be seen after intraabdominal surgery or surgery in an area that has been contaminated by feces. Mortality rates are about 25%, and poor prognosis factors are leukopenia, advanced age, renal failure, and intravascular hemolysis. *C. perfringens* (80–95%), *C. novyi* (10–40%), or *C. septicum* (5–20%) are common pathogens [66]. It is usually seen in association with gastrointestinal mucosal ulceration or perforation because *Clostridium* species are normal inhabitants of the gastrointestinal tract. *C. perfringens* may be isolated from as many as 20% of the women with nonsexually transmitted upper genital tract infections. The mere presence of *C. perfringens* in a wound does not mean that the patient will develop gas gangrene; it develops in only 1–2% of wounds in which that species can be isolated.

Early signs and symptoms of clostridial myonecrosis are tense edema in tissue that is extremely tender and pain that rapidly intensifies. If an incision is open, it is not uncommon to see a swollen, herniated muscle. There is frequently a serosanguinous, dirty discharge that has many gram-positive or gram-variable rods but few leukocytes. There may also be gas bubbles, and the secretions have a particularly sweet, offensive odor. The surrounding tissue frequently has crepitus. The skin becomes red to green-purple and then turns yellow before becoming a characteristic bronze color. The usual incubation period is about 2–3 days, but it can be as short as 6 h after the bacterial inoculation. With progression of the infection, the patient becomes obviously ill, pale, and sweaty, with increased pulse rate and decreased blood pressure. Temperature is usually elevated, but hypothermia may occur with shock. A positive wound culture may accompany the characteristic signs and symptoms of clostridial myonecrosis. X-ray or CT scan of the affected area frequently shows gas in deep tissues. Blood cultures grow clostridia in approximately 15% of the cases. It is common to find a decrease in hemoglobin and an increase in circulating leukocytes. Involved muscle is pale and edematous, with loss of elasticity, and it does not bleed or contract with stimulation. Histologic findings demonstrate coagulation necrosis of muscle fibers.

Clostridial myonecrosis is another infection that requires prompt and extensive débridement in the operating room. Cultures must be performed, and because clostridia may develop plasmid-mediated antibiotic-resistance, repeated cultures with sensitivity testing may be required if a patient is slow to respond. In addition to wide débridement, the treatment of choice is penicillin G at a dose of 1–2 million units every 2–3 h. Gram's stain also may indicate the presence of gram-negative bacteria, in which case coverage should be provided for those bacteria as well. Metronidazole, clindamycin, or carbapenems all of which have good in vitro activity against *C. perfringens* may be considered. Hyperbaric oxygen may be adjunctive, but its efficacy is uncertain.

Septic Pelvic Thrombophlebitis

Septic pelvic thrombophlebitis, also known as suppurative pelvic thrombophlebitis, is a disorder that has been diagnosed most frequently after antimicrobial therapy for pelvic infection after cesarean section or septic abortion, but it can be seen as a complication of infection after any type of pelvic surgery [67]. The mortality rate observed in 1917 was 52% after surgical therapy [68]. The use of antimicrobial prophylaxis and the enhanced antibacterial activity of current therapeutic regimens are presumed to be paramount in the disappearance of this potentially lethal infection. Septic pelvic thrombophlebitis is clot formation in the pelvic veins as a result of infection. It can be seen after hysterectomy, other pelvic operative procedures including brachytherapy, and in association with pelvic trauma or perirectal abscess. Classically, there is relative venous stasis before phlebitis that develops adjacent to pelvic infection. The intimal lining of the veins is invaded by bacteria, including Enterobacteriaceae, especially *E. coli*, aerobic and anaerobic streptococci, and *Bacteroides*. The veins involved may be the ovarian, hypogastric, or uterine, with essentially equal involvement in the right and left sides. If common iliac veins are involved, clot formation is more frequently seen on the left for unknown reasons. Infected clot may embolize to the lungs, kidneys, liver, brain, and spleen.

Presentation is essentially that of a fever of unknown cause, and the physician must rule out infections such as pyelonephritis, pneumonia, and pelvic or abdominal abscess. Persistent fever associated with tachycardia after clinical response to antimicrobial therapy for a pelvic infection is the most common presentation. In most cases clinical manifestation are not distinguishable; occasionally it may be possible to palpate tender cords in the vaginal fornices. In patients with bacteremia and septic emboli, chills are observed in two thirds of the patients, fever up to 41°C, and the variations in temperature may be quite hectic. Dyspnea, tachypnea, pleuritic pain, cough, hemoptysis, restlessness, anxiety, and perhaps angina may all be seen with septic embolization.

Compatible clinical presentation and CT or MRI scan are used for diagnosis [69]. Criteria for diagnosis of venous thrombosis using CT studies include enlargement of the involved vein(s), sharply defined vessel walls enhanced by contrast media, and a low-density intraluminal mass [70]. Diagnosis using MRI is based on intense intraluminal signals from clot in involved veins and a lack of signal with normal blood flow in uninvolved vessels; no contrast agent is needed. Blood culture should be performed if there is suspicion of septicemia. A ventilation-perfusion scan or contrast enhanced spiral CT scan should be performed if there is a suspicion for pulmonary embolization. A gallium scintiscan may be necessary to identify very small septic embolic foci in the lungs.

Early treatment of venous thrombosis was surgical [68]. The first to advocate the use of anticoagulants in addition to antibiotics were Schulman and Zatuchni [71]. In some cases antibiotics alone may have been adequate and can be used in patients in whom anticoagulation can be detrimental [72]. In the largest published study of heparin therapy, the mean time to become afebrile was 2.5 days, and the average duration of heparin therapy was 8 days [73, 74]. It was unnecessary to initiate anticoagulation therapy in patients without evidence of emboli. Thromboembolism, during or after treatment with heparin has not been reported [75]. Antibiotic therapy must be continued. If there is significant improvement in the pulse rate and temperature pattern within 12–48 h after addition of heparin, reassessment is mandatory. Treatment with low molecular weight heparin has not been studied or standardized for this condition.

Noninfectious Causes of Fever

Not all patients with gynecologic malignancy and fever have an infection. Pulmonary embolus, drug-related fever, and tumor-related fever represent the main noninfectious sources of fever, but others, such as factitious fever and underlying collagen vascular disorder, must also be considered. The use of procalcitonin and neopterin levels have been suggested to help distinguish between infected and noninfected patients, although further studies are needed to validate these tests [76].

Pulmonary embolus should be considered in a bed-bound or postoperative patient with any combination of fever, chest pain, dyspnea, or an abnormal chest radiograph. Patients with bulky pelvic tumors are also at risk. A high level of suspicion is important and spiral chest CT scans or ventilation-perfusion scans may establish diagnosis; in rare instances a more definite pulmonary angiogram may be performed. Therapy remains anticoagulation with low molecular weight heparin. For patients who are unable to tolerate these drugs or who continue to have pulmonary emboli despite therapy, inferior vena caval filter are required.

Any antibiotic may cause fever [77]. Patients typically develop fever and a diffuse maculopapular rash after several days of therapy, although, eosinophilia is a helpful sign, when present. Mild elevations in liver function tests may be present though nonspecific. Atypical presentations of drug fever, including patients without rash or those who develop fever weeks into therapy or after completion of therapy, can also occur. The diagnosis is usually made by discontinuing the antibiotic and observing the patient. It is important to remember that some drug fevers may take as long as a week to resolve. Supportive measures, such as antipyretics and antipruritics, may decrease symptoms.

The diagnosis of tumor fever can be made only after systematic exclusion of all other potential causes of fever. Most patients with tumor fever have metastatic disease in the liver or lung. The fever may be as high as 40°C and patient often feels relatively well when afebrile. Patient suspected of having tumor fever, a clinical trial of broad-spectrum antibiotics is given. If the fever does not abate and no other clear infection source is evident, the likelihood of tumor fever increases.

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Chapter 19
Central Nervous System Infections in Cancer Patients

Victor Mulanovich and Amar Safdar

Abstract Central nervous system (CNS) infections represent an important complication in cancer patients undergoing therapy. These infections are often difficult to diagnose, a high level of suspicion, prompt investigation, and institution of appropriate and early therapy remains critical for improved outcomes. A wide variety of viruses, bacteria, mycobacteria, fungi and parasitic meningeal, and brain disease makes empiric selection of antimicrobial therapy a daunting task. The factors that assist in the selection of initial therapy includes predisposing factors such as: (a) presence of prosthetic devices, (b) surgical manipulation, (c) host's immune defects either related to underlying malignancy, antineoplastic chemotherapy, or (d) complications arising from stem cell transplantation to name a few. For instance, patients with severe neutropenia have an increased risk for bacterial meningitis due to Gram-negative organisms, and fungal brain abscesses, where as patients with profound cellular immune defects are susceptible to *Listeria monocytogenes* infection, Cryptococcal meningitis and recrudescent herpesviruses, and toxoplasmosis. In evaluation of patients with CNS infections a knowledge of noninfectious causes that are clinically difficult to distinguish from an infection also need to be considered. In this regard, neoplastic meningitis, paraneoplastic syndrome, and recently described chemotherapy-induced reversible posterior leukoencephalopathy syndrome, are to name a few. Mental confusion and fever related to a drug is an important consideration in this population.

Keywords Encephalitis • Meningitis • Brain abscess • Shunt infection • Cancer • Transplantation • Noninfectious brain inflammation

Overview

Central nervous system (CNS) infections represent an important and difficult to diagnose complication of cancer and its therapy. Its presentation and differential diagnosis are affected by factors pertaining to the patient, the type of malignancy and its treatment. Patients may be at risk of CNS infection because of environmental exposure, such as mosquito bites transmitting viral encephalitis, or previous infections that may reactivate secondary to immunosuppressive treatments or stem cell transplantation (SCT). Hospitalizations increase the risk of colonization and infections with resistant bacteria. Cancer itself, such as hematologic malignancies, may cause immunocompromise. Treatment of malignancy often predisposes to CNS infection, in particular SCT, neurosurgical interventions, use of immunosuppressants, and chemotherapy-induced neutropenia.

The list of potential pathogens is large. A rational diagnostic approach has been presented in the past [1, 2]. We advocate following a methodical approach:

1. Identification of the clinical syndrome based on history, clinical exam, radiology, magnetic resonance imaging (MRI) if possible, although computed tomography (CT) of the brain may be used, and basic cerebrospinal fluid (CSF) results (if available). Four major neurologic syndromes, which may overlap to some degree, which will be discussed, are as follows: encephalitis, meningitis, brain abscess, or postsurgical infections.

2. Consideration of patient factors relevant to the particular syndrome, such as environmental exposures, age, type of malignancy, immunosuppression, history of neurosurgery. Noninfectious causes that may mimic infection should be entertained. Based on these factors, a list of potential pathogens that will be targeted with diagnostic tests and empiric treatment (steps 3 and 4) will be formulated.

3. Request of specific diagnostic tests, such as CSF cultures, polymerase chain reaction (PCR) testing for specific viruses and serology. Investigate extraneural sites of infection that may provide a diagnosis by means such as

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blood cultures, sinus, or pulmonary imaging. Use stereotactic needle aspirate for diagnosis and treatment of a CNS abscess if indicated.

4. Empiric antimicrobial treatment while awaiting for an etiologic diagnosis.

The etiologic diagnosis may not be reached in a high percentage of patients. In this case the efficacy of empiric treatment has to be assessed by serial performance of clinical and radiologic exams and/or repeat CSF analysis. Disease progression may require performing brain biopsy in some cases.

We will discuss such an approach in the following pages.

Infectious Syndromes and Management

Encephalitis

Encephalitis is an inflammatory process in the brain parenchyma. Its hallmark is deterioration of cortical function, often referred to as encephalopathy. Other than infection, encephalopathy can be caused by autoimmune disease and/or vasculitis, neoplasias and paraneoplastic syndromes, metabolic derangements, hypoxia, trauma, drugs and toxins, vascular pathology (including hypertension, hemorrhage and ischemia), and nonconvulsive status epilepticus [3, 4].

In the United States there are ~19,000 hospitalizations each year with a diagnosis of encephalitis (An annual rate of 7.3 hospitalizations per 100,000 population) and 1,400 deaths. Although more than 100 different infectious agents have been identified as causative agents of encephalitis, the etiologic agent is not detected in the majority of cases. Khetsuriani et al. found no specific cause in 59.5% of encephalitis-associated hospitalizations from 1988 to 1997 [5]. The California Encephalitis Project identified the etiologic agent of only 29% of 1,570 prospectively identified immunocompetent patients with encephalitis between 1998 and 2005, despite extensive testing [4].

Infectious agents may cause encephalitis directly, when they invade the brain parenchyma or its supporting structures, or indirectly, when extraneural infection triggers it. These "parainfectious encephalitides" may be immune-mediated (e.g., acute disseminated encephalomyelitis (ADEM)) or occur when an infection-induced metabolic catastrophe leads to cerebral dysfunction, as in septic encephalopathy [3].

Clinical manifestations of encephalitis include fever, confusion, altered level of consciousness, and/or behavioral abnormalities. Fever may be absent or low grade, especially in the elderly and immunosuppressed. Altered mental status may range from mild lethargy to deep coma. The patient may be agitated, hallucinating, may have mood changes or frank psychosis. Generalized or focal seizures are frequent. Focal neurologic deficits such as aphasia, ataxia, or hemiparesis reflect the most affected brain regions. Meningeal inflammation is often present and, if significant, the term meningoencephalitis may be more appropriate [6].

The approach to the patient with infectious encephalitis takes into account his/her immune status, history of recent infectious syndrome such as fever and rash, diarrhea or upper respiratory infection, recent vaccination, and presence of sepsis or systemic inflammatory response syndrome. The following four groups are considered:

(a) *Encephalitis in an immunocompetent host who happens to have cancer*: The causative agent is often the same as encountered in noncancer patients. Epidemiologic data may help direct the investigation for an etiologic agent. Age, season of the year, geographic locale, diseases prevalent in the area, insect or animal contacts, travel, recreational or occupational activities may point towards a specific etiology and determine further diagnostic testing. The most common causes in the U.S. are herpes simplex virus (HSV), varicella zoster virus (VZV), and enteroviruses, which may also present as aseptic meningitis or as meningoencephalitis [4, 5]. Cases of Influenza encephalitis/encephalopathy have been reported since the 1918 pandemic (encephalitis lethargica) and with increased frequency in Japanese children. The onset of symptoms is within a few days of the first signs of infection; the mortality rate is 30% [7].

(b) *Encephalitis in an immunosuppressed host*: Reactivation of dormant infections, de novo infection with opportunistic pathogens and severe manifestations of less virulent ones occur in these patients. Herpesviruses cause persistent or latent infection in most humans and reactivate after solid organ or SCT or are transmitted from the donor to the transplant recipient. HSV remains an important consideration but is rare, maybe because the most immunocompromised patients receive prophylaxis. Human herpesvirus-6 (HHV-6) reactivates in ~50% of SCT patients 2–4 weeks posttransplant and may cause encephalitis, with predilection for the hippocampus, in a small number of patients, usually within the first 100 days posttransplant [8–10]. Preemptive therapy for HHV-6, triggered by high-level viremia, did not show advantage in preventing encephalitis in one Japanese study [11]. Cytomegalovirus (CMV) may affect the ependymal lining of the ventricles causing ventriculoencephalitis. Progression is rapid, MRI may show enhancement of the affected areas. CMV PCR may be positive in blood and/or CSF. High-level viremia, retinitis, or extraneural involvement may be present and provide a clue to the diagnosis [12]. VZV rarely causes CNS infection, cases of granulomatous cerebral angiitis following ophthalmic

zoster [13, 14], clinically resembling a stroke, and progressive chronic encephalitis manifested in MRI as spherical white matter lesions without surrounding edema scattered throughout the white matter, have been reported in immunocompromised patients [15]. Epstein–Barr virus (EBV) can cause encephalitis and meningitis after primary infection or reactivation, in immunocompetent and immunocompromised hosts. Encephalitis is frequently accompanied by focal neurologic abnormalities. EBV-associated posttransplant lymphoproliferative disease (PTLD) presents usually within a year of transplantation and affects the CNS in 19% of cases [16–18].

West Nile virus (WNV) may be transmitted by mosquitoes, blood transfusion, or transplantation from a viremic donor, leading to meningoencephalitis after solid organ and hematopoietic SCT. Movement disorders and flaccid paralysis are often present. Patients receiving chemotherapy or otherwise immunosuppressed may also develop severe WNV disease [19–21].

Progressive multifocal leukoencephalopathy (PML) is caused by the polyomavirus JC. Eighty five percent of cases are associated with HIV infection. Immunosuppressive drugs such as corticosteroids, alkylating agents, purine analogs and some monoclonal antibodies (such as rituximab, natalizumab, etanercept, etc.), calcineurin inhibitors, and other drugs used mainly for the treatment of malignancies and in transplantation account for most of the rest. Cases have been described after SCT including autologous transplants. MRI findings include periventricular and subcortical white matter lesions that do not enhance and are not space occupying. PCR for JC virus in CSF has a sensitivity of 80% and specificity of 95%. Treatment is ineffective; cidofovir has been used with poor results. Withdrawal of immunosuppression is recommended [22–27].

Toxoplasma encephalitis occurs in SCT patients as subacute progressive or severe acute encephalitis. Altered mental status and focal neurological signs are common. Chorioretinitis, pneumonia, and multiorgan involvement are reported. Graft versus host disease (GVHD) is a predisposing factor. Diagnosis relies in finding multiple ring-enhancing lesions on MRI and *Toxoplasma* PCR in CSF or blood. Brain biopsy may be necessary [28–31]. CNS lymphoma, including PTLD, is the main differential diagnosis.

Acanthamoeba spp. and *Balamuthia mandrillaris* are free-living amebas that can rarely cause chronic granulomatous meningoencephalitis in patients with cancer and/or immunosuppression, including SCT. Diagnosis is difficult and requires culturing the organism from brain or skin lesion biopsies, so clinical suspicion is essential [32, 33].

Listeriosis, endemic mycoses, and *Mycobacterium tuberculous* are part of the differential diagnosis. Please refer to the appropriate chapters for a more detailed discussion.

(c) *Post-infectious or post-immunization encephalitis* is mediated by an immunologic response to an antigenic stimulus. ADEM accounts for the majority of cases. The usual latency is 4–21 days. Fever is present in 15% of adults and ~50% of children. Seizures occur in only 4% of adults and more frequently in children, often associated with fever. MRI usually reveals multifocal enhancing white matter lesions. The initial MRI may be normal, so repeat study it in 7–10 days is advised when the history of immunization and clinical presentation are suggestive [3].

(d) *Septic encephalopathy* is present in 50–70% of patients with sepsis [34]. It is defined as encephalopathy unexplained by lung, liver, kidney or cardiac dysfunction, or any of the previously discussed etiologies, in patients with an extraneural source of infection. It is a diagnosis of exclusion with no pathognomonic histopathology. It is most likely caused by mediators of inflammation that induce cerebral endothelial dysfunction and increased permeability of the blood-brain barrier. Ischemic changes are also found in patients dying from septic shock [3].

Diagnostic workup: Brain MRI is more sensitive and specific than CT in cases of suspected encephalitis [35]. Other conditions with similar presentation can be excluded. In ADEM, the MRI will show acute enhancing white matter lesions throughout the CNS [3]. CSF evaluation is essential. Viral encephalitis usually presents with mild mononuclear pleocytosis. Neutrophilic pleocytosis may be seen initially and may persist in WNV encephalitis. CSF protein is mild to moderately elevated. CSF eosinophilia suggests helminth infection, but is not specific. Low CSF glucose suggests bacterial infection (listeriosis, tuberculous), fungi or protozoa. Up to 10% of patients have normal CSF. Serology and PCR are the main diagnostic studies for viral agents. Viral cultures is of limited value; bacterial, fungal, and mycobacterial should be obtained [6].

Occasionally, the causative agent may be identified outside the CNS. Blood cultures may identify a bacterial pathogen (*Listeria*). Serum cryptococcal and CMV antigens and urine histoplasma antigen should be ordered if clinically indicated. In patients with respiratory symptoms, viral respiratory antigens or a PCR viral panel should be obtained from respiratory secretions. Diffuse pulmonary infiltrates may suggest *Mycoplasma* or viral infection; circumscribed infiltrates may be caused by infection with fungi, *Nocardia* or *M. tuberculous*.

Treatment recommendations: Since an etiologic diagnosis is not obtained in more than 70% of cases, empiric therapy directed at the most likely pathogens and treatable organisms is essential. Immunocompetent patients should be treated for HSV and VZV with intravenous acyclovir. Most patients are treated empirically for bacterial meningitis due to the clinical overlap (see next section). Listeriosis should be considered in pregnant, elderly, and immunocompromised patients,

Table 19.1 Causes of encephalitis, diagnostic method of choice, and recommended treatment in immunocompetent and immunocompromised patients. (1) Intraventricular γ-globulin for chronic or severe disease, (2) includes La Crosse, St. Louis encephalitis and Eastern, Western, and Venezuelan equine encephalitis viruses, (3) interferon-α-2b may be used for St. Louis encephalitis

Immunocompetent patients	Diagnosis	Treatment
Etiologic agent	Stool and throat cultures	Supportive 1
Enteroviruses	CSF RT-PCR	
HSV-1 and 2	CSF RT-PCR, MRI	Acyclovir
Varicella zoster virus	CSF PCR, MRI	Acyclovir
	DFA skin lesions	
Influenza A and B	Viral culture, antigen detection, PCR of respiratory secretions	Oseltamivir
West Nile virus	Serum+CSF IgM	Supportive
	CSF PCR	
Other mosquito-borne viruses 2	Serologic, CSF IgM	Supportive 3
HIV	HIV serology and RNA	HAART
Bartonella henselae (cat scratch disease)	Serology	Doxycycline or azithromycin (may add rifampin)
Rickettsia or *Ehrlichia*	Serology	Doxycycline
Immunocompromised patients		
Cytomegalovirus	CSF PCR, MRI	Gancyclovir+Foscarnet
Human herpesvirus 6	CSF PCR, MRI	Gancyclovir or Foscarnet
Epstein–Barr virus	CSF PCR, MRI	Supportive
JC virus	CSF PCR, MRI	Reverse immunosuppression
West Nile virus	Serum+CSF IgM	Supportive
	CSF PCR	
Listeria	Blood and CSF cultures	Ampicillin+gentamicin or trimethoprim/sulfamethoxazole
M. tuberculous	CSF AFB and culture	Four TB drugs per guidelines+Dexamethasone for meningitis
	CSF Gene-probe	
Coccidioides sp.	Serum+CSF antibodies and cultures	Azole or amphotericin per guidelines
Cryptococcus neoformans	Blood and CSF antigen and cultures	Amphotericin+flucytosine
Histoplasma capsulatum	Urine histoplasma antigen, CSF stains and culture	Liposomal amphotericin
Toxoplasmosis	Serum IgG (establish risk)	Pirimethamine+either sulfadiazine or clindamycin
	CSF PCR, MRI	
Postinfectious and postimmunization	MRI	Corticosteroids
		Plasma exchange
Septic encephalopathy	Diagnosis of exclusion	Treat underlying condition
		Supportive

and ampicillin added empirically. Rickettsial and ehrlichial infections may present with fever, headache, and altered mental status in patients at risk for tick bites, doxycycline should be added in patients with probable exposure to ticks. Serologic tests for these pathogens are of limited value.

In moderate to severely immunocompromised patients herpesviruses and endemic fungi are the most important treatable agents and gancyclovir and/or foscarnet, plus voriconazole or liposomal amphotericin B are part of the empiric regimen. Meningitis again should also considered, including *Listeria*. Ten percent of toxoplasma encephalitis cases occur in HIV-negative patients, mostly after transplantation. Treatment with pyrimethamine plus sulfadiazine or clindamycin is standard. Trimethoprim/sulfamethoxazole has been used successfully to treat toxoplasmosis in AIDS patients [28–31].

Table 19.1 lists the most important pathogens in the first two groups and the diagnostic test of choice and general recommendations for therapy.

Meningitis

Signs of meningeal irritation and CSF pleocytosis are the hallmarks of this syndrome. Acute meningitis commonly presents in hours to days, chronic meningitis is defined as symptoms, signs, and/or CSF abnormalities for at least 4 weeks. Many infectious agents can cause encephalitis, meningitis, or both. It is not infrequent to have a mixed presentation, the term meningoencephalitis applies to those cases, nevertheless, separation is useful for diagnostic and therapeutic purposes.

The classic triad of fever, neck stiffness, and altered mental status is present in only 44% of cases of acute bacterial meningitis, however, 95% present with at least two of the following symptoms: headache, fever, neck stiffness, or altered mental status. In addition, 14% of patients are comatose and 33% have focal neurologic findings on admission [36]. Elderly patients tend to present less frequently with meningeal signs, headache, or fever and more with altered mental status, thus requiring a higher index of suspicion [37]. Symptoms tend to be less severe with viral meningitis, in which prodromal flu-like symptoms and characteristic rashes may be important diagnostic clues [38, 39].

When meningitis is suspected, blood cultures should be obtained and lumbar puncture performed immediately. If CSF can't be obtained promptly, appropriate empiric antibiotics should be started without delay. Criteria for obtaining a CT scan prior to lumbar puncture in adults have been published and are based in a prospective study of 301 patients by Hasbun et al., which showed that abnormal CT findings in patients with bacterial meningitis were associated with the following risk factors: age ≥60 years, history of CNS disease (e.g., mass lesion, stroke or focal infection), immunocompromised state, recent seizure (≤1 week), abnormal level of consciousness, or focal neurologic deficits [40, 41].

CSF analysis shows considerable overlap between bacterial and viral causes of meningitis. Gram stain using cytospin techniques has a yield of 50–90% for different bacterial pathogens, but decreases by >20% points with prior antimicrobial treatment. Only positive cultures or PCR for a specific pathogen are diagnostic. Latex agglutination has fallen out of favor but is still recommended for pretreated patients with a negative Gram stain. CSF lactate concentrations ≥4 mmol/L are predictive of bacterial infection in postoperative neurosurgical patients and a normal serum C-reactive protein has a high negative predictive value for the diagnosis of bacterial meningitis [40–45]. The approach to meningitis can be categorized as follows:

Acute bacterial meningitis is a neurologic emergency and therapy should be initiated as soon as possible after the diagnosis is considered to be likely [41]. Cancer patients can be classified in three groups according to risk of infection:

(a) *Community-acquired*: The predominant organisms are *Streptococcus pneumoniae* and *Neisseria meningitidis*. *Hemophilus influenzae* is now rare, thanks to vaccination. *Listeria monocytogenes* and aerobic Gram-negative bacilli must also be considered in adults over 50 years. Empiric antibiotic coverage with vancomycin plus ceftriaxone or cefotaxime is recommended, with the addition of ampicillin when listeriosis is suspected. The use of dexamethasone in patients with suspected or proven pneumococcal meningitis either immediately before or concomitant with the first dose of antibiotics is now recommended [41, 46], no specific data for cancer patients is available.

(b) *Neutropenic patients*: Acute bacterial meningitis is uncommon and associated with high morbidity and mortality. It affects predominantly patients with hematologic malignancies. Lukes et al. [47] reported Gram-negative organisms in 29 of 43 CNS infections in neutropenic adults in 1984. *Listeria* was the most common Gram-positive organism. More recently, Sommers and Hawkins reported Gram-positive predominance in neutropenic pediatric cancer patients, most of them had an underlying hematologic malignancy [48]. Staphylococci and Streptococci caused ten infections and *Klebsiella* and *Pseudomonas* one each. *Stomatococcus mucilaginosus*, a facultatively anaerobic Gram-positive coccus, causes sepsis in neutropenic patients with mucositis and caused meningitis in leukemic and SCT patients [49]. Viridans streptococci have emerged as a cause of bacteremia in severely neutropenic patients with the following risk factors: chemotherapy with high-dose Ara-C, use of quinolones or cotrimoxazole for prophylaxis and/or oropharyngeal mucositis. Penicillin resistance is common and cases of meningitis with or without sepsis have been reported [50, 51]. Other Gram-positive bacteria that may cause meningitis in neutropenic patients include *Staphylococcus aureus* [52] and *Corynebacterium jeikeium* [53]. Empiric therapy with vancomycin plus cefepime or ceftazidime is reasonable for neutropenic patients with hematologic malignancy. Again, ampicillin should be started if *Listeria* is suspected.

(c) *Nosocomial meningitis* occurs in patients with three distinct types of underlying conditions:

1. Patients with history of neurosurgery, neurosurgical device (discussed later) or CSF leakage.
2. Immunocompromised patients.
3. Patient with a distant focus of infection (pneumonia, sinusitis or otitis).

S. aureus and S. pneumoniae are the most common organisms. *Streptococcus epiderdimidis*, enteric Gram-negatives and *Pseudomonas aeruginosa* are also reported. Empiric treatment with vancomycin plus cefepime, ceftazidime, or meropenem is recommended [41, 54].

Patients with nasopharyngeal carcinoma have anatomic changes in the upper respiratory tract that predispose them to sinusitis and otitis; they often receive radiotherapy and may develop osteoradionecrosis of the skull base, and therefore have an increased risk of bacterial meningitis, brain abscess, or cavernous sinus thrombosis [55].

Viral (aseptic) meningitis: Aseptic meningitis is defined by the absence of a bacterial pathogen. Viruses are the main cause. Age and immune status influence the severity of presentation. More than 90% of all viral meningitis is caused by

enteroviruses, which are transmitted primarily by fecal–oral contamination and less commonly by respiratory secretions. In temperate climates, most cases occur in summer and early fall. Gastrointestinal symptoms and rash are common. Enterovirus 71 presents with vesicular hand-foot-and-mouth disease [39]. HSV-1 and 2 can cause meningitis with or without genital or oral lesions. Recurrent episodes of aseptic meningitis (Mollaret's meningitis) have been linked to HSV-2 reactivation. VZV may also present as meningitis, the occurrence of herpes zoster may herald it [39].

WNV infection often presents as meningitis, which has lower mortality and less complications than WNV encephalitis. Additionally, acute flaccid paralysis similar to paralytic poliomyelitis was described in up to 10% of patients, and only half of them had concomitant meningitis or encephalitis [56]. Other viruses more commonly associated with encephalitis, such as St. Louis and La Crosse viruses, may present with meningeal signs and symptoms (Table 19.1). As with viral encephalitis, diagnosis of viral meningitis depends on epidemiologic clues, blood and CSF serology, and CSF PCR. Treatment, other than acyclovir for HSV and VZV, is supportive.

Other infectious causes of meningitis: Cryptococcal meningitis is a disease of patients with cellular immune deficiencies. Please refer to chapter 26 for a more detailed discussion. Infrequently, cases are described in "immunocompetent" patients and in patients with leukemia or SCT [57–59].

In the appropriate setting and with the right risk factors, Spirochetes (Lyme borreliosis, syphilis and *Leptospira spp.*), endemic fungi (*Histoplasma, Coccidioides, Blastomyces*), and *M. tuberculous* must be considered in the differential diagnosis. The presentation is usually subacute and sometimes chronic. Molds are extremely rare causes of meningitis in patients with hematologic malignancy. Few cases of *Aspergillus* and other molds have been described [60, 61].

Candida meningitis is a rare entity mostly limited to neonates and neurosurgical patients. McCullers et al. reported 12 patients with leukemia and *Candida* meningitis, eight had positive blood cultures and only one had an Ommaya reservoir. Autopsies on seven of eight revealed disseminated multiorgan disease. All had prolonged neutropenia and one had SCT [62]. The routine use of antifungal prophylaxis in high-risk patients with prolonged neutropenia has made this entity rare.

Non-infectious causes of meningitis: Connective tissue disease, malignancy, and drugs such as nonsteroidal anti-inflammatories and intravenous immunoglobulin [39, 63] may cause a meningitis syndrome.

Chronic meningitis: Defined as meningitis persisting for >4 weeks, is caused mainly by *M. tuberculous* and endemic fungi, especially *Cryptococcus*. *Histoplasma* causes chronic meningitis in children and individuals with impaired T-cell immunity and has been described in association with AML [64]. Lyme disease presented as lymphocytic meningitis in a patient with CLL [65], syphilis, and brucellosis can be considered if there are risk factors. Patients with hypo- or agammaglobulinemia can develop enterovirus chronic meningitis or meningoencephalitis, often fatal [66]. Enterovirus meningoencephalitis has been reported after rituximab therapy. Enterovirus PCR in CSF may provide the diagnosis. Response to high-dose intravenous immunoglobulin and the antiviral pleconaril has been reported [67, 68]. Parvovirus B19 caused chronic meningitis in a patient with ALL [69]. Noninfectious causes include neoplastic meningitis, sarcoidosis, lupus erythematous, vasculitides, and drug toxicity or reactions [70].

Brain Abscess

Brain abscess is a focal infection that begins as a localized area of cerebritis that develops a necrotic center. Well-vascularized (ring-enhancing on CT) tissue surrounds the area leading to the formation of a capsule that walls off the abscess. The process takes >14 days in experimental animal models [71].

The epidemiology, diagnosis, and management of brain abscesses changed radically with antibiotic and surgical treatment of dental, otic and sinus infections, the advent of CT scans and MRI, the introduction of stereotactic brain biopsies, and the increased incidence among very immunosuppressed patients, especially with hematologic malignancies and SCT.

Etiology and risk factors: Infection may spread from adjacent structures such as the paranasal sinuses, middle ear, and teeth, either directly or indirectly through venous drainage. Early antibiotic and surgical treatment of these infections has diminished its importance as a cause of brain abscess. Direct seeding in the case of postoperative infections will be discussed in the next section. Hematogenous spread from distant sources, especially endocarditis, line infection and pneumonia may also occur. The source of infection is not found in 20–30% of cases. Bacteria are by far the most common cause in immunocompetent patients. Table 19.2 shows the most frequent etiologic agents for each of the above mentioned categories [71–73].

Cancer patients are often immunocompromised, and the etiology of brain abscess is quite different. Patients most frequently affected are those with hematologic malignancies, SCT, and primary CNS tumors or brain metastases taking high doses of corticosteroids, often in association with temozolamide [74, 75]. A case series of 12 pediatric cancer patients with brain abscesses found 11 cases due to fungi, seven of them *Aspergillus*, two *Candida*, and one case of *L. monocytogenes*. Eight patients had leukemia (two had allogeneic transplants) and four had CNS tumors [76]. Three

Table 19.2 Brain abscess: risk factors and etiologic agents

Risk factor	Frequent etiologic agents
Contiguous source (Sinusitis, otic or odontogenic infection)	Aerobic and anaerobic streptococci
	Haemophilus sp.
	Anaerobes (*Bacteroides, Fusobacterium, Actinomyces*)
	Pseudomonas, Enterobacteriaceae (otogenic)
Hematogenous spread (Endocarditis, pulmonary, GI or urinary sources)	*Staphylococcus aureus* and streptococci
	Listeria monocytogenes
	Anaerobes (from lung of GI tract)
	Pseudomonas, Enterobacteriaceae (from lungs or urinary tract)
Postoperative infections	*S. aureus* and streptococci
	Pseudomonas, Enterobacteriaceae
Penetrating trauma	*S. aureus* and *S. epiderdimidis*
	Clostridium sp.
	Enterobacteriaceae
Immunocompromised host (Hematopoietic malignancy, stem cell transplant, high dose corticosteroids/other immunosuppressive agents)	Molds (mainly *Aspergillus*)
	Candida sp.
	Nocardia
	Toxoplasma gondii
	L. monocytogenes
	Other: *Trypanosoma, Mycobacteria*, bacteria (see above)

out of 13 patients with solid tumors with invasive aspergillosis had brain invasion [75]. The incidence of brain abscess is highest among SCT recipients, with reports of 2–5% [77–79]. Fungal pathogens accounted for 92% of cases. *Aspergillus* and *Candida* are the most common [76, 78]. The lungs, sinuses, and skin are frequently the source of CNS mold infections, while candidemia accompanies two thirds of *Candida* brain abscesses. Bacteria, especially Gram-negatives, and *Toxoplasma gondii* are seen with less frequency [78]. *Nocardia* sp. may also cause brain abscess, often originating in the lungs or skin. In patients from endemic areas of the Americas, *Trypanosoma cruzi* may reactivate and present as an area of localized encephalitis termed "chagoma." Donors infected with *T. cruzi* may transmit infection to transplant recipients [80, 81].

The classic clinical presentation includes dull, nonspecific headache, fever (seen in 50–80% of cases), focal neurological findings (30–60%), and seizures (20–30%). SCT patients have fever (83%) and altered mental status (50%) more commonly, with or without neurologic deficits [71, 73, 78]. Acute deterioration with meningismus may be due to abscess rupture into the ventricular space. Signs of increased intracranial pressure (altered mental status, nausea and vomiting) may herald herniation. Coma at presentation is an independent risk factor for mortality [71].

Diagnosis depends on imaging. Brain CT scan shows cerebritis as a focal hypodensity (edema) that enhances with contrast. The classic ring-enhancing lesion is associated with a mature brain abscess. MRI shows hypointense lesions with ring-enhancement following gadolinium administration in T1-weighted sequences. In T2-weighted images a hyperintense central area of pus is surrounded by a well-defined hypointense capsule and surrounding edema. Stereotactic brain biopsy allows for confirmation and identification of the causal organism. Positive blood cultures or identification of an extraneural source of infection (such as *Aspergillus* or *Nocardia* pneumonia, bacterial or fungal sinusitis or otitis) will help when biopsy or surgery is not an option. Lumbar puncture is infrequently done because of the risk of herniation and frequent negative results, unless there is associated meningitis.

In patients with cancer, differentiating between brain tumor (new or recurrent) and abscess is often difficult. Pus produces hyperintense signals on MRI diffusion-weighted sequences while necrotic tumor centers produce iso- or hypointense signals. Brain metastases and glioblastomas occasionally display hyperintense signals and may be confused with abscess. Intratumor hemorrhage may also limit the interpretation. CNS toxoplasmosis is difficult to differentiate from lymphoma and PTLD in SCT patients since both may present as single or multiple nodular or ring-enhancing lesions. Tuberculomas, histoplasmomas, cryptococcomas, aspergillomas, nocardiosis and, even more rarely, neurocysticercosis, schistosomiasis, and cerebral syphilitic gummas can be confused with a brain tumor or metastatic disease [82–84].

Antibiotic management of bacterial brain abscess is best directed by microbiologic diagnosis. Empiric therapy may be selected based on the likely bacterial etiology as listed in Table 19.2, however, since patients are often very ill and cancer patients may be at higher risk of resistant bacterial infections, broad-spectrum coverage with vancomycin 15 mg/kg every 8 h plus either meropenem 2 g every 8 h or the combination of metronidazole plus cefepime or ceftazidime are reasonable initial therapies while awaiting culture results.

Fungal brain abscess has shown poor response to traditional antifungals with or without surgery. Amphotericin B and liposomal amphotericin B were the most frequently used treatments [76–79]. The use of voriconazole has been reported to improve outcomes with complete or partial response in 28 (35%) of 81 patients. SCT patients had the worst response (15%) [85].

Stereotactic needle aspiration provides therapeutic drainage and specimens for culture and other studies [71]. Prior antibiotic therapy decreases culture positivity by 50% [73]. Open craniotomy is now rarely performed. Response to therapy is monitored with CT or MRI and duration of therapy is determined in part by radiologic resolution of inflammatory signs. Traditionally, 6–8 weeks of parenteral antibiotics have been recommended. Shorter intravenous courses followed by oral antibiotics have been used successfully even in patients who either could not have or refused aspiration or surgery [71, 86].

Postoperative Infections

CSF shunt infections: CSF shunts are used in the management of hydrocephalus, and have a proximal portion that enters the CSF space and a distal portion that may either drain internally to the peritoneal or pleural cavity or a blood vessel, or externally as in external ventricular drains (EVDs), used for temporary drainage. They may have reservoirs for intermittent percutaneous access [87].

EVD infection is defined as one positive CSF culture, except when skin flora is recovered, in which case a repeat positive culture or abnormal CSF and/or clinical findings consistent with infection are required. An average incidence of these infections is 10% although infectious complications have been seen in up to 27% in some series. Risk factors include the presence of subarachnoid or intraventricular hemorrhage, duration of catheter placement for >5 days, frequent manipulation of the EVD system, and repeat shunting [87–90]. Use of antibiotics for the duration of EVD placement to prevent infection is controversial, with some studies showing decreased incidence of infections while others show no change in incidence and selection of more resistant organisms [88, 91, 92]. Etiologic agents include skin flora such as coagulase-negative staphylococci and *S. aureus*, *Propionibacterium acnes* as well as resistant Gram-negatives commonly seen in ICU, including *Pseudomononas* sp., *Acinetobacter* sp. [93], and Enterobacteriaceae. *Candida* infections are infrequent and occur in patients with risk factors for candidemia and patients treated for bacterial CSF infections [94].

Internal shunt infections often mimic shunt malfunction, presenting with headache, drowsiness, and vomiting. Fever and CSF abnormalities are common. Only one third of patients develop meningeal irritation since most infections remain contained in the ventricles and are caused by low-virulence organisms, mostly skin flora (*Staphylococci*, *P. acnes*), and less commonly by Gram-negatives. Most infections present early after shunt placement or revision. CSF cultures obtained from the valve or ventricles have a higher yield than lumbar puncture. CT or MRI imaging may rarely show a brain abscess. Infection of the distal shunt portion may manifest as peritonitis or bacteremia depending on whether it drains in the peritoneum or the vascular system [87, 95].

Treatment of CSF shunt infections includes removal of its components, a new temporary EVD and intravenous antibiotics. Empiric coverage includes vancomycin plus either cefepime, ceftazidime, or meropenem. The timing of internal shunt reimplantation depends on the infecting organism and negativization of CSF cultures. Specific indications for use of the intraventricular route for antibiotic administration are not well established. They may be beneficial [41, 96]. Conservative treatment with antibiotics alone or "one stage" shunt replacement has a higher risk of relapse [41, 95, 96].

The Infectious Diseases Society of America has published treatment recommendations [41].

Postcraniotomy infections occur in <1 to >8% of intracranial surgical procedures [97] and may be superficial, such as scalp infections and bone flap osteitis, or deep, including meningitis-ventriculitis, brain abscess, and empyema. Most scheduled craniotomies are considered clean surgeries. Entry through the paranasal sinuses or mastoid is considered clean-contaminated, and open fractures from trauma are considered contaminated [98]. Antibiotic prophylaxis decreases the incidence of superficial but not deep infections and may select for more resistant organisms in the later [98, 99]. *S. aureus* is the most frequent pathogen followed by other Gram-positive bacteria, and, less commonly, hospital-acquired Gram-negatives. The risk of infection is higher in those with a preceding craniotomy, operative time >4 h, emergency or trauma surgery, external CSF leakage or early subsequent operation. In patients recovering from surgery for malignant glioma, it is difficult to differentiate clinically or by imaging between early recurrence of tumor, postoperative hyperperfusion, and intracranial infection. Fever and local signs of wound infection may be present. Infections tend to occur early, 70% in the first month and 85% within 2 months, while tumor recurrence usually occurs after 6 months, rarely before 3 months [100]. Surgical debridement and antibiotics are the treatment of choice. Empiric therapy is similar to CSF shunt infections.

Postoperative meningitis may be bacterial or aseptic, the later is likely a reaction to heme breakdown products, and posterior fossa surgery is a known predisposing factor. Empiric therapy followed by discontinuation if CSF cultures are negative after 3 days, provided the sample was taken before antibiotics were administered, was found prospectively to be an effective strategy in one study [101].

Noninfectious Problems that May Mimic Infection

1. Neoplastic meningitis is most commonly seen in patients with disseminated progressive cancer (60–70%), but in 5–10% of cases it may be the initial manifestation of cancer. The incidence varies according to tumor type, and is highest with some lymphomas and leukemias. The most common solid tumors include breast cancer (3%) and small-cell lung cancer (6%). Symptoms are varied, depending on the CNS territory invaded by the tumor. Headache, altered mental status, and ataxia are the most common (50%). Cranial nerve compromise (40%) and spinal symptoms (60%) are frequently reported. MRI shows leptomeningeal enhancement and tumor nodules in less than 60% and communicating hydrocephalus in

8–10%. CSF analysis may show pleocytosis (63%), elevated protein (80%), and decreased glucose (55%). Malignant cells are found in 50% on the first CSF sample and 25% more in the second one. Autopsy data shows up to 40% of patients with neoplastic meningitis lack positive CSF cytology. Thus, it may be difficult to differentiate from subacute or chronic meningitis and chemical meningitis [102].

2. Paraneoplastic neurological syndromes (PNS) may affect any part of the central and peripheral nervous system, the neuromuscular junction or muscle. In 50% of cases onconeural antibodies are found, suggesting an immune-mediated disorder. PNS are rapidly progressive and may cause severe disability. They are rare (less than 0.01% of cancer patients) and antedate the diagnosis of cancer in almost 80% of patients. Some may be confused with infection. Paraneoplastic encephalomyelitis is characterized by neuronal loss and inflammatory infiltrates in multiple areas of the CNS. Seventy five percent of patients have underlying small-cell lung cancer. Limbic encephalitis has a subacute onset with confusion and short-term memory loss, sometimes after a prodrome of fevers and headache. Seizures, hallucinations, and sleep disturbances may follow. Small-cell lung cancer, testicular tumors, and breast cancer are the most frequent underlying cancers. Treatment is directed at the tumor and immune modulation may be beneficial in select cases [103, 104].

3. Reversible posterior leukoencephalopathy syndrome (RPLS) was described by Hinchey et al. in 1996 in seven patients receiving cyclosporine or tacrolimus after transplantation or for aplastic anemia, one receiving interferon alpha for metastatic melanoma and seven more with either eclampsia (three patients) or acute hypertensive encephalopathy (four patients) [105]. RPLS presents subacutely with headaches (53%), visual symptoms (39%), seizures (87%), and altered mental status/encephalopathy (92%) [105, 106]. Blood pressure elevations can be severe or, more often, mild to moderate. The syndrome can be confused with acute encephalitis. Since the clinical presentation is nonspecific, diagnosis relies on MRI, which shows bilateral white matter abnormalities suggestive of edema in the posterior regions of the cerebral hemispheres. Other areas may be involved [105, 107]. Capillary leak caused by drugs that affect the endothelium or increase blood pressure or blood volume and secondarily tax endothelial function is the proposed mechanism. The posterior part of the brain has decreased sympathetic innervation and is thus believed to be more vulnerable [105–108]. RPLS is usually reversible within 2 weeks. Treatment includes discontinuation of the offending drug, control of hypertension, and supportive treatment. In a large series, malignancy was present in 32% and transplantation in 24% of cases of RPLS [106]. Reports of chemotherapeutic agents linked to RPLS continue to enlarge the list, now including platinum analogs (cisplatin, carboplatin), antimetabolites (gemcitabine), folate antagonists, anthracyclines, and vinca alkaloids. Growth factors, high-dose corticosteroids and antiangiogenic-targeted therapies such as Bevacizumab and sorafenib have been implicated. Many of this drugs cause hypertension and have the potential to cause endothelial damage. RPLS has been reported as soon as hours after drug administration and as late as 1 month later [108].

4. GVHD neurological involvement commonly manifests as neuromuscular problems. Angiitis of the CNS is a rare complication of allogeneic SCT. Patients present with acute or subacute focal neurological deficits, encephalopathy, or neuropsychological impairment approximately 2 years after transplantation. Gray and white matter ischemia and cerebral hemorrhages are found in autopsy. Most patients had history of acute and chronic GVHD [109–111]. Two cases of GVHD presenting solely as encephalitis in similar patients have been reported [112, 113].

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Chapter 20
Endocarditis in Oncology Patients

Sara E. Cosgrove and Aruna Subramanian

Abstract Although relatively uncommon in the general population with an incidence of 2–7 cases per 100,000 person-years, infective endocarditis (IE) is associated with significant morbidity and mortality. Recent studies suggest that the incidence of IE in oncology patients overall has increased and that it is reasonable to maintain a baseline suspicion in patients who present with the appropriate clinical scenario. An in-depth review of epidemiology, risk factors, clinical presentation, diagnosis, and medical and surgical management of IE in oncology patients is presented in this chapter.

Keywords Infective endocarditis • Antibiotic therapy • Diagnosis • Surgical intervention

Epidemiology

Although relatively uncommon in the general population with an incidence of 2–7 cases per 100,000 person years, infective endocarditis (IE) is associated with significant morbidity and mortality [1]. The incidence of IE in oncology patients has not been defined and traditionally is thought to be low. Some have hypothesized that because many oncology patients, particularly those with leukemia, have low platelet counts because of their disease or therapy, they are unable to effectively form the essential lesion of endocarditis – a mass of platelets and fibrin adherent to the endothelial surface of the heart within which circulating microorganisms have enmeshed. Indeed, in a study of the hearts at autopsy of 420 patients with acute leukemia between 1954 and 1964, none had endocarditis, although 7% had myocardial abscesses generally associated with disseminated infection [2].

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However, recent studies suggest that the incidence of IE in oncology patients overall has increased and that it is reasonable to maintain a baseline suspicion in patients who present with the appropriate clinical scenario. In a study evaluating a large international cohort of patients with IE, 230 (8%) of 2,772 patients had cancer [3]. Interestingly, in this same cohort, similar numbers of patients were on hemodialysis (8%), a recognized risk for IE due to long-term catheter use and frequent access of the vascular system, events that also often occur in oncology patients undergoing therapy. An additional analysis of this cohort specifically evaluated patients with both nosocomial and nonnosocomial healthcare-associated IE, which made up 34% of the cohort of patients with noninjecting drug use-associated IE. Of these patients, 16% had cancer and 15% were on immunosuppressive therapy. *Staphylococcus aureus* was the most common cause of infection, occurring in about 45% of patients, about half of whom had methicillin-resistant strains.

Very few studies specifically investigate IE in oncology patients (Table 20.1). Early case series focused on an association between long-term central venous access and risk of coagulase-negative staphylococcal bacteremia and subsequent endocarditis, predominantly involving the right side of the heart in patients with hematologic malignancy [4–6]. Indeed, this pathogen and *S. aureus* appeared to be the predominant causes of IE in the oncology population, while streptococci were reported infrequently. This more closely mirrored the distribution of pathogens in healthcare-associated IE and stood in contrast to the usual distribution of pathogens among patients with community-acquired native-valve endocarditis who were not injecting drug users in which one third to one half of cases were caused by streptococci [1, 3, 7]. Interestingly, the incidence of native-valve coagulase-negative staphylococcal IE might be even higher in the oncology population than had been described among patients with healthcare-associated IE, perhaps because of the frequency and duration of central venous catheterization in the former group. Also of interest in these series was the finding that IE developed despite the presence of thrombocytopenia in many cases.

Table 20.1 Studies of IE in oncology populations

Author	Year	Population	Number	Incidence	Type of malignancy	Predominant organisms	Notes
Liepman [4]	1980–1981	Adult leukemia patients	3	Not stated	AML (100%)	*S. epidermidis* (66%)	All with indwelling catheters and thrombocytopenia
Quinn [6]	1982–1983	Oncology center, adult allogeneic bone marrow transplant patients	3	3/246 (1.2%) patients undergoing BMT	Leukemia undergoing BMT	Coagulase-negative staph (100%)	All with Hickman catheters; all right-sided IE
Martino [5]	1986–1987	Adult allogeneic and autologous bone marrow transplant patients	7	7/141 (5%) patients undergoing BMT	Leukemia undergoing BMT (100%)	*S. epidermidis* (57%)	All with Hickman catheters; all right-sided; 5/7 with thrombocytopenia
Yusef [8]	1994–2004	Oncology center, adult patients	26	26/654 (4%) patients with echo requested to rule out IE	About half with hematologic malignancy and half with solid organ cancer	*S. aureus* (35%) Coagulase-negative staph (23%) *Enterococcus* spp. (11%) *E. coli* (8%)	45 patients with vegetations by echo; 19 with negative blood cultures – the authors speculate that most of these cases were NBTE; 69% of patients with IE had a central venous catheter; 31% had thrombocytopenia; 21 had left-sided

In a larger series of patients identified at a large oncology center between 1994 and 2004 which included patients with both hematologic (51%) and solid organ malignancy, *S. aureus*, coagulase-negative staphylococci, and Enterococcus species accounted for over two thirds of cases of IE in patients with positive blood cultures [8]. In contrast to previous series and although most patients with culture positive IE had central lines (69%), 21 (81%) of 26 patients had involvement of the mitral or aortic valves with only three patients having right-sided IE. Consequently, the risk of peripheral embolic events was high, occurring in 15 (58%) patients.

heart disease, hypertrophic cardiomyopathy, and the presence of a prosthetic valve, and host conditions, such as intravenous drug abuse and the presence of an indwelling central venous catheter or cardiac device. Prosthetic-valve endocarditis accounts for about 15–20% of patients with IE in recent studies [9, 10]. The risk of PVE is greatest in the first 6 months following valve replacement, but continues indefinitely. Most cases seen within the first year are caused by *S. aureus* and methicillin-resistant coagulase-negative staphylococci. After this time, the causative pathogens of PVE are similar to those of NVE, although the relative incidence of staphylococcal infections remains greater.

Risk Factors for IE

Risk factors for development of IE include both preexisting valvular abnormalities, such as rheumatic valve disease, degenerative heart disease, mitral valve prolapse, congenital

Clinical Presentation

Patients with IE have traditionally been divided into those with subacute presentations and those with acute presentations. The former is characterized by a more indolent illness that

develops over weeks with low-grade fevers and minimal cardiac dysfunction in patients with underlying valvular disease and is usually caused by organisms with lower virulence such as α-hemolytic streptococci (viridans streptococci). The later is characterized by an acute syndrome of systemic toxicity and rapid progression with intracardiac and extracardiac complications, is usually caused by *S. aureus,* and can occur on normal valves.

The majority of patients (~80–90%) present with fever, although it may be absent in patients either of advanced age, with chronic renal failure or who have received prior antibiotics. Other nonspecific symptoms include chills, anorexia, weight loss, myalgia, cough, and back pain. About 85% of patients with native-valve IE have heart murmurs, although this is usually related to the predisposing valvular lesion; only 10–40% of patients have a new or changed murmur. The classically described peripheral signs of IE are rarely seen in the modern era because patients are diagnosed before these sequelae of long-standing disease develop. These include petechiae which often involve the conjunctiva or distal extremities; splinter hemorrhages; Osler nodes which are painful nodules on the finger and toe pads; and retinal lesions known as Roth spots. However, clinical manifestations of embolic events are often seen because emboli occur in about 40% of patients. These include renal emboli that may present as flank pain or hematuria; splenic emboli that can manifest as left shoulder or left upper quadrant pain; septic pulmonary emboli indicated by pleuritic chest pain or back pain; emboli to the extremities which, if small, can cause capillary occlusion and painful spots on the fingers and toes, and if large, can involve arteries and lead to limb ischemia; and cerebral emboli which most commonly involve the middle cerebral artery. Neurologic events are common in IE, occurring in up to 25% of patients and also include hemorrhage, transient ischemic attack, meningitis, and mycotic aneurysm [11]. Any new neurologic signs, including persistent headache, should be evaluated by MRI and MRA or angiography.

Diagnosis and Investigation

The "modified Duke criteria" are the most commonly used algorithm for diagnosing IE (Fig. 20.1) [12, 13]. These criteria combine clinical, laboratory, and imaging data to estimate the likelihood of IE. While IE is unlikely if these criteria are not met, it is important to recognize that the original intent was to create a standardized definition for research purposes. Thus, if these criteria are not met, but there is a strong clinical suspicion for IE, additional patient evaluation and treatment, if appropriate, should ensue.

Adequate numbers of appropriately obtained blood cultures are crucial in diagnosing IE. The majority of patients with IE will have positive blood cultures – upwards of 90–95%. The most likely reason for negative blood cultures is prior receipt of antibiotics; thus, every effort should be made to obtain three sets of blood cultures with a minimum of 10 ml of blood in each bottle prior to the initiation of antibiotics. If a patient has a central venous catheter, no more than one set should be drawn from the line. In a patient with a subacute presentation who has received antibiotics and has no evidence of sepsis, progressive valvular dysfunction, or heart failure, antibiotics should be withheld for 2–3 days and blood cultures obtained off antibiotics. Unfortunately, this is often not possible in the oncology population, where patients are more likely to have infection with organisms that present acutely, such as *S. aureus*, or may be neutropenic or otherwise significantly immunosuppressed.

Follow-up blood cultures should be obtained to document clearance of bacteremia and again a few days after initial clearance. In addition, additional blood cultures should be drawn if a patient has a persistent fever or develops new fevers or other concerning symptoms while on therapy. Fever beyond 7 days may indicate failure of antimicrobial therapy or the presence of a myocardial abscess, focal extracardiac infection, emboli, or hypersensitivity to an antimicrobial agent.

Finally, if infection with an unusual or fastidious organism is suspected, discussion with the microbiology laboratory should occur regarding additional approaches to evaluation of blood cultures. In addition, serologic tests for infection with *Brucella* spp., *Legionella* spp., *C. burnetii*, *Chlamydia* spp., and *Bartonella* spp. can be obtained, usually in consultation with infectious diseases.

All patients with suspected IE should undergo echocardiography to assess for the size and location of vegetations, the presence of valve ring abscess, and any evidence of valvular or ventricular dysfunction. While the specificity of transthoracic echocardiography (TTE) for detecting vegetations is high (91–98%), the sensitivity is in the range of 45–60%, particularly when vegetations are less than 1 cm in size [14, 15]. In addition, TTE is a poor modality for evaluating prosthetic valves or assessing the presence of perivalvular abscess or leaflet perforation. When evaluating an echocardiogram result, it is important to know how the quality of the exam was graded by the cardiologist. A negative TTE of good quality can rule out most cases of IE when the likelihood of disease is felt to be low. However, if the quality of the exam is low or the patient is at intermediate to high risk of IE, a transesophageal echocardiogram (TEE) should be obtained. TEE has a sensitivity of ~90% for identifying vegetations and offers improved imaging of the pulmonic valves, prosthetic valves, and intracardiac complications due to IE [16].

Fig. 20.1 Modified Duke clinical criteria for diagnosis of infective endocarditis

Major criteria

Positive blood culture
- Two separate blood cultures yielding organisms that typically cause infective endocarditis (viridans streptococci, *Streptococcus bovis*, HACEK[a], *Staphylococcus aureus* or community-acquired enterococci without a primary focus)
- Persistently positive blood cultures (defined as positive blood cultures drawn more than 12 hours apart *or* all of three or a majority of four or more separate positive blood cultures, the first and last drawn at least 1 hour apart)
- Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer > 1:800

Evidence of endocardial involvement
- Echocardiography positive for infective endocarditis[b]
  Oscillating intracardiac mass on a valve or supporting structure in the path of regurgitant jets or on implanted material in the absence of an alternative anatomical explanation
  Abscess
  New partial dehiscence of a prosthetic valve
- New valvular regurgitation (change in pre-existing murmur is not adequate)

Minor criteria
- *Predisposing heart condition or intravenous drug use*
- *Fever* (≥ 38.0°C)
- *Vascular phenomenon* (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival hemorrhages or Janeway lesions)
- *Immunological phenomenon* (glomerulonephritis, Osler nodes, Roth spots or rheumatoid factor)
- *Microbiological evidence* (positive blood culture, but less than major criterion,[c] *or* serological evidence of active infection with an organism consistent with infective endocarditis)

[a]*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*

[b]TEE recommended in patients with prosthetic valves, complicated endocarditis, and who have possible endocarditis

[c]Excludes a single positive culture for coagulase-negative staphylococci or organisms that do not cause infective endocarditis

Source: Durack *et al. Am J Med* 1994; **96**: 200-9 and

Li JS *et al. Clin Infect Dis 2000;* **30***-633-8.*

Management

In addition to the aforementioned blood cultures and echocardiography, all patients should undergo a detailed history and physical examination, laboratory work, chest X-ray, and an ECG. A prolonged PR interval or intraventricular conduction disturbance on ECG can indicate a valve ring abscess, particularly in aortic valve infective endocarditis. New conduction abnormalities are highly specific for paravalvular infection, but are not sensitive [17].

Risk factors for relevant organisms should be taken into consideration when selecting empiric therapy for oncology patients with IE. Based on the epidemiology of IE in this population, coverage directed against *S. aureus*, including methicillin-resistant strains, and coagulase-negative staphylococci (CoNS) is recommended, usually with vancomycin.

Given that infections caused by Gram-negative bacilli, yeast, or fastidious organisms are rare causes of IE in oncology patients, initial coverage directed at these pathogens is unnecessary in most cases, unless there is a specific reason to have concern that they may be involved. The American Heart Association has issued guidelines for organism-specific antimicrobial therapy and treatment for the most common organisms in oncology patients is summarized in Table 20.2 and discussed in the organism-specific sections below [18].

The strongest indication for valve replacement in a patient with IE is development of congestive heart failure as delaying surgery in these patients has been associated with increased mortality [19, 20]. Other situations in which surgery should be strongly considered include myocardial invasion such as valve ring abscess or fistula formation, large

Table 20.2 Infective endocarditis treatment regimens

Infecting Organism	Antibiotic	Dose	Duration	Comments
Viridans streptococcal and *Streptococcus bovis* native-valve endocarditis				
1. Fully sensitive to Penicillin (MIC ≤ 0.12 mcg/ml)	Penicillin G	3 million units IV Q4H	4 weeks	
	OR			
	Ceftriaxone	2 g IV Q24H	4 weeks	
	OR			
	[Penicillin G or Ceftriaxone]	3 million units IV Q4H 2 g IV Q24H	2 weeks 2 weeks	Use 2 week regimen for uncomplicated cases only
	PLUS			
	Gentamicln	3 mg/kg IV Q24H	2 weeks	
	OR			
	Vancomycin	15 mg/kg IV Q12H	4 weeks	Use for severe Penicillin allergy only Goal Vancomycin trough 15–20 mcg/ml
2. Relatively resistant to Penicillin (MIC > 0.12 mcg/ml and ≤ 0.5 mcg/ml)	[Penicillin G or Ceftriaxone]	4 million units IV Q4H 2 g IV Q24H	4 weeks 4 weeks	
	PLUS			
	Gentamicin	3 mg/kg IV Q24H	2 weeks	
	OR			
	Vancomycin	15 mg/kg lV Q12H		Use for severe Penicillin allergy only Goal Vancomycin trough 15–20 mcg/ml
3. Penicillin MIC > 0.5 mcg/ml or nutritionally variant streptococci	Treat as Enterococcal endocarditis			
Viridans streptococcal and *Streptococcus bovis* prosthetic-valve endocarditis				
1. Fully sensitive to Penicillin (MIC ≤ 0.12 mcg/ml)	[Penicillin G or Ceftriaxone]	4 million units IV Q4H 2 g IV Q24H	6 weeks 2 weeks	
	+/-			
	Gentamicin	3 mg/kg IV Q24H	2 weeks	
	OR			
	Vancomycin	15 mg/kg IV Q12H	6 weeks	Use only for Penicillin resistance or severe Penicillin allergy (consider desensitization to Ampicillin or Penicillin) Goal Vancomycin trough 15–20
2. Relatively or fully resistant to Penicillin (MIC > 0.12 mcg/ml)	[Penicillin G or Ceftriaxone]	4 million units IV Q4H 2 g IV Q24H	6 weeks 6 weeks	
	+/-			
	Gentamicin	3 mg/kg lV Q24H	2 weeks	
	OR			
	Vancomycin	15 mg/kg IV Q12H		Goal Vancomycin trough 15–20 mcg/ml
Enterococcal endocarditis				
1. Low-level resistance to Gentamicin	[Ampicillin or Penicillin G]	2 g IV Q4H 3–5 million units IV Q4H	4–6 weeks	4 weeks of therapy in most cases 6 weeks for those with symptoms > 3 months or prosthetic valve
	PLUS			
	Gentamicin	1 mg/kg IV Q8H	4–6 weeks	Goal Gentamicin peak = 3–4 mcg/ml and trough <1 mcg/ml
	OR			
	Vancomycin	15 mg/kg lV Q12H	6 weeks	Use only for Penicillin resistance or severe PCN allergy (consider desensitization to Ampicillin or Penicillin)
	PLUS			
	Gentamicin	1 mg/kg IV Q8H	6 weeks	Goal Vancomycin trough 15–20 mcg/ml Goal Gentamicin peak = 3–4 mcg/ml and trough < 10 mcg/ml
2. High level resistance to Gentamicin but low-level resistance to Streptomycin	Replace Gentamicin with Streptomycin in above regimens	7.5 mg/kg IV Q12H		Goal Streptomycin peak = 20–35 mcg/ml and trough <10 mcg/ml

(continued)

Table 20.2 (continued)

Infecting Organism	Antibiotic	Dose	Duration	Comments
Staphylococcal native-valve endocarditis				
1. Methicillin susceptible	Oxacillin **OR** Nafcillin	2 g IV Q4H 2 g IV Q4H	Uncomplicated: 4 weeks Complicated: 6 weeks	Drugs of choice for MSSA Addition of Gentamicin 1 mg/kg IV Q8H optional Goal Gentamicin peak = 3–4 mcg/ml and trough <1 mcg/ml
2. Methicillin susceptible and non-severe PCN allergy	Cefazolin	2 g IV Q8H	Uncomplicated: 4 weeks Complicated: 6 weeks	Addition of Gentamicin 1 mg/kg IV Q8H optional Goal Gentamicin peak = 3–4 mcg/ml and trough <1 mcg/ml
3. Methicillin resistant or Penicillin allergy	Vancomycin	15 mg/kg IV Q12H	6 weeks	Use only for Methicillin resistance or severe Penicillin allergy (consider desensitization to Oxacillin or Nafcillin) Goal Vancomycin trough 15–20 mcg/ml
	OR Daptomycin	6–12 mg/hg IV Q24H	6 weeks	Use only for Methicillin resistance or severe Penicillin allergy (consider desensitization to Oxacillin or Nafcillin)
Staphylococcal prosthetic-valve endocarditis				
1. Methicillin sensitive	Oxacillin <u>PLUS</u>	2 g IV Q4H	6 weeks	
	Gentamicin **AND**	1 mg/kg IV Q8H	2 weeks	Goal Gentamicin peak = 3–4 mcg/ml and trough <1 mcg/ml
	Rifampin	300 mg PO Q8H	6 weeks after blood cultures have cleared	
2. Methicillin resistant or Penicillin allergy	Vancomycin <u>PLUS</u>	15 mg/kg IVQ12H	6 weeks	Consider desensitization to Oxacillin or Nafcillin if severe Penicillin allergy.
	Gentamicin **AND**	1 mg/kg IV Q8H	2 weeks	Goal Vancomycin trough 15–20 mcg/ml Goal Gentamicin peak = 3–4 mcg/ml and trough <1 mcg/ml
	Rifampin	300 mg PO Q8H	6 weeks after blood cultures have cleared	

vegetation >1 cm with large embolization or vegetation >1.5 cm even without vegetation, most cases of PVE caused by *S. aureus*, and failure to respond to antimicrobial therapy, including cases with infection with highly resistant organisms or yeast and mold [19, 21]. These patients should be evaluated early in the clinical course by a cardiovascular surgeon in case urgent intervention is required. In general, if a patient has a strong indication for surgery, it should not be delayed to wait for clearance of blood cultures as reinfection of implanted valves occurs relatively infrequently provided that the patient is on appropriate therapy at the time of the operation [19, 22]. Surgery should be delayed in patients whose course is complicated by neurologic events given the risk of intracerebral hemorrhage on cardiopulmonary bypass. In general, waiting 2–4 weeks after a large embolic infarct (>2 cm) and 4 weeks after intracerebral hemorrhage is recommended; shorter waiting periods may be possible with smaller lesions [23]. With regard to duration of antimicrobial therapy postoperatively, patients with negative blood and valve cultures should complete the already planned course of therapy. For patient with positive valve cultures and most

patients with PVE, a full course of therapy postoperatively should be given.

Etiologic Agents

Below the etiologic agents of IE most relevant to oncology patients are reviewed. IE caused by Gram-negative organisms, HACEK organisms, and causes of culture-negative IE are not further discussed.

Staphylococcus aureus

Bacteremia with *S. aureus* is relatively common in oncology patients, likely due to the high frequency of central venous catheter use in this population. In the general population, about one third of patients with *S. aureus* bacteremia will develop metastatic complications resulting either from hematogenous seeding of a distant site or from local extension

of infection [24–26]. These sites include bone and joints, especially when prosthetic material is present; the epidural space and intervertebral discs; intra-abdominal organs such as the kidneys and spleen; and heart valves, including previously normal valves.

Interestingly, in the oncology population, there may be a difference in the rate of the occurrence of metastatic spread of *S. aureus* depending on the presence of neutropenia. Nonneutropenic oncology patients appear to be at significant risk for seeding other sites in the setting of *S. aureus* bacteremia. In one study of 52 nonneutropenic patients in which the source of infection was device-related in 42%, tissue-infection related in 44%, and unknown in 13%, 17 (33%) patients developed metastatic infections, including eight cases of IE, six cases of bone and joint infection, and three cases of renal infection [27]. In a study that evaluated outcomes of 91 patients with catheter-related *S. aureus* bacteremia of whom 63% had solid tumors and 81% were not neutropenic at the time of bacteremia, 36 (40%) had at least one complication [28]. Patients with solid tumors had significant risk for intravascular complications which included 3 cases of IE and 15 cases of septic thrombosis. Of note, rates of receipt of TTE and TEE were low in the cohort – 35% and 12%, respectively – and only 22% of patients had a venous flow study to evaluate for venous thrombosis. Thus, the true incidence of IE and other endovascular infection in the setting of *S. aureus* bacteremia is likely underestimated.

In studies that have evaluated neutropenic hematologic malignancy patients, IE associated with *S. aureus* bacteremia has been observed in very few patients (range 0–0.5%) [29–33]. Rates of other metastatic complications were also low in these studies, although osteomyelitis, septic pulmonary emboli, and meningitis were observed rarely [30, 31, 34]. Hypotheses for these findings include early initiation of antistaphylococcal therapy because of empiric treatment of neutropenic fever and inability of prolonged survival of *S. aureus* organisms within neutrophils due to their absence [35].

An important caveat in interpreting these results is that the studies were all retrospective and did not comment on whether patients had aggressive evaluations for spread of *S. aureus* infection with TTE, TEE or other symptom-based imaging (e.g., magnetic resonance imaging of the spine to rule out an epidural abscess or osteomyelitis in a patient with significant back pain). Thus, the suggestion made by one author that shorter courses of therapy be considered in these patients should not be undertaken without a complete evaluation for metastatic seeding of *S. aureus*. It is also important to note that although these studies did not find a high rate of metastatic spread, many did find that *S. aureus* bacteremia among neutropenic patients was associated with an increased risk of septic shock and death relative to nonneutropenic patients [28–31].

Because the presence of *S. aureus* bacteremia is a significant risk factor for IE, all patients with *S. aureus* bacteremia should undergo echocardiography to rule out vegetations. Many experts recommend use of TEE based on its superior sensitivity for detection of IE as well as intracardiac abcesses and valvular perforation in patients with *S. aureus* bacteremia [36–38]. At a minimum, TEE should be performed if a patient has a prosthetic valve, permanent cardiac device, prolonged bacteremia (>48 h) or fever (>72 h), or cardiac conduction abnormalities OR if short-course, 2-week therapy is planned. Of note, while a TEE of native valves that does not identify evidence of endocarditis makes the diagnosis of endocarditis unlikely, other criteria, such as the absence of other metastatic foci, must be met before the decision is made to give a short course of therapy [39].

Every effort should be made to identify and drain abscesses and remove infected devices to maximize therapeutic response. Antimicrobial therapy of *S. aureus* IE is based on the organism's susceptibility to methicillin. Methicillin susceptible isolates should be treated with antistaphylococcal penicillins whenever possible, given their superior efficacy relative to vancomycin [40]. Cefazolin is an alternative in patients with nonsevere penicillin allergies and desensitization to an antistaphylococcal penicillin should be considered in patients with type 1 allergies to penicillin. Guidelines from the American Heart Association note that the addition of initial (first 3–5 days), low-dose, synergistic gentamicin (1 mg/kg IV Q8H) is optional in the treatment of IE caused by MSSA [18]. This practice has not been shown to improve patient outcomes, although it appears to reduce the duration of bacteremia by about a day in patients with MSSA native-valve endocarditis [41]. However, this minimal benefit is likely outweighed by the potential for nephrotoxicity, which was seen in 24% of patients in a recent clinical trial [42].

Treatment of methicillin-resistant *S. aureus* IE can be challenging. Vancomycin is generally considered the drug of first choice as it has been used to cure many patients over the past 40 years. However, vancomycin is slowly bactericidal and has been associated with prolonged duration of bacteremia and occasionally clinical failure. This failure has been seen in patients without evidence of vancomycin resistance using conventional microbiologic testing. Some patients are infected with heteroresistant MRSA where subpopulations of organisms have minimum inhibitory concentrations (MICs) of vancomycin indicative of reduced susceptibility (4–32 μg/ml) [43]. In addition, patients with MRSA with vancomycin MICs of 2 μg/ml may be at increased risk for clinical failure [44, 45]. Although the use of higher doses of vancomycin to improve response has not been well studied, current guidelines recommend vancomycin troughs of 15–20 μg/ml for treatment of serious MRSA infections including IE [46].

An alternative to vancomycin is daptomycin, a bactericidal lipopeptide that is FDA-approved at a dose of 6 mg/kg

daily for the treatment of *S. aureus* bacteremia and right-sided endocarditis based on a trial showing that it was as effective as standard therapy, consisting of initial low-dose gentamicin plus either vancomycin or an antistaphylococcal penicillin [47]. Because six patients in the trial had emergence of reduced susceptibility to daptomycin during the study, it has been suggested that higher doses of daptomycin (8–12 mg/kg daily) be used in seriously ill patients or those with left-sided IE [48, 49, 99].

Prosthetic-valve IE caused by *S. aureus* should be treated with three agents to avoid emergence of resistance. These include either an antistaphylococcal penicillin or vancomycin based on susceptibilities of the organisms plus low-dose gentamicin and rifampin. Rifampin should be started after blood cultures clear to minimize emergence of rifampin resistance and care should be given to assess for drug interactions [50]. Most patients with *S. aureus* PVE will require repeat valve replacement to optimize outcomes; therefore, cardiac surgeons should be involved in the patient's care from the time of presentation [21].

Coagulase-Negative Staphylococci

While CoNS have long been frequent pathogens in prosthetic-valve IE, they were the cause of 7.8% of cases of native-valve IE in a recent multicenter study [51]. In addition, they were the second commonest cause of IE in oncology patients in a study assessing endocarditis in this population [8]. Most CoNS IE is caused by *S. epidermidis*, although other species have been implicated such as *S. lugdinensis*, *S. hominis*, *S. saprophyticus*, and *S. haemolyticus*. The epidemiology of native-valve CoNS IE appears similar to that of native-valve *S. aureus* IE in that it is often healthcare-acquired and associated with indwelling catheters, hemodialysis access, and recent invasive procedures [51]. However, patients tend to have a longer duration of symptoms before the IE is detected, both because the organism can be more indolent and possibly because CoNS in blood cultures is often a contaminant and does not attract clinical attention. Indeed, it can be challenging to assess whether CoNS growing in blood cultures represents contamination or infection. In general, patients with true infection will have more than one set of blood cultures taken from different sites growing CoNS, particularly in the setting of endovascular infection. If such infection is suspected, blood cultures should be obtained peripherally; repeated blood cultures growing CoNS that are drawn from central lines may represent colonization of the catheter and not infection. It is relevant to note that although most of the reported cases of CoNS IE in oncology patients have been associated with a central catheter, some may have the

mucosa as a source, particularly in those with neutropenia [4–6, 52].

CoNS isolates from patients with suspected or proven IE should be speciated to rule out infection caused by *S. lugdunensis*, a species of CoNS known for its increased virulence manifested by valvular destruction and myocardial abscess formation [53]. In contrast to *S. epidermidis*, this organism is usually susceptible to antistaphylococcal penicillins which should be used preferentially for treatment. Because of high rates of resistance to antistaphylococcal penicillins among *S. epidermidis* isolates, vancomycin is generally the agent of choice for most cases of CoNS IE. Regimens for PV IE due to CoNS are the same as those for *S. aureus* and include a three-drug regimen and evaluation by a cardiothoracic surgeon.

Streptococci

Although streptococci have traditionally been considered the most common cause of IE in the community setting, they appear to be less common among patients with healthcare-associated IE, including oncology patients. Most streptococcal IE is caused by α-hemolytic streptococci, also known as viridans group streptococci. Within this group, the majority of cases are caused by *Streptococcus sanguis*, *Streptococcus mitis*, and *Streptococcus mutans* [54–56].

Interestingly, despite the infrequency of streptococcal IE, bacteremia due to viridans streptococci is relatively common in neutropenic patients with cancer, accounting for 15–30% of all bacteremias in this population [57]. Streptococcal bacteremia in neutropenic patients is associated with oropharyngeal mucositis, receipt of high doses of cytosine arabinoside, and recent chemotherapy while receipt of penicillin for prophylaxis and early receipt of antibiotics for neutropenic fever appear to be protective [57, 58]. The organisms most commonly isolated in this population are similar to those that cause IE, *S. sanguis*, *S. mitis*, and *S. oralis* [57, 58]. However, few cases of IE following viridans streptococcal bacteremia have been noted. Two cases (8%) of IE were reported in one study to have developed following viridans streptococcal bacteremia; one of the two patients had previous valvular abnormalities [57]. Nevertheless, if an oncology patient presents with multiple blood cultures growing viridans streptococci, IE should be ruled out with echocardiography, particularly if the patient has a history of underlying valvular disease. It should also be suspected in patients presenting with low-grade fevers and malaise over a period of weeks.

Treatment recommendations are based on the minimal inhibitory concentration (MIC) of penicillin and are described in Table 20.2; it is important to request for the MIC of penicillin if it is not reported by the microbiology

laboratory. The frequency of penicillin nonsusceptible viridans streptococci has increased among oncology patients, a finding likely related to the use of penicillin and ampicillin for prophylaxis [59–61]. Thus, empiric therapy for viridans streptococci bacteremia before the MIC of penicillin is known should be with vancomycin in the oncology population at most institutions. There is some controversy regarding the optimal therapy for penicillin-resistant viridans streptococcal IE; recommendations include high-dose penicillin plus low-dose gentamicin, ceftriaxone plus low-dose gentamicin, or vancomycin [62, 63].

Among other streptococcal species that cause IE, *Streptococcus bovis* deserves particular mention because of its association both with IE and with colonic neoplasm. There are two biotypes of S. bovis: biotype I is now termed *S. galloyticus* subspecies *gallolyticus,* biotype II is further characterized into strain 1, *S. gallolyticus* subspecies *S. lutetiensis,* and strain 2, *S. gallolyticus* subspecies *pasteurianus* [64]. When biotype I is isolated in blood cultures, IE is also present in 60–94% of cases, and underlying malignant or premalignant colonic lesions can be detected in 40–100% of cases [64–67]. Bacteremia with biotype 2 is associated with hepatobiliary disease and much less commonly IE or colonic neoplasm. As most microbiology labs do not distinguish between the two biotypes when reporting culture results, any patient with *S. bovis* bacteremia should undergo echocardiography as well as colonoscopy. *S. bovis* IE is treated in the same manner as viridans streptococcal IE.

Other streptococcal types include the *Streptococcus milleri* group (*S. anginosus*, *S. constellatus*, and *S. intermedius*) and the nutritionally deficient streptococci (*Abiotrophia defectiva*, *Granulicatella adiacens*, *Granulicatella para-adiacens*, *Granulicatella balaenopterae*, and *Granulicatella elegans*). Of the former group, *S. anginosus* is most likely to cause IE, but overall this occurs uncommonly. The nutritionally deficient streptococci are often tolerant to penicillin; thus combination therapy is often needed for cure [68].

Enterococci

Historically, enterococci are the etiology in ~6–10% of cases of IE, although this percentage appears to be higher among patients with healthcare-associated IE [1, 3, 7]. In addition, a recent multicenter study found that patients with enterococcus IE were more likely to have cancer than patients with IE caused by other organisms (21% vs. 8%) [69]. *E. faecalis* IE is significantly more common than *E. faecium* IE, and the most frequent sources are infection of the urinary tract, particularly in the setting of instrumentation, followed by infections involving the GI tract and central catheters [70]. Between 8 and 32% of patients with enterococcal bacteremia, either have or will develop IE and this risk is significantly increased if the isolate is *E. faecalis* or the patient has a prosthetic valve [71].

Oncology patients with enterococcal bacteremia should be assessed carefully for the possibility of IE, particularly if blood cultures are persistently positive or in the setting of a prosthetic valve. It is particularly important to establish the diagnosis because treatment for enterococcal IE may be different than treatment for a less severe enterococcal infection. Combination therapy with a cell wall-active agent (penicillin, ampicillin, or vancomycin) plus an aminoglycoside with enterococcal activity (gentamicin or streptomycin) is required to eradicate enterococci in IE because enterococci are inhibited but not killed by penicillin, ampicillin, and vancomycin alone. Enterococci with high-level resistance to gentamicin (MIC $500 \geq$ mg/l) should be tested for high-level resistance to streptomycin (MIC $\geq 2,000$ mg/l); streptomycin can be used if high-level resistance is not present. Neither gentamicin nor streptomycin should be used when there is high-level resistance to both. A possible alternative to aminoglycosides in the treatment of *E. faecalis* is the addition of ceftriaxone to ampicillin, which has been associated with clinical cure rates in 67.4% of patients [72]. Although uncommon, IE caused by vancomycin-resistant enterococcus has been reported and is associated with poor outcomes [73].

Fungi

Although infections caused by *Candida* and *Aspergillus* are common in patients with malignancy, IE due to these organisms is rare in this and in the overall population. Reviews of the published literature between 1965 and 2005 revealed 237 cases of *Candida* IE, 94 cases of *Aspergillus* IE, and significantly smaller numbers of IE caused by other yeast and molds [74, 75]. Only 33 of 2,760 (1.2%) patients in a multinational database of prospective cases of IE had infection caused by *Candida* (11 patients had other fungal organisms that were not defined further) [76]. In this cohort, the majority of organisms were *C. albicans* (48%), followed by *C. parapsilosis* (21%), *C. glabrata* (15%), and *C. tropicalis* (9%). Risk factors for candida IE included having a prosthetic valve, a short-term indwelling catheter, or recent coronary artery bypass grafting, but not malignancy. In a report evaluating 168 oncology patients with candidiasis studied at necropsy, 17 (10%) were found to have cardiac involvement, although none of these patients had a past history of cardiac disease [77]. Sixteen of the patients had leukemia or lymphoma. While all patients had abscesses in the myocardium and eight had mural endocardial involvement, no patients had valvular involvement. All patients with cardiac involvement had

evidence of disseminated infection and the majority had *Candida* growing in blood cultures. *Candida* IE should be considered in oncology patients who have risk factors for IE (prosthetic valve, other valvular abnormalities, indwelling catheters), blood cultures with growth of *Candida* that is usually persistent, and evidence of peripheral embolization, as large vegetations and associated embolic events occur commonly in this disease.

Combination of surgical and medical management is generally recommended for *Candida* IE. Amphotericin B is considered the drug of choice, largely based on more extensive clinical experience with this agent, although treatment with echinocandins has been successful in some reports [78]. Valve replacement surgery followed by 6–8 weeks of antifungal therapy is recommended. For patients who are unable to undergo surgery, long-term suppressive therapy with fluconazole is recommended and has been associated with cure in some patients.

Cardiac infection due to *Aspergillus* species is uncommon in oncology patients and generally manifests as myocardial abscesses, rather than IE, in hematologic malignancy patients with other evidence of disseminated fungal disease [2]. The majority of cases of *Aspergillus* IE reported in the literature occur in patients following cardiac surgery with prosthetic valves [79]. In the few reports of *Aspergillus* IE in oncology patients, patients develop initial *Aspergillus* infection during the time of severe myelosuppression and go on to develop vegetative lesions after recovery of their cell counts [80]. Premortem diagnosis can be difficult as patients generally do not have blood cultures that grow the organism, either because of intermittent fungemia or challenges with isolation of the organisms in routine blood culture media [81]. *Aspergillus* vegetations are often large and are frequently associated with embolization; in one series, the diagnosis was initially established in 7 of 35 patients when fungal forms were found in arterial emboli that had been removed [79]. *Aspergillus* IE has also been associated with macroangiopathic hemolytic anemia in patients with hematologic malignancies, and the appearance of this clinical syndrome should prompt echocardiography [80, 81]. In addition, a patient with persistent unexplained fever and known disseminated Aspergillosis should undergo echocardiography.

Aspergillus IE in oncology patients is associated with significant, almost universal, mortality, both because patients usually have disseminated disease at the time of presentation and because treatment is challenging. A combination of medical and surgical therapy is required. Resection of the vegetation and infected valve and removal of other areas of mural involvement should be undertaken. Traditionally, Amphotericin B has been used for therapy; however, there are emerging reports of use of voriconazole alone or in combination for treatment and recent guidelines suggest that voriconazole be considered as first-line therapy [34, 82, 83].

Prolonged suppressive therapy with voriconazole is indicated in most cases.

Nonbacterial Thrombotic Endocarditis in Oncology Patients

Nonbacterial thrombotic endocarditis (NBTE), previously called marantic endocarditis, results from the deposition of masses of fibrin and platelets that do not contain microorganisms or inflammatory cells on often-normal heart valves. Consequently, blood cultures do not grow organisms. Although the exact pathogenesis is not fully understood, the condition has been associated with both increased levels of circulating cytokines that may lead to endothelial damage and a hypercoagulable state with enhanced activation of platelets and the coagulation cascade [84, 85]. In addition, there appears to be an association between NBTE and the presence of disseminated intravascular coagulation. In one autopsy study, 71% of patients had both conditions [86].

The incidence of NBTE appears to be relatively high in oncology patients. In one study, TTE was performed on 200 ambulatory patients with solid tumors and 100 control patients without overt heart disease or known malignancy. Cardiac vegetations were detected in 19% of the solid tumor patients compared to only 2% of the control group [87]. Other studies have reported a lower incidence of NBTE in cancer patients (0.96–1.3%); however, these have been autopsy studies and some authors have suggested that, by the time autopsy occurs, many patients who may have had NBTE no longer have evidence of cardiac vegetation because of peripheral embolization [86, 88].

NBTE is most frequently associated with solid tumors, most commonly adenocarcinoma of the lung and pancreas. However, it has been described in patients with almost all malignancies, including those involving the gastrointestinal tract, breast, and prostate; melanoma; lymphoma; and multiple myeloma [87–91]. Most oncology patients with NBTE have disseminated metastatic disease, although occasionally NBTE is seen with localized tumors.

NBTE is characterized by small multiverrucous vegetations that are found in areas of high blood flow such as the line of valve closure of the mitral and aortic valves. Right-sided valvular involvement is uncommon. Because of the lack of inflammation, the vegetations do not strongly adhere to the valves, and consequently, while they rarely cause valvular damage, they tend to embolize easily. Embolism rates range from 14 to 91% with an average of 42% and clinically important sites of embolism include the cerebral, coronary, splenic, renal and mesenteric vessels and, more rarely, major peripheral vessels [89].

The most common and most morbid clinical presentation of NBTE is an acute neurologic event. In one autopsy study, cerebral embolic infarction was noted in 42 (49%) of 86 patients with NBTE; 32 (76%) patients were symptomatic with about half having a focal neurologic deficit only and half presenting with diffuse encephalopathy [92]. Most patients had widespread metastatic disease at the time of presentation and half died from cerebral or other infarcts. Patients with NBTE-related embolic strokes appear to have a particular stroke pattern on diffusion-weighted magnetic resonance imaging consisting of multiple, widely distributed small and large strokes [93].

In addition to neurologic complications, cardiac dysfunction caused by embolism to the coronary vessels can complicate NBTE; intramyocardial arterial thrombosis occurs in one quarter to one third of patients with 6.7–9% developing clinical significant myocardial infarction [94]. Embolism to the kidneys may result in hematuria, while embolism to the spleen may manifest as left upper quadrant pain.

The diagnosis of NBTE should be considered in any oncology patient with evidence of arterial or venous embolism or disseminated intravascular coagulation. An initial evaluation should include a careful physical exam to assess for other embolic lesions followed by relevant imaging studies to evaluate abnormal findings, several sets of blood cultures to rule out infective endocarditis, laboratory investigations to assess for the presence of disseminated intravascular coagulation, and TTE. If suspicion for NBTE is high and TTE does not show a vegetation, TEE should be considered as it appears to have a higher diagnostic yield in NBTE [95].

One of the main challenges in diagnosing NBTE is distinguishing it from infective endocarditis, particularly because many oncology patients are on antibiotics which can cause blood cultures to not grow organisms in the setting of infective endocarditis. Some differences between IE and NBTE are noted in Table 20.3. Specifically, patients with NBTE are less likely to have fever, leukocytosis, blood cultures growing organisms, and valvular destruction and its sequelae and are more likely to have associated disseminated intravascular coagulation and CNS and coronary emboli than patients with IE.

Treatment of patients with NBTE includes both systemic anticoagulation and treatment of the underlying malignancy. The latter is often difficult as many patients have advanced metastatic cancer, but surgical resection or shrinkage of tumors with chemotherapy or radiation may lead to resolution of NBTE [96]. Although there are limited clinical data regarding the efficacy of heparin in curbing embolic events associated with NBTE, it is considered the first-choice agent for anticoagulation. Traditionally, therapy has been with unfractionated heparin, although low-molecular-weight heparin may also be effective. Cessation of heparin has been associated with occurrence of additional embolic events and is not recommended unless the malignancy can be controlled. Despite the high frequency of subclinical and clinical cerebral embolism in NBTE, treatment with heparin does not appear to promote brain hemorrhage [97].

The role of cardiac surgery to treat NBTE is not well studied. It could be considered in patients with reasonable functional status who have severe valvular dysfunction that cannot be medically managed or recurrent embolic events despite anticoagulation [98]. Vegectomy rather than valve replacement may be possible in some cases if the valve structure remains intact. Subsequent risk of recurrent NBTE after these procedures has not been studied.

Table 20.3 Comparison of infective endocarditis and nonbacterial thrombotic endocarditis

Characteristic	Infective endocarditis	Nonbacterial thrombotic endocarditis
Fever	~90% of patients	Uncommon
New murmur	~10–40%	~15%
Leukocytosis	Common	Uncommon
Positive blood cultures	~90%	Uncommon
Involved valves	Left- and right-sided involvement	Right-sided involvement rare
Valvular function	Often impaired due to valvular invasion	Often unaffected
Frequency of emboli	15–40%	14–91%
Common sites of embolization	Renal > splenic > coronary > cerebral	Cerebral > coronary > renal > splenic
Pattern of cerebral embolism	Solitary lesion, territorial infarction, or multiple punctate lesions	Multiple, widely distributed, small and large strokes
Concomitant disseminated intravascular coagulation	Rare	Common

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Chapter 21
Skin Disorders Difficult to Distinguish from Infection

Sharon Hymes, Susan Chon, and Ana Ciurea

Abstract Dermatologists and infectious disease specialists are often called upon to evaluate skin lesions in cancer patients, especially when an infectious etiology is suspected. Many different organisms can affect the skin, and these are comprehensively reviewed in other chapters. This section will review some of the noninfectious skin eruptions that mimic cutaneous infections. These noninfectious diagnoses may be suspected after review of the patient history, and are often confirmed by skin evaluation and biopsy as indicated. The morphology of the primary skin lesion, the one that has not been manipulated or otherwise treated, often provides important diagnostic clues.

This chapter is intended to help the clinician generate a differential diagnosis when evaluating cutaneous lesions in cancer patients. Using the morphology of the primary lesion as a starting point, we then list the noninfectious diagnosis that could be considered and the infectious process it mimics.

Keywords Skin disorder • Mimic infection • Vesiculobullous lesions • Pustular lesions • Reactive neutrophilic dermatoses

Vesiculobullous Lesions

A vesicle is a sharply circumscribed fluid-filled blister measuring 0.5 cm or less, while a bulla is usually greater than 0.5 cm. The configuration may be solitary, grouped or annular, and the distribution may be localized or widespread. From an infectious disease point of view, vesicles and bullae are most often associated with viral eruptions, and these are frequently herpetic. Vesicles and bullae are also produced when an infectious pathogen produces necrosis of the over-lying skin. Isolated bullae, especially when on a background of erythema, may look like impetigo or cellulitis. However, many vesiculobullous eruptions in cancer patients are noninfectious, and alternative etiologies are reviewed.

Acute Dermatitis

Differential Diagnosis: Viral Exanthem or Cellulitis

Acute dermatitis is characterized by vesicles and bullae, often precipitated by allergic or irritant reactions caused by an exogenous agent contacting the skin. In the oncology setting, this is often seen under dressings or after the application of topical antibiotics (Fig. 21.1). When corresponding to the outline of the bandages, the bullae may be linear but not dermatomal, helping to distinguish this from herpes zoster. When the diagnosis is uncertain, a skin biopsy demonstrates the hallmark changes of spongiosis, characterized by inter- and intracellular edema in the epidermis, rather than the multinucleated giant cells characteristic of herpes infections. Although acute dermatitis is not in itself contagious, it is not uncommon for the lesions to become secondarily infected. On occasion, eczematous vesicles and bullae develop in a generalized and distant distribution from the original contact, a phenomenon known as autosensitization dermatitis. This should be distinguished from disseminated herpetic disease.

Mechanical Blisters

Differential Diagnosis: Viral Exanthem or Ecthyma

Mechanical blisters occur in areas subject to friction (Fig. 21.2), pressure, burns, or extravasations of toxic substances, including some types of parenteral chemotherapy. Chemotherapeutic agents may be irritants, which produce inflammation or phlebitis but not tissues necrosis, or they may be vesicants which

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Fig. 21.1 Acute dermatitis. There are prominent blisters, erythema, and crusting after the application topical Neomycin

Fig. 21.3 Purpura from injections in a patient with thrombocytopenia

Fig. 21.2 Friction blister. This larger blister marked by an *arrow* is secondary to rubbing from an ill-fitting shoe. The smaller blister on the left is from edema

Fig. 21.4 Coma bullae after a barbiturate overdose

are more tissue destructive [1]. Hemorrhagic bullae may occur at the site of subcutaneous injections, or at phlebotomy sites in thrombocytopenic patients. In these cases, the history will likely confirm the diagnosis (Fig. 21.3).

Coma Bullae

Differential Diagnosis: Viral Exanthem, Cellulitis, or Ecthyma

Also called barbiturate or neurologic blisters, coma bullae usually appear over sites of pressure and are sometimes associated with macular erythema or violaceous plaques. The etiology is multifactorial, but in some cases, a direct toxic drug effect has been implicated. Many drugs are excreted through the eccrine glands and presumably produce eccrine gland necrosis resulting in blister formation. Barbiturates are the most frequently reported causative agent [2, 3], but similar findings have been noted in association with other medications, as well as coma and central nervous system disorders [4]. These bullae have been reported in up to 4–5% in patients hospitalized for drug-induced coma, and although they typically occur in pressure areas on the extremities and trunk after several hours or days, the bullae occasionally appear as early as 1 hour after acute intoxication. In addition, areas not typically prone to pressure may be involved (Fig. 21.4) [5].

Edema and Lymphedema Bullae

Differential Diagnosis: Cellulitis

Large bullae may develop in the setting of acute exacerbation of edema or of anasarca, often on the distal lower extremities. Early on, they are tense and clear, and biopsy demonstrates spongiosis (inter and intracellular epidermal edema) with dilated dermal vessels. In the cancer patient, lymphedema bullae are a difficult management problem produced by extensive lymph node dissection, ionizing radiation therapy, or tumor obstruction. Chronic lymphedema produces characteristic skin changes including verrucous hyperkeratosis, fibrosis, and hyperkeratosis, which may become superinfected.

Diabetic Blisters

Differential Diagnosis: Cellulitis

The term bullosis diabeticorum was first introduced in 1967 [6] and refers to the development of spontaneous bullous lesions in patients with diabetes mellitus. The pathogenesis may be related to angiopathy or trauma, and the bullae tend to be clear and tense. This needs to be differentiated from infectious cellulitis.

Bullous Insect Bite Reaction

Differential Diagnosis: Ecthyma, Viral Exanthem, Cellulitis

This is an exaggerated response to insect bites resulting in papulovesicles, bullae, and occasionally necrotic lesions. This phenomenon has been reported primarily in the setting of chronic lymphocytic leukemia (CLL), but may also occur with other hematoproliferative disorders like mantle cell lymphoma, and human immunodeficiency virus infection [7, 8]. Prominent eosinophil infiltration and degranulation within these lesions likely contribute to the severity of symptoms [9]. Many patients have no recollection of the bite.

Bullous Graft-Versus-Host-Disease (GVHD)

Differential Diagnosis: Cellulitis

Acute and chronic GVHD may be vesicular or bullous [10]. In severe acute disease, there is damage at the epidermal–dermal junction that may be severe enough to allow the epi-

Fig. 21.5 Graft-versus-host disease with positive Nikolsky sign and epidermal detachment

dermis to separate completely from the dermis when traction or pressure is applied; this has been termed the Nikolsky sign (Fig. 21.5). Chronic sclerodermoid GVHD, like idiopathic scleroderma, may also exhibit bullae. Although the pathogenesis is unknown, biopsy shows typical fibrotic changes and dermal edema [11, 12]. As the bullae resolve, the slowly healing erosions and ulcerations should be monitored for secondary bacterial superinfection.

Bullous Drug Eruptions

Differential Diagnosis: Viral Infection

Bullous drug eruptions may be localized or widespread (Fig. 21.6). When localized, they are referred to as fixed drug eruptions, and are characterized by recurrence at same location following drug reexposure. This eruption, occurring 1–2 weeks after the first exposure and within 24 hours of reexposure, is characterized by a localized area of erythema and bullae which resolve with a "slate gray" color (Fig. 21.7).

A variety of medications may also produce autoimmune blistering, sometimes characterized by the deposition of linear IgA at the dermal–epidermal junction. This is of particular interest to infectious disease specialists as it has been reported with multiple antibiotics including vancomycin, beta-lactam antibiotics, trimethoprim-sulfamethoxazole, penicillin, metronidazole, and rifampicin [13]. It has also been reported after interferon [14], lithium carbonate, diclofenac, and glibenclamide [15–18]. Linear IgA deposition in the skin has also been associated with malignancy [19] including that of the esophagus [20], colon [21], and pancreas [22].

Fig. 21.6 Bullous drug eruption on background of erythema secondary to cytarabine

Autoimmune Bullous Dermatoses

Differential Diagnosis: Viral Infection, Scabies

Dermatitis herpetiformis is associated with thyroid disease, particularly Hashimoto thyroiditis [24], as well as enteropathy-associated T-cell lymphoma. Clinically, these very pruritic tiny vesicles may be suggestive of scabies infestation or herpes. The biopsy shows characteristic neutrophils in the dermal papillae and direct immunofluorescence shows granular deposits of IgA. Conversely, the incidence of non-Hodgkin's lymphoma is significantly increased in patients with dermatitis herpetiformis [25–27].

Pemphigus is an autoimmune blistering disease that affects skin and mucous membranes, with characteristic flaccid bullae and a positive Nikolsky sign (Fig. 21.8). Multiple drugs have been associated with the development of pemphigus. Drugs of interest to the infectious disease specialist include thiol drugs like ampicillin, drugs with an active amide group such as penicillins, nonthiol, nonamide drugs containing a phenol group such as cefadroxil and rifampicin [13, 28]. Other culprits include penicillamine, captopril, beta blockers, progesterone, heroin, and pyrazole compounds [15]. The eruption occurs a few weeks after starting the medication, and the diagnosis is made by histology which shows an intraepidermal vesicle with acantholysis, and direct immunofluorescence of perilesional skin which demonstrates IgG and/or C3 binding to the intercellular cement substance or keratinocyte cell surface [15].

Paraneoplastic pemphigus, also called paraneoplastic autoimmune multiorgan syndrome [29], was described by Anhalt et al. in 1990 as a mucocutaneous disease invariably associated with neoplasia [30, 31] including lymphomas,

Fig. 21.7 Fixed drug eruption characterized by well-demarcated erythematous to slate gray plaques, in this case secondary to naproxen

Phototoxic drug eruptions may also be bullous, with the characteristic finding of involvement in UV exposed areas. This has been described recently with paclitaxel [23].

Fig. 21.8 Pemphigus produces superficial blistering with crusts

CLL, Castleman disease [32], Waldenstrom macroglobulinemia, thymoma, retroperitoneal sarcoma, bronchogenic carcinoma [15], and mastocytosis [33]. The lesions are heterogeneous, but the patients classically develop severe mucosal erosions, stomatitis, and skin eruptions that may resemble other autoimmune bullous disorders, drug eruptions, lichen planus, or erythema multiforme [15](Fig. 21.9). The patients may develop bronchiolitis obliterans and pulmonary infiltrates. Immunoprecipitation demonstrates the presence of antibodies against the plakin family [15]. Antibodies to desmoglein 1 and 3, similar to those found in classic pemphigus, may play a role [34, 35] .

Bullous pemphigoid presents with tense skin blisters and, less commonly, mucosal involvement (Fig. 21.10). It is characterized by autoantibodies located in the hemidesmosomal complex of the skin basement membrane zone. It may occur

Fig. 21.9 Paraneoplastic pemphigus with epidermal denudation. This patient also had severe stomatitis

Fig. 21.10 Bullous pemphigoid produces tense and ruptured bullae on the legs of this patient

de novo, associated with other autoimmune disease or with systemic malignancy. Some antibiotics, including amoxicillin [36], cephalexin [37], and ciprofloxacin [38] have been reported to cause drug-induced disease. Bullous pemphigoid and mucosal scarring cicatricial (scarring) pemphigoid may occur as manifestation of immune dysregulation after stem cell transplantation [39, 40]. It is diagnosed by its histologic features, as well as positive direct and indirect immunofluorescence microscopy.

Porphyria Cutanea Tarda (PCT) and Pseudoporphyria Cutanea Tarda

Differential Diagnosis: Viral Infection, Bacterial Infection

PCT is caused by decreased catalytic activity of uroporphyrinogen decarboxylase. There are acquired and hereditary variants associated with a clinical spectrum of vesiculobullae, skin fragility, erosions, crusts, scarring dyspigmentation, hypertrichosis, photosensitivity, and occasional sclerodermoid changes (Fig. 21.11). This may be associated with hepatitis C [41], HIV [42], hepatoma [43], estrogen, alcohol abuse, and iron overloading, especially in cancer patients who have received multiple transfusions [44].

Pseudoporphyria is a rare photosensitive disorder that clinically resembles PCT but lacks the biochemical derangements in porphyrin metabolism. It is often drug induced and has been associated with nalidixic acid, tetracycline, chlorthalidone, pyridoxine, naproxen, furosemide, etretinate, cyclosporine, intravenous 5-fluorouracil, imatinib [45], and voriconazole [46, 47]. It has also been associated with end-stage renal failure [48] (Fig. 21.12).

Fig. 21.11 Porphyria cutanea tarda is characterized by skin fragility especially on the sun-exposed hands leading to erosions and bullae

Fig. 21.12 Pseudoporphyria characterized by subepidermal bullae in a patient with renal failure

Miliaria Crystallina

Differential Diagnosis: Herpes Viral Infection

Also known as sudamina, miliaria crystallina is characterized by a diffuse eruption of 1–2 mm superficial asymptomatic vesicles on a noninflamed base, sometimes appearing as "drops of water" (Fig. 21.13). These vesicles appear in crops, typically on the trunk. This eruption is often mistaken for disseminated herpes, but the onset is related to heat and humidity or the profuse sweating accompanying persistent febrile illness. The individual vesicles are extremely fragile, rupturing spontaneously or with slight friction, and resolve with a superficial desquamation. Therapy is generally not required because the eruption is self-limited.

Pustular Lesions

Sterile pustular lesions may be seen as solitary or over most of the body surface. They may be mistaken for bacterial, fungal, or superinfected herpetic infections.

Acute Generalized Exanthematous Pustulosis (AGEP)

Differential Diagnosis: Bacterial, Fungal or Viral Infections

AGEP is also known as a pustular drug eruption as 90% of cases are related to medication administration (Fig. 21.14). The eruption is of sudden onset and appears on average of 5 days after the medication is started; in 50% of cases it starts within first 24 h. Initially, there is a diffuse exanthematous erythema followed by eruption of multiple monoform nonfollicular pustules less than 5 mm in diameter. Widespread superficial desquamation occurs after a few days and fever is common along with systemic neutrophilia and eosinophilia. Once the inciting agent is discontinued, the eruption resolves within 15 days without sequelae [49]. In up to 80% of cases, pustular drug eruptions are secondary to antibiotics including beta-lactam antibiotics, macrolides [49], and cephalosporins [50, 51]. Pustular eruptions may also occur after imatinib [52].

Fig. 21.13 Miliaria crystallina is characterized by translucent, fragile vesicles secondary to sweat duct obstruction. This may be confused with herpetic infections

Fig. 21.14 Acute generalized exanthematous pustulosis produces large and small sterile, nonfollicular pustules, sometimes on an erythematous base

Reactive Neutrophilic Dermatoses

Differential Diagnosis: Bacterial, Fungal or Viral Infections

These are a spectrum of dermatoses that are mediated by neutrophils. They frequently have systemic manifestations and associations with underlying diseases, such as inflammatory bowel disease and internal malignancies. The management of these disorders with systemic corticosteroids and nonsteroidal immunosuppressive or immunomodulatory agents is common [53]. Sweet syndrome, pyoderma gangrenosum, Bechet disease, and bowel-associated dermatosis-arthritis syndrome are examples of these dermatoses.

Sweet syndrome and pyoderma gangrenosum may look like ecthyma, erysipelas, cellulitis, viral, fungal, and mycobacterial infections. These are neutrophilic disorders that often start with erythematous papules and plaques; they may resemble cellulitis or erysipelas [54]. In the case of Sweet syndrome, also called febrile neutrophilic dermatosis, these may become pustular or bullous (Fig. 21.15). The patients often develop an associated fever and peripheral leukocytosis, all of which resolve promptly with glucocorticoid therapy [55]. It is thought to be a hypersensitivity reaction of unknown cause characterized by infiltration of polymorpholeukocytes in the skin. The majority of cases of Sweet syndrome follow a febrile upper respiratory tract infection and therefore acute and self-limited. Other infectious agents that have been associated include Yersinia, Toxoplasma, Salmonella, and Mycobacterium. It has also been reported with inflammatory bowel disease, Behcet syndrome and drugs like trimetoprim-sulfamethoxazole and the granulocyte-colony stimulating factor [56]. Hematologic malignancies or solid tumors are present in about 10–15% of cases [55, 57]. The most common associated malignancy is AML but it can also be seen in association with CML [58], lymphomas, anemias, or polycythemias [55]. The lesions may precede the diagnosis of leukemia. Associated solid tumors are of any type, but most commonly genitourinary, breast, and gastrointestinal [53] .

Patients with pyoderma gangrenosum develop ulcers with a purple overhanging edge and prominent pathergy. It is also associated with rheumatologic disorders, malignancy, and inflammatory bowel disease (Fig. 21.16).

Behçet disease (BD) was named in 1937 after the Turkish dermatologist Hulusi Behçet, who first described the triple-symptom complex of recurrent oral apthous ulcers, genital ulcers, and uveitis [59]. This chronic mucocutaneous disorder is diagnosed by means of clinical criteria, defined by oral and genital apthae, pustular vasculitic cutaneous lesions, ocular, gastrointestinal, and vascular manifestations [60] (Fig. 21.17). Although more prevalent in the Middle East, Behcet disease has been reported all over the world. The skin lesions are pyoderma and furunculosis [60]. The ulcers in Behcet disease present as superficial gray erosions and deeply punched out erosions that affects the lips, gums, cheeks, and tongue. The apthous lesions, whether on the mouth or genitalia, begin as vesicles or pustules and tend to heal with scar formation [60].

Bowel-associated dermatosis-arthritis syndrome is a well-recognized complication in patients who have had jejunoileal bypass for morbid obesity. It consists of an influenza-like illness with increased temperature, chills, polyarthralgia, myalgia, and inflammatory papules and pustules that are 2–4 mm in diameter and that usually appear on the

Fig. 21.15 Acute febrile neutrophilic dermatosis (Sweet syndrome) with red nodules, plaques, and blisters on the hands. Pathology often confirms the diagnosis

Fig. 21.16 Pyoderma gangrenosum. The lesion on the left shows an erosion with a purple overhanging border and central necrotic bulla. The lesion on the right is earlier and hemorrhagic

Fig. 21.18 EGFR-induced acneiform pustulosis. Monoform papulo-pustules are present on the extremities secondary to epidermal growth factor receptor inhibitor in patient with colon cancer

Fig. 21.17 Behcet disease showing recurrent ulcerations on the skin and genital mucosa in a patient with iridocyclitis and apthae of the oral mucous membranes

extremities and the upper part of the trunk. It involves bacterial overgrowth causing complement activation with subsequent deposition of antibody complexes in skin and synovium [61]. Histology shows a perivascular lymphocytic infiltrate and a leukocytoclastic vasculitis of dermal capillaries. Pustular pyoderma gangrenosum and infections should be considered in the differential diagnosis.

Acneiform Eruptions

Differential Diagnosis: Bacterial or Fungal Folliculitis

Acne is a follicular disease characterized by abnormal kera-tinization, inflammation, presence of Propionibacterium acnes in sebum, and increased sebum production, under hor-

monal control. Precursor lesions are noninflammatory (comedo and microcomedo) and inflammatory (papules, pustules and nodules) on face and upper trunk. The inflam-mation is triggered by follicular wall rupture and subsequent immune responses that promote follicular plugging and microcomedo formation [62]. Drug-induced acne is usually abrupt in onset and monomorphous. In cancer patient on sys-temic corticosteroids, an acneiform eruption is not uncom-mon, but comedones are rarely seen. Antibiotics such as tetracyclines and isoniazid, as well as chemotherapeutic agents such as azathioprine, cyclosporin, and sirolimus may produce acneiform drug eruptions [13]. Patients on epider-mal growth factor receptor inhibitors, EGFRI, often have characteristic pustular eruptions, frequently associated with paronychia that is severe enough to significantly impact their lives [52, 63]. Rather than the diffuse pustulosis seen with AGEP, this eruption commonly found in an acneiform distri-bution on the face, scalp, chest, and back is characterized by a perifollicular lymphocytic infiltrate or suppurative neutro-philic folliculitis [1, 64] (Fig. 21.18).

Eosinophilic Folliculitis

Differential Diagnosis: Bacterial or Fungal Folliculitis

This presents as erythematous pruritic papules and pustules, some edematous, on face, trunk, extremities, and scalp. It has a male predominance with increased incidence in Japan. Typically, it has an abrupt onset that resolves in 1 week then reoccurs in crops several weeks later. It has been associated with HIV disease with CD4 counts <300.

Grover Disease

Differential Diagnosis: Bacterial or Fungal Folliculitis

Also know as transient acantholytic dermatosis, this disease is characterized by a sparse eruption, often of limited extent in persons over 50 years of age. The lesions are red papules and fragile vesicles that erode into scaly papules and plaques limited to the chest, shoulder girdle area, and upper abdomen. It is exacerbated by heat and often confused with bacterial folliculitis (Fig. 21.19).

Miliaria Rubra

Differential Diagnosis: Bacterial, Fungal, or Viral Folliculitis

Obstruction of the eccrine sweat duct may create small non-follicular red macules and papules topped by a vesicle or pustule, commonly called "prickly heat." This is not uncommonly seen at sites of occlusion, especially on the back of febrile immobile patients.

Neutrophilic Eccrine Hidradenitis

Differential Diagnosis: Cellulitis

This has also been termed chemotherapy-associated eccrine hidradenitis and appears at a mean of 8 days after infusion. It is characterized by painful erythematous papules and plaques,

Fig. 21.19 Grover disease (transient acantholytic dermatosis) is characterized by pruritic red–brown keratotic papules on the chest that may be confused with infectious folliculitis

Fig. 21.20 Neutrophilic eccrine hidradenitis. These painful, erythematous plaques on the breast may be confused with cellulitis

usually on the trunk [3]. Alkylating agents, anthracyclines, antimetabolites, platinum compounds, taxanes, vinca alkaloids, mitotic inhibitors, and G-CSF and GM-CSF may induce this disorder [1, 65–67] (Fig. 21.20).

Papulosquamous Lesions

A papule is a raised growth less than 1 cm; a plaque is a raised growth greater than 1 cm. Squamous lesions have characteristic epidermal changes such as scale. The distribution of the lesions helps to further refine diagnostic possibilities.

Dermatitis

Differential Diagnosis: Cellulitis or Superficial Fungal Infection

Also known as eczema, this skin condition has a variety of etiologies, usually described by the preceding adjective, i.e. atopic, contact or irritant dermatitis (Fig. 21.21). The classic skin findings are erythematous, often itchy, scaly patches, and plaques. Due to the chronicity and pruritic nature of this condition, long-standing lesions often become secondarily infected and 90% will be culture positive for *Staphylococcus aureus* leading to impetigo [68].

Pityriasis alba is a variant of atopic dermatitis characterized by hypopigmented patches that are associated with fine, sometimes powdery scale. The most common areas of involvement are the face especially the forehead and

Fig. 21.21 Irritant dermatitis from a breast prosthesis. This needs to be distinguished from cellulitis

Fig. 21.22 Radiation dermatitis with erythema that may be mistaken for infection

cheeks, but can also be seen on the trunk and extremities. The eruption can be preceded by mild asymptomatic erythema. The lesions are usually self-limited and do not require treatment. The hypopigmentation is due to a decreased number of melanocytes and decreased pigment production [69]. Potassium hydroxide examination of a superficial skin scraping can rule out cutaneous dermatophyte infections.

Stasis dermatitis often causes patchy or confluent erythema which must be differentiated from cellulitis. Excoriations or minimal trauma may precipitate erosions and ulcers which may become secondarily superinfected. When chronic venous insufficiency is present, examination of the lower extremities show various combinations of varicosities, dyspigmentation with hemosiderin deposition, or even fibrotic changes termed lipodermatosclerosis. Ulcers often occur around the medial malleolus. Both extremities may be affected with patches of dermatitis. Pruritis is more likely a feature of dermatitis, and pain more likely with cellulitis.

Dermatitis after ionizing radiation often produces persistent tender or edematous erythema which may be mistaken for cellulitis (Fig. 21.22). It is important to identify any superinfection, especially with organisms like *Staphylococcus aureus*, which may act as a superantigen and increase the inflammation [70, 71].

Drug eruptions may be papulosquamous, and when present in intertriginous areas are confused with dermatophyte or yeast infections. This has been reported with chemotherapeutic agents like gefitinib [72] and busulfan. Symmetrical drug-related intertriginous and flexural exanthema may also be seen is association with antibiotic therapy [73].

Psoriasis

Differential Diagnosis: Superficial Fungal Infection

Psoriatic plaques may be mistaken for cutaneous fungal infections due to their similar clinical appearance. This skin disease is a common affliction affecting over 2% of the general population, with a bimodal peak at the 3rd and 6th decade of life. The well-demarcated papules and annular plaques often are covered in a thick silvery scale and can be distributed all over the body with a predilection for the scalp, elbows, and knees (Fig. 21.23). When the morphology is annular or ring shaped, the lesions can mimic cutaneous fungal infections. Psoriasis of the hands and feet demonstrates erythema with diffuse scaling and thickened nails reminiscent of onychomycosis. Pustular eruptions of the hands and feet may also represent a form of psoriasis that can be indistinguishable from tinea and dyshidrotic dermatitis. Cancer patients who are placed on systemic corticosteroids and chemotherapy often find that their psoriasis improves, only to flare with pustular lesions when these drugs are withdrawn [74].

Fig. 21.23 Psoriasis vulgaris. Psoriasis produces an erythematous plaque covered with white or silvery scale which can be confused with fungal infection

Pityriasis Rubra Pilaris

Differential Diagnosis: Superficial Fungal Infection

This eruption often starts with erythema and scaling of the scalp and face and thickening of the palms and soles. Scaly, salmon-colored plaques and hyperkeratotic follicular- based papules are seen on the trunk and extremities. A characteristic finding is "islands of sparing" within the involved areas. Skin biopsy is helpful to distinguish this from psoriasis and fungal infection and a search for occult malignancy should be considered if the presentation is atypical, or in older patients.

Pityriasis Rosea

Differential Diagnosis: Superficial Fungal or Spirochete Infection

This is a two-phase inflammatory skin condition. The onset begins with a herald patch, which is a solitary erythematous papule or plaque, either oval or round, with a collarette of scale. At this stage, it can easily be misinterpreted as a fungal infection. Within 2 weeks, a diffuse truncal rash appears with similar lesions. Pityriasis rosea is postulated to be due to a viral infection although this is not proven [75]. A higher incidence of pityriasis rosea in the fall and winter has been observed. The disease is self-limited and resolves often with 6–8 weeks.

Mycosis Fungoides and Cutaneous T-Cell Lymphoma

Differential Diagnosis: Superficial Fungal Infection

There are many clinical variants, but the classic subtype begins with erythematous patches that may evolve into scaly erythematous plaques. The evolution of this condition can vary from asymptomatic, stable, and indolent or progressing to more serious disease with tumors, erythroderma, and blood involvement (Sezary syndrome). The subtle erythematous patches are nonspecific, and may resemble superficial fungal infection. The diagnosis of mycosis fungoides can be elusive and multiple biopsies with T-cell receptor gene rearrangement studies may also be necessary.

Purpuric and Petechial Lesions

Purpura or hemorrhage into the skin may be a sign of more serious disease in immunocompromised patients. Cancer patients are especially susceptible to polymicrobial opportunistic infections that present this way. When not infectious, vasculitis, the inflammation of the blood vessel walls, often precedes the purpura and can be caused by medications, neoplasms, or other systemic diseases, leading to significant morbidity and mortality. The most common purpuric dermatoses that can mimic underlying infections will be reviewed.

Leukocytoclastic Vasculitis

Differential Diagnosis: Bacterial or Fungal Infection

Leukocytoclastic vasculitis, an inflammation of the small dermal blood vessel walls often presents as macular or palpable nonblanchable purpura usually on the lower extremities or in areas of localized pressure (Fig. 21.24). The

Fig. 21.24 Leukocytoclastic vasculitis is characterized by purpuric confluent papulovesicles on the legs in this patient

Fig. 21.25 Disseminated intravascular coagulation. Purpura and tissue necrosis involving the abdomen, buttocks, and legs

diagnosis can be made clinically and confirmed by skin biopsy that shows inflammation of the small vessels with neutrophils, extravasated erythrocytes, and fibrinoid necrosis in the blood vessel walls.

Superficial Thrombophlebitis

Differential Diagnosis: Cellulitis

Characterized by inflammation and thrombosis in the superficial venous system, this condition results in erythema, swelling, and tenderness in the extremity.

This is to be distinguished from cellulitis, which is an infection of the underlying deeper dermis and subcutaneous tissue.

Disseminated Intravascular Coagulation (DIC)

Differential Diagnosis: Fungal or Bacterial Sepsis

This disorder of coagulation causes a consumption of clotting factors and the production of fibrin split products. Patients will have signs of blood loss as well as end-organ damage due to thrombosis of large and small vessels. Cutaneous findings include petechiae, purpura, bleeding from mucocutaneous orifices and wounds, soft tissue hematomas, acral cyanosis with possible ischemia, and necrosis (Fig. 21.25). The most common associated conditions are underlying infection, sepsis, trauma, malignancy, and transfusion reac-

tions. Therefore, a thorough investigation of all possible underlying causes is warranted in these cases [76].

Calciphylaxis

Differential Diagnosis: Ecthyma, Cellulitis, Deep Fungal, or Bacterial Infection

Calciphylaxis produces vascular calcification leading to ischemia of the skin and soft tissues (Fig. 21.26). It is most commonly seen in patients with chronic renal disease and hyperparathyroidism. Clinically, the involved areas develop reticulate, violaceous patches which are painful and may progress to necrosis. The exact etiology of calciphylaxis is unknown. Various theories propose either protein C dysfunction or exposure to sensitizing agents that then cause deposition of calcium in tissues [77, 78].

Fig. 21.26 Calciphylaxis characterized by stellate ulceration and hemorrhagic crusts can be confused with ecthyma

Petechiae

Differential Diagnosis: Rickettsial, Bacterial, or Fungal Infection

Petechiae are pinpoint nonblanchable erythematous macules due to leaking of blood into the skin. They occur in the setting of thrombocytopenia, abnormal platelet function, localized pressure or trauma, increase in intravascular venous pressure, or vitamin C deficiency. However, some Rickettsial infections can often start with small erythematous macules on the wrists and ankles with petechiae.

Lesions of the Adipose Tissue

Differential Diagnosis: Cellulitis, Deep Fungal, or Mycobacterial Infection

Panniculitis refers to diseases in which the major abnormality is an inflammation of the subcutaneous fat presenting as subcutaneous nodules. The clinical lesions are red-to-violaceous nodules and plaques that have a predilection for the legs. The nodules may be tender and ulcerated or they may remain asymptomatic and intact. Fat necrosis is usually present and associated with vascular changes. Histopathologically, the inflammatory processes may show considerable overlap. From the practical standpoint of diagnosis and management, patients with panniculitis can be placed into the following groups:

Cold Panniculitis

This is an acute, nodular, erythematous eruption with livedo mottling usually limited to areas exposed to the cold. It is commonly seen in children and women, and systemic diseases are not associated with this group of patients.

Pancreatic Panniculitis

Circulating lipases from pancreatic carcinoma and acute pancreatitis can produce fat necrosis that results in tender subcutaneous nodules that simulate erythema nodosum. Fever, eosinophilia, and arthralgia may accompany the disease (Fig. 21.27).

Fig. 21.27 Pancreatic panniculitis. Painless subcutaneous nodules of pancreatic fat necrosis

Nodular Vasculitis

This presents as tender, subcutaneous nodules of the calves of middle-aged women. The lesions are bilateral, often ulcerate, and recur over years. It has long been considered as a cutaneous hypersensitivity reaction to Mycobacterium tuberculous, but has also been associated with HIV [79] and hepatitis C [80] and drugs including dasatinib [81] and imatinib [82] (Fig. 21.28).

Septal panniculitis (Erythema nodosum, EN)

The most common form of inflammatory panniculitis with most cases occurring in young adult women. The eruption consists of bilateral, symmetrical, deep tender nodules 1–10 cm in diameter located pretibially. The onset is acute, frequently associated with malaise, arthralgias, arthritis, and leg edema. The nodules last a few days to weeks, appearing in crops, and then slowly involute.

EN is a reactive process, commonly associated with streptococcal, beta-hemolytic infection, usually within 3 weeks from the onset of the disease. Other associations

Fig. 21.28 Nodular vasculitis. Tender subcutaneous nodules on the calves of a middle-aged woman

include primary tuberculous, intestinal infection with Yersinia, Salmonella, or Shigella and in endemic areas, systemic fungal infections (coccidiomycosis, histoplasmosis, sporotrichosis, and blastomycosis) should be considered. Other noninfectious causes of EN include sarcoidosis, inflammatory bowel diseases, hematologic malignancies, pregnancy, and medications including oral contraceptives. Spontaneous resolution usually occurs within 3–6 weeks without scarring.

Sclerosing Panniculitis (Lipodermatosclerosis)

This occurs primarily on the medial lower legs of obese women older than age 40. However, this may occur in the setting of chronic lower extremity edema in the cancer patient. There is marked woody induration in a stocking distribution as a result of fibrosis of subcutaneous fat.

Traumatic panniculitis

Most commonly occurs on the trunk and breast in women. Lesions present as firm subcutaneous masses of variable tenderness, and may mimic mastitis.

Erythematous Lesions

The term erythema means redness (hyperemia) of the skin and most of the skin conditions in this category are blanchable. A number of skin conditions are referred as reactive erythemas: urticaria and angioedema, erythema multiforme, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), eosinophilic dermatosis, and gyrate erythemas. Confluent erythema may be mistaken for cellulitis, and the gyrate erythemas which are annular or polycyclic, may be confused with superficial fungal infections. These entities represent the cutaneous reaction to an underlying systemic process which may be infectious, malignant, or drug related. The primary lesions are erythematous plaques that are annular or arcuate, transient or fixed.

Urticaria and Angioedema

Differential Diagnosis: Cellulitis, Superficial Fungal Infection

Acute urticaria is a common, acute, self-limited eruption of smooth, pruritic erythematous papules and plaques produced by localized edema. They change in size and shape with time and are usually present for a few hours and less than 2 days. Chronic urticaria is defined as urticaria lasting longer than 6 weeks. Although urticaria results from transient dermal edema, angioedema results from deep swelling within subcutaneous sites. The etiology of an acute episode of urticaria can sometimes be determined, but chronic urticaria is often idiopathic. When the lesions are annular, it may be mistaken for tinea, and angioedema must be distinguished from cellulitis.

Erythema Multiforme (EM)/Stevens–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Differential Diagnosis: Disseminated Viral, Bacterial, or Fungal Infections

The lesions of EM may be macular, urticarial, and vesiculobullous (Fig. 21.29). The eruption has a predilection for the back of the hands, palms, soles, and the extensor surfaces of the limbs. They may spread to the rest of the body, or be generalized from the start. The macular lesions are bright red and well circumscribed and they frequently become urticarial within a few hours. Iris or target lesions are urticarial

Fig. 21.29 Erythema multiforme characterized by target lesions

patches with dusky centers and bright red active borders. Mucosal involvement begins with bullae that break very soon after formation and leave denuded areas that undergo a variety of changes. Healing of mucosal lesions takes place without scarring, unless there has been secondary bacterial infection. In the case of SJS, the lips, buccal mucosa, palate, conjunctivae, urethra, and vagina are frequently involved. It is often defined as severe erythema multiforme with mucosal involvement, visceral involvement, or both. These diseases are part of a continuum of immunologically mediated mucocutaneous diseases of varying degrees of severity. When the lesions become bullous, pustular, or necrotic, the differential diagnosis may include disseminated herpes, bacterial or fungal infection.

TEN is a severe reaction characterized by confluent blisters resulting in detachment of the epidermis from the dermis, leading to denudation of greater than 30% of the body surface area (Fig. 21.30). The differential diagnosis includes staphylococcal scalded skin syndrome (SSSS), which causes more superficial epidermal blisters that can be readily distinguished by skin biopsy.

EM, SJS, and TEN have multiple etiologies. Infectious diseases are the important causes of EM in children and young adults [83], whereas drug reactions [84–86] and malignancy [86] are more important factors in adults. Herpes simplex infection may be followed 7–10 days later by EM. The diagnosis may be established by biopsy, culture, or direct antigen immunofluorescence. Other etiologic infectious agents are Mycoplasma pneumoniae, Coxsackie B-5, influenza type A and echo viruses [87].

Erythema Annulare Centrifugum

Differential Diagnosis: Superficial Fungal, Bacterial, or Rickettsial Infection

The most common gyrate erythema is characterized by polycyclic, erythematous plaques, sometimes with trailing scale, that grow eccentrically and slowly (2–3 mm/day). The lesions disappear over several weeks and are replaced by new ones that follow a similar course, usually on the trunk, buttocks, and inner thighs (Fig. 21.31). Some cases are associated with dermatophyte infection elsewhere, but the lesions themselves do not contain fungus. It is rarely associated with internal malignancy such as Hodgkin's lymphoma [88], Mantle B-cell non-Hodgkin's lymphoma [89], breast carcinoma [90], CLL [91], myeloma [92], and tumors of the gastrointestinal tract [93]. The clinical presentation can mimic secondary syphilis, tinea corporis and cruris, Hansen disease, and Lyme disease.

Erythema Gyratum Repens

Differential Diagnosis: Superficial Fungal Infection

This uncommon, morphologically distinctive eruption is an indicator of serious disease, usually internal malignancy. Lesions consist of undulating wavy bands of slightly elevated

Fig. 21.30 Toxic epidermal necrolysis. Erythroderma and detachment of the epidermis and erosions affecting more than 30% body surface

Fig. 21.31 Erythema annulare centrifugum characterized by annular and polycyclic plaques with delicate scaling on the inner margin of the advancing edge on the legs

Fig. 21.32 Necrolytic migratory erythema with erythematous patches that blister centrally, erode, and heal with hyperpigmentation on the perineum

95]. Removal of the pancreatic tumor leads to resolution; however, in half of the cases, metastases have occurred at the time of diagnosis. Necrolytic acral erythema produces similar erythematous or gyrate lesions on the acral surface has been reported in association with hepatitis C [96].

scaly erythema over the entire body. Lesions migrate rapidly (up to 1 cm/day) and are characteristically concentric, giving the skin a "wood grain" appearance. This distinctive migratory eruption has been mostly associated with lung cancer, esophageal, and breast cancer. With adequate control of the cancer the dermatitis usually abates, however this may not be possible in cases of metastatic disease at diagnosis [94].

Necrolytic Migratory Erythema

Differential Diagnosis: Mucocutaneous Candidiasis

This rare syndrome is associated with glucagon-secreting tumors of the pancreas that occurs in periorificial, flexural, and acral areas and closely resembles the lesions associated with zinc deficiency. There are active erythematous, gyrate, or circinate borders with confluence [94, 95] (Fig. 21.32). Most patients have diabetes or glucose intolerance, and hyperglucagonemia, in addition to the rash. Other common manifestations include anemia, weight loss, diarrhea, atrophic glossitis, and angular cheilitis. Additional laboratory findings are low serum zinc level and hypoaminoacidemia. The eruption may resemble chronic mucocutaneous candidiasis, severe seborrheic dermatitis, and acrodermatitis enteropathica [94,

Chemotherapy-Induced Acral Blisters and Erythema (Palmoplantar Erythrodysesthesia Syndrome, Hand–Foot Syndrome)

Differential Diagnosis: Cellulitis, Viral Infection

This reactive and usually painful erythema of the hands and feet may be seen following chemotherapy with a variety of agents including cytarabine, doxorubicin, capecitabine, taxanes and 5-fluorouracil, and methotrexate [52, 97]. More recently it has been associated with some of the multikinase inhibitors, including sorafenib and sunitinib [52, 98]. Erythema is followed by blistering and superficial desquamation, associated with the dose and duration of infusion [1].

Granuloma Annulare

Differential Diagnosis: Superficial Fungal Infection

This is a granulomatous process which presents with annular and serpiginous plaques usually on the extremities (Fig. 21.33). They occur most often on the dorsum of

Fig. 21.33 Granuloma annulare producing annular plaques that can be confused with fungal infection erythema migrans associated with Lyme disease

Fig. 21.34 Hypereosinophilic syndrome with diffuse dermatitis and excoriations which may be confused with scabies

the hands and arms, then legs and feet. There is usually no significant scale. Biopsy of the indurated borders reveals a granulomatous dermatitis with histiocytic infiltration, degeneration of collagen and elastic fibers, and mucin deposition. The lesions are self-limited and must be distinguished from a fungal infection.

Eosinophilic Dermatoses

Differential Diagnosis: Bacterial, Fungal, Mycobacterial Infections

The eosinophilic dermatoses are a heterogenous group in which the histopathologic findings are characterized by many eosinophils in the inflammatory infiltrate. The most common causes include arthropod bites, drug eruptions, allergic contact dermatitis, and atopic dermatitis.

Granuloma faciale (GF) is a distinct disease characterized by a single or multiple red–brown plaques on the face. Although the clinical appearance is usually quite distinctive, it can be mistaken for syphilis and leprosy, and is resistant to therapy [99].

Eosinophilic cellulitis (Wells syndrome) presents as recurrent painful or pruritic erythematous indurated plaques, persistent urticaria, and eosinophilia, both peripheral and in the bone marrow. The pathogenesis of Wells syndrome is unknown, but so-called triggers have been described in some cases, including myeloproliferative diseases, insect bites, and drugs [100]. Toxocara canis and other parasitic disorders can present with clinical and pathological findings similar to Wells syndrome [101]. Wells syndrome often has a striking clinical presentation resem-

bling bacterial cellulitis and erysipelas, and usually improves dramatically after administration of systemic corticosteroids.

Hypereosinophilic syndrome is often a myeloproliferative disease defined as peripheral eosinophilia for more than 6 months, more than 1,500/µl absolute eosinophil count, lack of evidence of parasitic, allergic, or other known cause of eosinophilia, and signs and symptoms of multiorgan involvement, including the heart, central nervous system (CNS), skin, and respiratory tract [102, 103] (Fig. 21.34). Thromboembolic disease is not infrequent. Cutaneous lesions occur in more than half of all cases and range from pruritic macules, papules, and nodules to urticaria and angioedema. Ulcerated or nonulcerated nodules, erythroderma, and mucosal ulcerations are less common cutaneous manifestations. The differential diagnosis includes Churg–Strauss syndrome, parasitic infections (toxocariasis, strongylodiasis), and lymphoproliferative diseases [102, 103].

Ulcerative Lesions and Skin Tumors

Differential Diagnosis: Bacterial, Fungal, Mycobacterial, Parasitic Infections

An infectious etiology should always be considered when a skin ulcer develops in a cancer patient, especially when they are immunosuppressed. Noninfectious causes may be considered after this is excluded. Skin fibrosis and poor wound healing is frequently seen in the context of radiation fibrosis [70] or sclerodermoid GVHD [104] (Fig. 21.35). Mal perforans or neuropathic ulcers are associated with altered skin sensation resulting in the inability to detect and avoid skin trauma, and may be a consequence

of chemotherapy-induced sensory neuropathy. Neurotic excoriations may produce factitial changes that result in erosions and ulcers. Chronic nonhealing ulcers should be biopsied to rule out tumor, which may be primary or metastatic. At the same time, a tissue culture biopsy may be performed for fungal, mycobacterial, and bacterial culture. Primary and metastatic skin tumors may mimic infections or cellulitis, especially when the lymphatic system is involved (Fig. 21.36). Solitary tumors may resemble ecthyma or septic emboli (Fig. 21.37).

Hair and Scalp Lesions

Differential Diagnosis: Fungal and bacterial Infections

Alopecias may be divided into scaring and nonscarring forms. The scarring or cicatricial forms may present with sterile pustules and are often mistaken for infectious folliculitis, secondary to bacteria or dermatophytes (Fig. 21.38). In these neutrophilic dermatoses, follicular hyperkeratosis rather than infection is thought to play a role, although *Staphylococcus aureus* is commonly found [105]. Dissecting folliculitis may respond better to oral retinoids rather than to antibiotics [106]. Conversely, a rather bland, scaly alopecia is occasionally associated with the infiltration of neoplastic cells, which destroys hair follicles by inducing fibroplasia via inflammatory mediators. The most common neoplasm is metastatic breast carcinoma. Other causes include squamous and basal cell carcinomas, angiosarcoma, gastric carcinoma, placental site trophoblastic tumor, and mycosis fungoides [107].

Summary

A wide variety of cutaneous infections have been described in cancer patients. As clinicians, we know that these patients are often prone to commonplace skin problems which may be more difficult to recognize because of confounding factors

Fig. 21.35 Chronic leg ulcers developing in patient with poor wound healing from sclerodermoid GVHD

Fig. 21.36 Metastatic breast carcinoma mimicking cellulitis

Fig. 21.37 Leukemia cutis mimicking ecthyma or septic emboli

Fig. 21.38 Acne keloidalis mimicking a bacterial or fungal infection

like immunosuppression and pancytopenia. Unusual noninfectious skin lesions and paraneoplastic eruptions also occur in this setting. Teamwork between the infectious disease specialist, dermatologist, and pathologist is critical in distinguishing infectious lesions from dermatologic eruptions that mimic infectious disorders.

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Part III
Major Etiologic Agents

Chapter 22
Overview of Invasive Fungal Disease in Oncology Patients

Amar Safdar

Abstract The spectrum of invasive fungal disease has changed considerably in the past 2 decade. Since early 1990s, triazole prophylaxis has resulted in a significant decline in cases of invasive candidiasis among patients undergoing hematopoietic stem cell transplantation and those with acute leukemia. Recently, reduced rates of invasive mold disease following echinocandin and antimold triazoles use during the high-risk periods have ushered optimism. This trend in effective drug-mediated prevention has not been without setbacks including unexpected toxicity due to drug–drug interaction, and difficult-to-treat breakthrough fungal disease due to previously uncommon yeasts and filamentous fungi. The rise in virulent non-*albicans Candida* species and non-*Aspergillus* molds has, to some extent, compromised the recent advances in early diagnosis and effective antifungal therapy. As the understanding of hosts' genetic (polymorphisms) vulnerability to fungal disease improves, next generation of diagnostic assays (DNA proliferation, microarray and other technologies) gain clinical validation, approach toward mitigating underlying immune defects with recombinant cytokines, strategies to restore innate and adaptive immune dysfunction become feasible, and target-specific effective antineoplastic therapy is introduced in the cancer fighting armamentarium; these accomplishments in a new era for improved outcomes in cancer patients who are susceptible to invasive fungal disease.

Keywords Fungal infections • Aspergillosis • Candidiasis • Cancer • Leukemia • Bone marrow transplantation

The spectrum of invasive fungal disease has changed considerably in the past 2 decade. Since early 1990s, triazole prophylaxis has resulted in a significant decline in cases of invasive

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candidiasis among patients undergoing hematopoietic stem cell transplantation and those with high-risk hematologic malignancies [1]. An increase in non-*albicans Candida* breakthrough infections in patients given fluconazole prophylaxis [2, 3] appears to be a small setback as in a recent registry of over 2,000 cases of invasive candidiasis only 3% of these infections were seen in patients following stem cell transplantation whereas, 17% had solid-organ cancer, a group in whom antifungal prophylaxis is not given routinely [4]. Similarly, a significant decline in invasive mold disease has also been shown in randomized trials in patients given micafungin or posaconazole prophylaxis [5, 6]. These drugs have also not been without disadvantages such as unexpected drug–drug interaction and toxicity, problems arising from unpredictable bioavailability of the newer antifungal agents, and difficult-to-treat breakthrough fungal disease due to previously less common yeasts and filamentous fungi [7, 8].

Introduction of echinocandin drugs was an important addition in the existing choices for candidiasis therapy. The agents in this class such as caspofungin and micafungin have shown promising results in neutropenic patients with persistent fever, or for patients with invasive *Candida* species infections including fungemia, acute disseminated candidiasis, intra-abdominal infections, and *Candida* abscesses [9–11]. A similar benefit has been seen in randomized trials for the treatment of invasive aspergillosis in cancer and transplant population. Voriconazole had a significant impact on the overall survival in immunosuppressed patients with IA compared with the old standard of therapy [12]. As these agents have become widely used in susceptible cancer and transplant population, it was not unexpected to find improved outcomes among cancer patients with invasive mold infection. In a recent registry-based analysis of 234 HSCT recipients with fungal disease, the short-term mortality among patients with IA was comparable or less than the crude mortality noted in patients with invasive candidiasis (36 vs. 49%, respectively) [13]. This improved survival has been echoed in several recent reports of invasive aspergillosis in patients with hematologic malignancies and stem cell transplantation [14–16].

The research in understanding the immunopathogenesis of invasive fungal diseases has recently uncovered the central

role of innate immune defense pathways such as pattern recognition receptors (PRR) in preventing fungal colonization and fungal tissue invasion [17, 18]. These and other similar important advances in elucidating the complex host–pathogen interaction and the role of various facets of immune defenses that come in to play at different stages in fungal infection have opened the door for asking the very basic question; why certain patients with similar risk factors and exposure develop IFD and other do not? The association in hosts' genetic polymorphism and fungal colonization, invasive fungal disease and more importantly predictor of response to antifungal therapy, and disease recurrence remains in the early phase of exploration. There have been certain interesting observations, such as polymorphisms in genes encoding for Dectin-1 may increase the risk for colonization due to *Candida* species [19]. Individuals with Dectin-1 gene polymorphism along with other immune pathways such as TLR-4, IL-10, TNF receptor-2, and plasminogen may also have an increased susceptibility for invasive aspergillosis [20–25]. However, much work needs to be done to understand clinical impact of these apparently random single gene or gene-cluster polymorphisms on susceptibility for fungal disease, disease progression, response to antifungal therapy, and in what group of patients it is suitable to consider immunotherapy.

The immunotherapy for fungal infection is also gaining traction; this field has received a boost from the recent developments on understanding the host–pathogen immune interaction and role of various components of innate and more importantly adaptive cellular immune effector pathways in the development of invasive fungal disease [26–28]. Since the use of donor granulocyte transfusion in the early twentieth century, and awaking in the 1960s, and reawaking in the past decade, little progress was made in this field [29, 30]. This changed with the development of recombinant myeloid growth factors such as G-CSF and GM-CSF, furthermore, Th1 cytokines like interferon gamma that favorably influenced the natural course of invasive fungal disease in animal experiments and in nonrandomized clinical studies [31–33]. The field of adaptive immunotherapy for fungal disease is also gaining momentum in the recent years [34, 35] and future prospects look promising.

In conclusion, this section focuses on all clinically relevant aspects of invasive fungal disease in the immunosuppressed cancer and stem cell transplant patients. These include epidemiology, immunopathogenesis, clinical presentation, and diagnosis. The discussion on antifungal therapy is supplemented with chapters relating to issues regarding molecular and clinical bases for drug resistance, pharmacokinetic and pharmacodynamics of the antifungal drugs in the special host. The topic of current and future strategies for restoring innate and adaptive immune dysfunction is also presented. The recent accomplishments ushers an era for improved outcomes in cancer patients susceptible to and being treated for invasive fungal disease.

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Chapter 23
Diagnosis of Invasive Fungal Disease

Dionissios Neofytos and Kieren Marr

Abstract The diagnosis of invasive fungal infections (IFI) relies on the critical assessment of clinical presentation, associated risk factors, and careful interpretation of the appropriate diagnostic tests. Frequently, clinicians have to initiate antifungal therapy based on their clinical suspicion and without having made a definitive diagnosis, particularly in cancer or other critically ill patients. To complicate diagnosis, isolation of fungal organisms does not imply pathogenicity, especially from nonsterile sites, and may not necessitate treatment. Hence, making the diagnosis of an IFI in clinical practice requires suspicion of disease, mostly on the acuity and severity of clinical signs and symptoms, and necessitates careful consideration of findings. In this chapter we will review the traditional diagnostic modalities (culture, histopathology, and imaging) and recently developed diagnostic tools (BG, PCR, and GM EIA) for the diagnosis of IFIs. This review will focus on the diagnosis of the most commonly identified IFIs in cancer patients, specifically invasive candidiasis (IC), invasive aspergillosis (IA), and zygomycosis.

Keywords Invasive fungal infection • PCR • Galactomannan assay • Fungal antigen assays • CT scan • Beta glucan • Candidiasis • Aspergillosis • Zygomycosis

Introduction

The diagnosis of invasive fungal infections (IFI) relies on the critical assessment of clinical presentation, associated risk factors, and careful interpretation of the appropriate diagnostic tests. Frequently, clinicians have to initiate antifungal therapy based on their clinical suspicion and without having made a definitive diagnosis, particularly in cancer or other critically ill patients. To complicate diagnosis, isolation of fungal organisms does not imply pathogenicity, especially from nonsterile sites, and may not necessitate treatment. Hence, making the diagnosis of an IFI in clinical practice requires suspicion of disease, depends mostly on the acuity and severity of clinical signs and symptoms, and necessitates careful consideration of findings.

The identification of a yeast or mold in the mycology laboratory has – historically – been based on their appearance under the microscope and growth in culture. Isolation varies by the media used, the experience of the mycology laboratory personnel, and the occasional slow and cumbersome growth of certain fungi. In addition, blood cultures, considered the reference diagnostic test for the diagnosis of candidemia, have been associated with a sensitivity ranging from 50 to 70% [1–7]. Similarly, the sensitivity of tissue and bronchoalveolar lavage (BAL) cultures for *Aspergillus* spp. has ranged between 30–52 and 0–67%, respectively [8–21]. The need for faster and more sensitive diagnostic tests has led to the recent development and implementation of multiple tests to augment detection of microbial components, including the β-D-glucan (BG), fungal polymerase chain reaction (PCR), and the double-sandwich galactomannan enzyme immunoassay (GM EIA). However, the study of diagnostic tests for IFIs is limited mainly due to the absence of a reference standard other than histopathologic confirmation of diagnosis and insensitivity of this "gold standard." In this chapter we will review the traditional diagnostic modalities (culture, histopathology, and imaging) and recently developed diagnostic tools (BG, PCR, and GM EIA) for the diagnosis of IFIs. This review will focus on the diagnosis of the most commonly identified IFIs in cancer patients, specifically invasive candidiasis (IC), invasive aspergillosis (IA), and zygomycosis. The diagnostics of other yeasts and molds and endemic fungi, rarely encountered in cancer patients, will not be reviewed.

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Invasive Candidiasis

Clinical Syndromes

Two major clinical syndromes of IC among cancer patients will be discussed in this section: candidemia and hepatosplenic candidiasis. Cancer patients share multiple risk factors for candidemia by virtue of their underlying disease and therapies administered. Most commonly candidemia results from translocation of *Candida* spp. through the gastrointestinal tract due to mucositis caused by chemotherapy. In addition, most cancer patients have a central intravenous catheter, presenting additional risks for candidemia. Candidemia may be sustained despite administration of appropriate therapy, present as sepsis, and rapidly disseminate to involve other organs (e.g., endophthalmitis, osteomyelitis). A diffuse maculopapular skin rash may occasionally be observed among neutropenic patients with IC (Fig. 23.1). Patients with hematologic malignancies may also develop hepatosplenic candidiasis due to invasion of the portal venous system and subsequent spread of *Candida* spp. into the liver or/and spleen (see Sect. III). Hepatosplenic candidiasis may present with persistent fever, severe right-sided abdominal pain, abnormal liver function tests, and multiple liver, spleen, and/or kidney micronodular lesions on imaging tests.

Diagnosis of Candidemia

Microbiology and Culture

Although widely considered the "gold standard," blood cultures for the diagnosis of candidemia have been associated with a sensitivity historically ranging from 21.3 to 54% [1–7, 22]. The advent of lysis centrifugation has increased the diagnostic yield of blood cultures for the diagnosis of candidemia, albeit with limitations including higher rates of contamination and additional cost and required personnel [23]. For instance, a retrospective review of 41 confirmed cases of IC among 803 autopsies showed that blood cultures with lysis centrifugation were positive in 28 and 58% of patients with single-organ and disseminated IC, respectively [1]. Notably, the majority of patients with disseminated disease had a hematologic malignancy. The automated continuous monitoring blood culture systems and use of special fungal media have been used to increase our ability to identify *Candida* species [24]. Diagnosis has been reported to be better and faster when using the Mycosis IC/F medium, particularly for patients with *C. glabrata* candidemia [24]. Although special "fungal" blood cultures are not widely utilized, it appears that blood cultures in special media may increase the diagnostic yield. Prospective studies in specific patient populations are required before definitive conclusions can be drawn.

Candida speciation: The identification of *Candida* spp. may provide significant information about the source of candidemia (e.g., association between *C. parapsilosis* and intravenous central catheters) and the selection of the appropriate antifungal agent. The latter can be based on specific *Candida* spp. susceptibility patterns (e.g., *C. krusei* – resistance to fluconazole, *C. lusitaniae* – resistance to polyenes) or/and susceptibility testing, particularly important for *C. glabrata* (against the azoles) and *C. parapsilosis* (against the echinocandins). Historically, a germ tube test is performed for the differentiation of *C. albicans* (or/and *C. dubliniensis*) from other *Candida* species. Results can be available within 1–2 h, but the test requires sufficient growth of *Candida* that may further delay the diagnosis for 1–3 days. More recently,

Fig. 23.1 Disseminated maculopapular skin rash in a neutropenic patient with acute myelogenous leukemia with *C. tropicalis* candidemia

the germ tube test has been applied directly on positive blood cultures with a sensitivity and specificity of 87.1 and 100%, respectively, for the identification of *C. albicans* when compared to the results obtained from fungal colonies [25]. In clinical practice, the identification of germ tube-positive yeasts would imply the presence of *C. albicans,* usually susceptible to fluconazole. Germ tube-negative yeasts may include *C. krusei* which is inherently resistant to fluconazole and *C. glabrata* which may be or become resistant to fluconazole and other azoles. Notably, not all germ tube-negative *Candida* spp. are azole-resistant, as *C. tropicalis* and *C. parapsilosis* remain highly susceptible to fluconazole and *C. krusei* is susceptible to voriconazole.

The Peptide Nucleic Acid Fluorescent In Situ Hybridization (PNA-FISH) test has been studied and recently introduced in clinical practice for the rapid identification of *Candida* species. The PNA-FISH for *C. albicans* has had a sensitivity, specificity, positive, and negative predictive value of 99, 100, 100, and 99.3%, respectively [26]. More recently, a multicenter study evaluated the performance of a rapid two-color PNA-FISH assay for detection of *C. albicans* and *C. glabrata* directly from positive blood culture bottles [25]. Among 197 routine blood cultures positive for yeast by Gram stain, PNA-FISH test detected *C. albicans* and *C. glabrata* with a sensitivity of 98.7 and 100%, respectively, and a specificity of 100% for both. More data are required for the use of PNA-FISH test for the diagnosis of IC due to other *Candida* species.

Beta-D-Glucan Assay

Nonculture diagnostic tests, such as the BG assay, may be useful adjuncts for the diagnosis of candidemia. BG is a cell wall component of a wide variety of fungi and can be detected by its ability to activate factor G of the horseshoe crab coagulation cascade [27]. There are two different assays for the detection of BG: the Fungitec-G glucan (Seikagaku) and the Glucatell (or Fungitell) test (Associates of Cape Cod). The reagents used in these two tests are derived from different species of horseshoe crabs: the amebocyte enzymes from *Tachypleus tridentatus* for the Fungitec assay and the enzymes from *Limulus polyphemus* amebocytes for the Glucatell assay [27]. The former test has been extensively studied and used in Japan, whereas the latter has been cleared by the United States Food and Drug Administration (FDA) for the diagnosis of IFIs.

In one of the preliminary studies, BG was studied in serum samples from 283 patients with newly diagnosed acute myelogenous leukemia or myelodysplastic syndrome [27]. Twenty patients developed a proven or probable IFI; 11 of these IFIs were IC. Using a predefined cutoff value of 60 pg/mL, the sensitivity and specificity of a single positive specimen was 100 and 90%, respectively. The positive and negative

predictive value of the test was 43 and 100%, respectively. Notably, BG was positive at a median of 10 days before the clinical diagnosis of a proven or probable IFI was made. In another case-control study including patients from six different clinical sites in the US, a single blood sample was drawn from each subject within 72 h of the diagnosis of an IFI [28]. In that study, only a minority of patients had an underlying malignancy (28.8%) and IC was the most common diagnosis: 111 cases of proven (*n*=107) and probable (*n*=4) IC. Using a BG cutoff of 60 pg/mL, the assay had a sensitivity of 82.6% for IC. Notably, sensitivity differed among *Candida* spp., with the assay performing worse for *C. parapsilosis* (sensitivity: 72.2%).

Based on the above, the BG appears to be a promising tool for the diagnosis of candidemia in patients with hematologic malignancies, albeit with certain limitations. The optimal frequency of testing has not been established as yet. False positive results have been reported in patients requiring hemodialysis with cellulose membranes, use of cotton gauze and surgical sponges, administration of immunoglobulin products or antitumor polysaccharides (e.g., lentina, polysaccharide K, schizophyllan) [28–32]. There have also been reports of false positive GM results associated with bacterial infections (e.g., *P. aeruginosa*, *S. pneumoniae*), perhaps due to production of BG or similar molecules [33, 34]. Other limitations of the test include the variable performance among different *Candida* spp. (e.g., *C. parapsilosis*) and relative lack of specificity (other fungi, e.g., *Aspergillus* spp., *Pneumocystis* spp. produce this antigen). Finally, one needs to be considerate of the relatively low positive predictive value when applied on patient populations with a low prevalence of candidemia; hence, careful targeting of the assay to high-risk populations is necessary [35–37].

Polymerase Chain Reaction

There are few data to support the use of a PCR assay for the diagnosis of candidemia in cancer patients. In a study of 72 patients with a hematologic malignancy and neutropenic fever from Italy, the sensitivity and specificity of PCR for the diagnosis of IC were 92.9 and 97.6%, respectively [38]. Another group from Brazil evaluated the efficacy of a PCR assay for the diagnosis of candidemia in 225 patients with high risks [39]. With the minority of study subjects being cancer patients, the reported sensitivity, specificity, positive and negative predictive value were 72.1, 91.2, 65.9, and 93.2%, respectively. Similar observations come from studies on nonneutropenic intensive care unit patients [40]. Considering the relatively low sensitivity of blood cultures, PCR may prove to be a significant adjunct for the diagnosis of candidemia particularly in high risk patients, such as cancer patients. However, a major limitation of most PCR assays is

their relative lack of specificity, mostly due to high rates of contamination. The test may not be applicable to smaller institutions or resource-poor countries due to requirements for highly trained personnel, special equipment, and higher costs. The above will likely result in running PCR assays for the diagnosis of candidemia in batches rather than on a daily (or even more frequent) basis, thus minimally affecting time to diagnosis compared to more traditional diagnostic tests. Widespread use awaits standardization, commercialization, and further study.

Diagnosis of Hepatosplenic Candidiasis

Hepatosplenic candidiasis develops typically after *Candida* spp. invade the portal vasculature, disseminating to the liver and/or spleen. Clinical manifestations typically coincide with inflammation developed after resolution of neutropenia. Definitive diagnosis requires biopsy of hepatic lesions that may reveal hyphal forms consistent with *Candida* species. The diagnosis is suggested by the presence of multiple lesions of the liver and spleen, occasionally described as "bull's eye" appearing on abdominal CT scan or magnetic resonance imaging (MRI) (Fig. 23.2) [41]. Frequency of candidemia among patients with hepatosplenic candidiasis has historically ranged between 8 and 19% [41, 42]. While the constellation of fever, abdominal pain, elevated alkaline phosphatase, and liver lesions is suggestive of hepatosplenic candidiasis, multiple organisms, including bacterial and filamentous fungi, can cause a similar syndrome. Clinicians should also be aware that lesions (and symptoms) can get worse with progressive inflammation, despite appropriate antifungal therapy.

Fig. 23.2 Thirty nine-year old male patient with a history of acute myelogenous leukemia presenting with neutropenic fever, abdominal pain, elevated liver function tests and liver and spleen lesions on abdominal CT, consistent with hepatospenic candidiasis

Invasive Mold Infections

Clinical Syndromes

Invasive mold infections among immunocompromised hosts may present with local invasion (e.g., sinusitis, pulmonary involvement) or disseminate to involve multiple sites. Local invasion of the sinuses and lungs follows mold inhalation, and skin involvement most frequently occurs through direct inoculation. Spread of the organisms to other sites may happen contiguously (e.g., sinus to orbit and brain) or hematogenously (e.g., brain, skin, liver). Pulmonary invasive disease is the most commonly observed clinical syndrome due to molds among cancer patients. Multiple molds may cause disease, including *Aspergillus* spp., the Zygomycetes, and *Fusarium* species. Few clinical clues are typical with presentation. One classic finding is the presence of multiple maculopapular to ulcerated skin lesions, which, especially in the presence of positive blood cultures, is highly suggestive of fusariosis (Fig. 23.3) [43]. However, most other molds, including *Aspergillus* and the Zygomycetes may disseminate to involve the skin.

Diagnosis of Invasive Mold Infections

Imaging

Invasive mold infections affecting the lungs may present with different patterns on a chest CT, including small or large nodules, patchy, segmental, or wedge-shaped consolidations, peribronchial infiltrates with a tree-in-bud distribution, and cavitation [44, 45]. Systematic use of chest CT for the diagnosis of pulmonary IA can significantly decrease the time to diagnosis of IA among neutropenic patients [46, 47]. Improved outcomes based on early diagnosis of pulmonary IA with the use of the halo sign were observed in a study that analyzed the radiographic findings from 235 patients with pulmonary IA who participated in the Global Comparative Aspergillosis Study [48, 49]. Patients with a halo sign were more likely to survive by 12 weeks (71 vs. 53%, $p < 0.01$) and respond to the administered treatment (52 vs. 29%, $p < 0.001$), regardless of neutropenic status or underlying condition [48]. This may be, in part, due to the earlier recognition of IA and prompt initiation of antifungal treatment at an earlier stage leading to improved outcomes.

Two CT patterns have been associated with early and late pulmonary IA: the "halo" and the "crescent" sign, respectively (Fig. 23.4). Kuhlman et al. first described the significance of the halo sign on a chest CT for the diagnosis of IA in patients with acute leukemia [50]. This refers to a nodular

Fig. 23.3 Nineteen-year old male patient with relapsed acute myelogenous leukemia presenting 5 days after a mismatched related allogeneic HSCT with fever and multiple maculopapular skin lesions (**a**). His skin biopsy and blood cultures were positive for *Fusarium* species (**b**)
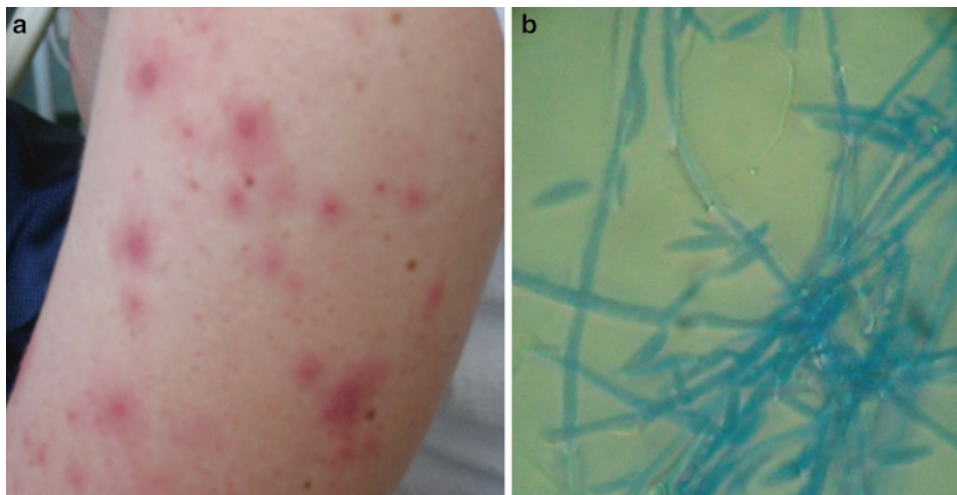
Fig. 23.4 Thirty nine-year old female patient with relapsed acute myelogenous leukemia presenting 3 months after a matched unrelated allogeneic HSCT recipient with cough, fever, and mild dyspnea. The patient was being treated with high dose corticosteroids for severe skin graft versus host disease. She was diagnosed with pulmonary invasive aspergillosis based on the halo sign shown on her chest CT and the presence of *A. fumigatus* in her bronchoalveolar lavage

lesion or mass surrounded by a halo of alveolar hemorrhage, showing as ground-glass attenuation on CT [50–53]. The halo sign may appear in 60–93% of neutropenic patients with pulmonary IA [3, 44–46, 48, 54]. Although the halo sign has been most frequently associated with pulmonary IA, other infections can present similarly, including other filamentous fungi (e.g., zygomycosis) and bacterial infections (e.g., *Pseudomonas* spp.) [53, 55, 56].

Historically, zygomycosis has been associated with sizable nodular, occasionally cavitary, lung lesions [57–59]. However, the majority of old studies have included mixed

patient populations, with diabetic patients representing a significant proportion [57–59]. In addition, most lesions described were based on chest XRs rather than CT scans [57–59]. More recent data suggest that presence of multiple (>10) lung nodular lesions (OR: 19.8; $p=0.012$) or a pleural effusion (OR: 5.07; $p=0.042$) may be more suggestive of pulmonary zygomycosis vs. IA among patients with an underlying hematologic malignancy [60]. Notably, the presence of the halo or crescent signs, cavity, or mass was not found to be a predictor of pulmonary zygomycosis. Although the above findings need to be further validated, they could – potentially – be useful in the differential diagnosis of hematologic patients with a suspected pulmonary invasive mold infection on imaging.

It is important to remember that these classic findings – halo and cavitation – are common in neutropenic patients. However, more recent studies are emphasizing that nonneutropenic patients with high risks, such as allogeneic HSCT recipients postengraftment with graft-versus-host-disease (GVHD), may present with variable radiographic findings. For instance, it has been reported that bronchopneumonias or focal infiltrates may be more common compared to isolated nodules in nonneutropenic allogeneic HSCT recipients with documented IA [61].

Histopathology and Microbiology

Histopathologic confirmation of sterile tissue invasion remains the "gold standard" to establish a proven diagnosis of an invasive mold infection [62]. The presence of septate narrow hyphal forms with acute angle branching is suggestive of *Aspergillus* spp., but other filamentous fungi (e.g., *Fusarium* spp., *Penicillium* spp., *Scedosporium* spp.) may

look similar under the microscope. The Zygomycetes appear with characteristic broad, nonseptate hyphae with right-angle branching when specimens are stained with calcofluor white or methenamine silver stains. Although suggestive, histopathologic findings do not definitively identify the pathogen. Microbiologic identification of the fungal genus and species should be pursued if feasible, as it may have important implications in the management of cancer patients with fungal infections.

However, culture of filamentous fungi is not easy. Sensitivity rates of sputum cultures for the diagnosis of pulmonary IA have ranged between 15 and 69%. Similarly, the sensitivity of tissue and BAL cultures for *Aspergillus* spp. has ranged between 30–52 and 0–67%, respectively [8–21]. Sensitivity rates of sputum and BAL cultures for the diagnosis of zygomycosis have been in the range of 25% [63]. Hence, cultures may be negative despite presence of disease. In addition, performing an invasive procedure (e.g., bronchoscopy) or obtaining tissue for a biopsy may not always be feasible. To further complicate the diagnostic process, isolation of a fungal organism does not necessarily imply pathogenicity. Fungal pathogens (e.g., *A. niger*) may represent mere colonization of the airway and incidentally growth in a sputum or BAL culture. Hence, interpretation of culture results necessitates careful consideration of the host and clinical presentation.

Galactomannan Antigen

Reiss and Lechmann were the first to report the detection of *Aspergillus* antigens for the diagnosis of IA [64]. Since then, significant progress has been made, eventually leading to the availability of commercial assays. Galactomannan is a polysaccharide present in the cell wall of *Aspergillus,* which is released during the growth of *Aspergillus* hyphae. Currently, the Platelia sandwich enzyme-linked immunosorbent assay (ELISA; BioRad, Marnes-La-Coquette, France) is the assay that has been most extensively studied and used. Positive and negative controls are included in each assay as well as a standardized serum specimen with 1 ng/mL of GM. The process may take up to 3–4 h and the assays are run in batches in most institutions. The optical density index (ODI) of each sample is used to define positivity, calculated by dividing the OD of each sample with that of the threshold control. ODI cutoffs have ranged between 0.5 and 1.5 in different studies, with an ODI of 0.5 suggested as the cutoff by the FDA. The Platelia GM EIA has been approved by the FDA for use only on serum samples; approval of the test on BAL is under evaluation.

The performance of the serum GM EIA has varied among studies, depending on the patient population and age, number of serum samples required to define positivity, certainty of diagnosis, administration of concomitant antibacterial and antifungal agents, and the ODI cutoff used [49, 65–71]. Sensitivity and specificity have differed based on the ODI cutoff ranging from 64–78 to 81–95% for ODI of 1.5 and 0.5 ng/mL, respectively [72] In a meta-analysis of 27 studies with a total of 4,000 patients, the overall sensitivity and specificity of the GM EIA for the diagnosis of IA (proven and probable) were 61% (95% CI 59–63%) and 93% (95% CI 92–94%), respectively [73]. The assay appeared to perform better in patients with an underlying hematological malignancy or among HSCT vs. solid organ transplant (SOT) recipients [73]. The latter may, in part, be due to the low prevalence of IA among most SOT recipients and the small number of SOT recipients included in these studies. The use of GM EIA may significantly quicken the diagnosis of pulmonary IA and affect the costs associated the management of this infection [66, 74].

Administration of piperacillin-tazobactam or amoxicillin-clavulanate has been associated with false positive results [47, 75–78]. In fact, in one study piperacillin-tazobactam was the only factor significantly associated with false positive GM EIA results in 38 of 42 (90.5%) patients with positive GM EIAs; the GM EIA was positive in 3 of 4 batches of piperacillin-tazobactam in this study [77]. The presence of organisms that share cross-reacting antigens (e.g., *Penicillium* spp., *Paecilomyces* spp., *Alternaria* spp., *Cladosporium herbarum*, *Acremonium* spp., *Alternaria alternata*, *Fusarium oxysporum*, *Wangiella dermatitidis*, and *Rhodotorula rubra*) may also decrease the specificity of the test [65, 79]. Severe mucositis and gastrointestinal GHVD following HSCT can occasionally lead to false positive results, likely due to translocation of GM across the intestinal mucosa during periods of reduced mucosal integrity. Younger age has been associated with lower specificity rates, predominately attributed to the high concentration of GM in children's food (e.g., cereals) [49]. Recent data suggest that the performance of the GM EIA may be variable for the different *Aspergillus* spp. with sensitivity being lower among patients with IA due to *A. fumigatus* (13%) compared to non-*fumigatus Aspergillus* spp. (49%; $p < 0.0001$) [80]. Finally, based on animal and human data, the performance of serum GM appears – in part – to depend on the fungal burden [66, 81–87]. In fact, administration of antifungal agents with mold activity has been found to decrease the sensitivity of GM EIA [67, 80].

GM EIA in other than blood specimens: GM is a water-soluble carbohydrate, and thus can be detected in fluids other than blood, including urine, BAL, cerebrospinal fluid (CSF), and pleural fluid. Sensitivity of the GM EIA in BAL has ranged between 60 and 100%, depending on the patient population studied, ODI cutoff used, certainty of diagnosis, and bronchoscopy performance [88–95]. False positive assays can occur when BAL is contaminated with galactomannan in the setting of airway colonization. Despite, specificity has been reported to be as high as 95% among HSCT and lung

transplant recipients [89, 93]. In a case-control study among HSCT recipients, Musher et al. reported a sensitivity and specificity of 76 and 94%, respectively, for the diagnosis of IA using the GM EIA on BAL samples at an ODI cutoff of 0.5 [89]. Notably, among 22 culture-negative BAL specimens from patients with IA, the sensitivity of the GM EIA was 59%, suggesting that more than half of HSCT recipients with a negative culture on their BAL could be diagnosed with this assay. In fact, 25 additional procedures were performed among 18 HSCT recipients with negative BAL cultures; the authors estimated that 8 of 12 additional bronchoscopies and 8 of 13 lung biopsies might have been avoided if the GM EIA was applied on the initial BAL [89]. The combination of GM EIA and early chest CT may result in earlier diagnosis of IA [82, 83]. Many institutions have started using the GM EIA on BAL specimens pending the clearance of the assay by the FDA.

The performance of GM testing in the urine has varied based on the patient population and method used for the detection of GM [96–101]. The sensitivity and specificity of antigenuria using the latex agglutination test among HSCT recipients with autopsy-proven IA were 57 and 53%, respectively, compared to 43 and 53% for antigenemia [96]. It has been suggested that the diagnostic yield of the urine GM EIA may increase if urine is concentrated by tenfold [100]. False positive results of urine GM have ranged between 8 and 47%, attributed to a variety of factors, including urine contamination with *Aspergillus* spp. [96, 98, 99]. GM can also be detected in the CSF of patients with central nervous system or pleural fluid of patients with lung disease, although most results come from case reports/series and more prospective data are required to make further conclusions [102–104].

Beta-D-Glucan Assay

The BG is a cell wall component of a variety of fungi, including *Aspergillus* species. It is being evaluated as a diagnostic aid for numerous IFIs, given its lack of specificity, with reasonable reported sensitivities. The sensitivity of the serum BG assay for the diagnosis of IA has ranged between 55 and 87.5% [28, 105–107]. For instance, in a retrospective review of 456 autopsies, 54 (11.8%) cases of proven IFIs were identified, 41 of which had a BG test performed within 2 weeks prior to death [35]. With the vast majority of IFIs (70%) being IA, the sensitivity and specificity of the BG assay at a cutoff of 60 pg/mL were 85.4 and 95.2%, respectively.

Polymerase Chain Reaction

The use of PCR for the diagnosis of IA in cancer patients has been studied using different blood products (e.g., whole blood, plasma, serum), BAL, and CSF [95, 103, 107–128]. Sensitivity and specificity of blood PCR for the diagnosis of IA have ranged between 64–100 and 63.5–100%, respectively [129]. PCR for the diagnosis of IA has been limited due to, in part, lack of standardization and commercially available assays [129]. Results have varied based on the specimen used (e.g., whole blood, plasma, serum, BAL), PCR technique (e.g., real-time vs. nested), DNA extraction methods, target genes (e.g., 18S vs. 28S rRNA vs. mtDNA), patient population studied (e.g., hematologic malignancy vs. other), or the number of samples tested [128]. For instance, testing serum may be less sensitive (55–70%) than whole blood (57–100%), perhaps as a result of the partial loss of fungal particles during processing [71, 111, 114, 122, 126, 130–132]. Sample volume may also affect the sensitivity of the test, with large serum volumes yielding higher sensitivity (100%) compared to smaller serum volumes (76.5%) [133].

A major limitation of the test is its relative lack of specificity due to – among others – potential contamination of the specimens during processing. The specificity of blood PCR for the diagnosis of IA in patients with a hematologic malignancy may increase from 37 to 89% when two consecutive positive samples are required to establish the diagnosis [108, 111]. The occasional homology of probes used with the DNA of other filamentous fungi may further increase the false positive rates observed in PCR assay results. Caution should be called here, as a "false positive" result may represent subclinical or early infection (early true positive) which might have affected the performance of the PCR assays in previous studies [116, 128].

PCR has been successfully applied to identify fungi in tissues and to further identify organisms to the species level. For instance, PCR and restriction fragment-length polymorphism analysis have been used retrospectively for the identification of the Zygomycetes in tissue [134, 135]. Moreover, two seminested PCR assays identifying *Aspergillus* spp. and the Zygomycetes were prospectively studied on respiratory tract biopsy samples from 56 immunocompromised hosts with suspected invasive mold infections [136]. Among 27 (48%) patients with histopathologically confirmed mold infections, 18 (66.7%), 6 (22.2%), and 3 (11.1%) were found to have IA, zygomycosis, and another mold infection, respectively. PCR was found to be significantly better compared to traditional cultures in detecting an invasive mold infection (26 of 27 vs. 17 of 27, respectively; $p = 0.006$).

Diagnosis of Invasive Fungal Sinus Disease

Sinus disease presents with fever, facial numbness or tenderness, and necrotic areas appearing as dark colored eschars in the nares or oral cavity. Concomitant neutropenia may result

in a subtle clinical presentation of sinus disease and hence lead to late diagnosis and worse outcomes. Clinical suspicion among patients at risk should prompt aggressive diagnostic work-up, including sinus CT scan or magnetic resonance (MRI) and sinus biopsy, if feasible [137, 138]. Necrotic lesions are not necessary to establish diagnosis. Invasive fungal sinusitis among cancer patients may also present as severe soft tissue edema and mucoperiosteal thickening on a CT scan [138]. Lesions are frequently unilateral and contiguous bone erosion may occur [138]. As imaging tests are not as sensitive for the diagnosis of invasive fungal sinusitis, diagnosis relies on biopsy and culture of the affected tissue. The absence of distinct lesions upon direct visualization of the sinuses should not exclude tissue biopsy. Concomitant sinus and lung disease may be suggestive of zygomycocis, although *Aspergillus* spp. and other molds, including the dematiaceous molds, may have similar presentations [60, 139–141].

Summary

Establishing the diagnosis of IFIs first depends on having an early and accurate suspicion of disease, depending on the knowledge of host risks and local epidemiology. In the past several years, availability of nonculture based assays to detect fungal antigens and nucleic acids have opened up new pathways to increase sensitivity of detecting fungi in tissues, although much needs to be learned about how to best utilize them in clinical practice.

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Chapter 24
Invasive Candidiasis in Management of Infections in Cancer Patients

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Abstract *Candida* infections are increasing. Nonalbicans *Candida* are now the most commonly isolated species in immunocompromised patients. The determination of serum beta-D-glucan may allow early diagnosis, but the best implementation of this new technology as screening or diagnostic test remains to be determined. From the therapeutic standpoint, the echinocandins have changed the management of invasive candidiasis due to their effectiveness and excellent safety and drug interaction profile.

Keywords *Candida* • Beta-D-glucan • Echinocandin • Neutropenia

Introduction

Candida is the yeast responsible for most human fungal infections, ranging in severity from mucocutaneous disease to multisystemic invasive disease. The incidence of systemic *Candida* infections, particularly candidemia, has increased significantly in recent years, being the fourth most common pathogen isolated in blood cultures [1]. Apart from *Candida albicans*, other species (nonalbicans) are being isolated more frequently and currently account for the majority of episodes of candidemia in many groups of immunocompromised patients [2, 3].

The diagnostic and therapeutic challenges presented by *Candida* infections are being met by advances in serologic markers and drug development. From the diagnostic standpoint, although blood cultures may be negative in invasive candidiasis [4], the use of beta-D-glucan offers the possibility of early diagnosis [5, 6]. From the therapeutic standpoint, even if widespread use of antifungal prophylaxis predisposes to infections due to species with intrinsic or acquired resistance

to some antifungal agents, the echinocandins offer an excellent therapeutic alternative with low toxicity and few interactions in cancer patients [7].

Candida colonization, the presence of the yeast on mucocutaneous surfaces without any sign of invasion, must be distinguished from infection, where there is a clinically evident pathological process with mucosal damage and inflammation. A culture of oropharyngeal, intestinal, or genital material that grows *Candida* species is clinically insignificant unless there are signs or symptoms of infection, as it is part of the normal flora.

Candidemia, the presence of *Candida* species in the blood, may be a manifestation of disseminated disease or it may sometimes reflect only a colonization of an indwelling intravenous catheter [8]. Nonetheless, all the cases of candidemia require treatment with an antifungal agent [9, 10]; it should never be assumed that removal of a catheter alone is an adequate therapy for candidemia.

Mortality rate in case on invasive candidiasis, particularly candidemia, remains high, but can be decreased by rapidly administered antifungal therapy [3, 11–14]. Cancer patients at highest risk for *Candida* infection may be potential candidates for prophylaxis or empirical or preemptive therapy [15].

Epidemiology

Invasive candidiasis is an increasingly important nosocomial infection, particularly in patients who are malnourished, long time hospitalized, and immunocompromised [1, 3, 8, 16, 17].

In Europe, an autopsy-based study showed an increase of invasive fungal disease over the last 10 years [18]. *Candida* infections affect patients with disrupted mechanical barriers (such as skin and mucous membranes, including the presence of central venous catheter) and with deficits in phagocytosis (e.g., neutropenia). Candidemia is now the fourth most common type of nosocomial bloodstream infection, accounting for 9% of cases in a national survey of United States hospitals from 1995 to 2002 [1], and *Candida* species are increasingly isolated from surgical site and urinary tract

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Table 24.1 Resistance patterns among different *Candida* species

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Amphotericin B	Echinocandins
C. albicans	S	S	S	S	S	S
C. glabrata	S-DD or R	S-DD or R	S-DD or R	S-DD or R	S to I	S
C. krusei	R	S-DD or R	S	S	S to I	S
C. lusitaniae	S	S	S	S	S to R	S
C. parapsilosis	S	S	S	S	S	S or rarely R
C. tropicalis	S	S	S	S	S	S

I intermediate; *S* susceptible; *S-DD* susceptible dose-dependent; *R* resistant

infections [19]. Moreover, there has also been an increase in bloodstream infections due to nonalbicans species of *Candida* [12, 13, 20], surpassing *C. albicans* in some series [2, 3]. *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei* seem to be more common in immunocompromised patients [12, 21], perhaps related to the selective pressure caused by antifungal prophylaxis with fluconazole [21–26]. However, other factors such as geography, age, and concomitant therapies may contribute as well [27–30]. Table 24.1 reports susceptibility of selected species to the most commonly used antifungals. Given that *C. krusei* is intrinsically resistant to fluconazole and *C. glabrata* is either resistant or exhibits a dose-dependent susceptibility, these are the species more common in case of fluconazole administration. Moreover, *C. glabrata* can cause also a breakthrough infection in case of prophylaxis with other triazoles, namely itraconazole [31]. Nosocomial *C. parapsilosis* infection is frequently related to indwelling catheter and parenteral nutrition by CVC has been reported [32].

The mortality in candidemia remains high with most recent randomized controlled trials reporting mortality in the 20–40% range [33–36], even if the attributable mortality is only 10–15% [33].

Pathogenesis

C. albicans is a part of the normal endogenous flora and is present in the gastrointestinal tract of 40–50% of individuals. Colonization is a mandatory first step in developing invasive candidiasis. Changes in endogenous flora which promote increased fungal growth on mucosal surfaces, together with damage of intestinal mucosa, can predispose patients to invasive infections. The loss of integrity of the gastrointestinal tract, as a result of either the disease or the cytotoxic chemotherapy, can create a portal by which *Candida* passes from the gastrointestinal tract into the bloodstream [37]. However, in the case of *Candida* catheter-related infections, including septic thrombophlebitis, the skin at the site of vascular catheter entry, rather than the gastrointestinal tract, is the most likely portal of entry [38].

Although the infecting strain is most often part of the host's endogenous flora, nosocomial acquisition of *Candida*

Table 24.2 Patients who are at increased risk of invasive candidiasis

Congenital deficit of cellular immunity
Deficit of cellular immunity secondary to infection (HIV)
Recipients of solid organ transplant
Recipients of hematopoietic stem cell transplant
Low birth weight infants

Table 24.3 Risk factors for invasive candidiasis in cancer patients

Neutropenia, secondary to chemotherapy or aplasia
Treatment with immunosuppressive agents (including glucocorticosteroids, chemotherapeutic agents, and immunomodulators)
Colonization with yeasts
Central venous catheter
Parenteral nutrition, particularly with high-concentration carbohydrate solutions
Prolonged broad-spectrum antibiotic therapy
High APACHE II scores
Acute renal failure, particularly if requiring hemodialysis
Prior surgery, particularly abdominal
Gastrointestinal tract perforations and anastomotic leaks
Bacteremia with enteric organisms
Severe mucositis
Total body irradiation
Graft versus host diseases with mucosal damage
Long-term hospitalization, with changes in endogenous flora

species has been described [19, 39, 40]. The organism has spread via contaminated solutions in some cases [39], whereas the hands of healthcare workers have been the probable source in others [40].

Risk Factors

Patients who are at increased risk of *Candida* infection and numerous risk factors for invasive candidiasis, which are particularly frequent in cancer patients during hospital stay, have been described and are outlined in Tables 24.2 and 24.3 [11–13, 20, 22, 41, 42]. Patients who are immunocompromised or admitted to intensive care units (ICU) have the highest risk of developing candidemia. In the case of cancer patients, next to granulocytopenia, the use of pharmacological doses of corticosteroids and indwelling catheters is the most important factor facilitating the development of candidiasis. Additionally,

chemotherapeutic agents associated with extensive gastrointestinal mucosal damage or abdominal surgical procedures further predispose to yeast infections.

Diagnosis

A positive blood culture remains a cornerstone for the diagnosis of invasive candidiasis. Cultures of nonsterile materials, such as pharyngeal swab, bronco-alveolar lavage, and urine, which grow *Candida,* should be carefully examined in consideration of clinical signs and risk factors for candidiasis in order to discriminate between a colonization and an infection.

Definitions

As for other invasive mycoses, the definitions of invasive candidiasis have been developed and modified [43, 44]. Proven invasive fungal disease due to *Candida* species requires a positive result of a histopathologic, cytopathologic, or direct microscopic examination of a sterile material from a normally sterile site (other than mucous membranes) showing pseudohyphae or true hyphae of *Candida*. Positive blood cultures also constitute a proven invasive fungal disease, if there are clinical signs or symptoms of infection or if predisposing host factors (especially neutropenia) are present.

Candidiasis is considered disseminated when after an episode of candidemia within the previous 2 weeks, there is visceral or ophthalmic involvement. These are indicated by the presence of small, target-like abscesses (bull's-eye lesions) in liver or spleen, or progressive retinal exudates on ophthalmologic examination. The signs and symptoms consistent with sepsis syndrome indicate acute disseminated candidiasis, whereas their absence denotes chronic disseminated disease.

Urinary infection due to *Candida* can be diagnosed in case of two positive results of culture of urine samples for yeasts in absence of urinary catheter or if there are *Candida* casts in urine in absence of urinary catheter.

Chronic disseminated candidiasis can be diagnosed as probable in the presence of characteristic target-like radiological lesions, demonstrated by CT, MRI, or ultrasound, as well as elevated serum alkaline phosphatase level, even if no microbiological confirmation is found.

Blood Cultures

Unfortunately, blood culture techniques are relatively insensitive. Moreover, studies from several decades ago showed that blood cultures were positive in only approximately 50% of patients who were found to have disseminated candidiasis at autopsy [4]. Since then, improved, more sensitive microbiological detection systems were developed. However, blood cultures are still often negative in patients with disseminated candidiasis and the diagnosis is often made on clinical grounds. Moreover, blood cultures require from 1 to 4 days to become positive, and in seriously ill patients, more rapid and sensitive diagnostic techniques are warranted. Thus, a number of noninvasive rapid diagnostic tests have been explored.

Nonculture-Based Methods

Noninvasive techniques, such as presence of *Candida* antigens, their metabolites, or antibodies in serum (mannan, enolase, antimannan antibodies), have been developed. However, their clinical utility is limited due to high rate of false positive and false negative results. The colonization with *Candida* can decrease the specificity of antibody assay, while the fact that immunocompromised hosts may be unable to produce antibodies can decrease test's sensitivity. Detection of circulating *Candida* antigens or metabolites seemed promising, but was proved to be insufficiently sensitive for clinical purposes [45, 46].

The newest indirect diagnostic test is based on the detection of beta-D-glucan, which is present in the cell wall of many fungi, including *Candida*, *Aspergillus*, *Fusariumm*, *Trichosporon*, *Saccharomyces,* and *Acremonium* infection [5, 47]. Serum beta-D-glucan was included among mycological criteria in new definitions of invasive fungal diseases [44], and several studies have reported its high sensitivity and specificity [5, 6]. It has been used as a screening test obtained twice a week in neutropenic patients [5] as well systematically twice weekly and then more frequently in the presence of fever during neutropenia [48]. Although the test seems useful, it remains unclear what the best screening or diagnostic strategy with beta-D-glucan can be in terms of efficacy and cost for the management of candidiasis in daily clinical practice. We have had cases of documented candidemia where a positive beta-D-glucan preceded the positive blood cultures by several days. The availability (or lack thereof) of results in real time is an important consideration that may make the implementation of the test difficult.

Molecular diagnosis with polymerase chain reaction (PCR) seems promising; however, it is time-consuming and lacks intralaboratory standardization. Therefore, it remains useful for clinical studies and is not routinely recommended [43, 44].

Radiological Signs

Chronic disseminated candidiasis (hepatosplenic candidiasis) is characterized by peripheral, target-like abscesses (bull's-eye

lesions) in liver or spleen. These lesions may be documented by ultrasound, computed tomography, and magnetic resonance [49]. Serial studies are often required, as the microabscesses may be undetectable during neutropenia, but manifest at the time of neutrophil recovery [50]. The radiological signs and symptoms can be strongly suggestive of invasive mycosis, but occasionally lymphoma, other fungal infections, and tuberculous or other disseminated mycobacterial disease may present a similar pattern.

Clinical Presentation

There are numerous clinical manifestations of diseases caused by *Candida*, which can be divided into mucocutaneous and deep organ involvement. Mucous membrane infections include oral candidiasis (thrush), acute atrophic candidiasis of the tongue, chronic atrophic candidiasis ("denture sore mouth"), angular cheilitis, and *Candida* leukoplakia. *Candida* esophagitis is an invasive infection of the esophageal mucosa. Other manifestations of mucocutaneous *Candida* infections are vaginitis, balanitis, paronychia, onychomycosis, and chronic mucocutaneous candidiasis.

The clinical forms particularly important in cancer patients will be reviewed in detail.

Esophagitis

Esophageal disease was believed to be initiated by direct spread from oral disease; however, it may occur frequently without thrush. It is frequent in patients with AIDS, cancer, particularly hematological malignancies, and in transplant recipients. According to an autopsy study from a cancer hospital, esophagus and stomach were the sites most frequently involved in gastrointerstinal candidiasis in these patients [51].

The most common symptoms include painful swallowing, a feeling of obstruction on swallowing, and retrosternal chest pain. Nausea and vomiting may also occur. Among the complications, hemorrhage and dissemination should be mentioned, particularly with involvement of the whole gastrointestinal tract in cancer patients.

The diagnosis is made definitively by biopsy during endoscopy; however, endoscopic appearance of ulceration and white patches (pseudomembranes) can be strongly suggestive.

Candidemia

The clinical manifestations of candidemia vary from mild fever to a full-blown sepsis syndrome (fever, chills, hypotension),

indistinguishable from severe bacterial infection. Of note, in cancer patients receiving corticosteroid therapy, fever might be absent, thus an episode of candidemia may be initially asymptomatic. Clinical signs of hematogenous spread of *Candida* include predominantly characteristic eye lesions (chorioretinitis, endophthalmitis) or skin lesions, both described further below. Rarely, muscle abscesses can form. Additionally, signs of multiorgan system failure may be present due to involvement of the organs like kidneys, heart, liver, spleen, lungs, eyes, and brain.

Skin Lesions in Disseminated Candidiasis

In case of disseminated candidiasis, different types of lesions have been described [52]. The most frequent ones are painless, nodular, small (0.5–1 cm in diameter), and pink to red. They may be either single or numerous, distributed over the entire body [53]. Most patients with these lesions are neutropenic and affected by disseminated candidiasis. Other possible lesions may resemble ecthyma gangrenosum [54] or purpura fulminans [55]. A punch biopsy and histological examination is the most accurate diagnostic method.

Chronic Disseminated Candidiasis (Hepatosplenic Candidiasis)

The clinical sign and symptoms of hepatosplenic candidiasis include fever, abdominal pain, hepatosplenomegaly, and an increase in markers of cholestasis, particularly alkaline phosphatase. Radiological imagining reveals the aforementioned characteristic target-like lesions. Most of these infections have occurred in severely immunocompromised patients and become manifest during their recovery from neutropenia.

Ocular Infection

The incidence of ophthalmologic lesions in case of candidemia ranges from 2 to 26%. The most common are endophthalmitis and chorioretinitis. Endophthalmitis can become evident up to 2 weeks after the diagnosis of candidemia and is correlated with the dissemination of fungal infection to other internal organs.

Clinical signs and symptoms include visual disturbances, such as blurring or floating scotomas, eye pain, and even blindness. However, cases of asymptomatic *Candida* endophthalmitis have been reported, thus a fundoscopic exam is mandatory in case of blood cultures positive for

Candida. Importantly, patients in the ICU may be too ill to report any symptoms.

Usually, on fundoscopic exam, the lesions are white, cotton ball-like, chorioretinal in origin, and can rapidly progress to involve the vitreous. Diagnosis can be made by the characteristic picture plus, in half of the cases, an episode of known candidemia. Unlike vitrectomy, aspiration of the anterior chamber is rarely diagnostic.

Diagnosis of ocular lesions is particularly important because they can cause permanent blindness and they may indicate underlying dissemination to other internal organs.

Endocarditis

Cardiac *Candida* infections are almost exclusively diagnosed in patients fitted with a central venous catheters or a prosthetic valve, in those undergoing cardiac surgery, and in drug addicts. Large vegetations are characteristic and, peripheral embolization phenomena are frequent. *Candida* endocarditis usually requires valve replacement and prolonged antifungal treatment [56], although a few case reports and case series show that medical management alone may be successful when there are contraindications to surgery [57–61].

Trombophlebitis

The infection of vascular prostheses or anastomoses is possible in patients undergoing vascular surgery with implementation of large prosthetic materials. Management usually requires catheter removal and drainage or resection of the vein, or intravenous treatment with echinocandin or AmB followed by fluconazole.

Intra-abdominal Infections

They are usually secondary to perforations of gastrointestinal tract or to abdominal surgeries, particularly when liver or biliary vessels are involved.

Urinary Tract Candidiasis

The clinical importance of candiduria remains unclear. Urinary catheters are frequently colonized with *Candida*, and catheter replacement can successfully resolve the presence of fungi in the urine. In case of asymptomatic candiduria, therapy is usually not indicated, with the exception of patients at high risk for disseminated candidiasis, such as neonates, neutropenic adults, or those undergoing urologic procedures. Cancer patients often belong to one or more of these categories, and the possibility of disseminated candidiasis should be considered and ruled out. Imaging of the kidneys and collecting system may be indicated. Symptomatic cystitis, when *Candida* is the only pathogen growing in urine culture, may require antifungal therapy. Fluconazole is generally the treatment of choice (and the only azole that achieves high enough concentration in the urine), but AmB may be necessary if the isolate is *C. glabrata*.

Prophylaxis and Treatment of *Candida* Infection

Systemic antifungal agents with activity against *Candida* include amphotericin B (AmB, both deoxycholate (AmB-d) [34, 62] and lipid formulations (L-AmB) [33], triazoles (fluconazole [63], itraconazole [64], voriconazole [65, 66], and posaconazole [67]), and echinocandins (micafungin, caspofungin, and anidulafungin) are presented in Table 24.4 [33, 34, 36]. Not all agents have been compared in all the different *Candida* infections and settings, so recommendations are based both on evidence and reasonable extrapolations [9].

Prophylaxis

Knowing which patients are at increased risk for candidiasis allows for selective use of antifungal prophylaxis. The main indications in cancer patients are prolonged neutropenia and hematopoietic stem cell transplantation. Randomized controlled trials have confirmed the efficacy of fluconazole (400 mg [6 mg/kg] daily) [68, 69], itraconazole [70, 71], posaconazole (200 mg 3 times daily) [72], voriconazole [73], and micafungin (50 mg daily) [74]. All these agents have shown to effectively prevent invasive candidiasis, but the clinical trials have been performed in different patient populations. In prolonged neutropenia (mainly acute leukemia), posaconazole 200 mg every 8 h was superior to fluconazole or itraconazole and was associated with improved survival [72]. Studies in stem cell transplantation have not shown superiority of any antifungal prophylaxis, although agents with activity against mold have the added advantage of resulting in less *Aspergillus* infections.

Treatment

The *Candida* infections most important in Oncology are mucocutaneous (thrush and esophageal), acute disseminated

Table 24.4 Systemic agents with activity against *Candida* spp.

Antifungal agent	Adult dose for systemic candidiasis/ candidemia	Described resistant species	Evidence-supported usage
Azoles	Inhibit ergosterol synthesis. Inhibit to various degrees some cytochrome P-450 isoenzymes, with decreased clearance of several drugs important in oncology, including vinca alkaloids, cyclophosphamide, calcineurin inhibitors, and sirolimus		
Fluconazole	800 mg loading, then 400 mg/day	*C. krusei, C. glabrata*	Prophylaxis during neutropenia and oropharyngeal and esophageal candidiasis therapy of invasive candidiasis
			Urinary tract *Candida* infection
Itraconazole	Avoid initiating an oral agent in cases of systemic candidiasis	*C. glabrata* may exhibit or develop decreased susceptibility	Prophylaxis during neutropenia and stem cell transplantation, esophageal candidiasis
Posaconazole			Prophylaxis during neutropenia and oropharyngeal and esophageal candidiasis
Voriconazole	400 mg (6 mg/kg) d12h for 2 doses, then 4 mg/kg/12 h		Candidemia, oropharyngeal and esophageal candidiasis, invasive candidiasis. Prophylaxis during neutropenia
Echinocandins	Inhibit synthesis of beta-glucan, a constituent of the cell wall. Only available for intravenous administration. Few toxicities. Few significant interactions (possible interaction cyclosporine A-caspofungin). Equivalent efficacy against *Candida* spp. J-shaped in vitro growth curve inhibition for some yeasts has unknown clinical significance. All are approved for use in candidemia as well as oropharyngeal and esophageal candidiasis, invasive candidiasis		
	Prophylaxis during neutropenia in stem cell transplant		
Caspofungin	70 mg loading, followed by 50 mg daily	*C. parapsilosis* sensu strictu may be resistant	Candidemia (equivalent to AmB-d)
Micafungin	100 mg daily		Candidemia (equivalent to L-AB)
			Prophylaxis during neutropenia in stem cell transplant
Anidulafungin	200 mg loading, then 100 mg daily		Invasive candidiasis (superior to fluconazole)
Amphotericin B	Binds to ergosterol and disrupts the osmotic integrity of the fungal cell wall. Lipid formulations seem to be equally effective, less toxic		
Amphotericin B deoxycholate lipid formulations	0.5–1 mg/kg/day	*C. lusitaniae* is resistant; *C. glabrata* may exhibit decreased susceptibility	
Amphotericin B lipid formulations	3–5 mg/kg/day		

candidiasis (candidemia), and chronic disseminated candidiasis (hepatosplenic candidiasis).

Mucocutaneous Candidiasis

For mild cases of mucocutaneous candidiasis, clotrimazole troches (10 mg 5 times daily) or nystatin suspension or pastilles may be used. For moderate-to-severe disease, fluconazole (100–200 mg daily) is usually the first-line agent. Fluconazole failures can usually be successfully treated with itraconazole or posaconazole. Voriconazole and amphotericin suspension may be used when the other regimens fail. For refractory cases, echinocandins (there is no evidence that there are significant differences in terms of efficacy between the three currently available) may used, but they may also be used as first-line agents if there are contraindications (e.g., drug interactions) for the use of the other agents. Amphotericin B deoxycholate (AmB-d) 0.3 mg/kg/day is also effective.

Candidemia and Acute Disseminated Candidiasis

Only a few multicenter randomized controlled trials have compared different treatment options for acute invasive candidiasis [34, 35, 62, 63, 75–77]. The IDSA guidelines appropriately distinguish between the treatment of suspected candidiasis and the treatment of documented candidemia and further separate neutropenic from nonneutropenic patients [9], based on the fact that most controlled trials of echinocandins have included only a few neutropenic patients.

In cases of suspected candidiasis in neutropenic patients, the options include caspofungin or another echinocandin or AmB (either deoxycholate 1 mg/kg or a lipid formulation (L-AmB) 3–5 mg/kg). In patients with hypotension, severe sepsis, or septic shock, many experts would still prefer AmB. Voriconazole or fluconazole IV should be considered only if the patient was not receiving azole prophylaxis. In nonneutropenic patients, the IDSA recommends (as expert opinion only, not evidence-based) an echinocandin of fluconazole as first-line therapy,

In documented candidemia, the choice will be influenced by the prior use of azole prophylaxis as well as the particular species of *Candida*. An echinocandin, AmB, or fluconazole may all be reasonable options depending on the circumstances. Patients who were on azole prophylaxis should receive an echinocandin or AmB. Regarding species-specific recommendation, for *C. glabrata* and *C. krusei* most experts would choose an echinocandin; *C. parapsilosis* is less susceptible in vitro to echinocandins, and in some trials, a disproportionate amount of the echinocandin failures were caused by this species.

The need to remove the intravenous catheter in neutropenic patients with candidemia has been questioned, based on the fact that the catheter may not be the portal of entry (as opposed to ICU-acquired candidemia, in which the catheter is usually to blame and should routinely be removed) [10]. However, in cases of candidemia, we usually remove and replace intravascular catheters when feasible [78].

Chronic Disseminated Candidiasis

Most successful experience in chronic disseminated candidiasis has been with AmB [79, 80] or fluconazole [81, 82]. Echinocandins have also reported to be successful [83, 84]. Accordingly, all these are endorsed by the IDSA as acceptable options for the treatment of this disease. The emphasis is on the prolonged duration of treatment (until resolution of the lesions, usually weeks) and the need for continued treatment during subsequent episodes of immunosuppression or neutropenia [9].

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Chapter 25
Management of Aspergillosis, Zygomycosis, and Other Clinically Relevant Mold Infections

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Abstract Invasive mold infections (IMIs) are a major cause of morbidity and mortality in severely immunocompromised hematologic malignancy patients and hematopoietic stem cell transplantations recipients. Invasive aspergillosis caused by *Aspergillus fumigatus* is the most common cause of IMI, but recent advances in the pharmacotherapy of fungal infections and an increase in the number of patients at risk have caused an epidemiologic shift towards infections with resistant non-*fumigatus Aspergillus* species and non-*Aspergillus* molds such as Zygomycetes. Patient outcome is a function of immune function recovery, early diagnosis, and multiple interventions, such as with broad-spectrum antifungal therapy and adjunct immunotherapy and surgery in select patients. In this chapter, we review the utility of new diagnostic modalities such as the galactomannan test, the 1,3-beta-D-glucan test, and fungal DNA tests in diagnosing IMIs early. We focus on modern antifungal agents (the lipid formulations of amphotericin B, the broad-spectrum azoles, and the echinocandins) and evaluate them in the context of evolving prophylactic, preemptive, and targeted therapies for IMIs.

Keywords Aspergillosis • Zygomycosis • Invasive mold infections • Prophylaxis • Prevention • Treatment

Brief Review of the Evolving Epidemiology of Invasive Mold Infections

Recent advances in oncology and transplantation have led to prolonged survival in critically ill and severely immunocompromised cancer patients. However, these patients' pleiotropic and profound immune defects (Table 25.1) have led to the emergence of invasive fungal infections (IFIs) and specifically invasive mold infections (IMIs) [1, 2].

Since the 1990s, the widespread use of fluconazole for antifungal prophylaxis has decreased the incidence of candidiasis, but increased the incidence of IMIs, especially aspergillosis. Invasive aspergillosis (IA) remains a leading cause of death in leukemia patients and stem cell transplantation (SCT) recipients, although recent reports have documented a decreasing mortality rate, perhaps reflecting earlier diagnosis and the use of voriconazole-based regimens [3, 4]. An alarming swift in the epidemiology of IA is the increasing incidence of non-*fumigatus Aspergillus* spp. that are resistant to antifungals like *A. terreus* and *A. ustus* [5, 6]. In addition, there is an increase in the incidence of uncommon and difficult-to-treat opportunistic molds such as Zygomycetes, *Fusarium* spp., *Scedosporium* spp., and phaeohyphomycetes [7, 8]. Zygomycosis in particular has emerged as a superinfection in patients on voriconazole, a broad-spectrum triazole that has no activity against Zygomycetes [9]. Voriconazole is the preferred agent for treatment or perhaps prophylaxis against IA in many hematology centers. This opportunistic mycosis poses a great challenge as it manifests clinical similarly to IA, there is no reliable method of early diagnosis, and delayed treatment that has activity against Zygomycetes is associated with a dire clinical outcome [10]. The decreasing autopsy rates in hematology units – at our center, current rates approach 7% in the leukemia and SCT units (K. Leventakos and D.P. Kontoyiannis, unpublished data) – disguise the true incidence of IFIs and IMIs. In addition, this vanishing "gold standard" makes it difficult to reliably assess the true utility of new diagnostics and therapies.

Diagnostic Criteria and Novel Diagnostics

Substantial delays in diagnosing IMIs remain a major impediment to their successful treatment. Recently, the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National

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Table 25.1 Risk factors for IFIs in HSCT recipients.

- History of IFI, especially IA or chronic systemic candidiasis, prior to transplantation
- History of ongoing steroid therapy or steroid therapy prior to BMT
- Underlying hematologic malignancy (AML, malignancy not in remission)
- Allogeneic transplantation (with unrelated cord blood recipients at highest risk)
- Duration of neutropenia >20 days
- Age >40 years
- History of cytomegalovirus disease or cytomegalovirus reactivation
- Colonized with fungi such as *Aspergillus* spp., *Fusarium* spp., zygomycetes, *Scedosporium* spp., and *Candida tropicalis*
- GvHD grade III or IV

Institute of Allergy and Infectious Diseases Mycoses Study Group revised their definitions of invasive fungal disease [11]. The revised definitions retain the original classifications of "proven," "probable," and "possible" IMIs. For most conditions, proven infections require proof of hyphal elements in diseased tissue. To characterize a case as probable, a host factor, clinical features, and a mycologic or nonculture-based surrogate marker (e.g., galactomannan, beta-glucan, or as determined by polymerase chain reaction [PCR]) must be present. Possible invasive fungal disease is more strictly defined to include patients with the appropriate host factors and sufficient clinical evidence of invasive fungal disease, but no mycologic evidence. For rare molds, the isolation of fungus in respiratory secretions, skin, and blood is not synonymous with invasive disease. Most such cases represent contamination or colonization, even among high-risk patients [8, 12]. For example, in our recent experience with the significance of the isolation of black molds at MD Anderson Cancer center, most of the cases did not represent infections [8].

In clinical practice, conventional diagnostic methods based on histologic evaluation and culture remain the cornerstones for diagnosing IMIs [13]. Cultures allow for speciation and susceptibility testing, which may provide useful treatment information. Invasive procedures such as biopsy may be required, but they may not be feasible in patients who are clinically unstable or severely hypoxic (in the case of bronchoscopy) or who have low platelet counts. Even when biopsy is feasible, it may not provide a specific diagnosis when culture remains negative as occurs in almost 50% of cases [14]. In addition, *Fusarium*, *Scedosporium*, and *Acremonium* spp. have histologic characteristics that cannot be distinguished from those of IA. In situ hybridization directed against ribosomal 18S RNA sequences can rapidly and accurately distinguish between these species [15]. Recent efforts have been oriented towards identifying a nonculture-based marker for rapid, reliable diagnosis. Thus, the identification of fungal antigens, metabolites, and DNA has enhanced current diagnostic modalities.

The galactomannan assay is the most studied of new diagnostic tests. Galactomannan is a heat-stable heteropolysaccharide that is released from the cell wall during hyphae growth in tissues. A double-sandwich enzyme-linked immunosorbent galactomannan assay (galactomannan detection threshold at concentrations as low as 0.5 ng/mL) has been approved by the U.S. Food and Drug Administration for use with serum samples [16]. False-positive results have been described in patients receiving beta-lactam antibiotics. Variables that reduce the fungal load and consequently reduce the levels of circulating galactomannan, such as antifungal prophylaxis and treatment, can alter the results [17, 18]. Galactomannan can be detected in bronchoalveolar fluid, urine, and cerebrospinal fluid, but these approaches have not been standardized.

1,3-beta-D-glucan is an integral cell-wall component in a number of pathogenic yeasts and filamentous fungi (exceptions include Zygomycetes, *Cryptococcus* spp., and *Trichosporon* spp.). A sensitive (1 pg/mL) colorimetric beta-glucan detection assay is now commercially available. The presence of beta-glucan in serum indicates the presence of fungal invasion, but it is not species-specific [19, 20]. False-positive results can occur in dialysis patients, immunoglobulin recipients, those exposed to glucan-containing gauge, and those treated with certain antimicrobials. It has been reported that the combination of galactomannan and beta-glucan improves the specificity (to 100%) and sensitivity (to 100%) of each test in high-risk hematologic patients by identifying false-positive reactions [20].

PCR – usually by amplifying ribosomal fungal DNA – has been regarded as a promising method of early detection of IA. One of the advantages of PCR is the capability of rapid detection and molecular identification of opportunistic molds besides *Aspergillus* [21]. However, these diagnostic platforms have not been standardized; thus they remain investigational.

Radiologic methods play a pivotal role in diagnosing IMIs [22]. Computed tomography (CT) findings – the most important being the "halo sign" and "air crescent sign" – have facilitated the diagnosis of pulmonary IMIs. The halo sign is highly specific for acute IA in severely neutropenic patients, but its sensitivity is low; it is also transient: 75% of initial halo signs disappear within a week [22, 23]. It has been reported that a positive halo sign may be associated with a better outcome in IA as it is a marker for early suspicion of and early therapy of IA [24, 25]. The radiologic distinction between IA and zygomycosis in high-risk leukemia or SCT patients is important because of the lack of reliable serologic methods for diagnosing zygomycosis. Single-institution retrospective studies have shown that the "reverse halo sign" and the presence of sinusitis, pleural effusion, ten or more lung nodules or reverse halo sign on chest CT are suggestive of zygomycosis [26, 27].

Current Systemic Antifungals with Mold Activity

Amphotericin B and its Lipid Formulations

Amphotericin B (AMB) is a broad-spectrum fungicidal polyene that has in vitro activity against most molds (the rare exceptions include *A. terreus*, *Fusarium solani*, and *Scedosporium* spp.). The common dose-limiting renal and infusion-related toxicities of D-AMB, an agent that has been in use for over 50 years, led to the introduction of three lipid formulations of AMB (LF-AMB): AMB lipid complex (ABLC), AMB colloidal dispersion, and liposomal AMB (L-AMB). All LF-AMBs have reduced nephrotoxicity compared with D-AMB because they functionally spare the kidneys [28]. IMI patients typically require prolonged therapy; these agents are preferred for systemic AMB-based therapy in high-risk cancer patients. Although no comparative trials between the lipid formulations of AMB and D-AMB in IMIs have been conducted, LF-AMBs appear to be equally efficacious and they are clearly less toxic than D-AMB.

An even more controversial issue is whether there are clinically meaningful differences between the various LF-AMB as there are, based mostly on preclinical data, differences with respect to the rate and extent of drug delivery to the respiratory tract, the most common site of involvement in IMIs. Specifically, ABLC results in substantially higher drug concentrations in lung tissue when compared with L-AMB; therefore, ABLC may result in more rapid and complete *Aspergillus* killing [29]. The current role of the LFABs in the treatment of IMIs remains significant because of their broad tissue distribution and spectrum that makes them favorable for preemptive strategies and for targeted therapies in a variety of documented IMIs progressing on a triazole or echinocandin-based therapy [30].

Second-Generation Triazoles

Voriconazole is an orally and intravenously available azole with high bioavailability (over 90%) and broad tissue distribution [31]. Voriconazole inhibits cytochrome P-450 14a-demethylase, which is an enzyme of the sterol biosynthesis pathway; it has a broad spectrum of activity against a variety of pathogenic molds, with the notable exceptions of Zygomycetes and *Scedosporium prolificans*. The drug is metabolized in the liver by CYP540; CYP540-inhibiting and -inducing agents and pharmacogenetic differences (e.g., idiosyncratic variations due to CYP2C19 polymorphisms) may dramatically change the drug's pharmacokinetics. Because of voriconazole's complex metabolism, dose-related toxicities, and

narrow therapeutic range, researchers have investigated the utility of therapeutic drug monitoring of voriconazole [32]. Even though the current data cannot establish a therapeutic range of voriconazole, a low level in a patient who does not respond to voriconazole therapy should lead to an increase of the regimen [33]. Common side effects of voriconazole include transaminase elevation and visual disturbances [34]. The latter is a rather unique side effect of voriconazole and is reversible upon discontinuation of the drug.

Posaconazole, an orally available analog of itraconazole, has the same mechanism of action as other azoles. On the basis of data from preclinical and salvage studies, posaconazole has an impressive spectrum of activity against molds, including Zygomycetes [35]. Its availability only as an oral formulation (it cannot be used in severely ill patients in the intensive care unit or in patients with gastrointestinal dysfunction) and poor absorption in undernourished patients or patients with mucositis are major limitations of its use. When posaconazole is administered after a high-fat meal, its bioavailability increases by 400%; thus, patients are strongly advised to take posaconazole after a good meal [36]. It is well tolerated and has few side effects, and it has a narrower drug interaction profile than voriconazole because it only inhibits CYP3A4 [37]. Limited data reveal an association between low posaconazole serum levels and suboptimal treatment outcome; that and posaconazole's unpredictable absorption support the use of routine therapeutic drug monitoring in some patients.

Validated assays have been developed for the new generation of triazoles and the results of several clinical trials suggest that therapeutic antifungal drug monitoring can be useful for reducing drug toxicity and optimizing efficacy. Further studies are needed to determine optimal timing of monitoring, to refine concentration goals, and to better delineate targeted monitoring for specific patient populations and clinical scenarios [38].

Echinocandins

The echinocandins inhibit (1,3)-beta-D-glucan synthase, which is the key enzyme for the production of beta-glucan, a critical component of the cell wall of many medically important fungi [39]. This inhibition results in disruption of the growing cell wall and the death of susceptible cells [40]. Laboratory ex vivo data support the immunopharmacologic mode of echinocandin action that enhances phagocytosis of fungal hyphae by means of beta-glucan unmasking [41]. All three Food and Drug Administration-approved echinocandins (caspofungin, micafungin, and anidulafungin) are water-soluble and are only available intravenously. They have linear pharmacokinetics, and because they are not CYP450

substrates or inhibitors, they have no drug–drug interactions, unlike members of the azole family [42–44]. This class of antifungals is extremely well tolerated, which is consistent with their unique, fungus-specific mechanism of action. All three echinocandins have a limited spectrum of activity in vitro against non-*Aspergillu*s molds.

IMI Prevention and Prophylaxis

Reports on nosocomial outbreaks of IMIs have linked cases to hospital construction, the absence of appropriate barriers between patients and the environment, and the presence of fungal spores in room air samples [45, 46]. A meta-analysis of 16 controlled trials found that HEPA filtration had no effect on mortality in neutropenic patients with hematologic malignancies and SCT recipients. Protected environments appeared to be beneficial, but there were insufficient data to support definite conclusions [47]. The Centers for Disease Control recommends the use of HEPA filters in allogeneic SCT recipient patients' rooms [48].

The optimal antifungal prophylactic has been an evolving issue, perhaps reflecting the introduction of several new agents in the clinical practice (Table 25.2). The emergence of IA in the last two decades necessitates the use of mold-active prophylaxis or fluconazole prophylaxis combined with effective surveillance (e.g., based on periodic galactomannan measure-

Table 25.2 Options for prophylactic use of antifungal drugs in HSCT recipients

No risk factors for IMIs

- *Autologous HSCT*: fluconazole (200–400 mg/day) starting at day 0 until the resolution of neutropenia and mucositis
- *Allogeneic HSCT*: fluconazole (400 mg/day) starting at day 0 for 75 days in myeloablative and nonmyeloablative allograft recipients

Risk factors for IMIs (only for allogeneic HSCT)

- *Voriconazole*: patients in whom *Aspergillus* (and *Candida* and other rare fungi) but not Zygomycetes is a major consideration, such as lack of iron overload, lack of concomitant diabetes, lack of infliximab for GvHD, and lack of prolonged prior exposure to voriconazole, but who have a history of cytomegalovirus reactivation or aspergillosis
- *Posaconazole*: patients in whom *Aspergillus* and Zygomycetes (and *Candida* and other rare fungi) are major considerations, such as iron overload, concomitant diabetes, chronic corticosteroids or infliximab for GvHD, recent cytomegalovirus reactivation, and prior prolonged exposure to voriconazole. Ambulatory patients with severe liver dysfunction or who experience intolerance to or prohibitory drug interactions with voriconazole (e.g., severe rash)
- *Echinocandins* (e.g., 50 mg/day of caspofungin intravenously): hospitalized or ambulatory patients in whom Zygomycetes is not a major consideration and who have severe liver dysfunction or experience intolerance to or prohibitory drug interactions with voriconazole or posaconazole
- *L-AMB* (2 or 3 times a week): patients who cannot take oral mold-active azoles or intravenous echinocandins and have normal renal function

ments and/or chest CT) to detect IA early [49]. Which of these two strategies is the most effective in specific patient subgroups is unknown. In addition, we do not know which antifungal agents and delivery methods (oral, inhaled, or intermittent intravenous) are the most effective. In a multicenter, randomized, nonblinded study, an echinocandin (micafungin) was found to be more effective than fluconazole [50]. In this study which has been questioned about the choice of study population and the prophylactic period length, micafungin was found to have superior efficacy. The lack of large comparative studies, the IV-only formulation of echinocandins, and reports for breakthrough mold infections makes echinocandins' role in prophylaxis needing more research [51].

Lipid formulations of AMB as prophylaxis have been tried either as daily administration, weekly, or twice weekly schedules. These agents' "depot" pharmacokinetic characteristics and long elimination times make them attractive for intermittent prophylaxis, avoiding the unreliability of azole-based oral prophylaxis in selected patients. The need for definite conclusions regarding safety and efficacy, since all current data come from noncomparative studies, can be answered by a well-developed randomized trial [52]. A recent study evaluated the effectiveness of aerosolized L-AMB in patients who at the same time were on fluconazole [53]. Fewer patients in the aerosolized prophylaxis arm developed IA; the most common reason for treatment discontinuation was cough. Further research is needed on the safety and efficacy of aerosolized polyenes.

In one study, prophylactic posaconazole was similar to fluconazole for prophylaxis against fungal infections among patients with graft-versus-host disease (GvHD) in overall mortality. Posaconazole was superior in preventing IA and reducing the rate of deaths related to fungal infections [54]. In a substudy of posaconazole pharmacokinetics in the GvHD population, patients with symptomatic diarrhea during acute GvHD had lower serum drug levels and tended to be more prone to infections due to their lower levels [55]. In another study of patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome, posaconazole prevented IFIs more effectively than did either fluconazole or/and itraconazole and improved overall survival [56]. These two studies' results are reflected in the most recent Infectious Diseases Society of America (IDSA) recommendations on prophylaxis in these patient groups [13]. According to these guidelines, antifungal prophylaxis with posaconazole can be recommended in HSCT recipients with GvHD who are at high risk for IA aspergillosis and in patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for IA. Prophylactic voriconazole was also compared with fluconazole and galactomannan monitoring in a large randomized trial in allogeneic SCT recipients. Both agents were administered for at least 100 days after allogeneic SCT [56, 57]. Fewer IFIs, especially IAs, were found in the voriconazole arm of this study, although

IFI rates were generally low because the population was at low or intermediate risk. Furthermore, the total mortality rates did not differ between the two arms of the study.

The use of second-generation azole as mold prophylaxis in high-risk patients is gaining acceptance, even though these drugs are more complicated to administer than is fluconazole. Issues that arise and need to be answered by future prospective studies are the need of therapeutic drug monitoring of these drugs and the changing validity of blood-based diagnostic assays because mold-active prophylaxis reduces their sensitivity [18]. In the current era of mold-active prophylaxis, it is needed to define which patients need to be covered with mold-active prophylaxis (and for how long) and which patients have less risk so that fluconazole is adequate as prophylaxis. Nevertheless, close evaluation for breakthrough infections is warranted for these patients. Finally, the increased survival of IMI patients in the setting of continuous immunosuppression necessitates secondary prevention strategies. For example, experience and data on the best treatment for relapsing IA are lacking. The high mortality rate of patients with relapsing IA shows that aggressive approaches (e.g., rapid tapering of immunosuppression, using a low threshold for switching to investigational antifungals, and antifungal therapy plus immune restoration strategies) are needed [58].

Empiric and Preemptive Therapy

The effectiveness of empiric antifungal treatment of neutropenic fever was documented in prospective randomized trials. L-AMB, voriconazole, and caspofungin were effective treatments in high- and low-risk patients with persistent febrile neutropenia [59–61]. A comprehensive strategy for this use of antifungal drugs is shown in Fig. 25.1. It is unclear whether the indiscriminate empiric use of antifungals or a measured approach that includes risk stratification, early use of chest CT, and nonculture serologic diagnostic (e.g., galactomannan assay or PCR) is the most efficacious, least toxic, and most cost-effective. The available options for the usage of antifungal drugs for preemptive therapy are shown in Table 25.3. A large randomized, nonblinded, European study (PREVERT trial) [62] did not show that preemptive approach is clinically more useful and more cost-effective compared to the traditional empiric approach. Future studies are needed that stratify patients by risk and use more sensitive methods for early diagnosis. There is no question that early antifungal therapy triggered by the detection of halo sign, an early radiologic marker of IA, is associated with better outcomes [24, 63, 64]. In addition, a single-institution retrospective study showed that a 1-week treatment delay of effective treatment compared with early treatment doubled the mortality rate in a case series of 35 patients with zygomycosis [10].
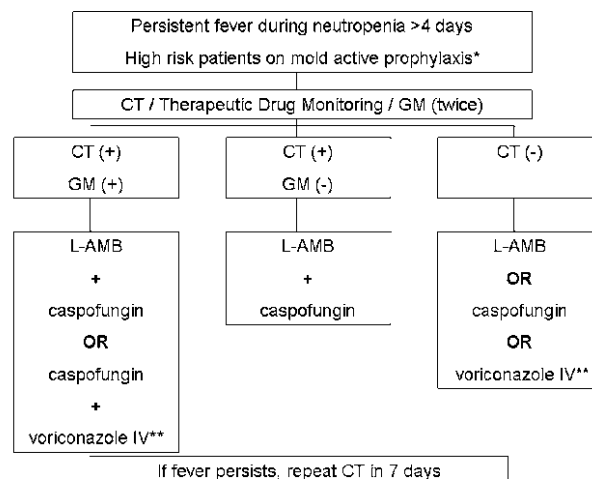
Fig. 25.1 Empiric management of fever in neutropenic SCT patients: use of antifungal drugs

Table 25.3 Options for preemptive therapy of IFIs

For suspected pulmonary mold infections	Voriconazole because *Aspergillus* is the most common mold infection, unless there are contraindications or a suspicion of voriconazole-resistant mycosis (e.g., zygomycetes infection)
	• 5 mg/kg/day of LF-AMB
	• Appropriate clinical and radiographic follow-up (including bronchoalveolar lavage or biopsy) coordinated with the infectious disease and pulmonary teams
Febrile BMT patients with twice-positive galactomannan assay results and no other signs or symptoms of infection	Trial of antifungal therapy (voriconazole, caspofungin LF-AMB) with an infectious disease consult
Patients on high-dose steroids for diffuse alveolar hemorrhage or idiopathic pulmonary syndrome[a]	Mold-active azoles such as voriconazole or itraconazole

[a]Rationale: patients with diffuse infiltrates early after transplantation who are negative for infection (on bronchoalveolar lavage or biopsy) are at high risk for subsequent mold infections because they are often treated with high doses of corticosteroids (4 mg/kg/day)

Targeted Therapy for Selected IMIs

Aspergillosis

Voriconazole has emerged as the preferred therapy for IA on the basis of results from a pivotal, large randomized nonblinded study comparing voriconazole with AMB-D (1–1.5 mg/kg/day) in 144 patients with documented IA [64].

This recommendation has been endorsed by several organizations, including the IDSA [13]. L-AMB was also endorsed as an effective alternative primary therapy on the basis of the results of a recent double-blind prospective trial that randomly assigned neutropenic leukemia patients to 3 or 10 mg/kg/day for 14 days, followed by 3 mg/kg/day (AmBiLoad trial) [63]. No statistically significant differences in the overall treatment response were found between the standard and high-dose regimens, but nephrotoxicity and hypokalemia were more common in the high-dose group.

The interest in combination antifungal therapy as primary therapy for IA developed from the observation that the preferred first-line drug, voriconazole, has failure rates approaching 70% in high-risk patients such as SCT recipients [64]. Therefore, it seems that there is much room for improvement, and the early administration of combined antifungal drugs may become an important treatment for IA [65]. A large randomized study is underway evaluating voriconazole plus placebo to anidulafungin plus voriconazole in patients with documented IA. This study hopefully will shed light on the true benefit of combined azole-echinocandin-based primary therapy.

Meanwhile, there are two points of special interest that should be noted in relevance to voriconazole-based combinations as primary therapy. Because voriconazole is used as front-line therapy for IA, it cannot be assumed that the combination of caspofungin and voriconazole will be effective in patients who do not experience a response to voriconazole. In addition, given the emergence of breakthrough Zygomycetes infections in patients undergoing voriconazole prophylaxis or empirical treatment, specific diagnoses are particularly important in high-risk patients because zygomycosis has a similar manifestation to that of IA. Similarly, the combination of an echinocandin and LF-AMB is unclear in IA. The results of small single-institution retrospective studies suggest that LF-AMB and caspofungin are effective against IA, especially as primary therapy [66]. A small prospective, randomized study comparing high-dose L-AMB (10 mg/kg/day) with low-dose L-AMB (3 mg/kg/day) and caspofungin in 30 IA patients (24 probable and six proven) (Combistrat trial) showed that combination therapy was associated with a better (but not statistically significant) response [67]. However, no firm conclusions could be drawn because of the small sample size and the undocumented status of most cases. In addition, it is unclear whether the combination of LF-AMB and echinocandin is beneficial in patients with IA that is refractory to LF-AMB given as monotherapy. Similar results were obtained in our retrospective study [68] and a recent observational prospective study of micafungin plus L-AMB in SCT patients with refractory IA [69]. It can be concluded that combination therapy for IA cannot be widely recommended; therefore, physicians should consider it on a case-by-case basis, accounting for clinical and laboratory evidence.

The effectiveness of salvage antifungal therapy is not known in patients with IA that is refractory or intolerant to voriconazole. Single-institution retrospective salvage studies have evaluated the combination of voriconazole and caspofungin [70]. A multicenter observational study assessed the effectiveness of caspofungin combined with other antifungal drugs in 53 patients with IA that was intolerant or refractory to front-line therapy. The combination of caspofungin and voriconazole resulted in a successful outcome in 54% of patients [71]. The complexities and biases in salvage therapy trials preclude firm recommendations. Combination antifungal therapy or immunotherapy with an LF-AMB, caspofungin, or posaconazole can be used [13].

Zygomycosis

Early diagnosis of zygomycosis is crucial because delayed AMB-based therapy results in poor clinical outcomes [10]. Posaconazole salvage therapy is promising. In a retrospective study that included 91 patients with zygomycosis, the rate of success (i.e., either complete or partial response) at 12 weeks after treatment initiation was 60% [72]. In a nonrandomized, multicenter, compassionate trial that evaluated oral posaconazole as salvage therapy for zygomycosis, the overall survival rate was 79%; survival was also associated with surgical resection of affected tissue and stabilization or improvement of the underlying illness [73]. In a recent study of diabetic patients with rhino-orbital-cerebral mucormycosis treated with combination polyene-caspofungin therapy, patients treated with ABLC and caspofungin had superior success [74]. Advances in our understanding of iron metabolism's role in zygomycosis pathogenesis have led us to use nondeferoxamine iron chelators, such as deferasirox, in combination treatment [75–77]. An open label trial of deferasirox and L-AMB is currently underway to assess their safety and tolerability (DEFEAT Study).

Fusariosis, Phaehyphomycosis, and Scedosporiosis

The rarity and opportunistic nature of fusariosis, phaehyphomycosis, and scedosporiosis prevent us from determining the optimal treatment regimen and precludes an organized experience for the treatment. Azole-based therapy (voriconazole and posaconazole) provides the best chance for survival, with or without LF-AMB, reduced immunosuppression, and adjunct immunotherapy (e.g., donor white blood cell transfusions [78]).

Summary

We have witnessed important advances in the treatment of IMIs during the last decades. The population at risk is continuously increasing, and the spectrum of emerging pathogens is endlessly expanding. Fortunately, our antifungal armamentarium includes newer antifungal drugs, and we have entered an era in which more sophisticated prophylactic and preemptive strategies and combination therapies can be tailored for patients on the basis of their unique epidemiologic characteristics and risk factors. Indeed, these new therapies will be tested in clinical trials that will establish evidence-based standards of care for patients with IMIs.

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Chapter 26
Cryptococcal Disease and Endemic Mycosis

Johan A. Maertens and Hélène Schoemans

Abstract *Cryptococcus* and the endemic fungi (*Histoplasma*, *Blastomyces,* and *Coccidioides*) can cause severe, even life-threatening, pulmonary and extrapulmonary disease in immunocompromised patients, including cancer patients and transplant recipients. This chapter describes the epidemiology, clinical manifestations, diagnosis, and treatment of these infections in patients with prolonged immunodeficiency.

Keywords Cryptococcus • Cancer • Immune suppression • Histoplasmosis • Blastomycosis • Coccidioidomycosis

Cryptococcal Disease

Cryptococcosis, a potentially life-threatening invasive fungal disease caused by the encapsulated, nonmycelial budding yeast, *Cryptococcus neoformans*, is a common opportunistic infection in acquired immunodeficiency syndrome (AIDS) patients and solid organ transplant recipients, but remains a relatively uncommon disease in patients with malignancy [1, 2]. This fungus is widely distributed worldwide and is particularly abundant in soil contaminated by pigeon droppings. In general, incidence rates below 2% have been found at autopsy surveys in cancer patients [3]. This low incidence can be partially due to the widespread use of azole prophylaxis (in particular fluconazole) and the routine empirical use of antifungals in many cancer patients at risk for cryptococcosis. As a consequence, most (retrospective) studies consist of case reports or small case series only. Hence, many aspects of the epidemiology and clinical features of cryptococcosis in cancer patients remain poorly documented.

The majority of *Cryptococcus* infections in immunocompromised patients are caused by *C. neoformans* var. *grubii* (serotype A) or var. *neoformans* (serotype D). *Cryptococcus gattii* (previously *C. neoformans* serotypes B and C) is responsible for a smaller proportion of cases, often in otherwise healthy immunocompetent patients in distinct geographic locations (northern Australia and Papua New Guinea and more recently Vancouver Island) [4]. Exposure to this ubiquitous environmental fungus is common, with the majority of people being exposed by the age of 5 years. Inhalation of basidospores is thought to be the primary portal of entry. Person-to-person transmission does not occur. Upon inhalation, these pathogens may be cleared, may be retained as dormant living yeast within pulmonary lymph nodes (similar to that of tuberculous), or may disseminate, depending on host immune response, virulence of the organism, and size of the inoculum. Cell-mediated immunity plays a critical role in the host defense and protective pulmonary inflammatory responses are dependent on interferon-gamma and tumor necrosis factor-α, leading to a Th1-weighted immunity [5].

Prior to the AIDS epidemic, only approximately 300 cases of cryptococcosis had been reported in the medical literature. Historically, cryptococcosis has typically been described in cancer patients with impaired T-cell immunity (e.g., patients with Hodgkin's disease) or in patients who received high doses of corticosteroids or purine analogs. As a result, patients with hematological malignancies, especially lymphoma and chronic leukemia, were predominant in older series [6, 7]. More recently, novel immunosuppressive monoclonal antibody therapies have been reported as emerging risk factors, including the use of infliximab, efalizumab, adalimumab (an anti-TNF-α monoclonal), and alemtuzumab, an anti-CD52 monoclonal that causes profound CD4 lymphopenia and that is used in the treatment of chronic B-cell malignancies, T-cell malignancies and solid organ transplants, and the use of antithymocyte globulin (ATG) [8, 9].

Clinical findings in cryptococcosis are generally caused by pulmonary and neurologic abnormalities, although the fungus can disseminate to virtually all organs of the body, including prostate and eye [10]. In addition, underlying immunodeficiencies (e.g., use of steroids) may attenuate the clinical signs and symptoms of cryptococcosis [10]. The onset of symptoms in immunocompromised patients is generally subacute, but rapidly progressive disease may occur [10, 11].

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Meningitis or meningoencephalitis and pulmonary cryptococcosis are the predominant manifestations in cancer patients [10].

Central nervous system cryptococcosis commonly results from dissemination from the lungs and usually presents as subacute meningitis with prominent neurological symptoms and defects. Patients frequently complain of unbearable headache, with or without fever. Other features include seizures, vomiting, visual disturbances, altered sensorium, hemiparesis, hemisensory signs, and cranial neuropathies [12]. These findings should always raise suspicion of cryptococcosis and need to be differentiated from other causes of meningitis, including tuberculous meningitis and carcinomatous or lymphomatous meningitis. Diagnosis of cryptococcosis with CNS involvement is based on positive *Cryptococcus* antigen titer, culture, or visualizing the organism by India ink staining of cerebrospinal fluid (CSF) [12]. *Cryptococcus* antigen testing (by latex agglutination test or ELISA) is almost always positive, except very early in the course of the disease (low fungal burden) and in certain patients with cryptococcomas [13]. However, a positive CSF culture remains the gold standard. Routine antifungal susceptibility testing is of little value because primary resistance is rare and cut-offs for susceptibility remain ill-defined. Neuro-imaging, computed tomographic (CT) scan, or preferably magnetic resonance imaging (MRI) of the brain with contrast should be carried out in all patients with cryptococcal meningitis to rule out space-occupying lesions [14]. A lumbar puncture with manometry is also highly recommended [15].

Cryptococcosis is an emerging respiratory mycosis and many HIV-negative patients infected with *Cryptococcus* will present with signs of pulmonary involvement [5]. However, the nonspecific constellation of symptoms of pulmonary disease, including fever, (dry) cough, chest pain, weight loss, dyspnea, night sweats, and hemoptysis, makes a differential diagnosis with other pulmonary conditions (e.g., tuberculous or lung metastasis) in cancer patients difficult. In some cases, pulmonary cryptococcosis may result in respiratory failure. The radiographic features of pulmonary cryptococcosis are clearly influenced by the underlying immune status of the patient [5]. Findings are nonspecific and can broadly be categorized into (1) solitary or multiple smooth or spiculated pulmonary nodules; (2) focal or multifocal consolidations; and (3) diffuse interstitial infiltrates. Lymphadenopathy and pleural effusions have also been reported. Diagnosis of pulmonary cryptococcosis requires culture and identification of the organism from a pulmonary specimen, and ideally, histopathologic evidence of tissue invasion. Sputum samples are the most readily obtainable samples, but are limited by decreased sensitivity. Invasive diagnostic procedures such as bronchoscopy with bronchoalveolar lavage (BAL), transbronchial biopsy, or percutaneous or open-lung biopsy will result in a higher diagnostic yield. *C. neoformans* will grow

on most bacterial and fungal culture media within 2–7 days [16]. Earlier studies have demonstrated that cryptococcal antigen testing of BAL samples (titer >1:8) was a very effective tool for diagnosing cryptococcal pneumonia [17].

Cryptococcus species are not considered normal respiratory flora in humans. Hence, especially among immunocompromised cancer patients, isolation from a respiratory sample must be considered significant. In these cases, a thorough search for dissemination and an accurate evaluation of fungal burden should be started, including serum cryptococcal antigen testing, fungal blood and urine cultures, and examination of CSF. Serum cryptococcal antigen detection (a titer of ≥1:4) is very accurate for diagnosing disseminated disease. In patients with cryptococcal meningitis, antigen positivity will be found in more than 90% of the tested CSF samples and in more than 80% of the tested serum samples. However, the diagnostic utility of the serum test is limited in patients with isolated pulmonary disease.

More unusual presentations of cryptococcosis include cryptococcemia, mimicking candidemia, and cryptococcal cellulitis, mimicking nonspecific panniculitis.

All infected immunocompromised patients, HIV-positive and HIV-negative, should receive antifungal therapy, even if they are asymptomatic. In addition, all these patients should have serum antigen titers obtained and a lumbar puncture performed with CSF cultures and antigen titers to determine CNS involvement. The goal of antifungal treatment in cryptococcal disease is to prevent dissemination, to sterilize infected tissue, and to prevent recurrence. Clearly, successfully achieving these goals will be closely related to the host immunity; therefore, different approaches have been recommended for immunocompromised and immunocompetent patients.

Recommendations for antifungal therapy of cryptococcosis in non-HIV-infected cancer patients are hampered by the paucity of data. However, given the high risk of fungal dissemination in all immunocompromised patients (albeit predominantly studied in HIV-positive patients), we still recommend an induction course of antifungal therapy, followed by consolidation and maintenance treatment [18]. Amphotericin B deoxycholate (0.7–1.0 mg/kg/day) plus flucytosine for 2 weeks remains the mainstay of induction therapy in most immunocompromised patients. A recent randomized controlled trial showed that high-dose amphotericin B deoxycholate (1 mg/kg/day) was significantly more rapidly fungicidal than standard-dose amphotericin B (0.7 mg/kg) in HIV-patients with meningitis [19]. In the context of preexisting renal impairment or concomitant use of nephrotoxic drugs (e.g., calcineurin inhibitors), substitution with liposomal amphotericin B (3–4 mg/kg) or amphotericin B lipid complex (5 mg/kg) is preferable. In addition, flucytosine, given at a dose of 100 mg/kg (orally or intravenously), remains the agent of choice for use in combination with

amphotericin B. Although many hemato-oncologists are hesitant to use flucytosine in cancer patients, particularly given its myelosuppressive properties, lack of flucytosine in the induction phase was independently associated with mycological failure at 2 weeks in a large prospective study in France in HIV-positive and HIV-negative patients [20]. Furthermore, less than 14 days of flucytosine therapy was independently associated with treatment failure at 90 days [21]. Although fluconazole (400 mg/day) is recommended as initial therapy for nonsevere, nonmeningeal disease [18], we still recommend initial therapy with amphotericin B and flucytosine for all cancer patients, especially in view of the poor outcomes seen in patients with initial dissemination. This combination induction therapy is then followed by consolidation with oral fluconazole 400–800 mg/day for a minimum of 8 weeks. Finally, in HIV-positive patients, fluconazole maintenance therapy (200 mg/day) is usually given for 6–12 months, depending on the CD4 cell count. The need for prolonged maintenance prophylaxis in HIV-negative patients is less clear-cut; the decision to discontinue should be based on host immune recovery and improvement in clinico-radiological findings. For instance, in a series from the MDACC, most patients did not receive more than 4 months of therapy [1]. The newer triazoles, voriconazole and posaconazole, have a role in the salvage setting. Echinocandins are not effective against cryptococcosis and therefore should not be used.

More recently, clinical research is focusing on the use of adjunctive immunotherapies, in particular the use of recombinant interferon-gamma, and on the use of heat shock protein 90 antibodies. Another important part of the integrated approach is the management of raised CSF pressure associated with cryptococcal meningitis, often requiring serial lumbar punctures or the (temporary) placement of shunts. Finally, cryptococcal immune reconstitution syndrome (IRIS) has also been reported in HIV-negative patients, including solid organ transplant recipients following tapering of immunosuppressive drugs and following T-cell recovery after alemtuzumab therapy. If IRIS patients deteriorate despite maintained antifungal therapy and controlled CSF drainage and if no alternative diagnoses have been found, a short course with corticosteroids may proof useful [18].

The outcome of cancer patients with cryptococcosis is ill-defined. A study from MSKCC found a significantly worse outcome for cancer patients than for HIV-infected patients [22] and a French study found underlying cancer to be the strongest predictor of fatal cryptococcosis among HIV-negative individuals [23]. However, a more recent case series from MDACC reported much better outcomes in cancer patients [1]. In this latter study, all patients who died of cryptococcosis had either lymphopenia or concurrent infections, a regular finding in these patients. According to a multivariate analysis in HIV-negative patients, age above 60 years, hematological malignancy, and organ failure were independent predictors of mortality [10]. Of note, cryptococcal infection does not preclude subsequent transplantation procedures, provided secondary prophylaxis is given. In the future, it is hoped that vaccines or boosting of the immunity will prevent or eliminate the disease.

Endemic Mycosis

Coccidioidomycosis

Although the exact incidence remains unknown, infection with *Coccidiodes immitis* is a very rare event in cancer patients, even in areas endemic for coccidioidomycosis (also known as valley fever). This finding may in part be explained by the frequent empirical use of antifungals in febrile cancer patients without a specific diagnosis, the low index of suspicion, and the lack of autopsy data.

In healthy individuals, this infection, which is endemic in the desert regions of the southwestern United States, in adjacent regions of Mexico, and in other areas of Central and South America, usually presents as a self-limiting, often asymptomatic pulmonary infection [24]. However, patients who have suppressed cellular immunity, including cancer patients, are at increased risk of developing extrapulmonary and disseminated disease. In a case series of 55 immunocompromised patients, dissemination was found in more than 20%, far exceeding the observed rate of 1 or 2% in immunocompetent individuals [25].

Most of the reports are hampered by small numbers of cases, but it seems that these infections are more frequent in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia, underscoring again the importance of deficiencies in T-cell immunity. Of note, these infections can be diagnosed months or years after the initial diagnosis of a hematological malignancy, either as primary infection or as reactivation of a previous episode [25]. More recently, an increased risk for coccidioidomycosis has also been reported following anti-TNF-α monoclonal antibody therapy [26]. Finally, in endemic regions, around 5% of solid organ transplant recipients have evidence of disease and, although prior coccidioidomycosis does not contraindicate transplantation, early identification and treatment or prophylaxis seems prudent [27].

Unifocal or multifocal pulmonary disease is present in 95% of the cases; dissemination may occur to skin, central nervous system, or other single organs. Only very few patients will present with disseminated disease without evidence of pulmonary involvement. In cancer patients, coccidioidomycosis carries a mortality up to 50%, albeit greatly increased by steroid treatment or cytotoxic therapy [25].

Rapid diagnosis is possible based on microscopic examination of respiratory specimens or tissues [28]. Cultures will be infrequently positive and are time-consuming. Detection of circulating antibodies (serological assays), although frequently used, yields questionable sensitivity and specificity [29]. More recently, a specific *Coccidiodes* enzyme immunoassay has been developed, detecting urinary antigen in 71% of immunosuppressed patients with moderately severe-to-severe disease. Specificity was high, but cross-reactivity occurred in 10% of patients infected with other endemic mycosis [30]. Recently, several smaller studies have demonstrated the usefulness of in-house-developed polymerase chain reaction assays in establishing the diagnosis.

Azole antifungals have clearly become the standard therapy for coccidioidomycosis [24]. Based on the Landmark study of Galgiani et al., itraconazole capsules 200 mg twice daily are preferred above fluconazole [31]. Posaconazole, structurally related to itraconazole, can be used in case of itraconazole failure. Amphotericin B deoxycholate or a lipid-based formulation can be used in patients unable to tolerate azole therapy or in patients with rapidly progressive disease. Although clinical efficacy with echinocandins has been seen in scattered case reports, their use cannot be recommended in the absence of clinical studies.

Blastomycosis

Infection with *Blastomyces dermatitidis* is endemic in the southeastern and south central states of the United States and the Great Lakes region, as well as in locations near the Missouri, Mississippi, and Ohio Rivers [32]. Although formerly thought to be more prominent in men in the fourth through sixth decade of life, recent data from the Nationwide Inpatient Sample Database fail to confirm this finding [33].

Systemic infection with *B. dermatitidis* usually follows an inhalation exposure. Alveolar macrophages then play a critical role in inhibiting transformation of the mold into the yeast phase and T-cells are the chief mediators of immunity to *B. dermatitidis*. Specifically, a Th-1 response is primarily responsible for effective immunologic control of infection [32].

The range of clinical symptoms associated with blastomycosis is broad. Almost any organ system can be involved, with severity ranging from mild-to-rapidly fatal, depending on the underlying immune status [34, 35]. The most common presentation is acute or chronic pulmonary infection. Patients with acute pneumonia present with mild-to-moderate flu-like symptoms with nonproductive cough, or more symptomatically with sputum, fever, and pleuritic chest pain. Chronic pneumonia is far more common and is characterized by nonspecific findings, such as low-grade fever, constitutional symptoms, and chronic productive cough. Chest radiographic features are nonspecific as well, demonstrating nodular or lobar infiltrates, often with cavitation. Skin and subcutaneous involvement is the second most frequent manifestation of blastomycosis [35].

Although the published experience is (very) small, recognition of blastomycosis in the expanding population of immunocompromised hosts is a real clinical problem. Indeed, blastomycosis affects less than 1% of solid organ transplant recipients in endemic regions, but causes ARDS or miliary disease in 15% of the infected patients [36]. This manifestation is associated with a 50–90% mortality rate, despite appropriate therapy. Also, stem cell transplant recipients and patients receiving chemotherapy are at risk [37]. The exact incidence rate remains unknown, but up to 40% of these infected patients will develop ARDS and miliary disease, resulting in a rapidly fatal outcome. HIV-infected patients are another population of interest; again, disease manifestations tend to be very severe with disease-related mortality rates approaching 40% within the first weeks [38].

Diagnosis, which is often delayed due to unawareness of clinicians of this possibility, rests heavily on culture and histopathology. However, the organism may take weeks to be isolated in culture and histopathologic examination requires a dedicated and well-trained pathologist. Given the low-to-very low sensitivities (complement fixation 9%, immune-diffusion 28%, ELISA 77%), most experts do not recommend using the currently available serological tests for diagnosis [39]. However, antigen can be detected in urine, serum, and bronchial lavage fluid using the routinely available *Blastomyces* enzyme immunoassay (MiraVista Diagnostics, Indianapolis, Indiana) [40]. High sensitivity and specificity of 93 and 98%, respectively, was noted in one study, comparing favorably against serological testing. In addition, serial testing may be a method to monitor disease progression [41]. However, the assay is somewhat limited by significant cross-reactivity with *Histoplasma capsulatum*.

Even in the absence of comparative clinical trial data, patients with moderately severe-to-severe forms of blastomycosis (such as most cancer patients) should receive initial therapy with amphotericin B, either deoxycholate (0.7–1.0 mg/kg) or lipid-based (3–5 mg/kg) for 1 or 2 weeks, followed by a consolidation therapy with itraconazole (200 mg bid, following a loading dose of 200 mg 3 times per day for 3 days) for at least 12 months (or lifelong in case of continued immunosuppression) [42]. Of note, given the erratic absorption of itraconazole, monitoring of serum itraconazole concentrations is strongly recommended. However, target serum levels and dose-adjustment protocols for itraconazole have not been established. Patients with central nervous system involvement should receive initial therapy with a lipid-based formulation of amphotericin B. The drug of choice for continued oral maintenance therapy in these particular cases is unclear, but voriconazole looks

promising, provided therapeutic drug monitoring is performed. Finally, patients presenting with ARDS due to blastomycosis may benefit from adjunctive therapy with corticosteroids and may suffer from infection-related adrenal insufficiency, underscoring the need for a multidisciplinary approach.

Histoplasmosis

Histoplasmosis, caused by *H. capsulatum*, is the most common endemic mycosis reported in immunocompromised patients, most likely because it is the most common endemic mycosis overall. The dimorphic fungus *H. capsulatum* is endemic in the Ohio and Mississippi River valleys and in Central and South America. In these areas, skin tests surveys demonstrate that over half of the population acquired histoplasmosis during infancy. Smaller foci of histoplasmosis also exist in southeastern Asia, Africa, and the south of Europe [43]. In general, healthcare providers in these areas are familiar with the recognition, diagnosis, and therapy of histoplasmosis. However, nowadays, an increasing number of cases are recognized in nonendemic areas, especially in immunocompromised patients with prior exposure to endemic areas, either through travel or residence [44]. In some of these cases, histoplasmosis occurs months to years later following low-inoculum exposure, making the diagnosis more difficult.

This fungus is abundantly present in soil contaminated by droppings from birds and bats, in old buildings, and in caves. Again, infection follows an inhalation exposure. Aerosolized microconidia are inhaled and phagocytized by alveolar macrophages. Upon phagocytosis, the organism converts to its yeast phase and disseminates throughout the reticuloendothelial system [45]. Once specific cell-mediated immunity develops, T cells will activate the macrophages, enabling them to kill the organism. However, in case of defective cell-mediated immunity, viable organisms will remain within these macrophages and cause progressive disease. Obviously, the severity of disease will depend on the burden of inhaled conidia and the host immune response. In severely immunosuppressed patients, even a small inoculum can cause severe pulmonary infection of disseminated histoplasmosis. Patients at increased risk include AIDS patients with low CD4 counts, those receiving corticosteroids and other immunosuppressive drugs, patients suffering from hematological malignancies and, more recently, patient receiving anti-TNF-α monoclonal antibodies; the risk for solid organ transplant recipients and stem cell transplantation recipients appears to be low, even in endemic areas. Of note, since *H. capsulatum* is a viable intracellular organism, it can be transmitted with donated organs. When diagnosis is made timely and adequate therapy is installed, mortality tends to be low, even in immunosuppressed patients. However, too often diagnosis is not established until late in the course, especially in nonendemic regions.

Patients who are immunosuppressed usually develop clinical picture of severe pneumonia or that of disseminated disease [46]. They appear ill, present with chills, high fever, dyspnea, dry cough, and chest pain, and can progress rapidly to acute respiratory distress syndrome. In case of dissemination, they manifest with severe signs of sepsis or organ failure: shock with ARDS, adrenal insufficiency, disseminated intravascular coagulation, central nervous system involvement, mucosal and skin lesions, pancytopenia, and markedly elevated liver enzymes. Hemophagocytic syndrome (with extremely high serum ferritin levels) has been reported occasionally as a detrimental complication of histoplasmosis.

Culture of the organism from involved tissue provides a definite diagnostic test, but is limited by delayed positivity for up to 4–6 weeks [43, 44]. Histopathology can provide a more rapid result (within days), but requires a pathologist skilled in recognition of fungal pathogens [29]. Hence, in acutely ill patients suspected for disseminated histoplasmosis, a tissue biopsy (e.g., bone marrow, liver, skin, etc.) for histopathologic evaluation should be performed without any delay [43]. In patients with pulmonary infiltrates, BAL with or without biopsies should be performed as soon as possible. Serological tests, although useful for diagnosis of histoplasmosis, lack sensitivity in disseminated disease, probably because of underlying immunosuppression. In addition, following acute infection, antibodies may persist for several years, incorrectly suggesting active disease in patients with other diagnoses, or (false) positive assays may result from cross-reactivity in patients with other endemic mycoses [29, 44].

The *Histoplasma* antigen sandwich enzyme immunoassay (offered by MiraVista Diagnostics, Indianapolis, Indiana) is very useful for the rapid diagnosis of disseminated histoplasmosis in HIV-positive patients [47, 48]. When available, antigen can be found within 24–48 h in approximately 90% of these patients with disseminated disease and in up to 75% of cases of acute pulmonary histoplasmosis. Urine specimens yield the highest sensitivity, but antigen can also be detected in other body fluids, including serum, CSF, and BAL fluid specimens. False-positive results have been reported in blastomycosis, paracoccidioidomycosis, penicilliosis, and occasionally in aspergillosis. However, one should realize that few data are available on the usefulness of this assay in HIV-negative immunosuppressed patients. Of note is that histoplasmosis may be a cause of false-positive results in the Platelia *Aspergillus* antigen assay (Bio-Rad Laboratories, Marnes-la-Coquette, France and Hercules, California); patients with invasive aspergillosis, however, do not exhibit false-positive *Histoplasma* antigen tests. Again, serial testing may be used to monitor antifungal therapy [49].

Antifungal therapy with amphotericin B (1–2 weeks) is indicated for all patients presenting with moderately severe-to-severe acute pulmonary histoplasmosis and severe progressive disseminated disease [50]. In a randomized trial in HIV-infected patients with severe disseminated histoplasmosis, liposomal amphotericin B (3 mg/kg daily) resulted in improved survival when compared with amphotericin B deoxycholate [51]. As the condition improves, a step-down therapy with itraconazole (200 mg twice daily following a loading dose of 200 mg 3 times daily for 3 days) can be initiated and continued for at least 12 months (or longer in case of persistent immunodeficiency) and until clinical findings have resolved [50]. Preferably, antigenuria should resolve before discontinuation of antifungal therapy. A short course of methylprednisolone (0.5–1 mg/kg/day) may be beneficial in patients with respiratory complications and ARDS. Less severe cases of pulmonary or disseminated histoplasmosis can be treated with oral itraconazole only. In every case, it is recommended to monitor serum itraconazole levels to ensure adequate absorption; a serum concentration above 1 µg/mL is recommended.

Patients with central nervous system histoplasmosis require special attention. They should be treated with higher-dose (5 mg/kg) liposomal amphotericin B, for at least 4–6 weeks, followed by prolonged oral maintenance therapy (at least 12 months) with an azole. The azole of choice in this particular setting remains unknown. Both fluconazole and itraconazole have been used, but also voriconazole and posaconazole have been used anecdotally. All echinocandins lack activity against *H. capsulatum*; they should not be used. Prophylaxis with itraconazole may be appropriate in specific circumstances in HIV-negative immunosuppressed patients. However, the best way of preventing histoplasmosis in immunocompromised patients might be via reduction of environmental exposure (specific recommendations are available from the National Institute for Occupational Safety and Health) [52].

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Chapter 27
Current Controversies in the Treatment of Fungal Infections

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Abstract With improved laboratory techniques and the availability of new antifungal agents, complexity in the treatment of invasive fungal disease has rapidly increased over the past decade, stimulating a debate on the best management strategies. In this chapter, we address four important areas of current uncertainty, including (1) the role of therapeutic drug monitoring for voriconazole and posaconazole, (2) the utility of in vitro antifungal susceptibility testing of yeasts and moulds, (3) the optimal treatment of zygomycosis, and (4) the value of combination therapy for invasive aspergillosis. For each topic, we examine the available evidence surrounding the ambiguity and then offer data-driven recommendations on how to proceed with management.

Keywords Voriconazole • Posaconazole • Drug level • Monitoring • Antifungal susceptibility testing • Combination antifungal therapy

Role of Therapeutic Drug Monitoring for Voriconazole and Posaconazole

The utility of therapeutic drug monitoring (TDM) hinges on certain attributes of a medication. These important qualities include (1) an unpredictable blood or tissue drug level, (2) evidence that the drug level correlates with either toxicity or efficacy, and (3) the availability of an accurate drug assay [1]. Drug levels are often influenced by several factors including absorption, metabolism, and drug interactions. As experience has increased with the newer extended-spectrum azoles, mounting evidence suggests that TDM may be necessary for these drugs. The following sections address the evidence for and against voriconazole and posaconazole TDM and are summarized in Table 27.1.

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Voriconazole

Despite excellent oral bioavailability, voriconazole drug levels are variable in healthy volunteers and patients [2–5]. Studies have demonstrated both metabolism and drug interactions to be important sources of this unpredictability.

The major mechanism of voriconazole elimination is hepatic metabolism through the cytochrome P450 system, including isoenzymes CYP2C9, CPY2C29, CYP3A4, and CYP2C19 [6]. The affinity of voriconazole appears to be highest for CYP2C19, and polymorphisms in this gene can result in variable rates of metabolism of the drug. Those with the wild-type allele ("extensive metabolizers") have up to fourfold decreased plasma concentration of voriconazole as compared to those homozygous for the "poor metabolizer" phenotype [7, 8]. Importantly, the estimated frequency of CYP2C19 polymorphisms is different among ethnic groups: 20% of Asians compared with 2–5% of Caucasians and African-Americans are poor metabolizers of the drug [1, 6, 8, 9].

Further, voriconazole interacts with many coadministered drugs as it is an inhibitor of several isoenzymes in the cytochrome P450 system (CYP2C19, CYP2C9, and CYP3A4) (see Table 27.2). The type of interaction depends on whether the coadministered drug acts as a substrate, inducer, or inhibitor of one of the noted P450 isoenzymes. Inducers or inhibitors of these enzymes may decrease or increase voriconazole plasma concentrations, respectively. For example, coadministration of efavirenz, an isoenzyme inhibitor, results in increased levels of voriconazole while rifampin, a potent isoenzyme inducer, reduces the mean area under the curve (AUC) and mean maximum concentration (C_{max}) of voriconazole by up to 95% [10, 11]. In some cases, the impact of voriconazole coadministration with another drug is hard to predict particularly when the two drugs have competing effects on the same isoenzyme [10].

Initially, based on data from six clinical trials ($n = 280$), no concrete relationship between voriconazole concentration and efficacy could be established [10]. However, more recent reports have correlated low voriconazole levels with poor outcome [12–15]. One study of 52 patients revealed

Table 27.1 Relevant voriconazole and posaconazole therapeutic drug monitoring (TDM) parameters

Drug	Predictable serum levels	Serum level correlated to efficacy	Serum level correlated to toxicity	Accurate assay available	TDM indicated	TDM targets
Voriconazole	No	More certain	Yes	Yes	Yes	Trough level between 1.0 and 5.5 µg/ml
Posaconazole	No	Less certain	No	Maybe	For specific scenarios	Steady-state level >0.5–0.7 µg/ml

Table 27.2 Major voriconazole and posaconazole drug interactions (% change in C_{max}, if available)

Voriconazole			Posaconazole	
Effects of other drugs on voriconazole	Effects of voriconazole on other drugs	2-Way interactions (levels of each drug affected)	Effects of other drugs on posaconazole	Effects of posaconazole on other drugs
Rifampin (↓93%) [a]	Sirolimus(↑700%) [a]	Rifabutin [a]	Rifabutin (↓43%)	Sirolimus (↑572%) [a]
Ritonavir (↓66–82%) [a]	QT prolongators [a, b]	Efavirenz [c]	Phenyoin (↓41%)	QT prolongators [a,b]
St. John's Wort (↓59%) [a]	Ergot alkaloids [a]	Other NNRTIs	Cimetidine (↓39%)	Ergot alkaloinds [a]
Barbiturates (↓) [a]	Cyclosporin (↑) [d]	Protease inhibitors	Efavirenz (↓45%)	Cyclosporine (↑) [d]
Cimetidine (→18%)	Tacrolimus (↑100%) [e]	Phenytoin	Boost	Tacrolimus (↑121%) [e]
Isoniazid (→)	Methadone (↑31–65%)	Omeprazole		Rifabutin (↑31%)
Amiodarone	Warfarin	Fluoxetine		Midazolam (↑30–126%)
	Statins	Oral contraceptives		Phenytoin (↑16%)
	Benzodiazepines			Ritonavir (↑49%)
	Calcium-channel blockers			Atazanavir (↑155%)
	Sulfonylureas			Vinca alkaloids
	Vinca alkaloids			Statins
	Other PPIs			Calcium-channel blockers
	Other SSRIs			Digoxin
	NSAIDS			Amiodarone

References [10, 28, 138]

PPI proton pump inhibitor; *SSRI* selective serotonin reuptake inhibitor; *NNRTI* nonnucleoside reverse transcriptase inhibitor

[a] Coadministration of the two medications is contraindicated

[b] QT prolongators/CYP3A4 substrates include terfenadine, astemizole, pimozide, cisapride, quinidine, and halofantrine among others

[c] Suggested dosing when coadministered is efavirenz 300 mg daily (decreased) and voriconazole 400 mg BID (increased)

[d] Cyclosporine dose should be reduced 50% with voriconazole and 25% with posaconazole coadministration

[e] Tacrolimus dose should be reduced 66% with voriconazole and posaconazole coadministration

unpredictable trough plasma voriconazole concentrations, ranging from ≤1 µg/ml in 25% to >5.5 µg/ml in 31%. Lack of response to therapy was significantly greater in patients with levels ≤1 µg/ml (46%, 6/13) than in those with levels >1 µg/ml (12%, 5/39) [13]. Smith et al. separately reported that of 28 patients who underwent TDM because of disease progression or drug toxicity, a random voriconazole concentration of >2.05 µg/ml was associated with a 100% favorable clinical response compared with a 44% (8/18) favorable response for patients with random plasma concentrations <2.05 µg/ml [12]. Of patients whose voriconazole dose was increased based on having a voriconazole level ≤1 µg/ml, 73% (8/11) survived. Finally, in an open-label treatment trial for IA, of the 5% of patients who had mean plasma levels consistently <0.25 µg/ml, none responded [14].

High levels of voriconazole have been associated with toxicity including visual symptoms [10, 16], hepatic dysfunction [14, 17], and encephalopathy [13, 18]. Based on data from ten clinical trials, 21% of patients receiving voriconazole experienced abnormal vision, color vision disturbance, or photophobia. Fortunately, these visual disturbances were reversible and rarely led to discontinuation of drug. More importantly, clinically significant transaminase elevations were seen in 12.4% (206/1655) of patients treated with voriconazole [10] and in an open-label voriconazole study, 6 of 22 patients with plasma concentrations >6 µg/ml experienced liver dysfunction or liver failure [14]. Finally, encephalopathy, which reversed upon drug discontinuation, was reported in 31% (5/16) of patients with a voriconazole trough level >5.5 µg/ml vs. none in patients with a level <5.5 µg/ml (*p*=0.002) [13].

Tests for voriconazole blood levels are becoming more widely available as high performance liquid chromatogrphy (HPLC), liquid chromatography-mass spectrometry (LC-MS), and bioassays have been developed [19, 20]. Of these, bioassays measure the antifungal effect of the patient's blood on a fungal strain and may give falsely high values, particularly if the patient is receiving other antifungal agents.

An international survey and proficiency study for measurement of antifungal azole plasma concentrations revealed that most laboratories used HPLC ($n=26/33$) or LC-MS ($n=6/33$) for drug level determination [20]. Overall, 82% ($n=57$) of voriconazole analyses were correctly reported within the predefined range and no statistically significant difference was found between methods. Voriconazole levels are available in many tertiary medical centers as well as from multiple reference laboratories which offer reasonable turnaround time [21, 22].

Voriconazole meets all important criteria for TDM: unpredictable blood levels due to variations in metabolism and significant drug interactions, evidence that low levels are associated with poor outcomes while high levels are associated with adverse effects, and an accurate and available test. With that said, studies rigorously establishing target drug levels or showing the efficacy of dose adjustment based upon drug level have not been conducted. Based upon the available data, we recommend voriconazole trough concentrations in patients with serious/life-threatening mycoses, in cases where there is concern about drug metabolism or interactions, or in cases of suspected treatment failure. Trough levels can be reliably checked 2–3 days after initiation of voriconazole, once steady-state levels are obtained (or at day 5 if no loading dose is given). Although the optimal concentration is not completely defined, we advocate a minimum target trough plasma level of 1 μg/ml. If levels are <1 μg/ml, we suggest increasing the dose by 50% and rechecking the level. In order to prevent toxicity, levels >5.5 μg/ml should be avoided.

Posaconazole

Posaconazole is only available orally and demonstrates moderate variability in absorption. Absorption is saturated at doses >800 mg and further increasing the dose has no affect on plasma concentrations. In healthy volunteers, a dosing interval of 200 mg 4 times per day demonstrated the greatest bioavailability [23, 24] and posaconazole C_{max} was increased with coadministration of an acidic beverage by 92% and with Boost® nutritional supplement by 60–137%. Posaconazole C_{max} was also increased by 96% when the drug was administered before and up to 337% when administered during or after a high-fat meal. Conversely, enhanced gastric motility and higher gastric pH decreased posaconazole maximum concentrations by 21 and 46%, respectively [25]. In a dose-finding study of 30 neutropenic, hematopoietic stem cell transplant (HSCT) recipients, interpatient pharmacokinetic variability ranged from 38 to 68% [26]. In a separate study conducted in HSCT recipients with graft versus host disease (GVHD), mean posaconazole concentrations (1.47 μg/ml)

were 54% higher in patients with chronic GVHD ($n=82$) compared with those with acute GVHD ($n=158$, mean concentration 0.958 μg/ml) [27].

There are several important drug interactions with posaconazole (see Table 27.2). Posaconazole is primarily metabolized via UDP-glucuronidation and rifabutin, phenytoin, and efavirenz can decrease posaconazole C_{max} by 39–45% in healthy volunteers via induction of this pathway [28]. Although not metabolized by the hepatic cytochrome P450 system, posaconazole inhibits it. Specifically, it affects CYP3A4 and increases plasma concentrations of several important coadministered medications [28].

One published trial links efficacy with posaconazole plasma concentrations [29]. In an open-label salvage study of refractory invasive aspergillosis (IA), patients with mean posaconazole average plasma concentrations (C_{av}) in the lowest (0.134 μg/ml), second (0.411 μg/ml), third (0.852 μg/ml), and fourth (1.250 μg/ml) quartiles had 24% (4/17), 53% (9/17), 57% (9/17), and 75% (12/16) response to therapy, respectively. On the other hand, secondary analysis of a phase III posaconazole prophylaxis trial found no correlation between plasma levels and clinical outcome. This finding may have been due to a lack of statistical power rather than an absence of a true difference as the low number of breakthrough mould infections precluded formal statistical comparison. Interestingly, the C_{av} for the three patients with breakthrough infections were all below the mean C_{av} (0.586 μg/ml) of those free from breakthrough infection ($n=188$) [30]. In the new drug application process, the FDA also examined the drug-exposure relationship in both phase III prophylaxis studies and found a significant increase in breakthrough invasive fungal infections in patients with posaconazole C_{av} <0.7 μg/ml [31]. Based on this, a cautionary warning was placed in the posaconazole package insert that lower posaconazole concentrations may be associated with an increased risk of treatment failure [28].

Hepatic dysfunction is the most common serious adverse effect noted in the posaconazole prophylaxis trials [28], but no studies have correlated posaconazole levels with this or any other toxicity.

As with voriconazole, posaconazole drug levels are available through several reference laboratories [32]. However, in the international proficiency testing program for measurement of antifungal azole plasma concentrations previously mentioned, only 62% ($n=26$) of posaconazole analyses were within the targeted concentration range [20]. Thus, more work is needed to establish an accurate test method for clinical use.

Posaconazole therefore meets some, but not all, requirements for TDM. Plasma levels are unpredictable and efficacy has been linked to plasma concentration according to one published trial. On the other hand, toxicity has not been associated with plasma concentration and more work is

needed to establish a reliable test method for determining blood concentrations. For these reasons, we do not suggest routine posaconazole TDM in prophylaxis and treatment. However, in cases of severe/life-threatening mycoses, concerns about drug bioavailability or interactions, and suspected clinical failure, we would recommend checking a steady-state level (3–5 h after a dose and ≥7 days after initiation of the drug). In such cases, concentrations <0.5–0.7 µg/ml should guide adjustment of the dosing schedule (e.g., switching the dosing interval from 2 to 4 times daily) or change to an alternative agent.

In Vitro Antifungal Susceptibility Testing for Yeasts and Moulds

Candida Species

Antifungal susceptibility testing first became important in the AIDS era when long-term fluconazole treatment for oral candidiasis bred clinical resistance [33]. Recognizing this, in 1982, the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) formed the Subcommittee on Antifungal Susceptibility Testing (SAST). Based on a collaborative study documenting unacceptably low interlaboratory agreement in Minimal Inhibitory Concentration (MIC) results [34], the committee set out to standardize a reference method for testing yeasts and to establish reference MIC ranges for quality control organisms [35]. Over the ensuing years, less labor-intense, commercially available methods of testing including broth microdilution [36–38], agar dilution [39–42], and disk diffusion [34, 43] have been favorably compared with the CLSI reference method, thus allowing for susceptibility testing of yeasts in most clinical microbiology laboratories [44].

The CLSI SAST also worked to create interpretative categories for *Candida* susceptibility results to several antifungal agents. Developing interpretive breakpoints for any organism–drug combination requires integration of the MIC distribution of the organism, pharmacokinetic and pharmacodynamic properties of the drug, and the relationship between the in vitro activity and outcome from in vivo and clinical studies. Using data generated by standardized testing methods, interpretive breakpoints for fluconazole, itraconazole, flucy-tosine, voriconazole, and the echinocandins against *Candida* species have been established and/or proposed [15, 45, 46].

MIC interpretative criteria for fluconazole were first published by Rex et al. [47, 48] and recently confirmed by Pfaller et al. [49]. In 1997, tentative fluconazole MIC breakpoints in *Candida* infections of susceptible (S; ≤8 µg/ml),

susceptible dependent upon dose (SDD; 16–32 µg/ml), and resistant (R; ≥64 µg/ml) were proposed [47]. Pooling the available clinical isolates, success rates for patients receiving fluconazole 100 mg/day were 98% (248/253), 78% (21/27), and 73% (16/22) for isolates with MICs ≤8, 16–32, and ≥64 µg/ml, respectively. For doses of fluconazole >100 mg/day, success rates for isolates with MICs ≤8, 16–32, and ≥64 µg/ml were 81% (122/150), 86% (24/28), and 46% (18/39), respectively. Because a dose of fluconazole >100 mg/day portended clinical success in the MIC 16–32 range as would be expected from pharmacokinetic analysis, the delineation of SDD was created.

Several caveats to the proposed breakpoints were noted. First, *Candida krusei* had higher MICs to and frequent clinical failure with fluconazole. Hence, *C. krusei* was deemed "intrinsically resistant" to fluconazole, obviating the need for MIC testing of this organism/drug combination [47, 50]. Second, the breakpoints were based mainly on cases of oropharyngeal candidiasis in HIV-infected patients (411/519 cases) and therefore needed confirmation in invasive disease. In 2006, the interpretive breakpoints for fluconazole and *Candida* were revisited using data accumulated in the interim from 12 clinical trials [49]. In the invasive candidiasis subset, successful treatment was seen in 77% (353/460), 71% (51/72), and 44% (31/71) for patients with isolates in the S, SDD, and R MIC ranges, respectively. The original breakpoints for fluconazole in *Candida* infection were thus confirmed.

Using an analytic plan similar to that employed for fluconazole, interpretive criteria for voriconazole have also been established. The MIC distribution for voriconazole was determined using a collection of 8,702 clinical isolates [15]. The MIC at which 90% of isolates were inhibited (MIC_{90}) was 0.25 µg/ml; 99% of isolates were inhibited at ≤1 µg/ml of voriconazole. Compiled data from 249 patients in phase III voriconazole trials revealed a significant correlation between MIC and investigator end-of-treatment assessment of outcome. For *Candida* species, the data supported the following MIC breakpoints for voriconazole: S ≤1 µg/ml; SDD 2 µg/ml; and R ≥4 µg/ml [15, 25].

Although the CLSI broth microdilution susceptibility testing method has been validated for posaconazole, the FDA has yet to approve a commercial test system for posaconazole and interpretive breakpoints for posaconazole to *Candida* have not yet been established. A study comparing MIC results for posaconazole to those for fluconazole and voriconazole against 10,807 isolates of *Candida* species was performed to examine the use of fluconazole or voriconazole as surrogate markers for posaconazole activity. Overall, the posaconazole MIC_{90} was 1 µg/ml; 96.9% of isolates had MIC ≤1 µg/ml. For comparative purposes only, investigators applied voriconazole breakpoints to the posaconazole MICs (S ≤1 µg/ml; SDD 2 µg/ml; R ≥4 µg/ml). Using this approach,

over 99% of fluconazole-susceptible isolates were "susceptible" to posaconazole, while only 47% (127/272) of fluconazole-resistant isolates were "susceptible" to posaconazole. Similarly, 98% of voriconazole-susceptible isolates were "susceptible" to posaconazole, while only 4% (4/92) of voriconazole-resistant isolates were "susceptible" to posaconazole [51]. This analysis, together with population MIC distributions, suggested that fluconazole and voriconazole are fairly reliable surrogate markers to predict posaconazole activity and that posaconazole and voriconazole have similar susceptibility profiles against *Candida* species.

The currently available echinocandins, caspofungin, micafungin, and anidulafungin, are highly active against *Candida* species. The three drugs have similar spectrum and potency, and scatter plots comparing *Candida* population MICs for the three agents show a high degree of correlation. Of 5,346 *Candida* isolates tested, the overall MIC_{90} for caspofungin was 0.25 μg/ml and 99.9% of isolates were inhibited by ≤2 μg/ml of caspofungin [45]. Interestingly, the caspofungin MIC_{90} for *C. krusei* (0.25 μg/ml), *C. parapsilosis* (1 μg/ml), and *C. guilliermondii* (1 μg/ml) was considerably higher than that observed for the three most common species of *Candida* recovered from blood (*C. albicans*, *C. glabrata*, and *C. tropicalis*; each with caspofungin MIC_{90} 0.06 μg/ml). The mechanism for this bimodal "wild type" MIC distribution for the echinocandins appears to be polymorphisms within the FKS1 gene, which encodes essential components of the glucan synthesis enzyme complex. A naturally occurring proline-to-alanine amino acid change at position 660 (P660A) in FKS1p is thought to account for this reduced echinocandin susceptibility [45, 52]. Fortunately, in clinical trials this FKS1 gene polymorphism was not associated with decreased clinical response, leading to speculation that this specific mutation may also confer decreased fitness for the organism. The decreased fitness, coupled with the excellent pharmacokinetics of the drug, may enable effective treatment for infections due to *Candida* species with MICs as high as 2 μg/ml with this polymorphism.

Several alternative mutations in the FKS1 gene have been correlated with higher echinocandin MICs, typically >2 μg/ml and usually ≥8 μg/ml, and clinical failure [15, 45, 53–55]. These mutations conferred equally high MICs (>2 μg/ml) to caspofungin, anidulafungin, and micafungin. Among 14 strains with such mutant FKS1p enzymes studied, caspofungin appeared to be the best surrogate marker for echinocandin "class resistance" [56].

The CLSI standardized method of testing the echinocandins against *Candida* species provides reliable and reproducible MIC results with good separation of the "wild type" MIC distribution from isolates of *Candida* with mutations in the FKS1 gene which confer an MIC >2 μg/ml, and presumably, clinical resistance. Fortunately, the number of isolates with such mutations remains rare despite widespread use of the echinocandins. CLSI currently recommends a breakpoint

for susceptibility of ≤2 μg/ml for the echinocandins. Because of the very small number of clinical isolates with an MIC >2 μg/ml, SDD and R categories have not been defined. Thus, until appropriate numbers of such isolates treated with echinocandins are available, any isolate with an MIC >2 μg/ml is currently considered "nonsusceptible" [45].

Interpretive breakpoints have not been established for *Candida* against amphotericin B (AMB) as the MIC population distribution is narrow (0.5–2 μg/ml) and studies have been unable to demonstrate a consistent clinical correlation within that range [35]. One demonstrative example is a series of clinical isolates from 107 patients treated with AMB for candidemia. Mean and median MICs for isolates from successfully treated patients were 0.33 and 0.5 μg/ml, respectively, which were almost identical to corresponding values for isolates from patients deemed clinical failures [57].

In summary, in vitro antifungal testing for *Candida* species correlates with clinical outcome and can offer important guidance in the care of patients. We recommend susceptibility testing for clinically relevant *Candida* species for which susceptibility is unpredictable (e.g., *C. glabrata* to fluconazole), isolates from patients with previous prolonged antifungal exposure, and isolates from patients demonstrating unexplained clinical resistance to a given agent.

Moulds

Standard methods for testing filamentous fungi have also been established [58]. However, caution is advised when correlating MIC data clinically as the relationship between in vitro and in vivo data has only been evaluated in animal models and case reports. The clinical relevance of testing moulds therefore remains uncertain and interpretive breakpoints of proven import have yet to be established.

Aspergillus Species

Per Table 27.3, the population MIC distributions of extended-spectrum azoles and AMB for *Aspergillus* spp. have been documented based on 2,088 clinical isolates from three different reports. The MIC_{90} of itraconazole, voriconazole, posaconazole, and AMB deoxycholate (dAMB) were 0.25–2, 0.5–1, 0.25–0.5, and 1–4 μg/ml, respectively [59–61].

Mechanisms to explain significant differences in MIC values among *Aspergillus* isolates for the extended-spectrum triazoles are beginning to be teased out. A review of all *Aspergillus fumigatus* isolates stored at a tertiary hospital in the Netherlands from 1994 to 2007 found that 2.6% (32/1219) of isolates had itraconazole MICs ≥4 μg/ml

Table 27.3 MIC_{90} for different antifungal agents to common fungal pathogens

	MIC_{90} or MEC_{90} [a]					
Organism	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Caspofungin	AMB
Candida albicans	0.5	N/A	0.15–25	0.06	0.06	0.5–2
C. glabrata	32	N/A	1–4	2	0.12	1–2
C. tropicalis	2	N/A	0.25	0.12	0.06	1–2
C. parapsilosis	2	N/A	0.06	0.12	2	1–2
C. krusei	64[b]	N/A	0.5–1	1	2	2
Aspergillus fumigatus	N/A	0.5–2	0.5	0.5	0.06	1–2
A. flavus	N/A	0.25–1	0.5–1	0.5	0.06	2
A. terreus	N/A	0.25–0.5	0.5–1	0.25	0.06	2–4
Zygomycetes[c]	N/A	8–32	16–128	1–4	>16	0.5–2
Fusarium species[d]	N/A	>8	>0038	>8	>8	2–4; 32
Scedosporium apiospermum	N/A	1–32	0.25	1	NR	8
S. prolificans	N/A	16–64	8	32	NR	16–32

References [43, 45, 51, 57, 59–61, 64, 68, 73, 75, 139–143]

AMB amphotericin B; *NR* not reported; *N/A* not applicable

[a] Using CLSI methodology M27-A3 and M38-A2; note for echinocandins, MEC_{90} used for testing moulds and MIC_{90} used for testing *Candida*

[b] *C. krusei* is considered intrinsically resistant to fluconazole and thus need not be tested; however, it has generally been found to be susceptible to voriconazole and posaconazole

[c] The zygomycetes include many important pathogenic moulds and the MIC_{90} for Itraconazole, Posaconazole, and AMB varies considerably between species

[d] *Fusarium* isolates demonstrated differences in MIC_{90} among species. *F. oxysporum* and *F. monoliforme* demonstrated lower MIC_{90} than other *Fusarium* spp.

as well as elevated MICs to voriconazole, posaconazole, and ravuconazole [62]. Ninety-four percent (30/32) of these isolates had a *cyp51A* gene mutation, which included a leucine for histidine substitution at codon 98 in conjunction with two copies of a 34-bp sequence in tandem in the gene promoter (TR/L98H). In a separate report, Verweij et al. described the TR/L98H mutation in nine patients with IA [63]. Of those treated with voriconazole (*n* = 3) or posaconazole (*n* = 1) monotherapy, 50% (2/4) died while the five patients receiving alternate treatment survived suggesting that the TR/L98H mutation produced clinically significant cross-resistance among all extended-spectrum triazoles.

Further elucidation of the resistance mechanisms for *Aspergillus* to the triazoles comes from a report of 771 *Aspergillus* isolates, including multiple species from around the world. Itraconazole MICs ≥4 µg/ml were demonstrated in 2.2% (*n* = 17) of isolates, but high MICs to itraconazole did not necessarily correspond to high voriconazole and posaconazole MICs [64]. This difference was subsequently explained in part by different mutations involving the *cyp51A* gene that conferred unique patterns of azole activity [65]. For example, G54 mutations led to high MICs for both itraconazole and posaconazole, while M220 resulted in high MICs for all four drugs [66]. Multiple different mechanisms of resistance, some of which are as yet unidentified, likely contribute to each organism's phenotypic profile. At this time, the CLSI broth microdilution method of testing appears to be reproducible enough to identify mould isolates with triazoles MICs ≥1 µg/ml [66].

Several studies have correlated high MICs to AMB with clinical failure, particularly for *A. terreus*. One study demonstrated that for *Aspergillus* spp. isolated from patients with invasive disease, AMB MICs <2 µg/ml were associated with survival (6/6), while MICs ≥2 µg/ml were associated with death (22/23). The latter group included all nine patients infected with *A. terreus* [67]. In a single-center review of proven IA cases, response to AMB was only 21% (5/24) for patients infected with *A. terreus*, which was significantly worse than the 48% (11/23) response for non-*terreus* *Aspergillus* infections [68]. In this study, of the 32 *A. terreus* isolates undergoing MIC determination, the MIC_{90} for AMB was 4 µg/ml compared with the voriconazole MIC_{90} of 1 µg/ml. Clinical confirmation of superior voriconazole activity for *A. terreus* came from a multicenter retrospective review of 83 cases of invasive *A. terreus* infection. Only 26.2% (11/42) receiving an AMB formulation as primary therapy survived vs. 64.7% (11/17) who received voriconazole as primary therapy (*p* = 0.01) [69]. Unfortunately, MIC data for those cases were not available.

All echinocandins appear to be active in vitro against *Aspergillus*. In a large study of 372 *Aspergillus* species isolates, the caspofungin minimum effective concentration (MEC) at which 90% of isolates were inhibited was 0.06 µg/ml, while 98.4% of isolates were inhibited at ≤1 µg/ml [60]. There are only a few reports of *Aspergillus* in vitro resistance to the echinocandins. One study examined the echinocandin MECs of *Aspergillus* isolates from nine cases of caspofungin breakthrough infection in an allogeneic stem cell transplant population. Of the four isolates examined, *A. ustus* and

A. nidulans had higher MECs (8 and 4 μg/ml, respectively) compared with MECs of 1 and 0.25 μg/ml for the two *A. fumigatus* isolates. A search for specific mechanisms of resistance was not done [70]. A second study evaluated a single isolate from a patient who failed caspofungin. Interestingly, while the broth microdilution MEC for the isolate was 0.25 μg/ml, the Etest® and an animal model indicated reduced caspofungin activity. Furthermore, although no FKS gene mutation was present, its expression was increased in the presence of drug suggesting that it played some role [71]. In the laboratory, researchers induced an *A. fumigatus* FKS1p mutation in the "hot-spot" region (serine-678-proline) and found an MEC ≥8 for all mutants [72]. Evidence linking echinocandin clinical failures to *Aspergillus* MEC is slim.

Non-Aspergillus Moulds

The MIC$_{90}$ of antifungal agents to several non-*Aspergillus* moulds is listed in Table 27.3. In general, AMB is the most active agent followed by posaconazole. For example, in vitro susceptibility testing of 217 zygomycetes revealed that, for *Rhizopus*, the MIC$_{90}$ to dAMB was 0.5 μg/ml and 100% of the isolates had MICs ≤1 μg/ml (*n*=86), whereas for posaconazole, the MIC$_{90}$ was 1 μg/ml and 80% of isolates had MICs ≤1 μg/ml (*n*=66) [73]. Although only eight isolates were tested, *Cunninghamella bertholletiae* had the highest MICs to dAMB compared with all other zygomycetes, which may account for the worse clinical outcomes reported with this infection [74]. By standardized testing methods, the echinocandins are inactive in vitro against zygomycetes and *Fusarium* species. In a compilation of two studies, the MEC of caspofungin to each zygomycosis tested (*n*=113) was ≥16 μg/ml [73, 75]. Also, in an exhaustive literature review, Espinel-Ingroff reported echinocandin MECs of ≥8 μg/ml to all 68 *Fusarium* spp. tested [76]. The data on echinocandin activity against other non-*Aspergillus* moulds are limited.

The most robust data correlating MIC with clinical outcomes for the non-*Aspergillus* moulds are from a report of in vitro susceptibility of 590 isolates collected from all phase III voriconazole trials [61]. The overall MIC$_{90}$ for voriconazole was 1 μg/ml. The 34 isolates with a voriconazole MIC ≥4.0 μg/ml included 9/9 zygomycetes, 10/13 *Fusarium solani*, 9/11 *Scedosporium prolificans*, and one isolate each of *S. apiospermum*, *A. fumigatus*, *F. oxysporum*, *F. proliferatum*, *Microascus cineus*, and *Scopulariopsis brevicaulis*. Of patients infected with these isolates with clinical data available, outcome was successful for only 38% (9/24) of patients infected with a mould with MIC ≥4.0 μg/ml compared with 52% (105/202) of those infected with a mould with MIC <4.0 μg/ml (*p*=0.0899). Correlation of in vitro data with clinical outcome for the echinocandins and AMB with non-*Aspergillus* moulds is scant.

Because of the laborious nature, lack of interpretive breakpoints, and unproven clinical correlation of mould in vitro susceptibility testing, most clinical laboratories do not routinely perform this testing, and similarly, we do not recommend routine in vitro susceptibility testing of filamentous fungi. More important in the selection of an appropriate antifungal agent is the correct identification of the mould, preferably to the species level, with choice of drug based on known population MIC distributions for the specific organism recovered. However, several notable exceptions for which susceptibility testing of filamentous moulds may help guide therapy include patients heavily pretreated with mould-active agents, patients failing to respond clinically, or patients with isolates for which MICs are not predictable. In such cases, a general rule of thumb for the triazoles and AMB is as follows: an MIC ≤1 μg/ml suggests that the drug may have in vivo activity against the organism and an MIC ≥4 μg/ml should prompt the choice of an alternative agent. Again, emphasis must be placed on the limitations of the data and that such information would be used only in conjunction with other parameters when deciding on treatment options.

Treatment of Zygomycosis

Historically, dAMB was the only active systemic antifungal agent for zygomycete infection. A literature review of 929 published cases of patients with zygomycete infection from 1940 to 2003 was performed, and in a multivariate model of risk factors for mortality, the odds ratio for dAMB vs. no antifungal therapy was 0.21 (95% CI 0.13–0.25, *p*=<0.001) and lipid AMB vs. no antifungal therapy was 0.10 (95% CI 0.04–0.24, *p*=<0.0001) [74]. Moreover, early antifungal therapy for this infection is critical. In a retrospective review of 70 consecutive hematology patients with invasive zygomycete infection, investigators found almost twofold higher mortality with delayed (≥6 days after diagnosis) AMB administration (49 vs. 83%) [77].

Unfortunately, the use of dAMB is accompanied by severe infusion reactions and renal toxicity. To minimize adverse effects, lipid formulations of AMB were developed. The currently available lipid AMB products include liposomal amphotericin B (LAMB), amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD). All three offer the broad antifungal activity of dAMB; however, ABCD is not frequently used secondary to increased infusion toxicity compared with dAMB [78]. No prospective head-to-head trial comparing the various AMB formulations in the treatment of invasive zygomycosis has been conducted.

While most experts now consider a lipid formulation of AMB to be first-line therapy for zygomycosis, there is no firm agreement regarding which of the lipid products (ABLC

or LAMB) is preferable and whether the addition of other agents is beneficial. The following section examines these areas of controversy.

In Vitro Data

As previously discussed, AMB is the most active agent in vitro followed closely by posaconazole. Although not reflected in MIC, one study demonstrated an immuno-modulatory activity of echinocandins against several moulds including *Rhizopus oryzae* [79]. In this study, administration of caspofungin increased mould cell wall β-glucan exposure and enhanced human neutrophil activity against the cell wall. Testing caspofungin in combination with posaconazole, Guembe et al. found a synergistic effect in all 12 zygomycete strains tested [80]. Perkhofer et al. tested 30 zygomycetes and found that combination of posaconazole and dAMB more often demonstrated a synergistic effect on zygomycete hyphae (40%) compared with zygomycete conidia (10%) [81].

Animal Data

The frequent central nervous system (CNS) involvement of zygomycete infection has engendered debate about which lipid formulation of AMB best penetrates the blood–brain barrier. Ibrahim et al. found that high-dose LAMB (15 mg/kg/day) was superior to LAMB 7.5 mg/kg/day and dAMB 1 mg/kg/day in a diabetic ketoacidosis (DKA) mouse model of disseminated zygomycosis [82]. In a recent head-to-head comparison of LAMB and ABLC in a disseminated *R. oryzae* mouse model, LAMB demonstrated significantly better survival in a DKA model and a nonsignificant trend towards improved survival in a neutropenic model [83]. CNS fungal burden in both models was significantly reduced with LAMB 15 mg/kg/day, ABLC 15 mg/kg/day, and LAMB 7.5 mg/kg/day, but not with ABLC 7.5 mg/kg/day as compared with placebo.

There are conflicting data regarding the activity of posaconazole in the mouse model. In both the DKA and neu-tropenic mouse models of disseminated *R. oryzae* infection, survival with posaconazole monotherapy was not significantly better than placebo and combination posaconazole plus LAMB added no benefit to LAMB alone [84]. However, in a neutropenic model of disseminated *R. oryzae* using two different strains, Rodriguez et al. showed that posaconazole monotherapy was better than placebo ($p < 0.05$), but inferior to dAMB ($p < 0.05$) [85]. In that model, the addition of posaconazole to dAMB enabled a lower dose of dAMB (0.3 mg/kg/day) to obtain a survival similar to the higher dose

monotherapy of dAMB (0.8 mg/kg/day). CNS fungal burden for one of the two *Rhizopus* strains was decreased signifi-cantly with combination therapy. Finally, a third mouse model found a lack of posaconazole activity to *R. oryzae*, partial activity for *Absidia corymbifera*, and a clear dose–response effect for *R. microsporus* [86]. In summary, posa-conazole had variable antizygomycete activity as a single agent, and for certain strains, posaconazole appeared syner-gistic when administered in combination with AMB.

Although not active in vitro, the echinocandins appear to have limited activity in murine models of disseminated zygo-mycete infection [87, 88]. Two reports of echinocandin–AMB synergy have been published, both of which demonstrated a significant improvement over AMB mono-therapy in mouse survival [89, 90]. The first study used ABLC plus caspofungin, while the follow-up study demon-strated a class effect by testing LAMB in combination with micafungin and anidulafungin. Why low doses of caspo-fungin and micafungin (1 mg/kg/day) and high doses of anidulafungin (10 mg/kg/day) conferred this benefit while micafungin 3 mg/kg/day and anidulafungin 1 mg/kg/day did not remains unexplained.

Clinical Data

Treatment success in humans has been reported with all three lipid AMB products; however, prospective clinical trials directly comparing the agents are lacking [74, 91–95]. A large review of the Collaborative Exchange for Antifungal Research database demonstrated a 52% clinical response (33/64 cured or improved) in patients with zygomycete infection treated with ABLC [96]. A review of 59 cases of zygomycosis in hematology units in Italy demonstrated 64% (7/11) cure with LAMB vs. 32% (6/19) success with dAMB [95]. A retrospective review of cases in Los Angeles found higher success rates ($p = 0.28$) with dAMB or LAMB (72%; 13/18) compared to ABLC (37%; 7/19) [97]. LAMB treat-ment success was 100% (4/4), but the small sample size and retrospective nature of the study considerably limit the strength of the finding. Although a dose–tolerance study found that LAMB could be given safely up to 15 mg/kg/day [98], studies of high-dose LAMB for the treatment of IA have shown increased toxicity compared to standard dosing [99].

The lack of an intravenous formulation and preclinical data suggesting less efficacy compared to lipid AMB has limited the use of posaconazole as first-line therapy for zygo-mycosis. With that said, the clinical experience with posa-conazole has been much more encouraging. The bulk of support comes from a retrospective compassionate-use study of 91 cases of zygomycosis either refractory to prior antifungal therapy (48%), or intolerant of prior antifungal therapy (10%),

or both (33%). In this difficult population, 60% of patients who received posaconazole had a favorable treatment outcome [100]. Importantly, investigators reported that the most deeply immunosuppressed patients received posaconazole plus lipid AMB in combination, and the favorable response rate in that subset was an encouraging 46% (6/13). Although not formally studied, the ability to give this agent orally as sequential therapy for patients who have responded to an initial course of lipid AMB has gained favor in many institutions.

Clinical data supporting the addition of an echinocandin to AMB are limited to a retrospective review of 34 patients with rhino-orbital-cerebral zygomycosis [97]. Most patients in the study had diabetes (83%) with only 10% having received a transplant. Treatment was successful for all six evaluable patients who received AMB–caspofungin combination therapy (one patient lost to follow-up) compared with 41% (14/34) in the AMB monotherapy group ($p = 0.19$). Taken in conjunction with the promising preclinical data, this study does lend support for adding an echinocandin in zygomycete infection. However, we emphasize that this small study requires validation as it was retrospective, had a select group of patients, and used various AMB formulations.

Bottomline is that current evidence from mouse models and humans slightly favors the use of LAMB, although ABLC has proven antizygomycete activity and is an acceptable alternative. Currently, a phase II, noncomparative clinical trial is underway to investigate the efficacy of high-dose LAMB (10 mg/kg/day) which may help clarify whether a higher starting dose is preferable. Until more convincing data become available, we do not advocate the routine addition of an echinocandin to lipid AMB for invasive zygomycosis.

Adjunctive Therapy

Iron chelation with deferoxamine has long been known to be a risk factor for zygomycete infection by acting as a siderophore to enhance iron uptake by the organism and promote its growth [101]. Newer iron-chelating agents including deferasirox have the opposite effect and steal iron from the zygomycete. Deferasirox has shown impressive antimould activity in vitro and in mouse models, and this agent was successful in one dramatic case report [102–104]. However, a second case report of a disseminated zygomycosis refractory to LAMB, caspofungin, surgery, and deferasirox was less encouraging [105]. A randomized, double-blind, placebo-controlled phase II clinical trial is underway to more rigorously evaluate the utility of adding deferasirox to LAMB for the management of zygomycosis.

In addition to iron-chelating agents, several novel therapies have been used to treat zygomycosis, including hyperbaric oxygen, GM-CSF, IFNγ, and granulocyte transfusions.

The use of these other adjunct therapies is currently supported by biological plausibility, in vitro data, and uncontrolled small case series. These strategies have been discussed in several recent reviews [101, 104, 106–109] in detail and are addressed in this book (Sect. III, Chap. 29 on Immune Enhancement and Cytokine Therapy in Patients with Difficult-to-Treat Fungal Infections).

Combination Therapy for Invasive Aspergillosis (IA)

Much interest has been generated over the utility of combination therapy for the treatment of IA as outcomes with monotherapy remain poor despite recent advances. For example, in the landmark trial comparing voriconazole with dAMB as primary treatment of IA, successful outcome was achieved for only 52.8% (76/144) of patients treated with voriconazole and 31.6% (42/133) of patients treated with dAMB [110]. Also, treating with high doses of LAMB did not offer improved efficacy in a randomized trial comparing standard dose (3 mg/kg/day) with high-dose (10 mg/kg/day) LAMB for primary treatment of invasive fungal disease (96% IA). Favorable response at the end of study drug administration (median 14.5 days) was only 50 and 46% for the low- and high-dose groups, respectively [99]. Other drugs with clinical efficacy in IA have published response rates of 40–42% for posaconazole [29, 111], 42% for ABLC [93], and 45% for caspofungin [112] in the salvage setting. This begs the question: can we improve on this 50% clinical response by using combinations of antifungal drugs?

Steinbach et al. exhaustively reviewed the literature from 1966 to 2001, reporting 249 cases where combination or sequential therapy was used for IA [113]. The authors found that 23 different antifungal combinations were used, resulting in clinical improvement for 63% of patients. Notably, the largest combination therapy cohorts included only ten patients and the review predated the use of voriconazole, posaconazole, and the echinocandins in the treatment of IA. Here we will examine the contemporary clinical trials published, which focus on the subject and which are summarized in Table 27.4.

Preclinical Data

In vitro and animal model data are conflicting; antagonism was shown using azoles with AMB in vitro and in an animal model (Lewis RE AAC 2002; Meletiadis JID 2006), while echinocandin synergy with both azoles and AMB has been demonstrated [114–121]. Steinbach et al. found synergy,

Table 27.4 Clinical combination studies of IA, 1966–2008 [a]

Author, year	Setting	Trial design	Study medications	EOT clinical response [b]	Day 90 survival [c]	Statistical significance?
Popp (1999)	Any cancer	Retrospective cohort	ITRA+dAMB dAMB	82% (9/11) 50% (5/10)	82% (9/11) 50% (5/10)	No (not powered to detect a difference)
Kontoyiannis (2005)	Heme	Retrospective cohort	ITRA+lipid AMB Lipid AMB	0% (0/11) 10% (10/101)	36% (4/11) 34 (34%)	No (p>0.05)
Chandrasekar (2005)	Any	Retrospective cohort	ITRA+ABLC ABLC	33% (30/90) 47% (132/278)	NR NR	NR
Marr (2004)	Heme/SCT	Retrospective cohort	CAS+VOR VOR	NR NR	63% (10/16) 32% (10/31)	Yes (HR 0.42, p=0.048)
Singh (2006)	SOT	Prospective, observational	CAS+VOR LAMB	NR NR	67.5% (27/40) 51% (24/47)	No (HR 0.58, p=0.12)
Maertens (2006)	Heme	Prospective open-label salvage	CAS+VOR CAS+AMB CAS+ITRA	54% (15/28) 50% (8/16) 29% (2/7)	Overall 45%; groups not specified	NR
Kontoyiannis (2003)	Heme/SCT	Retrospective cohort	CAS+LAMB	22% (5/23)	NR	N/A
Caillot (2007)	Heme	Prospective RCT	LAMB+CAS HD LAMB	66% (10/15) 27% (4/15)	100% (15/15) 80% (12/15)	Yes (EOT p=0.028) and No (Day 90 p>0.05)
Raad (2008)	Heme/SCT	Retrospective cohort, open-label salvage	CAS+HD LAMB HD LAMB POS	11% (4/38) 8% (4/52) 40% (21/53)	26% (10/38) 35% (18/52) 57% (30/53)	Yes: POS vs. Both LAMB groups (p<0.05) [b]
Denning (2006) [d]	Any	Prospective, open-label (87% salvage)	MICA+OLAT MICA	34% (65/191) 44% (15/34)	NR NR	NR
Kontoyiannis (2009) [d]	SCT	Prospective, open-label (91% salvage)	MICA+OLAT MICA	24% (22/90) 38% (3/8)	NR NR	NR

References [111, 123–132]

NR not reported; N/A not applicable; Heme hematologic malignancies; SOT solid organ transplant; SCT stem cell transplant; RCT randomized control trial; EOT end-of-therapy; HD LAMB high-dose LAMB (10 mg/kg/day in Caillot 2007; ≥7.5 mg/kg/day in Raad 2008)

[a] Studies including 10 or more subjects

[b] In Popp 1999, clinical response and survival were determined at EOT. In Konyotyiannis 2005, survival was determined on day 30. In Maertens 2006, clinical response and survival were both assessed on day 84 (not EOT)

[c] In Konyotyiannis 2005, clinical response and survival were determined at EOT. In Popp 1999, survival was assessed on day 84 (not EOT)

[b] In Popp 1999, clinical response and survival were determined at EOT. In Konyotyiannis 2005, survival was determined on day 30. In Maertens 2006, clinical response and survival were both assessed on day 84 (not EOT)

[c] In Raad 2008, LAMB 5 mg/kg/day was used alone or in combination for 80% of the primary antifungal therapy, potentially skewing the results for the HD LAMB group

[d] Kontoyiannis 2009 published the SCT subset of patients previously included in the cohort published by Denning 2006

additive effect, indifference, and antagonism in 36, 24, 28, and 11% of in vitro reports ($n=27$) and 14, 20, 51, and 14% of animal studies ($n=18$), respectively [113]. An important and relevant factor in interpreting and applying these results is that combination antifungal in vitro testing has not been standardized. In fact, a recent study sponsored by the CLSI SAST suggests checkerboard testing for combination antifungal activity is not reproducible across laboratories [122].

Clinical Data

In a retrospective review of patients who were treated for IA at Memorial Sloan-Kettering Cancer Center between 1995 and 1997, a favorable response was found in 82% (9/11) who received itraconazole (ITRA) plus dAMB vs. 50% (5/10) of those treated with dAMB alone [123]. Kontoyiannis et al. retrospectively compared treatment of IA in a hematologic cancer population with lipid AMB with and without ITRA and found similarly poor results with either strategy (0 vs. 10% favorable response, $p > 0.05$) [124]. Finally, in a large retrospective analysis of ABLC use, the subset of patients receiving combination ITRA plus ABLC had a 33% (30/90) favorable response vs. the 47% favorable response seen in the ABLC monotherapy group [125]. In this study, there was a concern for selection bias: the investigators treating IA with combination therapy likely were doing so in response to the severity of the infection. Overall, there was neither clear antagonism nor synergy with combination ITRA plus AMB in these studies.

Marr et al. retrospectively reviewed 47 hematologic cancer patients with IA at Fred Hutchinson Cancer Research Center from 1997 to 2001 who received voriconazole (VOR) salvage therapy after failing either dAMB or LAMB primary therapy. Beginning in 2001, caspofungin (CAS) was administered in combination with voriconazole for salvage treatment routinely. The 63% (10/16) 3-month survival for the combination therapy group was statistically superior to 32% (10/31) in the voriconazole monotherapy group [126]. Combination VOR plus CAS vs. lipid AMB for primary therapy of IA was studied in solid organ transplant recipients in a prospective, multicenter observational study [127]. Ninety-day survival and percent successful outcome were comparable between the two groups. Lastly, in an open-labeled, noncomparative salvage study of IA in a hematologic patient population, CAS was administered with other antifungal agents. Although small numbers precluded formal statistical testing, day 84 treatment successes for CAS when combined with VOR, AMB, or ITRA were 54% (15/28), 50% (8/16), and 29% (2/7), respectively [128].

A retrospective analysis of 23 patients with hematologic malignancy and IA in 2001 evaluated the combination of CAS plus LAMB. Six patients received the combination as primary therapy, while 17 patients received salvage CAS plus LAMB after failing LAMB monotherapy. Unfortunately, overall clinical response at the end of therapy was a dismal 22% (5/23). Study limitations included evaluation of response to treatment at 20 days (median) at which time many patients were still neutropenic and absence of a monotherapy comparison group [129]. A second retrospective analysis of combination of CAS plus LAMB was performed by Raad et al. [111]. The three comparator groups included CAS plus high-dose (HD) LAMB (LAMB ≥7.5 mg/kg/day), HD LAMB alone, and posaconazole alone. End-of-therapy treatment success and 12-week survival were significantly worse in the HD LAMB plus CAS and HD LAMB monotherapy groups as compared to the patients who received posaconazole alone. Notably, 80% of patients had received primary therapy with LAMB 5 mg/kg/day either alone or in combination with other antifungal agents, which potentially skewed the data toward favoring posaconazole. The HD LAMB and HD LAMB plus CAS groups did not have significantly different outcomes.

The only randomized trial of combination anti-*Aspergillus* therapy published to date included 30 patients with hematologic malignancy and proven or probable IA. Patients were randomized to CAS plus LAMB 3 mg/kg/day vs. monotherapy with HD LAMB 10 mg/kg/day [130]. At end-of-therapy, the CAS plus LAMB group had a 66% (10/15) favorable response which was statistically superior to the 27% (4/15) clinical response in the monotherapy group. Nephrotoxicity was also more common in the HD LAMB group (23 vs. 7%); however, 12-week survival was not statistically different. Until further study, it is unknown whether the superiority of CAS plus LAMB was simply due to the lower dose of LAMB or the addition of caspofungin. At a minimum, the combination appeared to be well tolerated and the good outcomes were encouraging.

Micafungin (MICA) was evaluated in a study of treatment for pulmonary IA as either primary or salvage therapy and as either mono- or combination therapy from 1998 to 2002. One hundred ninety-one patients received micafungin in addition to the antifungal therapy they had already been failing, most commonly AMB or ITRA. Those receiving combination therapy in the salvage group had a 35% (60/174) favorable response [131]. The subset of stem cell transplant patients from this study was subsequently examined and found to have a 24% (22/90) vs. 38% (3/8) favorable response when comparing the MICA plus other licensed antifungal therapy vs. MICA monotherapy groups [132].

Studies demonstrating the safety of both inhaled ABLC [133, 134] and inhaled LAMB [135] in the setting of antifungal prophylaxis have been published. However, whether an inhaled AMB compound would penetrate tissue sufficiently to synergize with systemic antifungal therapy for documented invasive pulmonary aspergillosis has not yet been evaluated.

While it appears that combination antifungal therapy may confer some benefit in IA, this has not yet been rigorously tested in a randomized trial.

Summary

In conclusion a number of important factors are driving the use of echinocandins in combination with other antifungal agents, primarily voriconazole and lipid AMB, which include:

- The need for better clinical outcomes in IA
- The biologic plausibility of using a cell wall-active (AMB, azole) and a cell membrane-active (echinocandin) agent in tandem
- The favorable adverse effect and drug interaction profile of echinocandins
- In vitro and preclinical studies generally suggesting synergy without evidence of antagonism
- Noncomparative retrospective and prospective cohorts demonstrating benefit
- A single small prospective randomized trial showing benefit but having several limitations

Updated 2008 IDSA guidelines for IA state the following: "There are insufficient clinical data to support combination therapy as routine primary treatment of invasive pulmonary aspergillosis. Although initial laboratory studies, case reports, and retrospective case series indicate encouraging findings, the efficacy of primary combination antifungal therapy requires a prospective, randomized, clinical trial to justify this approach" [136]. We support this view as do two recent comprehensive reviews [121, 137]. A phase III prospective, randomized, double-blind trial comparing voriconazole monotherapy vs. combination voriconazole plus anidulafungin for primary therapy of proven or probable IA currently enrolling should help definitively conclude the efficacy of azole–echinocandin combination therapy for this disease. Until such data is available, combination therapy should be reserved for patients in whom voriconazole monotherapy has failed or is contraindicated and for high-risk patients with unusual or resistant isolates. In such cases, current data would suggest combination with an azole–echinocandin or LAMB–echinocandin to be reasonable options.

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Chapter 28
Fungal Drug Resistance and Pharmacologic Considerations of Dosing Newer Antifungal Therapies

Russell E. Lewis and David S. Perlin

Abstract Recent advances in hematopoietic cell transplantation and a broadening array of salvage chemotherapy options have extended the survival of patients with hematological cancers, but can result in prolonged periods of immunosuppression and susceptibility to invasive fungal infections. Among these high-risk patient populations, systemic antifungal therapy is administered episodically or sometimes continuously for months or even years, increasing concerns for the development of antifungal resistance. As newer triazoles (voriconazole and posaconazole) and echinocandins (anidulafungin, caspofungin, and micafungin) have supplanted amphotericin B formulations as the preferred antifungal therapies for primary and secondary prophylaxis, pharmacokinetic variability inherent to the triazoles as well as emerging patterns of intrinsic and acquired antifungal resistance are becoming increasingly important factors in the long-term management of invasive fungal infections. In this chapter, we review recent data concerning antifungal drug resistance for these newer azoles and echinocandins, as well as key considerations in drug dosing.

Keywords Echinocandins • Glucan synthase • Fks1 • Caspofungin • Anidulafungin • Micafungin • Triazoles • Fluconazole • Voriconazole • Posaconazole • Itraconazole • Erg11 • Pharmacodynamics • Therapeutic drug monitoring

Introduction

Invasive fungal infections continue to be a source of extensive morbidity and mortality in severely ill cancer patients due to limitations in diagnostics and treatment [1]. More antifungal agents are available to treat invasive fungal diseases than at any time in the past decades [2]. Yet, the management of these serious infections in cancer patients remains problematic because these agents represent restricted chemical classes and targets. The aggressive use of antifungal therapy, especially triazole antifungals, correlates with a shift in the epidemiology of fungal infections, as non-*albicans Candida* species, *Aspergillus* spp., and other moulds, which have emerged as leading causes of infection in the heavily immunosuppressed cancer patients [3–6]. Unfortunately, many of these emerging fungi are not only difficult to differentiate [diagnose] from more susceptible pathogens, but are also frequently less susceptible to other classes of antifungal agents.

The epidemiological landscape of invasive fungal infections in cancer patients has been further changed by new approaches towards chemotherapy of hematological malignancies and hematopoietic stem cell transplantation (HSCT). Expanding use of purine analogs (i.e., fludarabine, cladarabine) and antilymphocyte monoclonal antibodies (i.e., rituximab, alemtuzumab) as well as other targeted therapies have reduced early nonrelapse mortality associated with remission-induction or salvage chemotherapy, but can result in persistent lymphopenia lasting months after bone marrow recovery [7–9]. Likewise, infectious diseases mortality in the early phases of HSCT (day 0–40) has decreased with nonmyeloablative conditioning regimens, peripheral blood stem cell sources, and hematopoietic growth factors that are associated with more rapid engraftment and shorter periods of neutropenia [10, 11]. As a consequence, fungal infections (especially moulds) are now encountered much later after stem cell engraftment (i.e., days 100–300) when graft versus host disease and high-dose glucocorticoid therapy predominate as risk

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factors for infection [12]. Metabolic factors in chronically immunosuppressed and transfusion-dependent patients, including hyperglycemia/malnutrition and iron-overload, further predispose this population to a widening array of fungal pathogens [13]. Cancer patients are more likely than ever to exhibit a complex mosaic of mixed immunosuppression and increased environmental exposures and are more likely to have received hundreds of days of antifungal therapy prior to developing a clinically evident invasive fungal infection [13, 14].

Overview of Antifungal Resistance Mechanisms

Successful therapy of invasive fungal infections is influenced by a variety of factors including host status, drug pharmacokinetic/pharmacodynamic properties, and pathogen drug susceptibility. Yet, it is the latter property of drug resistance that has the potential to broadly diminish the effectiveness of entire classes of therapeutics. Drug resistance is best defined as clinical failure following a standard therapeutic dose and course. Primary resistance is the most significant factor contributing to antifungal drug resistance and it results from the selection of inherently less susceptible species (Table 28.1). Secondary or acquired resistance is less prevalent and refers to the induction of a biochemical mechanism that confers reduced susceptibility on a previously susceptible strain. The emergence of drug resistance is multifactorial and is influenced by host immune status, duration of immunosuppression, underlying disease, and total drug exposure. Recent global antifungal surveillance studies demonstrate that resistance varies with geography, as well as clinical service and the severity of disease with hematology/oncology units often showing the highest levels [5]. Patient exposure to a prior antifungal agent is also a risk factor for the development of resistant mould infections [15]. In fact, the epidemiology of mould infections in the past decade reflects a shift toward drug-resistant non-*fumigatus Aspergillus* species, *Fusarium* species, and Zygomycetes [16–18]. Zygomycosis is now observed in nearly 7% of patients at autopsy [19]. Triazole resistance in susceptible species like *Aspergillus fumigatus* is more common than once thought with an annual prevalence of 1.7–6% observed in the Netherlands [20]. In addition, multitriazole resistance has been reported following primary therapy and/or prophylaxis [21–23].

Many aspects of secondary or acquired antifungal resistance are still poorly understood, particularly with respect to the in vivo regulation and expression of resistance mechanisms. Nevertheless, advances in molecular biology and genomic sequencing of pathogenic fungi have yielded progress in our understanding of mechanisms most frequently leading to antifungal resistance. These mechanisms can be broadly grouped into five general categories (Fig. 28.1):

- Decreased drug import or increased drug export (efflux) [1, 2]
- Overproduction or alteration of the drug target binding site [3, 6]
- Gain of function mutations in transcriptional regulators of antifungal resistance [4]
- Diminished intracellular drug activation or modification [5]
- Changes in biosynthetic pathways (especially sterol synthesis) that circumvent or attenuate the effects of antifungal inhibition or binding [7]

Importantly, multiple mechanisms are often expressed simultaneously and can result in cross-resistance (depending on the time, sequence, and length of antifungal exposure) between unrelated classes of antifungals [24]. For example, genome-wide profiling of *Candida albicans* during exposure to triazole antifungals have shown transient up-regulation of several resistance mechanisms simultaneously, including ergosterol biosynthesis *ERG3, ERG11*; efflux pumps-*CDR1, CDR2;* and a transcriptional regulator-*Tac1* that regulates the expression of efflux pumps [25]. Unlike resistance with antibacterials, the development of antifungal resistance is generally associated with longer courses of therapy and a more gradual accumulation of several resistance mechanisms that result in laboratory-detectable resistance [26].

Newer Triazole Antifungals and Fungal Susceptibility

The newer triazole antifungals, voriconazole and posaconazole, are synthetic derivatives of fluconazole and itraconazole with improved spectrum of activity against moulds (Table 28.1). Like other triazole antifungals, voriconazole and posaconazole inhibit ergosterol biosynthesis in susceptible fungi through inhibition of the fungal cytochrome p450 enzyme, 14α-demethylase (CYP51p) [27]. Inhibiting ergosterol biosynthesis results in the accumulation of toxic 14α-methylated sterols in the cell membrane, which disrupts phospholipid membrane fluidity and membrane-bound enzyme systems, arresting fungal cell growth [28]. Drug binding is mediated through interactions of nitrogen in the triazole rings with the CYP51p heme target site, while the remainder of the drug molecule binds to the apoprotein in a manner dependent on the individual structure of the azole. For posaconazole, extension of a lipophilic side-chain expands the potency and spectrum of the triazole against both yeast and moulds, including *Aspergillus* and some species associated with mucormycosis. For voriconazole, inclusion of an α-*O*-methyl group confers activity against *Aspergillus* and some *Fusarium* species (Table 28.1) [27].

Table 28.1 Systemic antifungals: spectrum of in vitro activity

	A. flavus	A. fumigatus	A. niger	A. lentulus	A. terreus	Fusarium	C. albicans	C. krusei	C. glabrata	C. parapsilosis	C. neoformans	Coccidioides spp.	Blastomyces spp.	Histoplasma spp.	S. apiospermum	Zygomycetes
Amphotericin B	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	±
Fluconazole	–	–	–	–	–	–	+	–	±	+	+	+	+	+	–	–
Itraconazole	+	+	–	–	–	–	+	±	±	+	+	+	+	+	–	±
Posaconazole	+	+	+	±	+	+	+	+	±	+	+	+	+	+	+	+
Voriconazole	+	+	+	±	+	±	+	±	±	+	+	+	+	+	+	–
Caspofungln	+	+	+	–	+	–	+	+	+	±	–	–	–	–	–	–
Micafungin	+	+	+	–	+	–	+	+	+	±	–	–	–	–	–	–
Anidulafungin	+	+	+	–	+	–	+	+	+	±	–	–	–	–	–	–

+ Susceptible; – nonsusceptible; ± mixed susceptibility

Fig. 28.1 Mechanisms of antifungal resistance

One drawback of exploiting fungal CYP-450 as a target for antifungal chemotherapy is the homology of these enzyme targets with mammalian CYP-450 involved in drug metabolism. Modifications to azole pharmacophore which enhance binding to the fungal CYP51p target (and improved spectrum) are frequently associated with increased binding to mammalian CYP-P450 enzymes, increasing the risk for drug interactions [29]. Both voriconazole and posaconazole inhibit human CYP3A4, the pathway responsible for the metabolism of 50% of clinically administered drugs [30]. Therefore, coadministration of voriconazole or posaconazole with drugs metabolized through CYP3A4 results in markedly decreased (i.e., 50–90%) metabolism/elimination of the second drug [29]. Similarly, administration of broad-spectrum triazoles with inducers of Phase I/II metabolism (rifamycins, phenytoin, carbamazepime, etc.) can result in low or undetectable levels of these antifungals [29]. While many of these interactions are not clinically significant, some interactions affecting the pharmacokinetics of drugs with a narrow therapeutic index for efficacy (e.g., chemotherapy agents, immunosuppressants used in transplantation) or the blood levels of antifungals needed to treat life-threatening fungal infections carry the potential for serious harm. Concurrent use of these drugs with voriconazole or posaconazole should either be avoided or proactively monitored with dosing guided by serum drug concentration monitoring [31, 32].

Pharmacokinetic Variability as a Contributor to Clinical Failure with Voriconazole

Voriconazole is available in both intravenous and oral formulation, which in healthy volunteers demonstrates excellent oral bioavailability (96%) [33, 34], but exhibits wide inter-subject pharmacokinetic variability due to the extensive saturable metabolism of this triazole. Several studies have demonstrated that most of this pharmacokinetic variability is due to differences in the ability of patients to metabolize voriconazole via CYP2C19 P450 enzyme [33–35]. Polymorphisms in the gene-encoding CYP2C19 are common and result in variable rates of voriconazole metabolism. Patients who are homozygous extensive metabolizers of

CYP2C19 have less than one-fourth the average voriconazole plasma concentrations of patients who are homozygous poor metabolizers and one-half the average plasma concentrations compared to patients who are heterozygous extensive metabolizers [36]. While these polymorphisms can occur in any individual, the homozygous poor metabolism genotype is found most frequently (14–19%) in patients of Asian descent [35, 37]. In contrast, the homozygous poor metabolism genotype is only found in 2–5% of caucasians, while 26–28% are heterozygous extensive metabolizers and 70–73% are homozygous extensive metabolizers [35, 37]. In the absence of individual genotyping, it may be difficult to predict a priori the dose of voriconazole that will result in therapeutic or potentially toxic drug concentrations in the bloodstream.

Beyond the genetic status, other factors that have been shown to influence voriconazole pharmacokinetics include age, liver disease, comedications that induce or inhibit CYP-P450 enzymes, and changes from intravenous (weight-based) therapy to a fixed oral dose of 200 mg twice daily. For example, the change from a standard intravenous maintenance dose of 4 mg/kg every 12 h to a fixed 200-mg tablet administered twice daily results in dose reduction of approximately 33% and significantly lower plasma drug concentrations [36].

Intra- and interpatient pharmacokinetic variability of voriconazole may be sufficiently large in patients with acute hematological malignancies or following HSCT to require drug dosing guided by plasma drug level monitoring [36]. In a series of articles from Northwestern Memorial Hospital (Chicago, IL), Trifilio et al. [38–40] found that 18–27% of adult allogeneic hematopoietic stem cell transplant recipients who receive standard oral voriconazole doses may have subtherapeutic drug exposures. Importantly, the subtherapeutic exposures could not be predicted based on daily or weight-based (mg/kg) dose of voriconazole alone (Fig. 28.2a) [38]. The investigators also noted a significant temporal effect of transplant on voriconazole plasma concentrations, with one
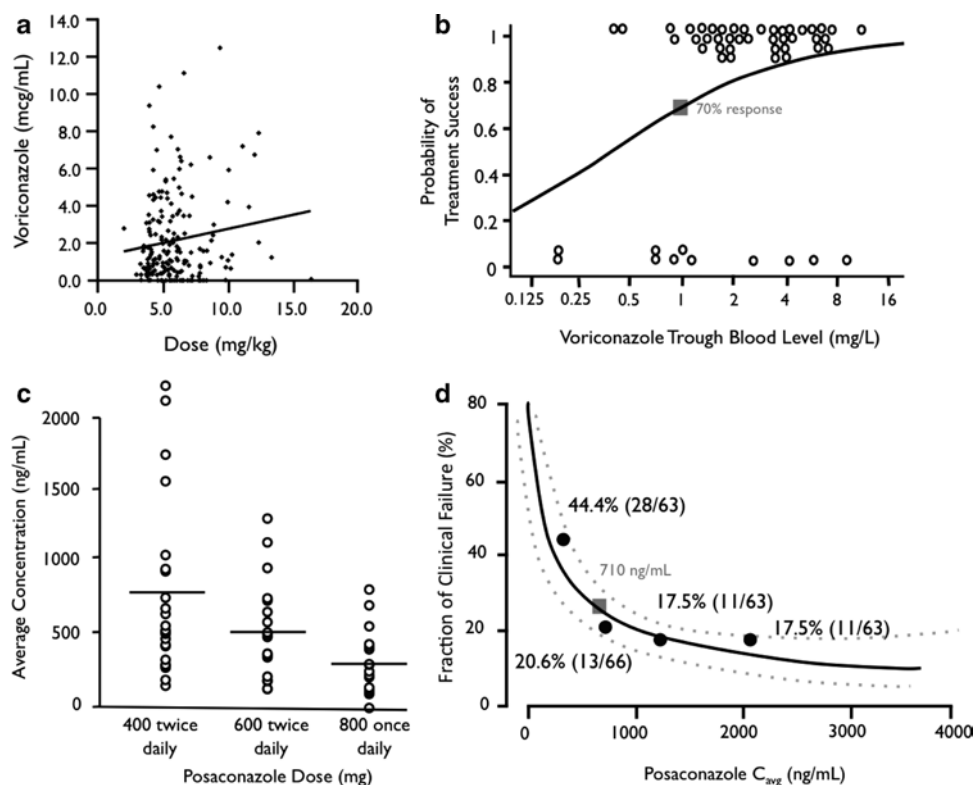
Fig. 28.2 Pharmacokinetic variability and relationship of plasma drug exposures to clinical failure for voriconazole and posaconazole. (**a**) Voriconazole trough concentrations exhibit a poor correlation with plasma trough concentrations [39]. (**b**) Logistic regression analysis of voriconazole trough concentrations from 52 patients receiving voriconazole for proven, probable, or possible invasive fungal infection demonstrating that log-transformed voriconazole trough level is a significant predictor of response to therapy: a twofold increase in blood level is associated with an OR for success of 1.8 (95% CI, 1.1–3.1; P = 0.03).

The logistic regression model indicates a 70% probability of response at a voriconazole trough concentration of 1 mg/L; [45] (**c**) Comparison of three posaconazole dosing schedule in febrile neutropenic patients revealing wide interpatient variability in drug exposure and dose-limited absorption; [54] (**d**) relationship between log-transformed posaconazole plasma exposures and risk of breakthrough invasive fungal infection during posaconazole prophylaxis; average drug concentrations <710 ng/mL were associated with an increased risk of breakthrough infection, P < 0.001 [36]

Table 28.2 Provisional guidelines for therapeutic drug monitoring of mould-active triazoles

Drug	Indication	Time of first measurement	Target blood concentration (μg/mL)-trough concentrations	
			Efficacy	Safety
Itraconazole	Routine during first week of therapy, lack of clinical response, GI dysfunction, suspected drug interactions	4–7 days	Prophylaxis >0.5; treatment >1–2	NA
Voriconazole	Lack of clinical response; GI dysfunction; suspected drug interactions; pediatric patients; severe hepatopathy, unexplained neurological signs or symptoms; monotherapy for documented infection	4–7 days	Prophylaxis >0.5; for treatment >1–2	Trough of <6
Posaconazole	Lack of clinical response; suspected poor absorption or compliance, concurrent H_2 or proton pump inhibitor therapy, possible drug interactions	4–7 days	Prophylaxis >0.5; for treatment trough >0.5–1.5	NA

Adapted from Andes et al. [36]

third of patients who previously determined to have therapeutic concentrations becoming subtherapeutic with subsequent tests – hence acceptability of a concentration on one occasion cannot be extrapolated to future concentrations in the same patient [41]. Therefore, close therapeutic drug monitoring and dose adjustment may be important in patients who have received an allogeneic HSCT due to the frequent use of prolonged voriconazole and changing liver function with GvHD.

Pediatric patients who receive voriconazole are at high risk for subtherapeutic dosing, due to their linear nonsaturable metabolism of the drug [42]. Maintenance doses of 7–14 mg/kg every 12 h may be required to achieve effective blood concentrations in children compared to the 6 mg/kg every 12 h recommended for adults. Because variability and subtherapeutic values are frequently observed in this population, monitoring of voriconazole plasma concentrations may be necessary in all pediatric patients receiving voriconazole [43].

Treatment outcome has been statistically linked to voriconazole plasma concentrations in several single-center retrospective and prospective studies [40, 44, 45]. In a prospective evaluation of 52 patients with invasive fungal infections who had over 180 concentrations determinations over 2,000 treatment days, patients with trough concentrations <1 μg/mL had lower clinical responses compared to patients with trough concentrations >1 μg/mL (50% vs. 90%, respectively; Fig. 28.2) [45]. Interestingly, reversible neurologic symptoms (confusion, hallucination, myoclonia) were observed in four patients with voriconazole trough concentrations >5.5 μg/mL – all of the patients were receiving the 2C19 inhibitor omeprazole. The probability of neurological symptoms in patients with voriconazole trough concentrations of 8 μg/mL or greater was >90%. Therefore, signs of encephalopathy occurring during voriconazole therapy should follow drug discontinuation or, if available in a timely fashion, plasma drug concentration determinations to ensure the patient does not have excessively elevated voriconazole plasma concentrations.

Toxicodynamic evaluation of data from Phase II–III clinical trials for voriconazole have demonstrated similar relationships between voriconazole plasma concentrations, the probability of developing self-limiting photopsia, and liver function test (LFT) abnormalities [46]. The median voriconazole plasma concentration for patients who develop visual abnormalities was 3.52 μg/mL versus 2.52 μg/mL in the symptom-free patients. However, therapeutic drug monitoring to reduce the risk of visual changes is not justified, due to the self-limiting and fully reversible nature of this adverse effect [36]. Hepatotoxicity with voriconazole is a greater concern and often manifests in the setting of multiple aggregate insults (i.e., viral reactivation, graft vs. host disease, high-dose chemotherapy, other medications). Therefore, assessment of a plasma voriconazole level could help identify whether excessive voriconazole exposures are potentially contributing to an evolving hepatotoxicity [36]. A toxicodynamic evaluation of voriconazole exposures and LFT abnormalities revealed the risk of significant abnormalities (defined as ≥2× upper limit normal for aspartate transaminase (AST) or alanine transaminase (ALT) or ≥3 mg/dL for total bilirubin) by 7–17% for every 1 μg/mL increase in random plasma voriconazole concentrations [46]. However, the overall risk for hepatic toxicity was low (<10%), suggesting that routine therapeutic drug monitoring to *prevent* hepatotoxicity is probably not useful beyond select situations of severe hepatic toxicity [47]. Provisional guidelines for monitoring voriconazole are presented in Table 28.2.

Pharmacokinetic Variability as a Contributor to Clinical Failure with Posaconazole

Unlike voriconazole, pharmacokinetic variability with posaconazole is primarily due to the saturable oral absorption of the drug, which is maximized with administration with

high-fat meals and in divided (three to four times daily) doses. Incomplete dissolution of the suspension in the gastrointestinal tract results in wide intra- and interpatient pharmacokinetic variability in both healthy volunteers and patient populations (Fig. 28.1c) [48–54]. Several factors have been shown to impact posaconazole absorption including high-fat meals, gastric pH (and the use of H_2 antagonists and proton pump inhibitors), mucositis, severe diarrhea, and the frequency of administration (due to saturable absorption) [36]. Administration of the oral posaconazole suspension with a high-fat meal (>50% of calories from fat) increases the mean AUC and maximum observed plasma concentrations (C_{max}) fourfold compared to fasted conditions [55]. Even a nonfat meal enhances posaconazole bioavailability, as mean AUC and C_{max} values increase 2.6- and 3-fold, respectively, compared with fasted conditions [55]. The importance of sufficient food intake for absorption of posaconazole can be problematic in cancer patients, particularly those who have nausea and vomiting, diarrhea and mucositis, or graft versus host disease involving the gut. Based on our clinical experience, one fourth to one third of patients with concomitant conditions or drugs that decrease posaconazole plasma concentrations have undetectable or near undetectable plasma concentrations at maximal doses (200 mg administered four times daily).

Although limited pharmacodynamic data are available, a single published trial that evaluated posaconazole as a salvage therapy reported the relationship of treatment response with randomly drawn plasma concentrations in a subset of 67 patients with refractory aspergillosis [56]. The patients in the lowest concentration quartile (≤0.13 μg/mL) had the poorest clinical response (20%). Patients with the highest response rates on salvage posaconazole therapy (70%) had average steady-state posaconazole concentrations of 1.25 μg/mL. Patients with plasma exposures in the middle two quartiles, 0.5–0.7 μg/mL, exhibited response rates of 53% [56].

A similar investigation of posaconazole plasma drug concentrations and risk of breakthrough fungal infection was explored in pivotal Phase III studies that examined the effectiveness of posaconazole prophylaxis in high-risk neutropenic patients or HSCT patients with graft versus host disease [57, 58]. Posaconazole concentrations were twofold lower in the cohort of patients who developed breakthrough invasive fungal infections ($n=5$) versus the cohort who did not develop infections ($n=241$; C_{avg} 0.611 vs. 0.922, respectively). Although these differences were not statistically significant due to the small numbers of patients who developed infection (2.4%), they do suggest that a threshold exposure level of posaconazole >0.6 μg/mL may be desirable to prevent the development of an invasive fungal infection [36]. Therefore, therapeutic drug monitoring of posaconazole

should be considered in patients with documented fungal infection or patients with suspected malabsorption who are receiving posaconazole prophylaxis. Guidelines for potential therapeutic drug monitoring approaches are outlined in Table 28.2.

Echinocandin Drugs and Fungal Susceptibility

The echinocandin class drugs, caspofungin, micafungin, and anidulafungin, are cyclic lipopeptides that inhibit glucan synthase, which is responsible for the biosynthesis of β-1,3-D-glucan, the central building block of fungal cell walls. Caspofungin, the first of this class, received FDA approval in 2001 for treatment of patients unresponsive to or who could not tolerate standard therapies for invasive pulmonary aspergillosis (IPA); it was followed by an expanded indication for empirical therapy in febrile neutropenic patients. Micafungin was approved in 2005 for the treatment of esophageal candidiasis and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation; the label was extended in 2008 to include patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis, and abscesses. Anidulafungin was approved in 2006 for the treatment of candidemia, esophageal candidiasis, *Candida* peritonitis, and intra-abdominal abscesses. Overall, these drugs display consistent pharmacokinetic–pharmacodynamic properties and demonstrate excellent safety and tolerability with few drug-related adverse events [59–61].

The echinocandin drugs are fungicidal with yeasts, including azole-resistant *Candida* strains [62], but they are only mildly fungistatic with most moulds causing irregular cellular and colony morphologies [63]. Although only caspofungin received an indication for treatment of invasive aspergillosis, all three echinocandin drugs show efficacy against *A. fumigatus* in animal models [64–66]. As weak in vitro antifungal agents against *Aspergillus* spp., the effectiveness of echinocandin drugs in treating such mould infections may reflect drug-induced changes at the surface cell wall in exposure of epitopes, such as glucans, which promote strong local immunological responses through the dectin and toll-like receptors [67, 68], as has been reported for *C. albicans* [69, 70]. Overall, the echinocandins show a more limited spectrum of activity than polyene or triazole drugs (Table 28.1). They are not effective against *Cryptococcus* spp., *Trichosporon* spp., *Fusarium,* and most Zygomycetes [71, 72]. In addition, some *Aspergillus* spp. such as *A. lentulus* spp., a sibling species of *A. fumigatus,* are resistant to echinocandin drugs [73].

MIC and Epidemiology of Echinocandin Resistance

The echinocandin drugs are highly active against *Candida* spp. where in vitro susceptibility testing by either standard CLSI or EUCAST methodologies reveals MIC values for a majority of strains in the submicromolar range [72, 74–76]. For this reason, the emergence of clinical isolates of *Candida* spp. with reduced susceptibility in normally susceptible strains is a concern for successful therapy. Yet, a complex relationship exists between MIC and clinical success, and an elevated MIC does not always foretell therapeutic outcome [77–79]. Modeling of pharmacokinetic and pharmacodynamic parameters in a neutropenic candidemia model revealed that a strong relationship exists between exposure and effect related to MIC, and the apparent discordance between MIC and clinical outcome is most likely related to a narrow MIC distribution window [80].

To assess in vitro drug susceptibility trends, more than 5,300 clinical isolates of *Candida* spp. collected globally over a 6-year period were evaluated for susceptibility to anidulafungin, caspofungin, and micafungin (Table 28.3) [76]. Overall, infecting strains retained their susceptibility over this period. In fact, it was determined for a wide range of species that greater than 99% of isolates were inhibited at ≤2 mg/mL for all echinocandin drugs [76]. On this basis, the CLSI Antifungal Subcommittee established a MIC ≤2 mg/mL, as an interpretive breakpoint for susceptibility of *Candida* spp. for all licensed echinocandin drugs [79]. The emergence of high MIC isolates of *Candida* above the breakpoint for normally susceptible strains is a risk factor for therapeutic failure, but a resistance breakpoint per se could not be assigned because of the small number of isolates evaluated [79]. It is important to recognize that as echinocandin drugs are exclusively delivered by intravenous route, they are extensively bound (97–99%) to serum protein [81], which modulates their antifungal properties [82–84]. The CLSI protocol M27-A3 does not take into account the influence of serum protein binding on the relative efficacy of echinocandin drugs, since it is a parameter that is difficult to standardize.

Breakthrough Infections and Fks Mutations

Breakthrough infections involving high MIC strains are encountered uncommonly. When they occur, mechanism-specific resistance has been reported for clinical isolates of *C. albicans, C. glabrata, C. krusei, C. dubliniensis, C. tropicalis,* and *C. parapsilosis* [85–94]. Breakthrough mould infections have also been reported following therapy with anidulafungin [95] or caspofungin [96]. Resistant isolates show cross-resistance across the entire class of echinocandin drugs. These strains retain sensitivity to other antifungal agents, which is consistent with a separate mechanism of resistance [97]. It is now well recognized that high MIC isolates of *Candida* spp. from patients failing therapy often contain amino acid substitutions in Fks subunits (Fks1p and/or Fks2p), which comprise the 1,3-β-D-glucan synthase complex [98]. The high MIC phenotype resulting from mutations in Fks subunits is a direct consequence of decreased biochemical sensitivity of glucan synthase to drug. Depending on the mutation, the drug sensitivity of the enzyme can be reduced several log orders, which renders the infecting strain highly cross-resistant to all echinocandin drugs [99]. This decreased biochemical sensitivity is observed as a comparable rise in the ED99 values for reduction of fungal burdens in animal models [86]. Yet, the fold decrease in enzyme sensitivity, as reflected in kinetic parameters IC_{50} or K_i, does not strictly correlate with an equivalent fold rise in MIC. Nevertheless, there is an unambiguous linkage between increasing values for these kinetic constants and MIC [99]. This tightly coupled relationship between K_i and MIC has been used recently to independently validate the new CLSI breakpoint of echinocandin drugs for *C. albicans* [99]. For caspofungin, nearly all clinical isolates containing *fks1* mutations were captured at MIC values ≥2 mg/mL, which fully supported the CLSI breakpoint. However, a threshold MIC value of ≥2 mg/mL was less inclusive for anidulafungin and micafungin, which typically display lower cut-off values [99]. These subtle differences are eliminated when MIC values are determined in the presence of serum, which allows 100% capture of *fks1*-resistant isolates at a breakpoint value of ≥2 mg/mL.

Table 28.3 In vitro susceptibilities of 5,346 clinical isolates of *Candida* species to anidulafungin, caspofungin, and micafungin

Species	Number of isolates tested	Anidulafungin		Caspofungin		Micafungin	
		MIC_{90}	% ≤2	MIC_{90}	% ≤2	MIC_{90}	% ≤2
C. albicans	2,869	0.06	100	0.06	100	0.03	100
C. glabrata	747	0.12	99.9	0.06	99.9	0.015	100
C. tropicalis	625	0.06	100	0.06	99.8	0.06	100
C. krusei	136	0.06	100	0.25	100	0.12	100
C. parapsilosis	759	2	92.5	1	99.9	2	100
C. guillermondii	61	2	90.2	1	95.1	1	100
All *Candida* species	5,346	2	98.8	0.25	99.9	1	100

Adapted from Pfaller et al. [76]

Fks-Mediated Resistance

The Fks mechanism of resistance is widely distributed among fungi accounting for echinocandin resistance in common *Candida* spp. [98]. Mutations conferring resistance are clustered in two highly conserved hot-spot regions of Fks subunits (Fig. 28.3). Most fungi contain multiple genes encoding glucan synthase, but the genes *FKS1* and *FKS2* are the most highly expressed. In *C. albicans* and several other *Candida* spp., *FKS1* is the most highly expressed of the genes and accounts for all resistance mutations. Resistance is dominant and mutation of a single allele in *C. albicans* is sufficient to confer a resistant phenotype [86]. In *C. glabrata*, *FKS1* and *FKS2* are expressed in nearly equal proportions, and hot-spot mutations conferring resistance occur readily in both genes [87, 91].

The Fks mechanism also helps account for reduced susceptibility in *Candida* spp. such as *C. parapsilosis* group and its siblings species *C. orthopsilosis* and *C. metapsilosis*. Most infections due to *C. parapsilosis* respond to primary echinocandin therapy [100]. Although clinical failures have been reported [85], there is evidence linking caspofungin usage to increased incidence of *C. parapsilosis* candidemia [101]. There is also a concern that the elevated baseline drug susceptibility may provide an initial step toward clinical resistance, especially in regions of the world like Latin America where *C. parapsilosis* infections are more common [102, 103]. Recently, it was demonstrated that a polymorphism in *C. parapsilosis* and related species at the C-terminal region of FKS1 hot-spot 1 confer moderate reduced sensitivity of glucan synthase to drug, which most likely accounts for the observed reduced susceptibility [104].

The Fks resistance mechanism appears ubiquitous within the fungal kingdom. In *A. fumigatus*, mutation of *FKS1* confers strong resistance to all echinocandin drugs [105]. Such mutations in *A. fumigatus* have not been observed clinically. However, a clinical strain with reduced susceptibility isolated from a patient on caspofungin therapy did show hyperexpression of *FKS1*, suggesting that an increase in the expression of the target can confer reduced susceptibility in *Aspergillus* [106].

Elevated MICs and Non-Fks Mechanisms

Echinocandin drugs induce enormous selection pressure on most fungi, since glucan synthase is required for cell growth, cell wall remodeling, and development [107]. Partial or complete inhibition of glucan synthase induces a wide array of compensatory cellular processes including cell wall integrity pathway and the molecular chaperones, such as HSP90 [108]. Many of these processes are regulated by the ubiquitous G-protein Rho1 and MAP kinase signaling cascades, which help modulate the cell wall in response to environmental stresses. These compensatory biological responses help account elevated MIC values [98] and have been implicated in the paradoxical effect, in which certain strains of *Candida* [109–111] and *Aspergillus* [112] become insensitive to drug at high concentrations. In at least one strain, a replacement of glucan as the major cell wall carbohydrate with chitin helped account for the phenomenon [110]. As drug levels required are above the highest serum levels achieved during normal patient dosing, the significance of the paradoxical effect based on animal models and limited clinical data remains unclear [111–113].

Summary

There is now convincing evidence that pharmacokinetic variability with newer mould-active triazoles contributes to the risk of clinical failure, and echinocandin resistance in breakthrough strains arises from genetic changes in two defined regions of the Fks subunits of glucan synthase. Therefore, patients with suspect absorption, poor clinical response, or unexpected toxicity should have determination of voriconazole or posaconazole plasma concentrations to determine if unexpectedly high or low drug exposures are contributing factors to lack of efficacy or observed toxicity. For echinocandins, the new susceptibility breakpoint provides a valuable measure of potential clinical response and could prove a useful determinant of emerging echinocandin resistance in *Candida* species. Yet, a direct assessment of Fks1 mutations may provide a more precise indicator of clinical outcome.

Fig. 28.3 FKS mutations (*yellow*) and polymorphisms (*blue*) in hot-spot regions conferring reduced susceptibility among *Candida* spp. Mutations in *green* do not confer changes in drug sensitivity

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Chapter 29
Immunotherapy for Difficult-to-Treat Invasive Fungal Diseases

Brahm H. Segal, Amar Safdar, and David A. Stevens

Abstract Opportunistic fungal diseases occur most commonly in highly immunocompromised patients, such as those with prolonged neutropenia or transplant recipients treated with intensive immunosuppression. Significant advances have been made in antifungal agents, which have led to improved therapeutic outcomes as well as a greater emphasis on antifungal prophylaxis targeted to the highly immunocompromised. In addition, we are gaining more knowledge about how our immune system recognizes fungi and protects us from fungal disease, while limiting potentially injurious inflammation and allergy. This knowledge has led to novel experimental approaches for immunotherapy. Progress in paving the way from promising preclinical approaches and limited clinical experience to properly conducted clinical trials has been poor – a reflection of invasive fungal diseases being relatively uncommon and the heterogeneity of the patient populations at risk, and insufficient funding for multicenter clinical immunotherapeutic trials. We describe our approaches to immunotherapy for severe and refractory invasive fungal diseases, realizing that important gaps in knowledge exist regarding benefit and toxicity. Future perspectives on immunotherapy are discussed.

Keywords Aspergillosis • Candidiasis • Fungal infection • Immunotherapy • Interferon-γ • Cytokines

Patients at Risk for Invasive Fungal Diseases

Yeasts and Dimorphic Fungi

Risk factors for invasive fungal diseases vary based on the specific fungal pathogen. *Candida* species are endogenous flora that colonize the skin, gastrointestinal, and vaginal mucosa. Candidemia generally requires disruption of barriers of the skin (e.g., from a central venous or dialysis catheter) or bowel mucosa (e.g., from mucotoxic chemotherapy or radiation) [1, 2]. Diseases caused by dimorphic fungi (e.g., histoplasmosis and coccidioidomycosis) occur in immunocompetent persons, but are more likely to be severe or disseminated in patients with compromised cellular immunity (e.g., HIV infection, transplant recipients) [3]. Host genes among different ethnic groups also appear to affect susceptibility to coccidioidomycosis [4]. *Cryptococcus neoformans* and *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) principally cause disease in patients with severe impairment in cellular immunity (Table 29.1).

Aspergillosis and Other Moulds

Risk factors for invasive aspergillosis and other moulds are complex. Patients at risk for invasive aspergillosis include those with prolonged neutropenia (e.g., following induction therapy for acute leukemia), hematopoietic stem cell transplant (HSCT) recipients, solid organ transplant recipients, advanced AIDS, and chronic granulomatous disease (CGD) [5].

In neutropenic patients, the degree and duration of neutropenia predict the risk of invasive mould diseases [6, 7]. Among allogeneic HSCT recipients, the early period of risk of invasive mould diseases corresponds to neutropenia following the conditioning regimen and later periods correspond to the intensity of immunosuppressive therapy required to control graft-versus-host disease (GVHD) [8]. In severe GVHD, global immune impairment occurs that affects both innate phagocyte function and cellular and humoral immunity. Several studies have reported the predominance of invasive aspergillosis cases occurring in the post-engraftment rather than in the neutropenic period in allogeneic HSCT recipients [9–16], with immunosuppressive therapy for GVHD and T-cell depletion [17] being principal risk factors.

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Table 29.1 Host defense deficits predisposing to invasive fungal diseases

Underlying diseases	Host defense impairment	Principal fungal pathogens
Acute myelogenous leukemia (AML), myelodysplastic syndrome, aplastic anemia	Neutropenia	*Candida* sp., *Aspergillus* sp., rarer moulds (e.g., zygomycetes, *Fusarium* spp., dark-walled moulds)
Acute lymphoblastic leukemia	Neutropenia; impaired cellular immunity due to corticosteroids	Similar spectrum as AML, plus *Pneumocystis jiroveci*
HTLV-1-associated hematological malignancies	Neutropenia; T-cell impairment	Similar spectrum as AML, plus *P. jiroveci*, *Cryptococcus neoformans*
Hematopoietic stem cell transplantation (HSCT) during neutropenia	Neutropenia	Similar spectrum as AML
HSCT during graft-versus-host disease	Global impairment in innate and antigen-driven immunity; risk of opportunistic infections related to intensity of immunosuppressive therapy for GVHD	*Candida* sp., *Aspergillus* sp., rarer moulds (e.g., zygomycetes, *Fusarium* sp., dark-walled moulds), *P. jiroveci*, dimorphic fungi, *C. neoformans*
Solid organ transplantation	Similar to allogeneic HSCT; risk of opportunistic infections related to intensity of immunosuppressive therapy to prevent allograft rejection	Similar spectrum as HSCT with GVHD
AIDS	T-cell impairment	Mucosal candidiasis, *P. jiroveci, C. neoformans*, dimorphic fungi; invasive aspergillosis is an uncommon complication of advanced AIDS (CD4 count <100 per μl; concurrent risk factors, e.g., neutropenia)
Collagen vascular diseases	Risk of opportunistic infections related to intensity of immunosuppression, e.g., dose and duration of corticosteroids, use of alkylating agents, TNF-α inhibition	Mucosal candidiasis, *P. jiroveci, C. neoformans*, dimorphic fungi; invasive aspergillosis is an uncommon complication
Chronic granulomatous disease	NADPH oxidase deficiency	Aspergillosis, rarer moulds

Purine analogues and alemtuzumab used to treat hematological malignancies (e.g., chronic lymphocytic leukemia) cause prolonged T-cell suppression that can persist from months to more than a year. Prophylaxis to prevent *P. jiroveci* infection is standard among alemtuzumab recipients. Indeed, multiple host defense pathways may be disabled by immunodeficiencies associated with the primary malignancy and cytotoxic and immunosuppressive agents.

Among solid organ transplant recipients, the intensity of immunosuppression to control graft rejection is the major predictor of opportunistic fungal and viral diseases. The incidence of invasive aspergillosis is higher after lung transplantation compared to other allografts [18]. *Aspergillus* species colonizing the airways in end-stage lung disease may be a source of fungal infection following single-lung transplantation [19].

The phagocyte NADPH oxidase is essential in host defense against aspergillosis and rarer moulds, as illustrated by chronic granulomatous disease (CGD), an inherited disorder of the NADPH oxidase complex in which phagocytes are defective in generating the superoxide anion and downstream reactive oxidant intermediates, hydrogen peroxide, hydroxyl anion, and hypohalous acid. CGD patients suffer from recurrent life-threatening bacterial and fungal infections, with invasive aspergillosis being a major cause of mortality [20, 21].

Principles and Challenges for Immunotherapy

The first decision point when considering immunotherapy for an invasive fungal disease is whether iatrogenic immunosuppression (e.g., corticosteroids) could be reduced or eliminated. This may not be feasible. For example, a certain level of immunosuppression is required for allograft survival following solid organ transplantation.

Immunotherapy must be tailored to the specific immunodeficiency that exists in a given patient population. This concept is straightforward for neutropenia in which the aim is to augment neutrophil number, e.g., by colony stimulating factors (CSF) or granulocyte transfusions. In GVHD, the immune impairment is more complex; the immunotherapeutic strategy may at best ameliorate some features of the immunocompromised state, but would not reconstitute for a sustained period all of the disabled host defense pathways. In addition, a potential exists that attempts to augment anti-fungal immunity may exacerbate GVHD (or prime allograft rejection in solid organ transplant recipients).

Finally, there is no adjunctive immunotherapy for invasive fungal diseases that has established efficacy. In the absence of modern, randomized, clinical trials, decisions about using

Table 29.2 Evidence supporting immune augmentation strategies to prevent and treat invasive fungal diseases

Host defense impairment	Immune augmentation (rating[a])
Neutropenia (absolute neutrophil count <500 per μl)	• Prophylactic G-CSF or GM-CSF in patients with at least 20% risk of developing neutropenic fever (2A) [28]
	• G-CSF or GM-CSF as adjunctive treatment for patients with fever and neutropenia (not routinely recommended) [28]
	• G-CSF or GM-CSF as adjunctive therapy for an invasive fungal disease (guidelines vary between 2A and 2B) [28, 98, 99]
	• Prophylactic granulocyte transfusions (not recommended)
	• Granulocyte transfusions as adjunctive therapy for an invasive fungal disease refractory to standard antifungal therapy (2B) [98, 99]
	• Prophylactic rIFN-γ (not recommended)
	• rIFN-γ as adjunctive therapy for an invasive fungal disease refractory to standard antifungal therapy (2B) [98]
Allogeneic HSCT recipients without neutropenia	• Reduce intensity of immunosuppressive therapy if feasible (uniform agreement)
	• Prophylactic G-CSF, GM-CSF, or rIFN-γ (not recommended)
	• G-CSF, GM-CSF, rIFN-γ, or combination as adjunctive therapy for an invasive fungal disease refractory to standard antifungal therapy (2B) [98]
Solid organ transplant recipients	• Reduce intensity of immunosuppressive therapy if feasible (uniform agreement)
AIDS	• Highly active antiretroviral therapy is the most effective mode to reconstitute immunity; be aware of immune reconstitution inflammatory syndrome [100]
	• rIFN-γ as adjunctive therapy for AIDS-associated cryptococcal meningitis (2B) [59]
Chronic granulomatous disease	• Prophylactic rIFN-γ (1A) [58]
	• Adjunctive rIFN-γ for invasive fungal disease (2B)
	• Granulocyte transfusions as adjunctive therapy for an invasive fungal disease refractory to standard antifungal therapy (2B) [101]
	• Adjunctive colony-stimulating factors (not routinely recommended)

[a]Level 1, uniform consensus based on high level of evidence (e.g., randomized trial); 2A, lower level of evidence than randomized trial, but recommended in authoritative guidelines; 2B, recommendation based on clinical experience, with lack of expert consensus

adjunctive immunotherapy reasonably entail consideration of a number of factors, including the following: (1) immunotherapy may be used as a salvage approach when standard antifungal agents fail; (2) the use of immunotherapy may be supported by in vitro studies and animal models; (3) limited support may exist from retrospective studies or early phase clinical trial data. Table 29.2 summarizes the level of evidence supporting immune-based therapies in specific patient populations.

Augmentation of Neutrophil Number

Colony Stimulating Factors

Normal myelopoiesis requires stem cell factor, interleukin 3 (IL-3), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which give rise to the colony forming unit-granulocyte/macrophage (CFU-GM). Granulocyte-colony-stimulating factor (G-CSF) acts at a later stage in concert with other growth factors to specifically drive granulopoiesis. The rationale for administration of recombinant CSFs is to accelerate myeloid recovery in patients with marrow failure either from an underlying hematological disorder or, more commonly, from cytotoxic chemotherapy.

CSFs can be administered as prophylaxis (prior to the onset of infection or neutropenia), or as adjunctive therapy to treat a suspected or documented infection. There is a substantial randomized database on use of prophylactic CSFs in patients receiving cytotoxic antineoplastic chemotherapy [22]. Primary (prophylactic) administration of colony stimulating factors CSFs has reduced the incidence of febrile neutropenia by approximately 50% in randomized trials in adults in whom the incidence of neutropenic fever was greater than 40% in the control group [23]. In patients with acute myelogenous leukemia, CSFs produce a modest decrease in the duration of neutropenia associated with induction chemotherapy, which in some studies has translated into a reduction in the duration of fever, use of antibiotics, and hospitalization [24, 25]. In one randomized study in patients receiving chemotherapy for acute myelogenous leukemia, prophylaxis with granulocyte-macrophage colony-stimulating factor (GM-CSF) led to a lower frequency of fatal fungal infections compared to placebo (1.9 versus 19%, respectively) and reduced overall early mortality [26, 27]. This degree of reduction in invasive fungal diseases has not been observed in other randomized studies of prophylactic CSFs; in addition, the value of CSFs in preventing fungal diseases in patients receiving mould-active prophylaxis has not been established.

The American Society of Clinical Oncology (ASCO) [28] and National Comprehensive Cancer Network [29] have established authoritative guidelines related to which patients should receive prophylactic CSFs. The principal rationale

for prophylactic CSFs is to reduce the incidence of neutropenic fever. ASCO guidelines advise a prophylactic CSF when the risk of neutropenic fever is approximately 20% and no other equally effective regimen that does not require CSFs is available [28].

The rationale for CSFs for established infections (referred to as adjunctive therapy, as opposed to prophylaxis) stems from both the quantitative and qualitative effects of these agents on phagocytic cells. In neutropenic patients with life-threatening infections, survival is strongly influenced by the rapidity of neutrophil recovery [30]. Although the benefit of a CSF for established infections in neutropenic patients is unproven, ASCO guidelines reasonably advise that a CSF be considered in serious infections, such as invasive fungal diseases [28].

Some studies in vitro [31] and in animal models [32, 33] show that G-CSF or GM-CSF add to antifungal activity when combined with antifungal agents. A Phase II randomized study of G-CSF plus fluconazole for invasive candidiasis and candidemia in non-neutropenic patients showed the safety of G-CSF, but was not powered for efficacy [34].

There are insufficient data to guide whether G-CSF or GM-CSF is preferred as adjunctive therapy for an invasive fungal disease. G-CSFs act only on neutrophils, whereas GM-CSF also accelerates the proliferation of the monocyte–macrophage system, and is a potent activator of monocytes and macrophages [35].We do not know if the broader effect of GM-CSF on innate effector cells translates to clinical benefit in patients with invasive fungal diseases.

In allogeneic HSCT recipients, G-CSF, but not GM-CSF, may result in Th2 skewing of lymphocytes and promote the development of T regulatory cells, which could dampen a desired pro-inflammatory effect [36, 37]. G-CSF given after T-cell depleted haplotype-mismatched transplantation was associated with faster neutrophil recovery, but prolonged cellular immune dysfunction [38]. Prospective, randomized trials are required to assess the short-term benefits versus long-term immune consequences of CSFs in allogeneic HSCT.

Another gap in knowledge is whether CSFs are safe and effective as either prophylaxis or adjunctive therapy in non-leukopenic patients with severe impairment in phagocyte function. GM-CSF has been demonstrated to reverse the steroid-induced depression of macrophage activity against *Aspergillus* conidia [39]. However, in case reports of patients with neutropenia, CSF therapy has been linked to pulmonary hemorrhage in patients with pulmonary aspergillosis [40]. Triggering of inflammatory reactions by CSFs could produce undesirable deterioration of organ functions. Intensive immunosuppressive corticosteroid-based regimens for GVHD cause global impairment of phagocyte effector functions and disable reconstitution of antigen-specific immunity, though circulating neutrophil counts are generally normal. There are no clinical data to support prophylactic CSFs in non-neutropenic patients, and they should not be used as

prophylaxis in this setting in the absence of supporting clinical trial data. In severely immunocompromised non-neutropenic patients (e.g., allogeneic HSCT recipient) with a refractory invasive fungal disease, it is reasonable to consider adjunctive GM-CSF to augment qualitative macrophage and neutrophil functions. We emphasize that the data on safety of CSFs in non-neutropenic patients is retrospective [41] and, outside of a clinical trial, should generally be reserved for when standard therapy fails.

Granulocyte Transfusions

The rationale for granulocyte transfusions is to provide transient elevations in circulating neutrophil counts for the neutropenic patient with a life-threatening infection until myeloid recovery occurs. Important concerns about the toxicity of granulocyte transfusions exist, including acute pulmonary reactions, HLA alloimmunization (which could render patients refractory to platelet transfusions and potentially impair myeloid engraftment following HSCT), and transfusion-associated infections, such as cytomegalovirus (CMV).

With more effective antibiotics, the interest in granulocyte transfusions waned in the 1980s. In the 1990s, the impetus to reexamine the role of granulocyte transfusions stemmed from improvements in donor mobilization methods. G-CSF and dexamethasone mobilization leads to as much as a tenfold increase in the yield of granulocytes that translates to improved levels of circulating neutrophils in neutropenic recipients [42]. The increase in circulating neutrophils tends to be sustained for 24–30 h following transfusion, as a consequence of prolonged circulating half-life of G-CSF mobilized granulocytes [43]. The qualitative functions of G-CSF- and steroid-mobilized neutrophils are intact based on in vitro bactericidal activity, respiratory burst, migration to experimental skin chambers, and localization to sites of inflammation.

Price et al. [44] conducted a phase I/II study of granulocyte transfusions derived from unrelated, non-HLA-matched, community donors, following G-CSF and dexamethasone mobilization. Chills, fever, and oxygen desaturation of ≥3% occurred in association with 7% of transfusions, but did not limit therapy. Eight of 11 patients with bacterial infections or candidemia survived, but all eight patients with invasive mould infection died. This study showed the safety and feasibility of using community donors for granulocytapheresis donations. The Transfusion Medicine and Hemostasis network of the National Heart Lung and Blood Institute is currently in the planning stages of a randomized study of adjunctive granulocyte transfusions in neutropenic patients with severe bacterial and fungal infections.

Currently, there is no justification outside of a clinical trial to use granulocyte transfusions either as prophylaxis or

in cases of documented infections that are likely to respond to conventional therapy. We reserve granulocyte transfusions for patients with prolonged neutropenia and life-threatening infections refractory to conventional therapy. Filamentous fungi are likely to constitute the majority of such refractory infections. Infusions of amphotericin B should be separated by several hours from granulocyte transfusions to avoid pulmonary toxicity [45]. In some highly alloimmunized patients, transfused granulocytes are rapidly consumed and are likely to have more toxicity than benefit [46]. Monitoring of post-transfusion granulocyte counts is advised. CMV-seronegative granulocyte donors should be used in allogeneic HSCT recipients where both the allograft donor and recipient are CMV-seronegative [47].

Recombinant Interferon-γ

Interferons are immune modulators that regulate the expression of numerous genes that mediate inflammation. Interferon-α is a cornerstone of therapy for chronic hepatitis C infection [48]. Several laboratories have shown that interferon (IFN)-γ augments the antifungal activity of effector cells (macrophages and neutrophils) ex-vivo against a variety of fungal pathogens, including *Candida albicans*, *Histoplasma capsulatum*, *Coccidioides* species, *C. neoformans*, and *Aspergillus* species [49–51]. Data in mouse models using cytokine depletion, gene knockout mice, and administration of exogenous cytokines have been instrumental in establishing the conceptual basis for immunotherapy in invasive mycoses and in paving the way to early clinical trials [52]. We will focus our discussion on rIFN-γ because the database is the most developed.

IFN-γ is produced by lymphocytes (CD4+, CD8+, and NK cells) as well as macrophages and perhaps neutrophils [53]. It is induced by a number of signals, including IL-12 and IL-18 [54, 55] and in turn induces hundreds of genes, including its own inducers [56, 57]. Exposure to various pathogens can stimulate at least two patterns of cytokine production by CD4+ T cells. Th1 cells are defined by production of IFN-γ, lymphotoxin and IL-2, and Th2 cells by production of IL-4, IL-5, IL-9, IL-10, and IL-13. The antimicrobial activity induced by IFN-γ encompasses intracellular and extracellular parasites, bacteria, fungi, and viruses. In patients with hematologic malignancies, use of rIFN-γ as adjunctive therapy for invasive fungal diseases has attracted substantial interest.

Recombinant IFN-γ is licensed as a prophylactic agent in patients with CGD based on a randomized trial in which IFN-γ reduced the number and severity of infections in CGD by about 70%, regardless of antibiotic prophylaxis or genetic subtype of CGD [58]. Despite the widespread use of prophylactic rIFN-γ in CGD, invasive fungal diseases have remained a persistent problem with an incidence of 0.1 fungal infections per patient year predating routine mould-active prophylaxis [20].

The value of rIFN-γ as adjunctive therapy for established fungal infection is unknown. Pappas et al. [59] conducted a phase II placebo-controlled study of adjunctive rIFN-γ in patients with AIDS-associated cryptococcal meningitis. rIFN-γ was well tolerated and the IFN-treated group showed a trend toward improved combined clinical and mycologic success.

Studies in vitro, in animal models [60], and limited patient data provide a rationale for adjunctive IFN-γ for invasive aspergillosis [61]. rIFN-γ augmented human neutrophil oxidative response and killing of *Aspergillus fumigatus* hyphae in vitro and acted additively with G-CSF [62]. It prevented corticosteroid-mediated suppression of neutrophil killing of hyphae [63]. rIFN-γ also enhanced killing of *A. fumigatus* hyphae by human monocytes [64]. Administration of rIFN-γ to CGD patients augmented ex vivo neutrophil-mediated damage of *A. fumigatus* hyphae [65].

Dignani et al. [66] reported successful outcomes using rIFN-g paired with CSFs in four patients with leukemia and refractory fungal disease. One concern about rIFN-γ in allogeneic HSCT recipients is the potential for worsening GVHD. Safdar et al. [67] retrospectively evaluated rIFN-γ use in 25 allogeneic HSCT recipients with proven or suspected invasive fungal disease. rIFN-γ was well-tolerated and did not result in marrow suppression or worsening of GVHD. In another retrospective analysis, combination granulocyte transfusions and rIFN-γ appeared to be safe in neutropenic patients with hematological malignancies and severe infections [68]. This database is exploratory and does not permit conclusions about efficacy of rIFN-γ as the sole immune adjuvant or paired with CSFs and/or granulocyte transfusions.

We reserve rIFN-γ for patients with life-threatening invasive mould infections refractory to standard antifungal therapy. Such decisions are necessarily based on retrospective analyses and anecdotal data. Pairing rIFN-γ with G-CSF or GM-CSF is another reasonable option in the setting of refractory fungal disease, though we emphasize that the clinical experience is anecdotal and that the efficacy of this approach is not established.

Antifungal Agents as Immunomodulators

Another area of research interest relates to the immunomodulatory effect of antifungals. Fungal cell wall constituents on opportunistic fungi are ligands for Toll-like receptors (TLR) and other innate pathogen recognition receptors [50, 69, 70]. Recognition of pathogen-associated molecular patterns by

TLRs, either alone or in cooperation with other TLR or non-TLR receptors (e.g. Dectin-1), induces signals responsible for the activation of the innate immune response. Several studies have demonstrated a crucial involvement of TLRs in the recognition of fungal pathogens such as *C. albicans*, *A. fumigatus*, and *C. neoformans* [50, 70–74]. In vivo, antifunga;s decrease the antigen load, which alone can help restore Th1 responses.

One example of the immunologic effect of antifungals is the infusional toxicity of amphotericin B that likely results from release of proinflammatory cytokines from monocytes [75, 76]. Other antifungal agents may have more indirect effects on host cell responses. Amphotericin B deoxycholate and liposomal amphotericin B have distinct effects on TLR signaling and antifungal activity of murine neutrophils [77]. Empty liposomes attenuated the immunopathology in experimental aspergillosis [78]. Echinocandins cause structural changes in the fungal cell wall, including blebbing and cell wall rupture [79, 80]. The beta-glucan constituent of the fungal cell wall is recognized by specific host cell pathogen recognition receptors and elicits immunologic responses [69, 81–85]. Echinocandins can unmask the beta-glucan constituents of fungal cell walls of Candida and filamentous fungi, leading to modulation of the immune response in macrophages and neutrophils [86–88]. In addition, compensatory cell wall synthesis pathways are likely to be induced by beta-glucan depletion [89], which may further alter antigenic cell wall epitopes. Other possibilities for antifungal-cytokine interactions includes the probability that cytokines can enhance uptake of antifungals by effector cells, and that effector cell antifungal mechanisms (e.g., oxidative metabolites) act synergistically with antifungal effects on fungi. Antifungals also appear to increase pro-inflammatory cytokines at a transcriptional level, inhibit anti-inflammatory cytokines, act synergistically with cytokines to induce protective proinflammatory responses, and prime effector cells for a second signal from cytokines. In vivo, antifungals decrease the antigen load, which alone can help restore Th1 responses.

We do not know the clinical significance of the immunomodulatory properties of antifungal agents. To gain at least correlative data, it would be useful if immunologic studies were included as secondary endpoints in future clinical trials.

Summary

There is currently insufficient proof that any immune-based therapy is effective for invasive fungal diseases. Knowledge of the immunopathogenesis of fungal infections has paved the way to promising strategies for immunotherapy at the preclinical level. These include strategies that increase phagocyte number, activate innate host defense pathways in phagocytes and dendritic cells, and stimulate antigen-specific immunity, such as vaccines [90–94]. Newer approaches, with supporting preclinical data, include infusion of donor T cells sensitized against *Aspergillus*, the use of monoclonal antibodies directed against protein and/or carbohydrate epitopes of pathogenic fungi, or against cytokines which depress the Th1 response, synthetic immunomodulators which act as TLR agonists [95], the therapeutic use of collectins, such as mannose-binding lectin [96], or gene therapy to deliver cytokines to the infected host [96a]. Studies of adjunctive immunotherapy for established infection should target specific well-defined patient groups to maximize the likelihood of detecting a treatment effect. Kullberg et al. [97] reasonably suggest that Phase I and II studies of immunotherapies focus on laboratory surrogates likely to predict efficacy (e.g. augmenting neutrophil number or type I cytokine responses) that would pave the way to larger studies that evaluate clinically relevant endpoints (e.g., survival, successful control of infection).

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Chapter 30
Cytomegalovirus in Patients with Cancer

Morgan Hakki, Per Ljungman, and Michael Boeckh

Abstract Human cytomegalovirus (CMV) is a common opportunistic infection after hematopoietic cell transplant (HCT) and is less frequently encountered among patients undergoing cytotoxic chemotherapy for various malignancies. Both primary infection and reactivation can result in substantial morbidity and mortality in the immunocompromised host. Therefore, the prompt recognition and treatment of CMV infection is critical. This chapter will outline the diagnosis, prevention, and treatment of CMV, focusing on the HCT recipient since it is this population that is at greatest risk for, and bears the largest burden of, CMV infection and disease.

Keywords Cytomegalovirus • Cancer • Stem cell transplant

Virus Structure and Replication

CMV, along with human herpesvirus (HHV)-6 and HHV-7, is a member of the beta (β) subfamily of the herpesviridae. The virion consists of a double-stranded DNA genome encased in an icosahedral capsid. Surrounding the capsid are the tegument (or matrix) and an outermost lipid membrane.

The genome contains approximately 230,000 base pairs of DNA that encode approximately 200 proteins [1, 2]. CMV genes are named based on their position within each segment of the genome. For example, UL97 is the 97th open reading frame (ORF) in the unique long segment. Some genes also have names based on historical usage or homologies to genes of other herpesviruses; UL55, for example, is also known as glycoprotein B.

CMV grows in a limited number of cell lines in the laboratory, such as diploid human fibroblasts, endothelial cells, and macrophages. During human infection, however, CMV has been found in a wide range of cells, including endothelial cells, epithelial cells, blood cells including neutrophils, and smooth muscle cells [3]. The presence of CMV in these cells may contribute to dissemination and transmission.

The ability to persist in a latent state in which evidence of viral replication is undetectable but replication-competent virus is present is a hallmark of herpesviruses. In the case of CMV, little is known about the site or mechanisms of latency. Since CMV can be transmitted from seropositive blood donors, a blood component is likely to be one site of latency. Several studies indicate that cells of the granulocyte-monocyte lineage harbor latent CMV [4–6]. Transplantation of solid organs clearly can transmit CMV, so it is possible that cells other than those mentioned above can harbor and transmit latent CMV.

CMV and Host Immunity

Adaptive Immunity

The importance of a competent immune system in controlling CMV replication is manifested by the clear association of immunosuppression with CMV infection and disease. The role of humoral immunity in controlling CMV replication is not clear. While antibodies to multiple different CMV proteins, primarily glycoproteins B (gB), and H (gH), develop during infection, they do not appear to prevent primary infection in adults, but rather may function to limit disease severity [7–11].

CMV provokes a robust CD8+ cytotoxic T lymphocyte (CTL) response and the percentage of circulating CD8+ T cells in healthy individuals that are CMV-specific may be as high 40% [12–17]. The most dominant proteins targeted by CD8+ T-cell responses are the products of UL123 (IE-1), UL122 (IE-2), and UL83 (pp65) [14, 17–23]. The importance of intact T-cell mediated cellular immunity in controlling CMV replication is demonstrated by studies correlating the lack of CMV-specific CD8+ CTL responses with CMV

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infection, and the reconstitution of CMV-specific CD8+ CTL responses with protection from CMV [24–28]. The presence of multifunctional CMV-specific CD8+ T cells have been associated with less recurrent CMV reactivation in seropositive hematopoietic cell transplant (HCT) recipients.

After HCT, detectable CMV-specific CD4+ T-cell responses are associated with protection from CMV disease [24, 29–31]. The lack of CMV-specific CD4+ T-cell is associated with late CMV disease and death in patients who have undergone HCT [32]. CMV-specific CD4+ cells likely function at least in part by helping to maintain robust CMV-specific CD8+ cell responses [28, 33].

Innate Immunity

Less is known about the role of innate immunity in controlling CMV replication, but evidence exists indicating that this arm of the immune response is indeed required to control CMV replication. CMV triggers cellular inflammatory cytokine production upon binding to the target cell, mediated in part by the interaction of gB and gH with toll-like receptor (TLR) 2 [34–36]. Polymorphisms in TLR2 have been associated with CMV infection after liver transplantation [37]. In mouse studies, TLR3 and TLR9 proved to be important components in limiting murine cytomegalovirus (MCMV) replication [38, 39].

Natural killer (NK) cells represent another arm of the innate immune response and have been shown to limit MCMV replication in mice [25, 40–44]. In humans, a deficiency in NK cells is associated with severe CMV infection

(among other herpesviruses) [45]. The genotype of the donor activating killer immunoglobulin-like receptor (aKIR), which regulates NK cell function, is associated with the development of CMV infection after allogeneic HCT [46–48]. These findings require validation in independent cohorts.

Finally, polymorphisms in chemokine receptor 5 (CCR5), IL-10, and monocyte chemoattractant protein 1 (MCP-1) have been associated with CMV reactivation and disease after allogeneic HCT [49]. Validation of these associations in independent cohorts is lacking at this time.

Immune Evasion

Numerous CMV-encoded genes function in immune evasion by inhibiting apoptosis [50], MHC-I restricted antigen presentation [51], and interferon-mediated pathways [52–55]. CMV also encodes several homologues of cellular proteins, including MHC class-I molecules, chemokine receptors, IL-10, TNF receptors, and CXC-1 homologues, that function to help CMV evade the host immune response [56–60].

Diagnostic Methods

Several assays are available to assist in the diagnosis of CMV. The strengths and limitations of these assays are summarized in Table 30.1. The serologic determination of IgG and IgM has an important role in determining a patient's risk for CMV infection after transplantation (see below, Section E)

Table 30.1 Methods utilized in the diagnosis of CMV infection and disease

Assay	Tumaround time	Advantages	Disadvantages
Histology	24–48 h	Specific	Low sensitivity
		Useful in determining invasive disease	Utility limited to tissue biopsy specimens
Serology	<24 h	Provides prognostic information regarding risk of CMV during HCT	Not useful in diagnosis of acute infection or disease
Culture	Up to 6 weeks	Specific	Low sensitivity
		Allows for phenotypic antiviral susceptibility testing	Long assay time
Shell vial	24–48 h	Specific	Low sensitivity compared to molecular assays
		More rapid than culture	
		Test of choice on BAL fluid	
pp65 antigenemia	<24 h	Rapid	Unable to perform in setting of profound neutropenia
		More sensitive than culture	Not as sensitive as PCR
		Provides approximate quantitation of viral load	Only validated on whole blood
Quantitative DNA PCR (qPCR)	<24 h	Most sensitive assay	Requires technical expertise
		Highly specific	Not validated on BAL fluid, tissue biopsy specimens Interlaboratory variability
		Provides direct quantitation of viral load	
pp67 mRNA NASBA	<24 h	More sensitive than culture	Less sensitive than DNA qPCR
		Specific for replicating virus	Qualitative
			Requires technical expertise

or during immunosuppressive therapy, but is not useful in the diagnosis of CMV infection or disease. Growth of CMV in tissue culture takes several weeks, limiting its clinical usefulness as a diagnostic tool. Culture-proven viremia is highly predictive of CMV disease, but is of limited utility for screening since this finding frequently coincides with the onset of symptomatic disease [61–63].

The shell vial technique, in which monoclonal antibodies are used to detect CMV immediate-early proteins in cultured cells, can be performed within 18–24 h after inoculation. This assay is not sensitive enough to use for routine blood monitoring [62], but is highly useful on bronchoalveolar lavage (BAL) fluid in the diagnosis of CMV pneumonia and in tissue samples to diagnose CMV gastrointestinal disease [64].

The presence of characteristic CMV "owl's eye" nuclear inclusions in tissue specimens is useful in the diagnosis of invasive CMV disease (Fig. 30.1a). This method has relatively low sensitivity, but can be enhanced by use of immunohistochemical techniques to identify CMV antigens (Fig. 30.1b) even when classic inclusions may not be evident.

Advances in molecular diagnostic techniques that do not rely on the growth in CMV in tissue culture have dramatically improved our ability to diagnose CMV.

The detection of the CMV pp65 tegument phosphoprotein in peripheral blood leukocytes offers a rapid, sensitive, and specific method of diagnosing CMV viremia. In this assay, peripheral leukocytes are spread on a glass slide and stained with a fluorescent antibody directed against pp65. The number of positive cells is reported per number of total leukocytes on the slide, thereby providing a rough quantitative assessment of the circulating viral load. In the transplant setting, a positive CMV pp65 assay has been shown to predict the development of invasive disease [65, 66]. Since this assay relies on the detection of pp65 in circulating leukocytes, it may not be reliable in patients with profound leukopenia. The predictive value of this assay has not been validated when performed on other body fluids such as BAL fluid.

Quantitative polymerase chain reaction (qPCR) relies on the amplification and quantitative measurement of CMV DNA. qPCR testing has become the standard method for detecting CMV in blood (either whole blood or plasma) and spinal fluid at many, if not most, institutions, for several reasons. PCR is the most sensitive method for detecting CMV [67], thereby prompting treatment initiation in cases of CMV disease that have been missed with the pp65 antigenemia assay [68]. At the same time, qPCR maintains high specificity. In addition, it is very rapid, with results usually available within 24 h. qPCR also provides a direct quantitative measurement of CMV viral load and viral load kinetics, which are accurate predictors of CMV disease after transplantation [32, 69–72]. This facet of qPCR may enable the development of institution-specific viral load thresholds for beginning treatment, thereby avoiding unnecessary treatment of patients who are at low risk of progression to disease.

Although PCR has been used on BAL fluid [73], viral load cut-offs have not been defined, and while the sensitivity and negative predictive values are very high, the specificity and positive predictive values are not known.
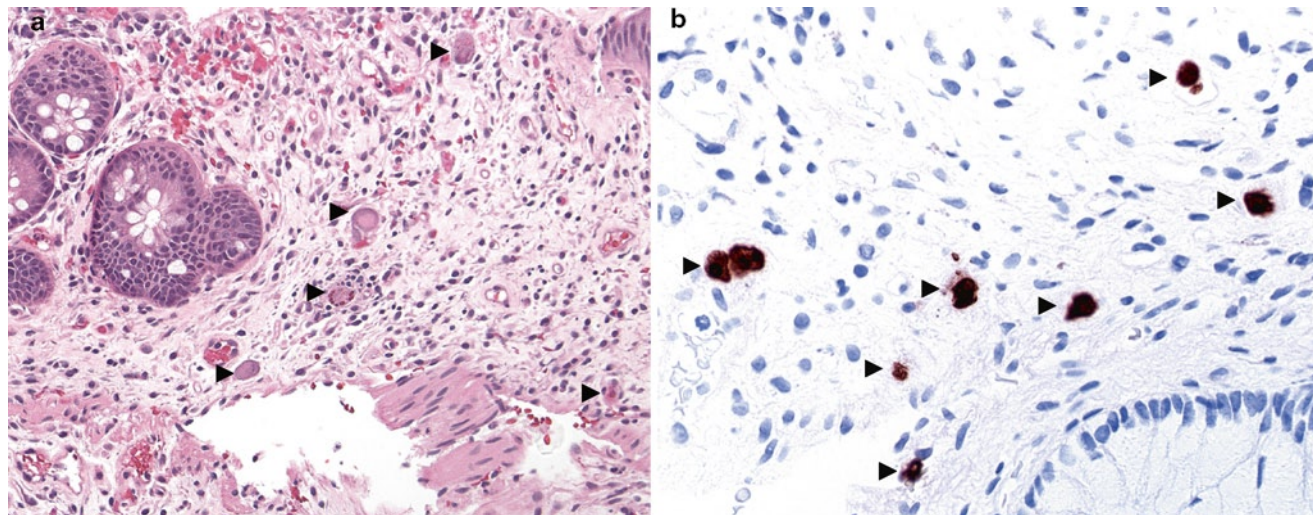
Fig. 30.1 (a) Hematoxylin and eosin (H&E) stain (20× magnification) of a transverse colon biopsy specimen from a patient day +46 after HCT demonstrating nuclear and cytoplasmic inclusions in CMV-infected cells (*arrowheads*). (b) Anti-CMV immunostaining (Dako, 40× magnification) of the same specimen, demonstrating CMV-infected cells (*arrowheads*). Photomicrographs courtesy of Dr. Howard Shulman (Fred Hutchinson Cancer Research Center)

The detection of CMV mRNA by nucleic acid sequence-based amplification (NASBA) on blood samples has proven to be as useful as DNA PCR or p65 antigenemia for guiding pre-emptive therapy after HCT [74, 75]. However, this method has not been as widely adopted as the pp65 antigenemia- or PCR-based assays.

Clinical Manifestations

Care must be taken to distinguish CMV "infection" from CMV "disease." CMV infection simply indicates the detection of CMV in plasma, whole blood, urine, or throat samples in asymptomatic CMV-seronegative patient (primary infection) or CMV-seropositive patients (reactivation of latent virus or superinfection with another strain of CMV) [76, 77].

International definitions of CMV disease have been published and generally denote the presence of symptoms and signs compatible with CMV end-organ involvement along with the detection of CMV using a validated method in the appropriate clinical specimen [78]. Almost any organ can be involved in CMV disease and therefore CMV infection has protean manifestations. Fever is perhaps the most common manifestation, but may be absent in patients receiving high-dose immunosuppression.

Pneumonia is the most important clinical manifestation of CMV disease due to its high associated mortality. Patients who have undergone autologous or allogeneic HCT have mortality rates of 60–90% [79–81]. This unacceptably high mortality rate has not changed much in the past 20 years, indicating that the management of these patients has not yet been optimized.

CMV pneumonia often manifests with fever, nonproductive cough, hypoxia, and interstitial infiltrates on radiography (Fig. 30.2a, b). Rarely, nodules may be observed on radiography (Fig. 30.2c). The onset of symptoms can occur over 1–2 weeks, often times with rapid progression to respiratory failure and the requirement for mechanical ventilation.

The diagnosis of CMV pneumonia is established by detection of CMV by shell vial, culture, or histology in BAL or lung biopsy specimens. While pulmonary shedding of CMV is common, the detection of CMV in BAL fluid from asymptomatic patients who underwent routine BAL screening at day 35 after HCT was predictive of subsequent CMV pneumonia in approximately two-thirds of cases [82]. Therefore, the presence of CMV in a BAL specimen in the absence of clinical evidence of CMV disease must be interpreted with caution.

We do not recommend PCR testing on BAL fluid since there is little data correlating CMV DNA detection by PCR in BAL fluid with CMV pneumonia. However, due to the high negative predictive value afforded by its high sensitivity, a negative PCR result can be used to rule out the diagnosis of CMV pneumonia [73].

CMV can affect any part of the gastrointestinal tract from the esophagus to the colon. Esophagitis typically results in odynophagia, while abdominal pain and hematochezia occur with colitis. Ulcers extending deep into the submucosal layers are seen on endoscopy, and visual differentiation of these lesions from other processes that may affect the gastrointestinal tract in these populations, such as graft-versus-host disease, is often difficult. The diagnosis of gastrointestinal disease relies on detection of CMV in biopsy specimens by culture and/or histology (Fig. 30.1a, b). Given the relative lack of sensitivity of each method, both methods should be used on biopsy specimens to diagnose CMV disease. Notably, gastrointestinal disease can occur in the absence of CMV detection in the blood [83, 84].

Retinitis is relatively uncommon after HCT [85–88]. Decreased visual acuity or blurred vision are typical presenting symptoms, and approximately 60% of patients will have involvement of both eyes [86]. Most cases present later than
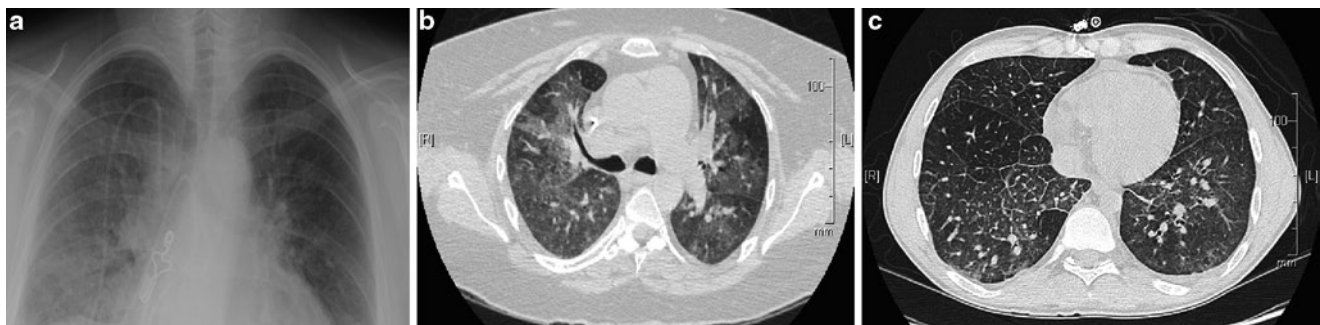
Fig. 30.2 (**a**) Chest radiograph demonstrating bilateral infiltrates in a patient post-HCT with CMV pneumonia. (**b**) Chest computed tomography of the same patient in (**a**). (**c**) Chest computed tomography demonstrating lower lobe nodules in a different patient, also post-HCT, with CMV pneumonia

day 100 after transplantation and are associated with prior CMV reactivation, delayed lymphocyte engraftment, and graft-versus-host disease (GVHD) [86].

Other manifestations, including hepatitis, encephalitis, and infection of the bone marrow resulting in myelosuppression, are all rare with current preventative strategies.

Risk Factors

Allogeneic HCT Recipients

In the setting of allogeneic HCT, the most important risk factor is the serological status of the donor and recipient. CMV-seronegative patients who receive stem cells from a CMV-seronegative donor (D−/R−) have a very low risk of primary infection. Primary infection can still occur if CMV is transmitted in transfused blood products or is acquired via sexual contact or through contact with another individual with primary CMV infection (e.g., via saliva).

Approximately 30% of seronegative recipients who receive stem cells from a seropositive donor (D+/R−) will develop primary CMV infection due to transmission of latent CMV via the allograft. While the risk of CMV disease is low due to pre-emptive treatment of CMV infection, mortality due to bacterial and fungal infections in these patients is higher than in similarly matched D−/R− transplants (18.3 versus 9.7%, respectively) [89]. The reason for this is not entirely clear, one hypothesis being that CMV infection after HCT has additional immunomodulating effects ("indirect effects") that increase a patient's susceptibility to infection with other, unrelated organisms.

Without prophylaxis, approximately 80% of CMV-seropositive patients will experience CMV infection after allogeneic HCT. Again, current preventative strategies have resulted in a substantial decrease in the incidence of CMV disease, which had historically occurred in 20–35% of these patients [90]. While a CMV-seropositive recipient is at higher risk for non-relapse mortality (NRM) than a seronegative recipient [91, 92], the impact of donor serostatus when the recipient in seropositive remains controversial. Some studies have reported a beneficial effect of having seropositive donor with regards to a reduction in relapse- or NRM, whereas other studies have found no such benefit [93–104]. A large CIBMTR study is presently underway to reconcile these controversial findings. However, although the effects on NRM and overall survival are controversial, the D−/R+ serological combination has been reported as a risk factor for delayed CMV-specific immune reconstitution [105–108], CMV reactivation [106, 109], late CMV recurrence [110], and CMV disease [72, 106, 111].

Other risk factors for CMV infection after allogeneic include the use of mismatched or unrelated donors, recipient HSV serostatus, malignant (versus nonmalignant) underlying disease, T-cell depletion, as well as posttransplant factors such as the use of steroids at doses greater than 1 mg/kg body weight/day and acute and chronic GVHD [69, 72, 111–117]. Whether the source of stem cells (peripheral blood versus bone marrow) has a significant impact on the development of CMV infection and disease is not clear, as several studies have yielded conflicting results [111, 115, 116, 118, 119]. Interestingly, the use of sirolimus for GVHD prophylaxis appears to protect against CMV infection, possibly due to the inhibition of cellular signaling pathways that are co-opted by CMV during infection for synthesis of viral proteins [111, 120].

Late CMV Infection After Allogeneic HCT

Whereas, CMV was typically seen by 100 days after allogeneic HCT [121], in the current era of pre-emptive ganciclovir therapy, it has become a significant problem after day 100 following allogeneic HCT [32, 110, 122]. In the absence of specific preventative measures, 15–30% of allogeneic HCT patients will experience late CMV infection and 6–18% will consequently develop disease [32, 69, 110, 123–125]. Late CMV infection is strongly associated with NRM [110].

Several factors predict the development of late CMV infection, including early (before day 100) CMV infection or disease, lack of CMV-specific immune reconstitution, acute or chronic GVHD, and lymphopenia [24, 30, 32, 110, 112]. Measures such as prolonged courses of therapy and continued weekly surveillance are warranted in these patients in order to reduce the risk of late CMV disease [32, 125, 126].

Nonmyeloablative HCT

The use of matched, related nonmyeloablative conditioning regimens generally results in a less CMV infection and disease early after HCT compared to standard myeloablative regimens [113, 126]. However, by 1 year after HCT, the risk of CMV infection and disease is similar among nonmyeloablative and myeloablative groups [116, 126, 127]. Conditioning regimens that include T-cell depletion show no reduction in CMV after nonmyeloablative transplantation compared to myeloablative regimens [128], and matched, unrelated nonmyeloablative transplantation carries the same risk of CMV infection and disease as does myeloablative transplantation [126].

Autologous HCT and Umbilical Cord Blood Transplantation

After autologous transplantation, approximately 40% of seropositive patients will have detectable CMV infection [79, 129]. While CMV disease is rare after autologous transplantation [118, 130–132], the outcome of CMV pneumonia is similar to that after allogeneic HCT [79, 133, 134]. Risk factors for CMV disease after autologous transplantation include CD34+ selection, high-dose corticosteroids, and the use of total-body irradiation or fludarabine as part of the conditioning regimen [118]. Therefore, while CMV is not typically considered a significant pathogen after autologous HCT, certain patients who are at high risk for CMV in this setting merit routine surveillance and pre-emptive therapy.

Umbilical cord blood transplantation (CBT) is a technique that is now utilized when a suitable donor for bone marrow or peripheral blood stem cell transplantation is not available [135]. Since most infants are born without CMV infection, the transplanted allograft is almost always CMV-negative. Among CMV-seropositive recipients who do not receive antiviral prophylaxis, the rate of CMV infection after CBT is 40–80%, with one study reporting 100% [136–140]. When patients receive prophylaxis with high-dose valacyclovir after CBT, it does not appear that CBT entails a significantly greater risk of CMV infection and disease than does peripheral blood stem cell or bone marrow transplantation [115, 141].

Prevention of CMV Infection and Disease

Pretransplant Risk Reduction

CMV serological status of the recipient and donor should be assessed as early as possible prior to HCT, as this is the most important predictor of subsequent CMV infection. For the seronegative recipient, the main goal is to prevent primary CMV infection. Therefore, recipients who are CMV-seronegative before allogeneic HCT should ideally receive a graft from a CMV-negative donor. Weighing the factor of donor CMV serostatus compared to other relevant donor factors, such as HLA-match, is difficult. No data exists indicating whether study HLA-matching is more important compared to CMV serostatus in affecting a good outcome for the patient. Given the choice, an antigen-matched donor for HLA-A, B, or DR would most likely be preferred to a CMV-negative donor. For lesser degrees of mismatch, (allele-mismatches or mismatches on HLA-C, DQ, or DP), the CMV serostatus of donor should be considered as a factor even if the match was poorer. Compared to other donor

factors such as age or blood group, a CMV-seronegative donor would have preference.

The transfusion of blood products represents a significant source for CMV transmission in D−/R− patients [142]. To reduce this risk, blood products from CMV-seronegative donors or leukocyte-reduced, filtered blood products should be used in this setting [143–145]. It is not clear which strategy is the most effective [146, 147], and no controlled study has investigated whether there is an extra benefit from the use of both methods.

Posttransplant Risk Reduction

Immunoprophylaxis

Intravenous immune globulin (IVIG) is not reliably effective as prophylaxis against primary CMV infection [148, 149]. Similarly, negative results were observed using a CMV-specific monoclonal antibody [150]. Likewise, the effect of immunoglobulin on reducing CMV infection in seropositive patients is modest, and no survival benefit among those receiving immunoglobulin has been reported in any study or meta-analysis [151–156]. Therefore, the prophylactic use of immune globulin is not recommended [157].

Antiviral Prophylaxis and Pre-Emptive Therapy

The prophylactic or pre-emptive use of antiviral agents after HCT has markedly reduced the incidence of early CMV disease and has improved survival among certain high-risk populations [62, 68, 112]. Prophylaxis denotes the routine administration of antivirals to all at-risk patients regardless of the presence of active CMV infection. Pre-emptive therapy, on the other hand, withholds antiviral therapy until CMV infection is detected, but prior to the development of CMV disease.

Both approaches have their benefits and drawbacks. Since prophylaxis involves the treatment of all at-risk patients, close monitoring is not required when ganciclovir or foscarnet are used, making this the easier strategy conceptually and useful in situations where rapid, sensitive CMV diagnostic methods are not available. Additionally, prophylaxis may prevent the indirect effects associated with CMV infection. However, since not all at-risk patients will experience CMV infection, prophylaxis strategies result in some patients receiving the drug unnecessarily, thereby exposing the patient to potential drug-related toxicities without discernable benefit. This is not an issue with pre-emptive treatment, since by definition all patients who receive treatment will have active CMV infection.

The success of the pre-emptive treatment strategy is largely dependent on the early detection of viremia. This, in turn, depends on access to rapid, sensitive CMV surveillance methods, and on strict adherence to a surveillance testing schedule. By allowing a limited amount of viral replication, pre-emptive therapy may stimulate immune responses and thereby promote CMV-specific immune reconstitution [24]. Since both strategies are equally effective in preventing CMV disease [68], most transplant centers have moved towards pre-emptive strategies as pp65 antigenemia and DNA PCR-based diagnostics techniques have become readily available [158–160]. The quantitative nature of modern PCR assays now allows to define threshold of viral load for different risk situation, thereby taking full advantage of the high sensitivity of the assay and, at the same time, limiting the use of antiviral drug treatment [161].

More recently, there has been great interest in utilizing methods to determine CMV-specific immune reconstitution after HCT as an additional means to stratify risk of CMV infection and disease ("immune monitoring") and further tailor surveillance and pre-emptive therapy strategies. The types of assays used, their strengths and limitations, and their predictive value in terms of CMV infection and disease after transplantation have been extensively reviewed elsewhere [12, 162]. The utility of measuring T-cell responses as a guide for withholding therapy was evaluated in a small pilot study involving HCT recipients more than 100 days after transplant [105]. While promising, the use of immune monitoring in this fashion requires validation in larger, randomized trials before it can be recommended.

Antiviral Agents

Several antiviral drugs with activity against CMV are available once the decision is made to employ either prophylaxis or pre-emptive treatment (Table 30.2). High-dose acyclovir reduces the risk for CMV infection and possibly disease [163, 164]. Valacyclovir is the valin-ester prodrug of acyclovir and is better absorbed, thereby attaining higher serum concentrations than acyclovir. High-dose valacyclovir is more effective than acyclovir in reducing CMV infection and the need for pre-emptive therapy with ganciclovir after HCT, although the impact of this on survival after HCT is not clear [165]. Routine monitoring for CMV infection is still required if valacyclovir or acyclovir prophylaxis is used. Ganciclovir is a nucleoside analog of guanosine that acts as a competitive inhibitor of deoxyguanosine triphosphate incorporation into viral DNA. A CMV gene, UL97, encodes a phoptotransferase that converts ganciclovir to ganciclovir monophosphate. Cellular enzymes then convert ganciclovir monophosphate to the active triphosphate form. Ganciclovir is currently the first-line agent for CMV prophylaxis and pre-emptive treatment barring contraindications. Intravenous ganciclovir has been demonstrated to reduce the risk of CMV infection and disease compared to placebo, but did not improve overall survival [68, 166–168]. Neutropenia occurs in up to 30% of HCT recipients during ganciclovir therapy [169], thereby placing the patient at risk of invasive bacterial and fungal infections [68, 166, 169]. Neutropenia often responds to dose reduction and support with granulocyte-colony stimulating factor, but occasionally discontinuation

Table 30.2 Antiviral agents used for prophylaxis, pre-emptive therapy, and treatment of CMV disease after HSCT

Agent	Toxicities	Dose based on reason for use		
		Prophylaxis	Pre-emptive therapy	Treatment of disease
Acyclovir	Local injection reactions (IV), nephrotoxicity, headache, neuropsychiatric, nausea	IV: 500 mg/m² t.i.d. PO: 800 mg 4×/day or 600 mg/m² 4×/day if <40 kg	Not recommended	Not recommended
Valacyclovir	Gastrointestinal up set, neutropenia, neuropsychiatric, nephrotoxicity, TTP/HUS	2 g 3–4×/day (>40 kg)	Not recommended	Not recommended
Ganciclovir	Neutropenia, anemia, thrombocytopenia, nephrotoxicity	Induction: 5 mg/kg b.i.d. Maintenance: 5 mg/kg/day	Induction: 5 mg/kg b.i.d. Maintenance: 5 mg/kg/day	Induction: 5 mg/kg b.i.d. Maintenance: 5 mg/kg/day
Valganciclovir	Neutropenia, headache, nausea, diarrhea, nephrotoxicity	Not established	Induction: 900 mg b.i.d. (>40 kg) Maintenance: 900 mg q.d. (>40 kg)	Not established
Cidofovir	Nephrotoxicity, neutropenia, ocular hypotony, uveitis, acidosis	Not established	Induction: 5 mg/kg/week×2 doses Maintenance: 5 mg/kg every other week	Induction: 5 mg/kg every other week Maintenance: 5 mg/kg/every other week
Foscarnet	Nephrotoxicity, metabolic abonormalities, urethral irritation, anemia	Induction: 60 mg/kg b.i.d. Maintenance: 90–120	Induction: 60 mg/kg b.i.d. Maintenance: 90 mg/kg/day	Induction: 60 mg/kg t.i.d. Maintenance: 90 mg/kg/day

of ganciclovir is required, in which case foscarnet is typically the second-line agent of choice. Measurement of ganciclovir concentrations can be helpful to guide therapy and reduce the risk for toxicity especially in the situation of preexisting renal impairment.

Valganciclovir is the orally available prodrug of ganciclovir and achieves serum concentrations at least equivalent to intravenous ganciclovir [170–172]. The results of several uncontrolled studies suggest that valganciclovir is comparable to intravenous ganciclovir in terms of efficacy and safety when used as pre-emptive therapy after allogeneic HCT [170, 173–175]. As of the writing of this chapter, no data comparing valganciclovir to intravenous ganciclovir in the setting of a randomized, controlled trial have been published. Preliminary data from a randomized trial has been presented indicating little or no difference in efficacy or toxicity compared to intravenous ganciclovir [176]. Until more data is available, caution should be exercised when choosing valganciclovir as pre-emptive therapy.

Foscarnet is a pyrophosphate analog that binds directly to and competitively inhibits the CMV DNA polymerase. Foscarnet is generally considered to be as effective as ganciclovir for pre-emptive therapy after allogeneic transplantation [177]. However, three uncontrolled studies have documented cases of breakthrough CMV disease during foscarnet therapy [178–180]. These findings, combined with commonly encountered toxicities of foscarnet, have led to the use of foscarnet as a second-line agent when ganciclovir is contraindicated or not tolerated.

Cidofovir is a cytosine nucleotide analog that does not require phosphorylation by viral enzymes for antiviral activity. Cellular enzymes convert cidofovir to cidofovir triphosphate, which then inhibits the CMV DNA polymerase. The long half-life of cidofovir allows a once-per-week dosing schedule. However, the major toxicity with cidofovir – acute renal tubular necrosis – limits its utility after HCT and it should therefore be considered third-line therapy after ganciclovir and foscarnet [181].

Monitoring for CMV Infection and Initiation of Pre-Emptive Therapy

The current approach to prophylaxis and pre-emptive therapy has been recently summarized [157]. With the exception of those receiving ganciclovir prophylaxis, all patients who have undergone allogeneic HCT, regardless of pretransplant donor and recipient serostatus [182], should be monitored on a weekly basis for CMV infection using pp65 antigenemia, DNA PCR, or mRNA NASBA. If a pre-emptive strategy is used, the initial detection of CMV in peripheral blood after allogeneic HCT should prompt the initiation of antiviral therapy and a thorough evaluation of the patient in order to assess for signs and symptoms concerning for CMV disease [183].

Various durations of pre-emptive antiviral treatment have been explored. Initial studies administered ganciclovir until day 100 after engraftment, which ultimately entailed approximately 6–8 weeks of therapy in the average recipient. Studies from the mid 1990s using short courses (2–3 week) of ganciclovir based on negative PCR assays at the end of therapy were generally effective; however, resumption of pre-emptive therapy was necessary in approximately 30% of patients [62, 177, 184]. Most centers now continue antiviral treatment until the designated viral marker is negative and the patient has received at least 2 weeks of antiviral therapy [161]. If less sensitive markers than DNA PCR, such as the pp65 antigenemia assay, are used, then pre-emptive therapy should be continued until two negative assays are obtained [177]. If a patient is still viremic by PCR or pp65 antigenemia assay after 2 weeks of therapy, treatment should be extended at maintenance dosing until clearance is achieved. It has been shown that a low rate of viral load decrease is a risk factor for later-occurring CMV disease [72].

Monitoring is generally performed until day 100 after engraftment or longer in patients at risk for late CMV disease. The ideal duration and frequency of CMV monitoring in the later transplantation periods have not been determined [125, 126].

Routine monitoring of autograft recipients is not recommended, with the exception being high-risk patients as described above [159, 160, 183].

Special Populations

Patients with CMV infection occurring prior to planned allogeneic HCT have a very high risk of death after transplantation [185]. After transplantation, a patient with documented pretransplant CMV infection should either be monitored for CMV very closely (i.e., twice weekly), or be given prophylaxis with ganciclovir or foscarnet.

The optimal approach to CMV after CBT is not clear. One study described successful pre-emptive treatment with ganciclovir [140], while others combined high-dose valacyclovir prophylaxis with continued monitoring and pre-emptive therapy [115]. Due to initial experience in Seattle suggesting a high rate of infection and disease early posttransplant, the latter approach, coupled with ganciclovir prophylaxis for the week prior to transplant and continued CMV surveillance posttransplant, has been adopted.

Antiviral Resistance

Drug resistance is relatively uncommon after HCT but can occur with all drugs used for the treatment and prophylaxis of CMV and can be fatal [186]. Risk factors for drug resistance include prolonged (months) antiviral therapy, intermittent low-level viral replication in the presence of drug due to profound immunosuppression or suboptimal drug levels, and lack of prior immunity to CMV [187]. Drug resistance should be suspected in patients that are on an appropriate dosage of an antiviral drug and who have increasing quantitative viral loads for more than 2 weeks. After start of antiviral therapy in treatment-naïve patients, an increase in the viral load will occur in approximately one-third of patients and is likely due to the underlying immunosuppression, not true drug resistance [66]. If a patient has received ganciclovir before transplantation or if viral load increases occur in the late setting where most patients are not antiviral drug naïve anymore, drug resistance should be suspected.

An approach to the patient with suspected drug-resistant CMV is presented in Fig. 30.3. Since ganciclovir is used as a first-line agent in most cases of CMV infection, resistance to this antiviral is the most commonly encountered problem.

Resistance is due most often to mutations in the UL97 gene, and less often to mutations in the UL54-encoded DNA polymerase. UL97 mutations that confer resistance have been described and genotypic assays are available for diagnostic analysis in reference laboratories [188]. Phenotypic testing can be performed, but this type of assay is time-consuming and is therefore not as helpful as rapid genotypic testing in guiding patient management. However, since different UL97 mutations confer varying degrees of ganciclovir resistance, some cases of genotypically-defined ganciclovir-resistant CMV may still respond to ganciclovir therapy, especially at higher doses [189]; therefore care must be taken in interpreting genotype results.

If ganciclovir resistance is documented or suspected, foscarnet is generally the second-line agent of choice. Unlike ganciclovir, foscarnet activity is not dependent on phosphorylation by the UL97 gene product; thus, CMV that has acquired ganciclovir resistance due to UL97 mutations will still be susceptible to foscarnet [190]. Studies evaluating the utility of combination therapy of foscarnet and ganciclovir for ganciclovir-resistant CMV disease have been inconclusive and therefore this strategy is not routinely recommended [191]. Resistance to foscarnet can occur and is due to


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┌─────────────────────────────────────────────────────────────┐
│ Suspicion of ganciclovir (GCV) or valganciclovir (VGCV)      │
│ resistance:                                                   │
│ Rising viral load after two weeks of ongoing GCV or VGCV      │
│ therapy                                                       │
│ Prior GCV or VGCV exposure                                    │
│ Symptomatic disease after or during extended GCV or VGCV      │
│ therapy                                                       │
└─────────────────────────────────────────────────────────────┘
                              │
                              ▼
                  ┌───────────────────┐
                  │ UL97 genotyping   │
                  └───────────────────┘
                              │
                              ▼
          ┌───────────────────────────────────────────┐
          │ Presence of UL97 mutations conferring      │
          │ resistance?                                │
          └───────────────────────────────────────────┘
                  │                       │
                 Yes                      No
                  │                       │
                  ▼                       ▼
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| Change to foscarnet **Less commonly used (input from expert recommended):** Cidofovir[a] Combination GCV+Foscarnet High-dose GCV (with GCSF support as needed) Leflunomide Artesunate | UL54 genotyping **Pending UL54 genotyping results:** If high-risk patient, symptomatic disease, or rapidly increasing viral load, switch to foscarnet If stable viral load and clinically silent infection, continue GCV or VGCV at current dose or consider higher-dose GCV therapy (with GCSF support as needed) |

[a]Genotyping of UL54 DNA polymerase is recommended to evaluate for mutations conferring cross-resistance to cidofovir

Fig. 30.3 Approach to the patient with suspected ganciclovir- or valganciclovir-resistant CMV

mutations in UL54. Interestingly, cross-resistance between foscarnet and ganciclovir does not occur, as mutations in UL54 conferring resistance to foscarnet occur in regions distinct from those conferring ganciclovir resistance [192].

Since cidofovir is not phosphorylated by the CMV UL97 gene product, it is active against ganciclovir-resistant UL97 mutants. However, certain UL54 mutations can confer causes cross-resistance between ganciclovir and cidofovir [190, 192]. Therefore, additional genotype testing of UL54 is indicated to evaluate for potential cross-resistance conferring mutations. There is limited experience with cidofovir for treatment of ganciclovir-resistant CMV, and its toxicity profile precludes its routine use as second-line treatment for ganciclovir-resistant CMV.

Drugs presently under evaluation, such as maribavir (especially at high doses), CMX001, an oral cidofovir derivative, and AIC 246, a inhibitor for late DNA synthesis, may also provide therapeutic options in the future [193–195]. Other licensed drugs with possible anti-CMV activity include the arthritis drug leflunomide and the antimalaria compound artesunate [196–198]. None of these are approved by European or American regulatory authorities for the treatment of CMV. Another potentially useful approach is to use the immunosuppressive drug sirolimus as adjunct therapy since it may impair CMV replication by regulating cellular signaling pathways, and has in fact been shown to reduce the risk of CMV reactivation after HCT and renal transplantation [111, 120].

Vaccination

Given the costs and toxicities associated with antiviral therapy, a vaccine to prevent CMV infection would be of substantial benefit. Indeed, the Institute of Medicine has given the development of a CMV vaccine highest priority [199]. Thus far, most vaccine candidates have yielded mixed results [200]. Recently, a phase I trial of a bivalent vaccine containing plasmids encoding gB and pp65 showed promising results in CMV-seronegative vaccine recipients, but not CMV-seropositive recipients, which is a limitation common to many CMV vaccine candidates [201]. Since it is the seropositive transplant patient who is at greatest risk for CMV infection, more work is required to provide protective immunity in these patients after HCT.

Management of CMV Disease

As mentioned earlier, the diagnosis of CMV disease requires documenting the presence of CMV in the appropriate diagnostic specimen, coupled with symptoms and signs consistent with CMV. For gastrointestinal disease, standard therapy generally entails induction treatment with an intravenous antiviral, most often ganciclovir, for 3–4 weeks followed by several weeks of maintenance. Shorter courses of induction therapy (2 weeks) are not as effective [202]. There is no role for concomitant intravenous immunoglobulin (IVIG) in the treatment of gastrointestinal disease [203]. Recurrence of GI disease may occur in approximately 30% of patients in the setting of continued immunosuppression and such patients may benefit from secondary prophylaxis with maintenance antivirals until immunosuppression has been reduced. Foscarnet can be used as an alternative if neutropenia is present. Valganciclovir as maintenance treatment for gastrointestinal disease has not been well studied but may be reasonable if symptoms are improved, systemic viremia is suppressed, and there are no factors that would impair the absorption of an orally-administered medication, such as severe gastrointestinal GVHD.

Several studies established the current standard of care for CMV pneumonia, which is treatment with ganciclovir (or foscarnet as an alternative agent) in combination with IVIG [204–207]. These studies showed improved survival rates compared to historical outcome results. There does not appear to be a specific advantage of CMV-specific immune globulin (CMV-Ig) compared to pooled immunoglobulin [205]. However, in specific clinical situations, such as volume overload, CMV-Ig may be preferred. Several studies have raised doubt regarding the beneficial effect of concomitant IVIG [208, 209]. However, while the use of IVIG remains a controversial topic, it is still considered as standard of care at many centers until more data regarding its utility is available.

CMV retinitis is typically treated with systemic ganciclovir, foscarnet, or cidofovir, with or without intraocular ganciclovir injections or implants [86, 210–212]. Fomivirsen is an antisense RNA molecule that targets mRNA encoded by CMV and is approved as second-line therapy for CMV retinitis in patients with AIDS [213].

Other manifestations of CMV disease, such as hepatitis and encephalitis, are uncommon and are typically managed with intravenous ganciclovir. The duration of therapy for these manifestations has not been well-established and should be tailored to the individual patient.

Adoptive Immunotherapy

HCMV-specific T cells can be generated via several different mechanisms in attempts to passively restore cellular immunity after transplantation [12]. Several groups have reported a beneficial impact of adoptive immunotherapy on HCMV

viral loads in patients who had undergone HCT [214]. Despite these seemingly promising results, scientific questions remain unanswered (such as the optimal cell type and dose for infusion) and technical hurdles persist (widespread availability of clinical grade reagents) that preclude adoptive immunotherapy from becoming a routine clinical procedure at the current time.

CMV in the Non-HCT Setting

While not typically thought of as a commonly-occurring opportunistic infection among non-HCT cancer patients, the incidence of CMV disease increased between the years 1964 and 1990, likely due to the development of fludarabine and high-dose cyclophosphamide based regimens for the treatment of leukemia and lymphoma [215–219]. The highest rates, 8.8 and 11.4%, were seen in patients with chronic lymphoblastic leukemia and lymphoblastic lymphoma, respectively. More recently, the incidence of CMV disease, specifically pneumonia, appears to have declined, perhaps due to improved preventative strategies [220].

The increasing use of immunomodulating monoclonal antibodies poses a new and perhaps the greatest risk for CMV infection outside of the HCT setting [221]. Alemtuzumab is an anti-CD52 monoclonal antibody that results in CD4+ and CD8+ lymphopenia that can last for up to 9 months after administration. CMV infection typically occurs during the period of maximal immunosuppression, which is 3–6 weeks after alemtuzumab therapy [222, 223]. When alemtuzumab is used for the treatment of CLL, NHL, and T cell prolymphocytic leukemic, the rate of CMV reactivation typically ranges from 10 to 66%, depending on the underlying disease and whether alemtuzumab is given as first-line or salvage therapy [224–228], although one study reported 100% [229]. Approximately, 4–29% of CMV infections in this population will be symptomatic, manifesting primarily with fevers [222, 225, 229]. The precise incidence of visceral CMV disease in this population is not known.

The optimal approach to the patient being treated with alemtuzumab is not clear. Several studies have documented the efficacy of prophylactic valganciclovir or ganciclovir in preventing CMV infection during alemtuzumab therapy [230–232]. Other studies used pre-emptive therapy with oral ganciclovir or valganciclovir once CMV was detected, in addition to withholding further alemtuzumab treatment, to successfully prevent CMV disease [225, 233]. Which strategy is superior in this population is not known. If routine prophylaxis is not used, patients receiving alemtuzumab should be monitored for CMV infection for a period of approximately 2 months after receipt of the last dose [183, 222, 234]. Detection of CMV by either PCR or pp65 antigenemia during alemtuzumab therapy should prompt a thorough evaluation for evidence of end-organ disease. Symptomatic infection or the presence of visceral disease always requires treatment, but the optimal management of asymptomatic infection is not clear, as many patients with asymptomatic CMV infection may not develop CMV disease despite the absence of anti-CMV therapy. Options in the latter situation include the administration of antivirals versus continued close viral monitoring combined with clinical observation [159]. Controversy also exists regarding the question of whether to withhold further alemtuzumab therapy in the setting of CMV infection. Some do not feel that asymptomatic CMV infection requires discontinuation of alemtuzumab [183, 222, 229, 235, 236], but several studies have withheld alemtuzumab treatment during CMV viremia [225, 231] and therefore this practice has been advocated by some groups [237]. Thus, the optimal approach to the patient receiving alemtuzumab is not clear at the present time and will certainly require further study.

Routine screening of asymptomatic patients with hematological malignancies undergoing treatment with conventional chemotherapy, hyperCVAD, fludarabine, or rituximab is not recommended due to the relatively low rate of CMV disease [238].

Summary

While much progress has been made in the prevention of CMV disease after HCT over the past decade, several issues remain. Increasing the specificity of pre-emptive therapy by combining detection of viremia with monitoring of CMV-specific T-cell immunity merits evaluation in a randomized trial. CMV pneumonia still carries a poor prognosis that outcome has not significantly changed in the past 20 years. Therefore, other strategies, such as combination antiviral therapy, should be studied in this setting in order to improve outcome. Additionally, the benefit provided by IVIG in the treatment of CMV pneumonia needs to be determined. New treatment and vaccination options for CMV are urgently needed because the currently available drugs have major limitations, such as toxicity and resistance. Novel drugs such as lipid cidofovir [239], a novel nonnucleoside inhibitor [194], as well as leflunomide and artesunate, deserve a systematic evaluation. Vaccination may also play an increasing role in the future prevention of CMV infection and disease.

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Chapter 31
Epstein-Barr Virus, Varicella Zoster Virus, and Human Herpes Viruses-6 and -8

Mini Kamboj and David M. Weinstock

Abstract Epstein-Barr virus (EBV), varicella zoster virus (VZV), and human herpes viruses-6 (HHV-6) and -8 (HHV-8) present unique management challenges to clinicians who care for patients with cancer. Although latent infection by these organisms is either common (HHV-8, VZV) or essentially ubiquitous (EBV, HHV-6), clinical manifestations vary widely in frequency and severity. Syndromes caused by EBV, VZV, HHV-6, and HHV-8 span from highly contagious infections (e.g., varicella) to monoclonal malignant populations (e.g., endemic Burkitt's lymphoma). Within this broad spectrum are polyclonal cellular proliferations (e.g., Multicentric Castleman's disease) that obscure the traditional boundary between infection and cancer. Despite the availability of acyclovir and related compounds, these Herpes viruses continue to cause significant morbidity and mortality in patients with cancer. Newer therapies that modulate the host immune response, either by vaccination or the infusion of targeted lymphocytes, have generated significant interest and are already available in some centers.

Keywords Herpes • Cancer • Infection • Epstein-Barr virus • Varicella zoster virus • Human herpes virus-6 • Human herpes virus-8

Introduction

Eight herpes viruses are known to cause clinical syndromes in humans: herpes simplex viruses 1 and 2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (see Chap. 30), and human herpes viruses-6 (HHV-6), -7 (HHV-7), and -8 (HHV-8). These organisms have double-stranded DNA genomes within an icosadeltahedral capsid and a glycoprotein envelope derived from the membrane of infected cells.

Upon entry into a human host, Herpes viruses can establish lifelong infection that roughly divides into three phases. First (primary infection), viral replication within host cells leads to cell lysis, viral dissemination, and further cellular infection. Primary infection can be subclinical or produce a syndrome with characteristics that vary based on the immune competence, genetic background, and age of the host. Primary infection is resolved by the host's innate immune system and results in the production of neutralizing antibodies.

In the second phase (latency), the organism achieves a quiescent equilibrium with the host adaptive immune response, primarily by reducing the number of genes expressed from the viral genome. Other factors that contribute to viral persistence within latently infected cells include viral microRNA, chemokine homologs, cytokines, and modulators of immune recognition.

In the third phase (reactivation), the organism reestablishes lytic viral replication by expressing genes necessary for the production and release of infectious virus. The balance between lytic and latent infection is highly complex and poorly understood. In fact, subclinical lytic infection can be either continuous or episodic for many Herpes viruses and results in asymptomatic viral shedding in saliva and other fluids. Characteristic clinical syndromes (e.g., herpes zoster) manifest when the extent of lytic viral infection exceeds an ill-defined threshold. The loss of immune competence, specifically the cytotoxic T-cell response, generally favors symptomatic lytic reactivation and more severe clinical complications. Acyclovir (and related antivirals) are only effective against lytic infection (primary or reactivation), as viral kinases that phosphorylate acyclovir to its active form are not expressed during latency.

The γ-herpes viruses HHV-8 and EBV are notable for their ability to induce both nonmalignant and malignant proliferations of latently infected cells. These proliferations are a teleologic conundrum, as they create a selective disadvantage for hosts infected by the organism without favoring viral transmission. The γ-herpes viruses utilize a vast array of mechanisms to promote cellular survival and replication. Yet, only a miniscule fraction of latently infected cells

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progress to become pathologic proliferations. The rarity of these proliferations argues that tumors derived from latently infected cells represent an unintended by-product of the latent program that requires additional factors, including the stochastic acquisition of complementary mutations and the failure of immune surveillance.

In this chapter, we will review aspects of infection caused by VZV, HHV-6, EBV, and HHV-8, which are pertinent to clinicians who care for patients with cancer. We will focus on the diagnosis, management, and prevention of traditional infections. The panoply of cellular proliferations, both malignant and nonmalignant, that are associated with γ-herpes viruses has been reviewed elsewhere [1–4]. HSV-1 and HSV-2 will also not be further discussed, although primary and reactivation syndromes caused by these organisms occur frequently in immunocompetent and immunocompromised patients with cancer. Finally, HHV-7 does not appear to be a common cause of morbidity in patients with cancer [5].

Varicella Zoster Virus

Epidemiology and risk factors. VZV infections occur worldwide. The organism produces two distinct clinical syndromes, primary varicella (chicken pox) and herpes zoster (shingles). Primary varicella is mostly a disease of childhood in temperate areas and of adolescent to early adulthood years in tropical areas [6]. Primary varicella is highly contagious and, unlike other Herpes viruses, is transmissible via the respiratory route.

During primary varicella, the virus establishes latency in the afferent neurons of dorsal root and cranial ganglia. Reactivation can manifest as herpes zoster (i.e., shingles), although only 15% of persons infected with VZV ever develop herpes zoster [7, 8]. VZV reactivation induces a profound anti-VZV T-cell response. Thus, second episodes of herpes zoster are rare in the general population, but occur more frequently in persons with impaired cell-mediated immunity [9].

Immunodeficiency, either from cancer or its treatment, is a risk factor for VZV disease and dissemination. In a population study of adult patients within 5 years after cancer diagnosis [10], the cumulative incidence of VZV disease was 625/100,000 person-years, a rate 5 times higher than the general population [11]. However, the incidence of VZV disease among patients with cancer varies widely based on several factors that primarily affect immune competence, including patient age, underlying tumor type, and cancer treatment.

Cell-mediated, rather than innate or humoral, immunity is the primary protector against VZV reactivation. Patients with underlying solid tumors treated with standard doses of cytotoxic agents (e.g., platinum compounds, vinca alkaloids, taxanes, and anthracyclines) generally have rates of VZV disease which are similar to age-matched controls, and complications other than postherpetic neuralgia are rare [12–14]. Dose-intensive regimens that include these agents increase the risk for VZV disease [15–18], although marginally. Even among patients with acute myelogenous leukemia, who typically retain some extent of adaptive immunity, less than 2% develop VZV disease [14, 19–22].

In contrast, patients with underlying lymphoproliferative disorders [20, 23–25] are at high-risk for VZV disease and severe complications. In the absence of routine acyclovir prophylaxis, 10–25% of adult and pediatric patients with acute lymphocytic leukemia (ALL) or Hodgkin's lymphoma develop VZV disease [14, 19–21, 25], with an annual incidence of approximately 6% and the highest attack rates among patients who receive combined chemotherapy and radiation. Among the latter, disseminated infection develops in approximately one quarter of cases and up to 15% experience a second episode of herpes zoster.

Newer chemotherapies that profoundly suppress cell-mediated immunity can *markedly* increase the risk for VZV disease. These include the purine analogs fludarabine, pentostatin and cladribine [26–28], alemtuzumab [29], temozolomide [30, 31], and bortezomib [32, 33]. Routine chemoprophylaxis against VZV should be strongly considered in patients treated with these compounds.

The widespread use of varicella vaccine (Varivax) to prevent infection by wild-type VZV has already reduced the overall incidence of VZV disease among children in the US [34]. As the age of vaccinated patients increases, it is likely that the epidemiology of VZV disease among patients with cancer will undergo dramatic shifts. Presumably, the lower rates of latent infection by wild-type VZV will result in fewer and less severe episodes of herpes zoster among vaccinated patients. However, the possibility also exists that immunity among vaccinated patients may be reduced compared to patients who experienced wild-type varicella, placing them at higher risk for "reinfection" by wild-type strains during or after cancer therapy. Epidemiologic studies to discern the effects of childhood VZV vaccination on the risk for VZV disease among patients with cancer will be essential for developing future prophylaxis and treatment strategies.

Hematopoietic stem cell transplant (HSCT) recipients. VZV disease among HSCT recipients typically occurs more than 30 days after transplant, when myelopoiesis and innate immunity are restored, but adaptive immunity is highly deficient. The median time to the onset of VZV disease after HSCT is approximately 5 months (Table 31.1), but varies widely between centers based on differences in the duration of prophylaxis after HSCT with acyclovir or related agents. Symptomatic VZV disease develops in 16.6–46% of HSCT recipients within 2 years after transplant [35–42].

Table 31.1 Summary of reports describing varicella zoster virus (VZV)-related illness in hematopoietic stem cell transplant (HSCT) recipients

References	Years	Population	Graft type	N	Rate	Timing of VZV-related illness after HSCT	Comments
Safdar et al. [40]	1996–2005	Adult and pediatric	UCB	97	11%	100% after day +100	All seven cases had chronic GVHD
Koc et al. [37]	1992–1997	Adult	Allogeneic	100	41%	12% by day +100 88% by +24 months	Disseminated infection in 17% of cases
Leung et al. [38]	1991–1998	Pediatric	Autologous and allogeneic	109	30%	73% by +12 months	11% visceral and 48% cutaneous dissemination
Schuchter et al. [41]	1983–1987	Adult and pediatric	Autologous	153	28%	60% by +6 months 91% by +12 months	5% visceral, 15% cutaneous dissemination Acyclovir used in 79% of cases
Wacker et al. [42]	1979–1987	Pediatric	Autologous	236	23%	87% by +6 months	13% cutaneous dissemination Antiviral used in 85%
Han et al. [36]	1974–1989	Adult and pediatric	Autologous and allogeneic	1,186	18.3%	15% by +6 months 86% by +18 months	6% visceral, 26% cutaneous dissemination
Atkinson et al. [35]	1970–1976	Adult and pediatric	Allogeneic and syngeneic	89	46%	Median onset +5 months	
Locksley et al. [39]	1969–1982	Adult and pediatric	Autologous and allogeneic	1,394	16.6%	80% by +9 months	13% visceral, 23% cutaneous dissemination Acyclovir used in 9.6% of cases

GVHD graft-versus-host disease; *UCB* umbilical cord blood; *disseminated* cutaneous dissemination

Fig. 31.1 Herpes zoster with cutaneous dissemination (courtesy of Dr. Ying Taur, Memorial Sloan-Kettering Cancer Center, New York, NY)

However, a large fraction of the remaining patients experience subclinical VZV reactivations that can be inferred by the acquisition of VZV IgG within the years after HSCT [43].

Like other herpes viruses, recipient-derived virus causes the vast majority of VZV disease after allogeneic HSCT. Thus, prior infection of the recipient by VZV is the strongest predictor of VZV reactivation after transplant. Some studies have reported that graft-versus-host disease (GVHD) and its treatment increase the risk for VZV reactivation and disseminated disease [37, 39]. Among autologous HSCT recipients, type of underlying malignancy appears to be an important factor, with the highest incidence of VZV infection among patients with underlying lymphoma [41].

Clinical manifestations. The clinical manifestations from VZV disease among persons with and without cancer largely overlap, although immunocompromised patients have a higher risk for cutaneous and visceral dissemination. Visceral VZV dissemination typically manifests as pneumonitis, hepatitis, and/or encephalitis [44–50]. Additional neurologic complications include vasculitis, meningitis, leukoencephalopathy, ganglionitis, postherpetic neuralgia, polyradiculopathy, myelitis, ventriculitis, and necrotizing angitis [47, 48, 51, 52]. Pulmonary and neurologic symptoms typically develop a week after the onset of rash [44].

A rare, but important, syndrome results from visceral involvement in the absence of cutaneous lesions [53, 54]. A delay in antiviral treatment is commonly fatal in these cases, so VZV should be considered in highly immunocompromised patients who present with idiopathic severe abdominal pain, unexplained transaminitis, or the syndrome of inappropriate antidiuretic hormone (SIADH) [55–58].

A few unique aspects of VZV infection have been reported in patients with cancer. For example, herpes zoster may have a predilection for previously irradiated areas or sites of tumor involvement [10, 14, 24]. Disseminated herpes zoster can also mimic primary varicella in immunocompromised patients [39, 44]. This is known as "atypical generalized zoster" and is characterized by skin lesions that appear in a nondermatomal distribution and have the same umbilicated "dew-drop" appearance classically seen with primary varicella (Fig. 31.1). Finally, VZV reinfection has been described in patients with cancer, although the distinction between a second episode of primary varicella and atypical generalized zoster can be exceedingly difficult [59]. Cases of reinfection described in the literature have generally been mild and seldom encountered in clinical practice [59, 60].

Laboratory diagnosis. Tissue culture remains the gold standard for the diagnosis of VZV infection. Direct immunofluorescence assays that use a monoclonal antibody against glycoprotein E are widely available. These assays have largely supplanted the Tzanck smear, as their turnaround time is a few hours and they can reliably distinguish between VZV, HSV, and pox viruses [61]. PCR is commercially available and is useful for identifying VZV DNA in cerebrospinal fluid [62–64], bronchoalveolar lavage [65], and tissue. PCR in conjunction with restriction fragment length polymorphism (RFLP) analysis is the most common approach for strain identification, either in the setting of a suspected outbreak or to distinguish between wild-type and vaccine strains [66, 67].

Serological testing remains the standard for identifying immunity and is routinely performed in HSCT candidates and other patients at high-risk, especially when considering chemoprophylaxis. A number of serological tests are available, including latex agglutination [68] and enzyme-linked immunosorbent (ELISA) assays. Fluorescent-antibody staining of membrane antigen (FAMA) [69, 70] is the most sensitive assay for VZV IgG, but remains only an investigational tool [70].

Treatment. Acyclovir was licensed in the United States in 1982 based on studies demonstrating its superior activity when compared to vidarabine (Ara-A) for the treatment of VZV disease. Despite its widespread use in the general population, acyclovir-resistant VZV remains exceedingly uncommon.

Among immunocompromised patients with herpes zoster, acyclovir is associated with fewer treatment failures compared to vidarabine. Acyclovir also shortens both the duration of culture positivity and the interval to clinical resolution [71–74]. In a placebo-controlled, double-blinded study of immunocompromised patients with herpes zoster, acyclovir 1,500 mg/m²/day reduced cutaneous dissemination and visceral spread. Acyclovir curtailed disease even when started more than 3 days after the onset of rash [74].

High-dose oral acyclovir (800 mg five times daily) has comparable efficacy to intravenous acyclovir in selected patients with cancer and localized herpes zoster [75]. The newer antivirals, valacyclovir and famciclovir, have largely replaced high-dose acyclovir for this indication because of their superior bioavailability. Famciclovir, an oral prodrug of penciclovir, administered at 500 mg three times daily has comparable efficacy to high-dose oral acyclovir for the treatment of localized zoster in HSCT recipients and patients with cancer who are >12 years old [76].

Valacyclovir is a prodrug of acyclovir with 3–5-fold higher bioavailability. In a recent study, patients with solid tumors actively receiving chemotherapy and/or radiation and patients with lymphoma were randomized to receive treatment for VZV disease with valacyclovir dosed at either 1 or 2 g thrice daily. No differences were noted between the doses in median time to crusting of lesions or zoster-associated neurasthenia [77].

Studies of oral antivirals in patients with cancer are limited to the treatment of localized zoster in selected patients. As such, there are no definitive criteria for which cancer patients can be safely treated with oral therapy. In the authors' experience, cancer patients with primary varicella or disseminated herpes zoster should receive an initial course of intravenous therapy. Among patients with herpes zoster involving only a single dermatome, those with solid tumors who are not actively receiving cytotoxic chemotherapy, those with hematologic malignancies who are in complete remission and have not received therapy for more than 6 months, and HSCT recipients who are not receiving immunosuppressive therapy can be safely treated with oral therapy. Many patients who do not satisfy these criteria can be treated with a brief course of intravenous therapy until no further lesions have developed and older lesions have begun to crust, and then switched to oral therapy to complete a 7–14 day course. More immunocompromised patients (e.g., active lymphoid malignancy, HSCT recipient) may benefit from continuing therapy until all lesions are crusted.

Antiviral therapy with acyclovir in immunocompromised patients with primary varicella decreases the risk of progression to pneumonitis [78, 79]. Among immunocompetent persons, this effect appears to depend on the institution of therapy in the first 72 h after the onset of rash. Whether the delay of therapy beyond 72 h negates any benefit in immunocompromised hosts is not known. However, it is likely that, similar to the treatment of herpes zoster in these patients, "better late than never" applies. The recommended dose for treating primary varicella is 10 mg/kg every 8 h. In children, the starting dose should be 500 mg/m² every 8 h. Continuous infusion with acyclovir 2 mg/kg/h has been tried in severe infections, although the data to support its use are sparse [80]. The total duration of intravenous or oral therapy depends upon the degree of underlying immunosuppression and response, following the same tenets as outlined for herpes zoster.

Humoral immunity to VZV is important for protecting against primary infection, but its role in limiting the extent of either primary or reactivation disease appears to be negligible. Thus, the use of adoptive VZV immune globulin (VZIG or VariZIG) to treat infection or prevent the dissemination of localized disease is not recommended [81, 82]. VZV immunoglobulin preparations remain in limited supply and should be reserved for scenarios where their application offers a demonstrated benefit.

Prevention and infection control. Nosocomial transmission of VZV has occurred frequently between patients with cancer. Aggressive infection control efforts to prevent and mitigate this transmission are essential [83–85]. Guidelines published in 2000 from the Infectious Disease Society of America, American Society for Blood and Marrow Transplantation, and Centers for Disease Control include several recommendations for infection control efforts pertinent to VZV [86], including the use of barrier precautions in patients with known or suspected VZV infection and postexposure prophylaxis for patients possibly exposed to VZV.

Patients with VZV are potentially infectious beginning 4 days prior to the onset of rash. Because primary and disseminated VZV can be transmitted by the airborne route, patients with VZV disease should be isolated with airborne (negative pressure room, N95 or higher level respirators or masks) and contact (gowns and gloves) precautions, in addition to standard precautions. After an exposure, VZV antibody testing should be performed as quickly as possible. Susceptible (i.e., VZV nonimmune) but asymptomatic patients should be isolated with appropriate precautions beginning 10 days after exposure and continuing until 21 days after the last exposure. VZV immune globulin (Ig) administered within 96 h after exposure has moderate efficacy in the prevention and mitigation of primary infection [87, 88]. VZV Ig can lengthen the period from exposure to the onset of symptoms. Thus, isolation should be lengthened to 28 days after exposure for patients who receive VZV Ig.

Because reinfection is very uncommon, seropositive patients do not require VZV Ig prophylaxis unless there is a substantial concern that antibodies were passively acquired, such as through the administration of intravenous immune globulin (IVIG) [59, 88]. VZV Ig is recommended for all HSCT recipients whose serostatus in unknown or who are seronegative after an expo-

sure [86]. VZV Ig should be considered in all nonimmune patients with cancer, especially adults and those with impaired cell-mediated immunity, as primary varicella causes significant morbidity and mortality [89]. Nonspecific IVIG is a reasonable substitute if VZV Ig is unavailable [81, 90].

Antivirals. Acyclovir and the newer antivirals are an attractive alternative to VZV Ig for postexposure prophylaxis, as they are readily available and inexpensive. The data to support their use is primarily limited to studies of healthy children [91–93]. Nonetheless, chemoprophylaxis with these agents is likely to be beneficial in immunocompromised patients. In addition to VZV Ig (if available), the authors offer valacyclovir 1 g tid prophylaxis to nonimmune, immunocompromised adults (including allogeneic HSCT recipients) exposed to VZV until 22 days after exposure (or 28 days if VZV Ig is also administered) [59, 94].

Vaccination to prevent VZV disease. Both VZV vaccines that are currently licensed by the FDA contain live VZV derived from the attenuated Oka strain. Thus, immunocompromised patients who receive these vaccines could develop VZV infections caused by the vaccine virus.

Varicella vaccine. Between the two vaccines, Varivax contains a lower titer of virus and is approved for the prevention of primary varicella. Varivax is immunogenic in selected children with lymphoreticular malignancies, acute leukemias, and autologous HSCT recipients [95–99]. The incidence of zoster among patients with acute leukemia who had received varicella vaccine has been lower than or similar to patients with a history of wild-type varicella [100–102]. One study of 13 children with ALL receiving maintenance chemotherapy tested two doses of Varivax 3 months apart. The seroconversion rate increased from 19 to 94% with a second dose of vaccine. One of the 13 children developed a possible case of vaccine strain varicella [103]. In a second study, five of 52 children with ALL developed varicella-like illness after receiving Varivax [104]. Postmarketing surveillance identified six additional cases of disseminated Oka strain infection in immunocompromised patients [105].

A 4-year-old girl with ALL developed fatal disseminated varicella from Oka strain virus, despite vaccination 5 months after achieving a complete remission. She presented with fulminant hepatic failure 5 weeks after receiving the vaccine [106]. Although varicella vaccination may be considered in selected patients with underlying cancer, more studies are needed before the safety and timing of varicella vaccine in high-risk patients are defined. Nonfatal, secondary transmission of vaccine strain virus has also been reported in immunocompromised patients [107, 108].

Zoster vaccine. In 2006, a higher dose of Oka strain vaccine (Zostavax) was licensed in the US for the prevention of herpes zoster in adults more than 60 years old. The titer of virus in Zostavax is at least 14 times greater than the titer in

Varivax, which is believed to correlate with a higher likelihood of causing symptomatic VZV disease. As such, Zostavax is contraindicated in HSCT recipients and persons with hematologic malignancies other than leukemia in remission. The vaccine may be administered to selected patients with other cancers, although at least 1 month prior to the initiation of therapy or no sooner than 3 months after the completion of treatment [109]. The authors are generally reluctant to administer Zostavax to any patient with cancer within 1 year after receiving chemotherapy or radiation. Although the prevention of herpes zoster remains a priority from a public health perspective, the potential risk of Zostavax in this population remains too poorly defined.

Other preventive strategies. Vaccination of close contacts and healthcare workers, aggressive outbreak investigation, and postexposure prophylaxis and furloughing for nonimmune healthcare workers are mainstays for reducing nosocomial VZV transmission [86]. Although the risk for transmission of vaccine strain virus is low, healthcare workers who develop a rash after VZV vaccination (Varivax or Zostavax) should avoid all contact with immunocompromised patients until the rash has cleared [110]. If inadvertent exposure to a vaccine recipient with a rash occurs, postexposure prophylaxis may be considered for highly immunocompromised, nonimmune patients who are not receiving acyclovir or other antiviral medications with activity against VZV. The vaccine strain virus is sensitive to acyclovir and related compounds.

Antiviral prophylaxis. Widespread use of chemoprophylaxis with acyclovir and related compounds has substantially reduced the rate of visceral dissemination and mortality related to VZV among high-risk patients [39, 42, 73, 111, 112]. Yet, even considering the considerable morbidity of herpes zoster in immunocompromised patients, antiviral prophylaxis against VZV reactivation is generally not recommended [113]. Studies of long-term antiviral prophylaxis are primarily limited to HSCT recipients and have confirmed that acyclovir reduces the incidence of herpes zoster during the treatment period [114–121]. Unfortunately, a significant fraction of patients will develop herpes zoster within a year after discontinuing antiviral prophylaxis, such that the overall rate of herpes zoster is not significantly reduced by a limited period of prophylaxis. Presumably, chemoprophylaxis suppresses VZV reactivation, which prevents VZV-specific immune reconstitution. In contrast with HSCT recipients, other patients with cancer at high-risk for developing VZV due to immunosuppressive chemotherapy are likely to reestablish immunity upon the cessation of immune suppression. Therefore, the same "rebound" in VZV incidence may not be observed in these patients.

Although the overall fraction of HSCT recipients who experience VZV reactivation was not reduced in the prophylaxis studies, the VZV disease that developed after discontinuing

prophylaxis (typically 6–12 months after HSCT) was generally localized and mild [117, 119]. Allogeneic HSCT recipients who required immunosuppression after stopping antiviral prophylaxis had a greater likelihood of developing VZV disease. That increased risk was reduced by continuing antiviral prophylaxis [114, 115, 119–121].

In general, the authors favor long-term prophylaxis to prevent VZV reactivation among very high-risk patients, including HSCT recipients and those receiving alemtuzumab, purine analogs, or high-dose corticosteroids. For example, we use acyclovir (1,200–1,600 mg daily in divided doses) or valacyclovir (500 mg twice daily) prophylaxis in all VZV-seropositive allogeneic HSCT recipients who are receiving immunosuppressive drugs, including those receiving systemic therapy for GVHD. Patients who received T-cell depleted or CD34-selected allografts are typically offered prophylaxis against VZV for at least 12 months after HSCT. The duration of prophylaxis may also be guided by the measurement of T-cell immune responses [122].

Human Herpes Virus-6 (HHV-6)

HHV-6 is an essentially ubiquitous β-Herpes virus that causes exanthema subitum (roseola) in children. Symptomatic reactivation is believed to be exceedingly rare in immunocompetent hosts, but can develop during periods of severe immunodeficiency. HHV-6 reactivation can cause hepatitis, pneumonitis, encephalitis, and a viremic syndrome characterized by fever, rash, and myelosuppression.

HHV-6 encephalitis classically manifests as anterograde amnesia and seizures that result from limbic involvement [123], possibly reflecting a viral tropism for hippocampal astrocytes [124]. Pleocytosis and elevated protein are present in the cerebrospinal fluid of one half to two thirds of patients with HHV-6 encephalitis. In these patients, characteristic abnormalities on MRI include nonenhancing, low attenuation lesions involving the gray matter and occasionally the white matter. These findings can be quite subtle and not visible by CT scanning [125, 126].

Recently, several studies have reported high rates of HHV-6 reactivation among allogeneic HSCT recipients [5, 123, 127–131]. Serial PCR monitoring of serum identified HHV-6 DNA in 50–70% of unselected allogeneic HSCT recipients within 30 days after transplant. In most cases, these reactivations were asymptomatic and associated with only a single positive sample, although higher DNA titers were predicted for GVHD, CMV reactivation and nonrelapse mortality. The highest incidence (80–100%) of reactivation was observed among recipients of umbilical cord blood grafts, as these grafts presumably lack any pathogen-specific immunity.

HHV-6 is susceptible to ganciclovir, foscarnet, and cidofovir in vitro, but has reduced susceptibility to acyclovir. Because the diagnosis of HHV-6 is often presumptive and a positive serum PCR does not prove causality, the decision whether to institute one of these drugs can be extremely difficult. Ganciclovir is myelosuppressive and both foscarnet and cidofovir are highly nephrotoxic, especially in combination with calcineurin inhibitors. Nonetheless, some centers routinely perform preemptive serum PCR screening for HHV-6 among umbilical cord blood transplant recipients and institute foscarnet in those with a positive PCR and symptoms consistent with HHV-6 disease, including persistent fever, delayed engraftment, or neurologic symptoms. No randomized data are available to evaluate the benefit of this approach.

Epstein-Barr Virus (EBV)

EBV infects more than 95% of humans in the first two decades of life. Transmission of EBV is most frequently horizontal through the passage of infected saliva. Vertical, sexual, blood, and transplant-mediated transmission also occur. Among children, primary infection is typically asymptomatic. Infection in adolescence or later in life is frequently accompanied by infectious mononucleosis, a syndrome of lymphocytosis, lymphadenopathy, and splenomegaly caused by the vigorous primary CD8 T-cell response against EBV-infected B cells.

B cells are believed to be essential for EBV persistence as patients with X-linked agammaglobulinemia (who lack B cells) do not develop persistent EBV infection. EBV gains entry into B cells via the CD21 receptor on the B-cell surface. The mechanism for EBV entry into epithelial, mesenchymal, and T cells, which lack CD21, remains unclear.

EBV is associated with a wide array of lymphoid and nonlymphoid proliferations in both immunocompetent and immunocompromised hosts (Table 31.2). The clonality of these proliferations can be determined by assaying the number of tandem repeats present in the episomal EBV genome. Proliferations whose cells contain a common number of tandem repeats are monoclonal, while proliferations that include variable numbers of repeats are polyclonal.

In immunocompetent hosts, the diagnosis of EBV infection can be made by assaying for heterophile antibodies. PCR of serum, plasma, or whole blood can be useful for diagnosing EBV reactivation or latent proliferations, although PCR assays vary widely and the benefit of preemptive PCR screening in high-risk patients remains largely unproven [132, 133].

EBV proliferations in highly immunocompromised hosts. EBV causes a range of pathologic disorders in immunocompromised patients, from fever to posttransplant lymphoproliferative disorder (PTLD) to monoclonal non-Hodgkin's

Table 31.2 Abridged compilation of malignant and nonmalignant proliferations associated with the γ-herpes viruses, Epstein-Barr virus (EBV) and human herpes virus-8 (HHV-8) [1, 2]

Epstein-Barr virus	Human herpes virus-8
Nonmalignant disease	
Infectious mononucleosis	Bone marrow failure
Chronic active infection	syndrome
Oral hairy leukoplakia	Multicentric Castleman's
	disease
Malignant lymphoid disease	
Immunodeficiency-associated B cell lymphomas	Plasmablastic lymphoma
	Germinotropic lymphoma
Posttransplantation lymphoproliferative disorder	Endemic lymphoma
	Primary effusion lymphoma
Lymphomatoid granulomatosis	Secondary effusion
Primary effusion lymphoma	lymphoma
Burkitt lymphoma	
Classical Hodgkin lymphoma	
Extranodal NK/T cell lymphoma, nasal type	
Virus-associated hemophagocytic syndrome	
Malignant nonlymphoid disease	
Lymphoepithelioma-like carcinoma	Kaposi's sarcoma
Nasopharyngeal carcinoma	
Breast carcinoma	
Hepatocellular carcinoma	
Leiomyosarcoma	
Follicular dendritic cell sarcoma	

lymphoma. A wide variety of immunodeficiency-associated B cell lymphomas occur in immunocompromised patients. Among primary effusion lymphomas, EBV is found in some cases, while HHV-8 is present in all cases. These arise from either lytic reactivation or the outgrowth of latently infected B cells.

Among HSCT recipients, the highest incidence for EBV-related proliferations occurs in the first 6 months after transplant, and the vast majority of cases develop during the first year. In allogeneic HSCT recipients, the virus is typically derived from the recipient while the B cells are donor-derived. Risk factors for EBV-related pathology in these patients are primarily related to T-cell immunodeficiency, including transplantation from an unrelated or HLA-mismatched donor, in vitro T-cell depletion of the allograft, the use of anti-T-cell antibodies, and chronic GVHD.

Treatment. Primary EBV can be highly fatal in patients with severe T cell defects. In these cases, acyclovir or related compounds may be beneficial, although published evidence is lacking. Available treatments for EBV-related B cell proliferations are either cytotoxic (i.e., chemotherapy and radiation) or immune-mediated. Among the latter, the anti-CD20 monoclonal antibody rituximab induces long-term remission in approximately half of HSCT recipients with EBV

reactivation [133], but is less effective for solid organ transplant recipients. For the latter, withdrawing immunosuppression can induce complete responses.

In patients who lack EBV-specific immunity, either due to immunoablation or primary immunodeficiency, adoptive cellular therapy can provide EBV-specific immunity and engender responses against EBV-associated proliferations [134]. In the allogeneic HSCT setting, immunity against EBV can be transferred by donor lymphocyte infusion [135]. However, nonselected donor lymphocytes also place the recipient at high-risk for developing GVHD. An alternative is to generate allogeneic EBV-specific T cells in vitro, a method now widely used at a few centers and associated with essentially no risk for causing GVHD. The group at Baylor University has pioneered the development of multivalent T cell products with activity against EBV, cytomegalovirus, and adenovirus [136]. A possibility currently being tested is that partially or fully HLA-matched, third-party (i.e., not from the donor or recipient) EBV-specific T cells will retain activity against EBV proliferations in the recipient. If so, T cells specific to EBV or other infectious agents could be taken "off-the-shelf" and given to a wide range of affected patients.

Human Herpes Virus 8 (HHV-8)

Although Moritz Kapoŝi first described his eponymous sarcoma in 1872, it was not until the early 1990s that epidemiologic studies suggested Kaposi's sarcoma (KS) is a sexually transmitted disease, and not until 1994 that the organism was identified by subtraction cloning [137]. Like EBV, HHV-8 is a γ-herpes virus that maintains latency in B cells and is associated with a variety of malignant and nonmalignant proliferations (Table 31.2). Also like EBV, transmission of HHV-8 is primarily through infected saliva, but can occur via other routes.

Unlike EBV, HHV-8 infects only 1–5% of persons in developed countries and up to 50% of persons in other regions, most notably Africa. Serum serology is the standard assay for demonstrating prior exposure (and latent infection), while immunohistochemistry on tissue sections is useful to confirm the presence of HHV-8 in Castleman's disease, KS, or non-Hodgkin lymphoma. HHV-8 infection can be diagnosed by serum PCR, although this method may be overly sensitive. Previous PCR studies have erroneously implicated HHV-8 in a variety of diseases where it is unlikely to be involved [2].

Primary HHV-8 infection is probably asymptomatic in most cases, although a mononucleosis-like illness has been reported. Among immunodeficient hosts, HHV-8 can widely disseminate and infect endothelial cells and a variety of bloodborne

mononuclear cells. Dissemination can cause a syndrome of severe myelosuppression in transplant recipients [138, 139].

HHV-8 is susceptible to ganciclovir, foscarnet, and cidofovir in vitro, although like EBV, there is sparse evidence demonstrating its efficacy in patients. Immune reconstitution is effective in reversing KS in patients with AIDS and, when this is a viable option, is likely to be the most effective therapy against many HHV-8 associated processes in patients with cancer.

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Chapter 32
Respiratory Viruses

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Abstract The respiratory viruses as a group are the most common cause of an acute infectious illness in developed societies. The immunocompromised state of many cancer patients constitutes the basis for the frequent failure of the host to promote a normal and rapid recovery from an acute respiratory viral infection and results in a more severe and prolonged infection that causes significant morbidity and mortality in these patients. Those respiratory viruses that are most prevalent and most prone to produce lower respiratory illnesses and pneumonia in healthy hosts, RSV, influenza viruses, and parainfluenza viruses, are those most likely to cause severe illness and pneumonia leading to hospitalization in immunocompromised persons. However, viruses less prone to produce a lower respiratory illness but that are highly prevalent, such as rhinoviruses, may frequently be associated with severe illness. The limited availability of antivirals and vaccines for the acute respiratory viruses means that these infections will continue to be important for many years and dictate a need for utilizing infection control procedures as much as possible, particularly in hospitals and institutions, so as to minimize spread. Efforts to develop specific vaccines are important as their use could prevent as well as reduce exposure of cancer patients to these viruses. Development of specific antivirals is important for use in immunocompromised patients as normal recovery mechanisms may be seriously impaired.

Keywords Influenza • Cancer • Transplant • RSV • Adenovirus • Metapneumovirus

Introduction

Community respiratory virus infections were once primarily considered to be infections of children and generally nonserious. However, over the past two decades, it has become clear that these viruses can cause serious infections that require medical attention, particularly in infant, elderly, and immunocompromised patients. Historically, the most common causes of respiratory infections in cancer patients were thought to be opportunistic bacteria and fungi, but newer diagnostic methods have revealed that respiratory viruses can cause serious morbidity and mortality in such patients, including leukemia patients and hematopoietic stem cell transplant (HSCT) recipients.

Many viruses are known to cause respiratory tract infections, but the most common in hospitalized cancer patients are influenza viruses, respiratory syncytial virus (RSV), and parainfluenza viruses (PIV) [1, 2]. However, all respiratory viruses can cause respiratory infections in cancer patients including rhinoviruses, enteroviruses, coronaviruses, human metapneumoviruses (hMPVs), adenoviruses, as well as cytomegaloviruses, herpes simplex, and varicella zoster viruses. In this chapter, we discuss the common clinical presentations, diagnostic methods, treatments, and prevention measures for respiratory virus infections in general and in cancer patients in particular (Table 32.1).

Data from September 2008 to February 2010 (18-month period) at our institution (Fig. 32.1) demonstrate the cyclical pattern of the three major respiratory viruses: RSV, influenza, and PIV. During the 2009–2010 season, influenza infections in our cancer patients were reported starting July 2009 with a peak in October 2009 due to the pandemic A (H1N1) influenza virus. More recently, a total of 181 cases of influenza, parainfluenza, and RSV were identified at our institution between 1 September 2009 and 28 February 2010 (Fig. 32.2). Of these cases, most were in HSCT recipients (45%).

Respiratory Syncytial Virus

Most RSV infections occur in infants and young children throughout the world [2, 3]. In the United States, these infections usually occur from late fall to the end of spring, with a peak from January to February; few cases are reported during

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Table 32.1 Syndromes and their commonly associated viruses

Syndrome	Commonly associated viruses	Less commonly associated viruses
Common cold	Rhinoviruses, coronaviruses	Influenza and parainfluenza viruses, enteroviruses, adenoviruses
Influenza-like illness	Influenza viruses	Parainfluenza viruses, adenoviruses
Croup/laryngitis	Parainfluenza viruses	Influenza viruses, respiratory syncytial virus, adenoviruses
Bronchitis/bronchiolitis	Respiratory syncytial virus	Influenza and parainfluenza viruses, adenovirus
Pneumonia	Influenza viruses, respiratory syncytial virus, adenoviruses	Parainfluenza viruses, measles, cytomegalovirus, varicella zoster virus, herpes simplex virus
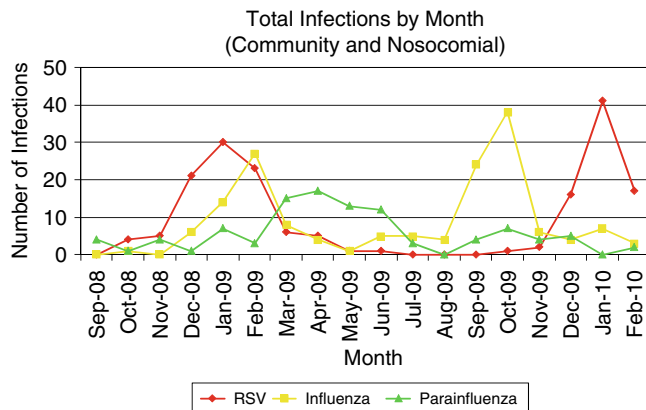
Fig. 32.1 Community and nosocomial infections per month for RSV, influenza, and parainfluenza virus at M.D. Anderson Cancer Center between September 2008 and February 2010
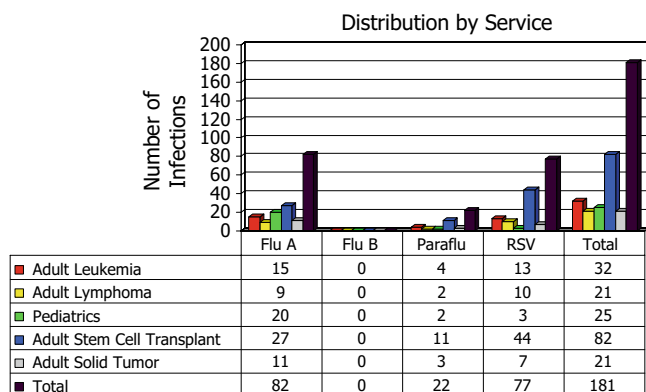
Fig. 32.2 Distribution of the infections caused by RSV, influenza, and parainfluenza virus by different services at M.D. Anderson Cancer Center that occurred between September 2009 and February 2010

the summer [2–4]. RSV is a member of the *Paramyxoviridae* family and the genus *Pneumovirus*. It is an enveloped single-stranded RNA virus approximately 150–300 nm in diameter that is contained in a helical nucleocapsid surrounded by a lipid envelope. This envelope bears two glycoproteins: the G protein, which attaches to the cell surface, and the F (fusion) protein, which enables the internal components to enter the cell after fusion of host and viral membranes and to initiate replication. Both glycoproteins are integral to pathogenesis [2, 3, 5]. There are two groups of RSV viruses, groups A and B [2–5].

Clinical Presentations

RSV infections can present with a wide array of upper or lower respiratory symptoms. The incubation period is 4–6 days in adults. In infants and young children, the primary infection starts in the upper respiratory tract, with rhinorrhea, low-grade fever, and cough; it may progress to lower respiratory infection (LRI) (bronchiolitis or pneumonia), at which stage most patients seek medical attention [3, 6]. It is also likely to involve the sinuses and the middle ear. RSV is known to cause apnea in infants, although the mechanism of this action remains unknown. Older children and adults typically present with upper respiratory tract symptoms, but may also have constitutional symptoms such as fever and malaise [3, 7]. RSV upper respiratory infections (URIs) can also progress to the lower respiratory tract, particularly in institutionalized adults and those with severe combined immunodeficiency, leukemia, HSCT, and in lung transplant recipients [2, 8, 9]. These patients may present with wheezing and shortness of breath, with or without underlying comorbidities or known hyperactive airways. Almost 35% of elderly patients with RSV infections report wheezing [8–11].

Infections in Immunocompromised Patients

Patients with weakened immune systems because of malignancy, chemotherapy, steroid use, HSCT, or solid organ transplantation are at high risk for developing severe illnesses. They also tend to have a longer duration of infection, with a varied presentation [12, 13]. Leukemia patients and solid organ and stem cell transplant recipients are particularly at risk, with the latter being at high risk for pneumonia and death prior to engraftment [11].

Leukemia Patients and HSCT Recipients

RSV infections begin as URI, but progress to LRI in 30–60% of HSCT recipients, leading to respiratory failure with significant morbidity and mortality; some early studies described a mortality rate of 70–100% [14, 15]. In HSCT recipients, the risk factors for progression to LRI

include lymphopenia, older age, stage of malignancy, graft-versus-host disease, and no ribavirin treatment [16–19]. Torres et al. [20] found that a high APACHE II score and not giving aerosolized ribavirin treatment were independent predictors of progression to pneumonia in leukemia patients; those with URI who were treated with aerosolized ribavirin were less likely than untreated patients to develop pneumonia (68 vs. 96%, $p < 0.01$) and die with RSV infection (6 vs. 36%, $p = 0.1$). The overall mortality rate in the study was 10% [20].

Solid Organ Transplant Recipients

Solid organ transplantation patients with RSV infection may present with dyspnea, cough, fever, and wheezing which progress to pneumonia in more than 70% of patients [21]. In lung transplant recipients, a higher frequency of RSV pneumonia has been reported, but the mortality rate is low; the mortality rate is also low in kidney transplant recipients [21]. In pediatric liver transplant patients, Pohl et al. reported a mortality rate of 17% for RSV pneumonia with early infection onset and preexisting lung disease as predictors of severe disease [22].

Other Immunocompromised Patients

In children, genetic polymorphisms in cytokine and chemokine-related genes (interleukin [IL]-4, IL-8, IL-10, IL-13, and CCR5) and genes related to potential virus-cell surface interactions or cell signaling (TLR-4, CX3CR1, SP-A, and SP-D) have been associated with severe RSV infections [23].

Data on HIV patients with RSV infections are scarce; however, a cohort study by Miller et al. [24] performed in the winter of 1994–1995 found no evidence of influenza, RSV, parainfluenza, adenovirus, or enterovirus infections in the bronchoscopic alveolar lavage fluids of 44 HIV-1-positive patients.

Diagnosis

RSV can be diagnosed on the basis of the clinical presentation in infants with LRI during an outbreak period [3]. RSV infections in adults cannot be clinically differentiated from other viral infections that cause upper respiratory symptoms. For a specific diagnosis, RSV must be detected in respiratory secretions. Nasal aspirates or washes are most likely to give a positive RSV test in young children. If a nasal aspirate or wash cannot be obtained, a nasopharyngeal swab or throat swab may be used. Because immunocompromised or intubated patients are more likely to develop an LRI due to RSV, tracheal aspiration or bronchoalveolar lavage should be performed [8, 25]. The gold standard for diagnosing RSV remains the identification of virus causing typical syncytia in cultures of HEp-2 cells [25]. Viral cultures may take 2 days (shell vial cultures) and up to 2 weeks (routine cultures) to become positive, making isolation less relevant in most clinical settings. Other available methods include antigen detection by enzyme-linked immunosorbent assay (ELISA), immunoflourescence assay, and polymerase chain reaction (PCR) tests. Fan et al. [26] reported a sensitivity of 65–95% for RSV detection using rapid antigen testing with ELISA. PCR tests have been shown to be more sensitive than direct antigen detection [27, 28].

Treatment

For most immunocompromised patients, RSV treatment is focused on reducing symptom severity and preventing progression to LRIs. Nonsteroidal anti-inflammatory drugs and antihistamines have been used in patients with a URI. Ribavirin, a nucleoside analog, has in vitro activity against RSV and has been approved by the United States Food and Drug Administration for the treatment of RSV infections in children. Two schedules of aerosolized ribavirin have been used in immunocompromised patients: continuous and intermittent. On the continuous schedule, a daily dose of 6 g (concentration, 20 mg/mL) is delivered over 18 h via a small particle aerosol generator unit, administered via a face mask in a tent. On the intermittent schedule, a concentration of 60 mg/mL is delivered over 3 h every 8 h.

Aerosolized ribavirin may be beneficial in certain adults and children with LRIs. Its early use has been shown in some retrospective studies to reduce morbidity and mortality in HSCT recipients [3, 29] and patients with hematologic malignancies, particularly when the infection is treated early on [30]. However, its effectiveness in solid organ transplantation patients remains unknown [31]. An RSV-specific monoclonal antibody (Palivizumab) did not demonstrate a therapeutic benefit in a major study conducted in children [32]. Although the combination of ribavirin and intravenous immunoglobulin (IVIG) or palivizumab has not been evaluated in a randomized trial, it is sometimes used in severely ill patients with RSV pneumonia, especially HSCT recipients, given that they have high mortality rates from this infection [3, 11, 14]. In patients at risk for progression to LRI, aerosolized ribavirin should be considered at an early stage. A recent trial demonstrated that both the intermittent and continuous schedules of aerosolized ribavirin were effective at preventing progression to LRIs in 91% and 80% of patients with RSV URIs and hematologic malignancies (including HSCT recipients), respectively [33].

Prevention/Vaccination

RSV infection may be acquired nosocomially, thus specific infection control measures should be implemented when dealing with patients with known or suspected infections. Briefly, patients should be isolated in private rooms when possible, and appropriate personnel protective equipments should be used (i.e., disposable gloves, masks, and gowns) [34]. No licensed vaccine is available for RSV; however, two agents, RSV-IVIG and palivizumab, have been used to prevent RSV infection. RSV-IVIG has been studied in children younger than 24 months with severe lung disease and those who were born prematurely [35], but it was removed from the market in 2003. A randomized double-blind placebo-controlled study in children found that palivizumab recipients had a 45% relative reduction in RSV hospitalizations ($p = 0.003$). Twenty-one children (3.3%) died in the palivizumab group vs. 27 (4.2%) in the placebo group with no deaths attributable to palivizumab [36]. Palivizumab is easier to administer than regular IVIG, which must be given over 4–6 h, and does not interfere with other vaccinations. However, RSV-IVIG and IVIG may provide additional protection against other respiratory viruses as well [35, 37, 38].

Influenza Viruses

Influenza viruses infect both the upper and lower respiratory tracts. Outbreaks are common every winter, although the severity of the disease varies considerably. Influenza viruses belong to the *Orthomyxoviridae* family, with influenza types A, B, and C constituting one genus. These RNA viruses are enveloped and measure about 80–120 nm in diameter. The designation of the viruses into types is based on the stable antigenic characteristics of the nucleoprotein and the matrix protein antigens. Influenza A and B viruses have surface glycoproteins known as hemagglutinins (HA) and neuraminidase (NA). Three hemagglutinin subtypes (H1, H2, and H3) and two neuraminidase subtypes (N1 and N2) have been described for the influenza A viruses that infect humans. Major antigenic changes in the glycoprotein (basis for new subtypes) are called antigenic shift and can cause pandemics; minor antigenic changes occur frequently, are called antigenic drift, and cause the annual epidemics. Influenza B has only exhibited minor antigenic drift [3, 39]. The 2009 pandemic influenza A (H1N1) contains segments present in North American swine for years, but is a new reassortant virus that acquired M and NA gene segments from a Eurasian adamantane-resistant swine influenza virus [40].

Clinical Presentation

Influenza typically has a short incubation period and an abrupt onset of symptoms, such as headache, fever, chills, myalgia, and malaise, along with respiratory symptoms of runny nose, cough, and sore throat. It can also present as a febrile URI or with constitutional manifestations only or with few-to-no respiratory symptoms.

Influenza can progress to pneumonia in otherwise healthy persons, but particularly in patients with comorbidities such as lung diseases, heart disease, diabetes mellitus, renal diseases, and hemoglobinopathies, in immunocompromised individuals, residents of nursing homes or chronic care facilities, and in individuals over 65 years of age [41].

Primary pneumonia occurs when the influenza virus directly involves the lung and should be suspected when clinical symptoms progress to high fever, dyspnea, and hypoxemia [42]. Influenza virus infections also affect the epithelium of the tracheobronchial tree, leading to impaired defense and a secondary bacterial pneumonia.

Infections in Immunocompromised Patients

Influenza infections can increase morbidity and mortality rates in cancer patients [2].

Leukemia Patients and HSCT Recipients

In a study of leukemia patients with influenza infections, 39% of patients developed pneumonia [43], with cough and dyspnea being the most common manifestations. Half of the patients had lymphopenia [43]. The incidence of influenza infection in HSCT recipients is reported as 0.4% [44], with a mortality rate up to 38% [43], mainly due to respiratory failure. In one study [44], 17% of patients who developed influenza after HSCT presented with pneumonia; of those who presented with URIs, 14% experienced progression to LRI. Risk factors associated with progression to LRI were lymphopenia and days from transplantation (i.e., pneumonia developed more commonly among those infected earlier after transplantation); whereas use of systemic steroids and autologous stem cell transplantation appeared to be protective. X-ray findings include a diffuse interstitial pattern or focal pulmonary infiltrates [45].

Solid Organ Transplant Patients

Among patients with solid organ transplantation, lung transplant recipients are at the highest risk for influenza virus infection [46]. The initial presentation in these patients may not always be in the respiratory tract, as illness can present with nonspecific gastrointestinal symptoms; however, patients who required hospitalization always presented with pneumonia [47]. Progression to bronchiolitis obliterans, which is a characteristic of chronic lung rejection after infection, was also reported. In patients postrenal transplantation, influenza pneumonia is often acute, with high fever, cough, dyspnea, cyanosis, leukopenia, and thrombocytopenia [48].

Table 32.2 Recent antiviral resistance pattern for different influenza strains[a,b]

	Oseltamivir	Zanamivir	M2 inhibitors[c]
2009 H1N1	Susceptible	Susceptible	Resistant
Seasonal H1N1	Mostly resistant	Susceptible	Mostly susceptible
Seasonal H3N2	Susceptible	Susceptible	Susceptible
Influenza B	Susceptible	Susceptible	Resistant
Avian H5N1	Susceptible	Susceptible	Variable

[a]Centers for Disease Control and Prevention. http://www.cdc.gov/h1n1flu/recommendations.htm
[b]WHO Guidelines for the Pharmacologic Management of Pandemic (H1N1) 2009 influenza and other influenza viruses. http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html
[c]Amantadine and rimantadine

Diagnosis

Influenza infection can only be diagnosed clinically in persons exhibiting the classic syndrome during an epidemic. However, because other viruses can produce the same syndrome and influenza infection can produce other respiratory syndromes, a confirmatory test detecting the virus or viral antigens in nasal washes, throat swabs, respiratory tract secretions, or bronchoalveolar lavage specimens is needed in sporadic cases and in immunocompromised patients. Viral culture remains the gold standard for diagnosis, but can take up to 72 h to yield results [49]. Sputum and nasal washes or nose swabs are superior to throat swabs for diagnosis [50]. Rapid antigen testing using immunoflourescence assays, enzyme immunoassays, and PCR-based testing are used frequently in clinical settings [51]. The results of these tests can be obtained in hours and can have good sensitivity (72–95%) and specificity (76–84%) if obtained early from those with more severe illnesses [52]. PCR-based assays are more sensitive than rapid antigen testing for diagnosing influenza A and B, but are not often used because of availability and cost [51]. Samples should be obtained within 24–48 h of the appearance of symptoms for the most accurate results.

Treatment

Two classes of drugs are available to treat influenza infections [53]: the neuraminidase inhibitors, zanamivir and oseltamivir, which are active against influenza A and B viruses; and the M2 inhibitors, amantadine and rimantadine, which are only active against influenza A viruses [54]. Amantadines are not effective against influenza B and resistance has been reported for 2009 novel H1N1 virus; resistance to oseltamivir has increased for the seasonal H1N1 virus (Table 32.2) [55, 56].

Therapy should be initiated as early as possible, preferably within 48 h after symptom onset [57]. Zanamivir and oseltamivir have been used extensively to treat both influenza A and B; both were shown to reduce the mean duration of symptoms by 1 day when used within 48 h of symptom onset [58]. Both neuraminidase inhibitors have been shown to significantly decrease the incidence of complications associated with influenza such as development of pneumonia when compared to placebo [59]. The most common side effects of oseltamivir are nausea and vomiting, although other toxicities have been reported. Central nervous system side effects such as anxiety, insomnia, impaired thinking, confusion, lightheadedness, and hallucinations have been reported with amantadine use. Newer NI inhibitors including parenteral preparations are under development [60].

Prevention/Vaccination

The mainstay of influenza prophylaxis in the general population is the administration of influenza vaccine. Annual vaccination has been recommended for many years for people at high risk for complications, including those older than 65 years, residents of nursing homes or other facilities, adults and children with chronic pulmonary or cardiovascular conditions, adults and children hospitalized during the previous year, women in the second and the third trimesters of pregnancy, immunocompromised patients, healthcare workers, and family member of those at high risk prior to the onset of influenza season [41]. The American Committee on Immunization Practices has recently recommended vaccination for all persons for whom there is no contraindication [61].

Currently, there are two types of vaccines available, an intramuscular (inactivated virus vaccine) and an intranasal (attenuated virus vaccine). The intranasal form is to be used only in healthy individuals between the ages of 2 and 49 years;

it should not be used to vaccinate immunocompromised patients [62]. Individuals with a significant allergy to eggs or those with acute febrile illness should not be given vaccine [63]. The Advisory Committee on Immunization Practices recommends that immunocompromised individuals be vaccinated prior to influenza season and receive daily chemoprophylaxis with an antiviral medication during community outbreaks [41].

Influenza chemoprophylaxis may be used in patients at high risk for complications if the vaccine is contraindicated or not likely to be completely protective. Antiviral drugs should be administered to patients within the first 6 months of HSCT, those with documented graft-versus-host disease, unvaccinated healthcare workers who care for immunocompromised individuals, and residents of long-term care institutions during outbreak periods [64]. The American Society for Blood and Marrow Transplantation (ASBMT) 2009 guidelines [65] for prevention of infection in HSCT recipients recommend annual inactivated influenza vaccine before the beginning of the season and before stem cell transplant. The vaccine may be given 4–6 months after HSCT. They also recommended prophylaxis and preemptive treatment during community and nosocomial outbreaks of influenza A for HSCT recipients regardless of the vaccination status in those who are within 24 months of the transplant or in those with more than 24 months posttransplant, but have GVHD and/or are on immunosuppression. The drug to be used for chemoprophylaxis depends on the susceptibility pattern of the outbreak virus.

Parainfluenza Viruses

PIV are enveloped, single-stranded RNA viruses that belong to the *Paramyxoviridae* family. The envelope contains two glycoproteins, one with both HA and neuraminidase activity and the other with fusion activity. There are five types that share certain antigens with other members of the *Paramyxoviridae* family [3, 66]. Of the five, PIV-3 is the most prevalent, with most adults demonstrating the presence of antibodies [67]. PIV-3 infections may be epidemic in the spring and summer, but may also occur through the year; PIV-3 is associated with pneumonia and bronchiolitis in infants. PIV-1 and 2 are associated with croup in children which occurs as outbreaks every 2 years in the fall; PIV-4A and 4B cause only mild illnesses [67, 68].

Clinical Presentation

PIV infections have a wide spectrum of presentations, from a simple URI to a life-threatening complication such as pneumonia. The incubation period is usually 2–6 days.

Young children may present with coryza, sore throat, hoarseness, and cough with chest X-rays revealing interstitial infiltrates. In adults, most infections are mild, but in immunocompromised individuals, the infection can progress to a lower respiratory tract illness including pneumonia and cause prolonged illness and even death [3, 67, 69].

Infections in Immunocompromised Patients

Immunocompromised individuals are at risk for a PIV infection that can progress to pneumonia. A study at our institution found a higher rate of progression among leukemia patients than among HSCT recipients [70].

Leukemia Patients and HSCT Recipients

PIV usually presents as an URI. In a large study in HSCT recipients over several years, PIV infections were documented in 7.1% of cases, with 78% being community-acquired [71]. Patients who have undergone HSCT are at particular risk for developing severe PIV-associated pneumonia [71–74]; Wendt et al. [72] reported a mortality rate up to 30%. Coinfections (*Aspergillus fumigatus* being the most common) and mechanical ventilation were found to be significant risk factors for PIV pneumonia-associated mortality in one study [71]. Other factors associated with progression include neutropenia within 1 month prior to infection, an APACHE II score higher than 15, and pulmonary coinfection; this study also found a mortality rate around 20%, with no difference between those treated and those not treated with aerosolized ribavirin [70].

Solid Organ Transplant Patients

Patients who have undergone solid organ transplantation do not appear to be at increased risk for developing severe PIV illness, but only a few studies have been reported [75, 76]. One of these studies in lung transplant patients found PIV infections in 11% of patients, all of whom developed pneumonia, but the majority (74%) were treated with aerosolized ribavirin and all but one recovered [75].

Diagnosis

Except for croup in young children, the clinical pattern of PIV infection is similar to that of other respiratory viruses and cannot be distinguished on the basis of symptoms alone. During a community outbreak, a presumptive diagnosis can be made; however, confirmation in laboratory tests may be

appropriate in immunocompromised individuals. The virus can be detected in respiratory tract secretions, nasal washes, nasal swabs, throat swabs, and bronchoalveolar lavage specimens. Viral culture remains the gold standard for diagnosis, but can take days to yield a result [3, 77]. Rapid antigen detection by immunofluorescence or ELISA is most commonly used and can have a sensitivity of as high as 75–95% [78]. Recent PCR-based assays have sensitivities up to 100%, with high specificity [26, 79].

Treatment

Management of PIV infection is mostly supportive as no PIV-directed antiviral therapy has been licensed by the U.S. Food and Drug Administration. Ribavirin has been shown to be active against the virus in vitro and in animal models and has been used occasionally to treat immunocompromised patients with severe PIV infections [80]. One case series reported a decrease in PIV viral loads and clinical improvement after aerosolized ribavirin treatment in children with severe immunodeficiency [81]. Nichols et al. [71] reported that aerosolized ribavirin did not reduce viral shedding or mortality rates in HSCT recipients after the infection had progressed to the lower respiratory tract. Our data also showed no apparent benefit of aerosolized ribavirin on the mortality rate in HSCT recipients and leukemia patients [70]. On the other hand, a combination of methylprednisolone and intravenous or oral ribavirin has, apparently, been used successfully to treat PIV pneumonia in a HSCT and a heart transplant recipient, respectively [82, 83].

Prevention/Vaccination

Currently, no licensed vaccine is available for the prevention of PIV infection. Hence, infection control measures play an important role in containing the spread of the infection. Patients with suspected or confirmed infections should be isolated, and personnel protective equipment should be used.

Adenovirus

Human adenoviruses are DNA viruses belonging to the *Mastadenovirus* genus of the Adenoviridae family which measure about 70–80 nm in diameter [3, 84]. There are at least 51 known human serotypes divided into subgenera A to F based on the DNA genome and pattern of hemagglutination [84]. Adenovirus infections are reported most frequently in infants and children and can occur throughout the year;

however, they may cause serious infections in immunocompromised patients. After a primary infection in childhood, adenoviruses establish latency in adenoidal tissues along with lifelong persistence of specific antibodies [84, 85].

Clinical Presentation

Adenovirus infections are transmitted by either inhalation of aerosolized virus, inoculation of the virus into conjunctival sac, or through the fecal-oral route [3, 84]. Subgroup A, type 31 and various types from subgroups B and C have been associated with pneumonia and hepatitis [86]. Serotypes 4, 7, 14, and 21 are associated with outbreaks of acute respiratory disease in military recruits, mostly in winter and spring [3]. Types 1, 2, 5, and 6 are most common in children and present as an acute upper respiratory tract illness which can progress to lower respiratory disease; types 3 and 7 are less common, but can cause severe disease. In adults, infections due to adenovirus are characterized by sore throat and gradual onset of fever. Cough, coryza, and regional lymphadenopathy are commonly seen. The most common clinical symptoms besides respiratory symptoms are fever and diarrhea [3].

Infections in Immunocompromised Patients

Leukemia Patients and HSCT Recipients

Adenovirus infections are common after HSCT and can occur as a localized illness or as part of a disseminated disease. It has been associated with delayed engraftment and graft failure. Infections due to adenovirus in HSCT recipients have a reported incidence of 0.5–3% [87, 88] and are more commonly reported in allogeneic HSCT recipients than in autologous transplant recipients (6 vs. 0.92%) [87]; however, the mortality rate can be as high as 75% in both groups [87, 89]. Some reports also suggest that the incidence of adenovirus infection in patients after HSCT may be rising due to transplantation practices [90, 91]. Disseminated infection may occur without respiratory tract symptoms and disease can develop in almost any organ causing gastrointestinal disease, hepatitis, nephritis, pneumonia, conjunctivitis, thrombotic thrombocytopenic purpura, pancreatitis, or hemorrhagic cystitis. Viremia may be present, but is not detected in all cases of disseminated disease [92].

Adenovirus is known to be fatal even in the absence of any respiratory tract involvement; however, if pneumonia is present, the mortality has been reported to be higher (80 vs. 50%) [87]. Coinfections with *Aspergillus* spp. and bacteria such as Nocardia, *Legionella* spp., and *Mycobacterium tuberculous* are frequently seen in this patient population [90, 93]. Risk factors for adenovirus infections include GVHD, unrelated

donor, total body irradiation, T-cell depletion, younger age (<7 years old), chronic disease, and recent transplantation [90, 91, 94, 95]; the degree of T-cell depletion and posttransplant suppression of T-cell function are the most important ones [92]. Adenovirus types 5 and 21 are associated with severe infections in HSCT recipients [95].

Solid Organ Transplant Patients

There are a few reports of adenovirus infections in solid organ transplant patients in whom the virus involved the donor organ and led to pneumonia, hepatitis, hemorrhagic cystitis, nephritis, enterocolitis, or disseminated disease. In patients with previous liver transplantation, adenovirus pneumonia had a reported prevalence of 1.5% with a mortality rate of 66% [96]. Serotype 5 is known to be associated with hepatitis [96, 97], whereas serotypes 1 and 2 are more commonly associated with pneumonia. In lung transplant recipients, one study found adenovirus infection to be an early complication following surgery with a prevalence rate of 1.3% [98]. Progressive adenovirus infections are known to be associated with graft loss, progression to bronchiolitis obliterans, or death [99].

Diagnosis

Adenovirus infection should be suspected in cases of acute respiratory disease in military recruits or during outbreaks. In most cases, infection caused by the virus cannot be differentiated from those caused by other respiratory viruses from the clinical presentation alone [3]. A definitive diagnosis can be established by viral culture or the detection of specific viral antigens.

Viral culture remains the gold standard for identification of adenovirus. Nasopharyngeal aspirate or swab, throat swab, sputum samples, or bronchoalveolar lavage can be used, depending on the site of the infection. A cytopathic effect is seen in human cell lines such as HeLa (cervix), A549 (lung), HEK (human embryonic kidney), and HEp-2 (larynx) by strains of adenovirus except for types 40 and 41. Adenovirus 40 and 41 grow well in HEK 293 cells. Adenovirus-specific Enzyme Immunoassay (ELISA) or immunofluorescence assay can be used to detect the presence of virus in clinical samples. These rapid tests suffer from a sensitivity of only about 50%; PCR-based assays can detect adenovirus DNA from a variety of clinical specimens and has better sensitivity [100, 101]. Viral load quantification is a useful tool to measure prognosis and monitor clinical response [102, 103]. Viral loads higher than 1×10^6 copies/mL have been associated with an increased likelihood of death [104, 105].

Treatment

There have been no randomized clinical trials for the treatment of adenovirus infection in immunocompromised patients. Most patients are managed using symptom-based treatment and supportive therapy. Cidofovir is currently being used in immunocompromised patients since it has been shown to decrease plasma viral loads in HSCT recipients [106]. Although cidofovir is active against all strains of adenovirus in vitro, only retrospective data are available on the efficacy of cidofovir in HSCT [106–109] and solid organ transplant recipients [110]. Nephrotoxicity is commonly encountered with this drug and it should be used with caution. There are two accepted regimens: 5 mg/kg every 1–2 weeks, or 1 mg/kg 3 times per week, with the latter being associated with less nephrotoxicity [110]. Orally active ether lipid-ester prodrugs of cidofovir (S)-HPMPA are under development with some promising results in in vitro experiments and phase I trials [111]. When tested against five adenovirus serotypes, they were shown to be more active than the unmodified parent compounds [111].

Intravenous ribavirin has been used in a few reported cases, but results were conflicting [112–114]. Finally, another treatment option using adenovirus-specific donor T-cells infusion has been shown to be feasible and effective in protecting children from complications due to adenovirus infection and causing a significant decrease in viral loads [115].

Prevention/Vaccination

Currently, there are no vaccines available for adenovirus infection other than the oral partially attenuated vaccines contained in enteric-coated capsules with use restricted to the military [116]. Only routine infection control practices are recommended for civilian populations where special precautions must be taken for contact and droplet exposure. In HSCT recipients at high risk from adenovirus infection, weekly PCR surveillance of viremia and preemptive treatment with cidofovir can be used [92, 117].

Rhinovirus

Rhinoviruses are members of the *Picornaviridae* family. They are nonenveloped, single-stranded RNA viruses that measure about 15–30 nm. The capsid of the virus is icosahedral and contains 60 copies of four polypeptides each. A canyon on the viral surface contains the attachment site for the host-cell receptor, with most rhinoviruses using this site to attach to the intercellular adhesion molecule-1 receptor expressed on the

surface of host cells [3, 118]. More than 100 serotypes of the virus have been isolated, making a vaccine unlikely in the near future [3, 119, 120].

Rhinoviruses are proven to cause 15–40% of common colds in adults [3]. Each year, adults experience 2 or 3 colds, whereas children may experience 8–12 [3, 120]. Children are the major reservoir for rhinoviruses with infection rates decreasing with age. Although infections occur throughout the year, peaks may occur in the fall and spring. This infection is primarily due to the deposition of the virus on the nasal mucosa. This can occur via self-inoculation or contact with infected secretions such as small- and large-particle aerosols (respiratory droplets) [3, 118, 120].

Clinical Presentation

Individuals with rhinovirus infections may be asymptomatic. When symptoms occur, they are typically those of the common cold: most commonly rhinorrhea and sneezing, which are associated with nasal congestion. Infections due to rhinovirus have an incubation period of 1–4 days. Adults characteristically experience sneezing, nasal obstruction and discharge along with cough, and a sore or scratchy throat. Sinuses are commonly involved so that the illness is rhinosinusitis. Symptoms may last for 4–9 days and usually resolve with no complications. Fever is not usually associated with adult illness [3, 121]. Children, on the other hand, may experience fever, cough, and nasal discharge and obstruction. In addition, the duration of symptoms may be longer. Although bronchitis, bronchiolitis, and bronchopneumonia have been reported in children, rhinovirus is not usually a major cause of lower respiratory illness [3, 122]. However, they are an important cause of exacerbations of asthma and chronic obstructive pulmonary disease in children and adults and of LRI in the elderly [3, 119].

Infections in Immunocompromised Patients

Leukemia Patients and HSCT Recipients

A retrospective study in adults with rhinovirus infections who had undergone HSCT found that 32% of patients developed and eventually died of pneumonia [123]. One patient was found to have a coinfection with *Aspergillus* spp. on autopsy; most of the other patients had interstitial pneumonitis and/or acute respiratory distress syndrome [123]. A study performed at another institution reported that 55% of HSCT recipients with rhinovirus infections developed pneumonia and 33% died [124].

Other Immunocompromised Patients

In a study of community-acquired pneumonia in immunocompromised patients (after HSCT or solid organ transplantation, with HIV infection, or receiving steroids or chemotherapy), rhinovirus was responsible for about 12% of cases, with a mortality rate of 18% [125]. These findings suggest that rhinovirus may cause more severe complications in immunocompromised patients than previously thought.

Diagnosis

Many viruses cause common cold symptoms, and a definitive diagnosis cannot be made only on the basis of the presenting symptoms but rhinoviruses are most commonly associated with colds. A definitive diagnosis can be made by isolating the virus from nasal washes or other nasal secretion specimens in tissue culture. Newer diagnostic methods such as real-time reverse-transcription PCR (RT-PCR) have been used; however, these tests are not frequently performed given the self-limited nature of most infections.

Treatment

No specific antiviral treatment is available for rhinovirus infections. Most cases are managed with supportive care using antihistamines, decongestants, and nonsteroidal anti-inflammatory drugs.

Prevention

Given the number of rhinovirus serotypes known to cause infection, an effective vaccine is unlikely to be developed in the near future. Infection control measures such as hand washing and isolating patients who are known or suspected to have rhinovirus infections can help contain the spread of the virus.

Human Metapneumovirus

hMPV belongs to the subfamily *Pneumovirinae* of the *Paramyxoviridae* family. The virus was discovered in 2001 and is genetically similar to RSV. hMPV is an enveloped RNA virus that is known to cause URIs and LRIs in all age groups [126]. Although hMPV infections are more common in children, a recent study revealed an infection rate of 4.5% in adults with acute upper respiratory illness; 11% of patients required hospitalization [127].

Clinical Presentation

hMPV usually causes a mild infection of short duration (about 3–5 days) and is self-limiting. The incubation period is 4–6 days [128]. The most common presenting symptoms in adults are cough, nasal congestion, rhinorrhea, dyspnea, hoarseness, and wheezing [127]. Children often present with cough, rhinitis, fever, and wheezing [129, 130].

Infections in Immunocompromised Patients

A recent study of patients with hematologic malignancies revealed a 9% incidence of hMPV infection. Nine of the 22 patients who had undergone HSCT had pneumonia; three of these patients died [131]. Another study in HSCT recipients detected the presence of hMPV in 3% (in 5 out of 163) of bronchoalveolar lavage specimens. These 5 patients presented with fever, cough, nasal congestion, and sore throat within the first 40 days after transplantation. The infection progressed to respiratory failure, pulmonary hemorrhage, and culture-negative septic shock. The mortality rate was 80% (4 of 5 patients) [132].

Diagnosis

hMPV's growth in culture is slow and unreliable, which makes this method of diagnosis impractical. The presenting symptoms are similar to those of other infections that cause an acute respiratory illness, making clinical diagnosis impossible. PCR-based methods have been used to diagnose the infection in some centers.

Treatment

No specific antiviral therapy exists for hMPV infections. In vitro studies have demonstrated that ribavirin has activity against the virus [133]; however, no clinical studies have been reported. Immune serum globulins may neutralize the virus as demonstrated in one in vitro study [133]. Anecdotally, a lung transplant recipient with respiratory failure secondary to hMPV pneumonia was treated successfully with aerosolized ribavirin [134].

Prevention

The use of general preventive measures for patients with known or suspected hMPV infections can help reduce the rate of transmission. No vaccine is currently available for this virus.

Coronavirus

Coronaviruses are single-stranded RNA viruses that measure about 80–160 nm in diameter. They are enveloped with club-shaped projections, giving them a crown-like appearance – hence the name [3, 135]. Coronaviruses can cause diarrhea in infants and may play a role in demyelinating diseases of the central nervous system [3, 136]. Coronaviruses are difficult to grow in vitro; some strains can only be grown in human tracheal organ cultures. The major antigenic types that cause diseases in humans are 229E, OC43, HK, and NL63 viruses which cause common colds and may also cause lower respiratory tract illnesses in young children, and SARS-CoV, which causes a severe acute respiratory syndrome [3, 137, 138].

Coronaviruses are found in all tropical, subtropical, and temperate climates. Most infections occur in the late fall, winter, and early spring [3, 139]. Cyclical outbreaks of these infections may occur every 2–4 years. Respiratory infections due to HCoV-229E and HCoV-OC43 strains probably spread in a manner similar to rhinovirus, i.e., via direct contact with infected secretions or aerosol droplets [3].

Clinical Presentation

The clinical manifestations of coronavirus infections are similar to those of rhinovirus infections. The most common symptoms are rhinorrhea, throat congestion, and fever. The middle ear may also be affected, leading to effusions and acute otitis media, especially in children [3, 135]. The incubation period is 1–3 days and the duration of the illness is shorter than that of rhinovirus infections, a mean of 6–7 days. The subtype SARS-CoV has a slightly longer incubation period of 4–5 days.

Infections in Immunocompromised Patients

In immunocompromised adults, coronaviruses can cause lower respiratory tract infections [3, 140]. A recent case series found that the infection rate among immunocompromised patients was significantly higher when compared to immunocompetent patients (8.8 vs. 4.5%) [141]. No large studies have been conducted in cancer patients or other immunocompromised individuals, but a few cases have been reported. Folz and Elkordy [140] reported a patient who had undergone autologous HSCT and was diagnosed with a coronavirus LRI. The patient developed a fever, sore throat, cough, and severe hypoxia and was treated successfully using supportive measures. Kumar et al. [142] described a patient who developed a fatal severe acute respiratory syndrome (SARS) after liver transplantation.

Diagnosis

Epidemiologically, these infections should be suspected during the late fall or winter or during an outbreak. However, no practical method is available to confirm the infection except PCR-based tests. These are used to diagnose coronavirus infections at some institutions [3, 143].

Treatment

Similar to rhinovirus, no specific antiviral therapy is available for coronavirus. Most patients respond well to supportive treatment with nonsteroidal anti-inflammatory drugs, decongestants and antihistamines.

Prevention

General preventive measures must be used around patients with coronavirus infections; hand washing, disposing of infected material carefully, and proper disinfection can help prevent the spread of the virus. No vaccine against the virus has been developed.

Enterovirus

Enteroviruses are single-stranded RNA viruses that can multiply in the gastrointestinal tract. They belong to the *Picornaviridae* family, but are relatively stable at a low pH. The virus is surrounded by an icosahedral capsid comprising four viral proteins. It has no lipid envelope and is not susceptible to alcohol, ether, or detergents. Poliovirus is the prototype of this group, but nonpolio enteroviruses have a wide spectrum of manifestations including acute respiratory illnesses [3, 144].

Enterovirus infections are more common in developing countries and socioeconomically depressed areas and are associated with poor hygiene and sanitation. They can occur throughout the year, but the peak occurs in the summer and fall [3, 145]. They can be transmitted by direct contact with feces during activities such as cleaning and diaper handling.

Clinical Presentation

The clinical picture of enterovirus infections is similar to that of rhinovirus infections; no specific symptoms are associated with the virus.

Infections in Immunocompromised Patients

Immunocompromised patients have been reported to develop central nervous system infections, chronic disseminated infections, and a dermatomyositis-like syndrome with enterovirus infection. In a study of respiratory tract infections in hematologic malignancy patients, 3% of patients had enterovirus infections; most (66%) were HSCT recipients with 33% of these developing pneumonia [131]. A study from Spain reported on four HSCT recipients who developed enterovirus infections, with a mortality rate of 75% (3 of 4) [146]. These findings demonstrate that immunocompromised patients may be at risk for lower respiratory tract infections and death from an enterovirus infection [3, 131, 146].

Diagnosis

Most enteroviruses can be isolated in cell cultures from nasopharyngeal or throat swabs. PCR-based testing is used to amplify the viral RNA from throat swabs, cerebrospinal fluid, and tissues. For diagnosis, isolation of the virus from the throat is more clinically significant than from stool because this virus has a shorter duration of shedding from the throat.

Treatment

Most enterovirus infections are self-limiting and do not require specific treatment. Intensive care may be required for central nervous system, cardiac, and hepatic infections. IVIGs have been used in some patients with severe infections, but no specific antiviral therapies are available [3, 147].

Prevention

General infection control measures must be undertaken around patients with enterovirus infections. Special attention must be paid to hand hygiene. Material in contact with or soiled by feces should be handled carefully and discarded with proper precautions.

Summary Comments

The respiratory viruses as a group are the most common cause of an acute infectious illness in developed societies. The variety of viruses that can cause infection and illness in all age groups and their presence in high frequencies throughout the year describe the risk of exposure of all persons at all

times including immunocompromised persons residing in the community. The immunocompromised state of many cancer patients constitutes the basis for the frequent failure of the host to promote a normal and rapid recovery from an acute respiratory viral infection and results in a more severe and prolonged infection that causes significant morbidity and mortality in these patients. Those respiratory viruses that are most prevalent and most prone to produce lower respiratory illnesses and pneumonia in healthy hosts, RSV, influenza viruses and PIV, are those most likely to cause severe illness and pneumonia leading to hospitalization in immunocompromised persons. However, viruses less prone to produce a lower respiratory illness but that are highly prevalent, such as rhinoviruses, may frequently be associated with severe illness. Although not generally considered respiratory viruses, the Herpes viruses are known to produce respiratory infection and disease, sometimes severe, in immunocompromised patients (Table 32.1). A historically important virus, measles virus, is now rarely encountered because of widespread vaccination.

The limited availability of antivirals and vaccines for the acute respiratory viruses means that these infections will continue to be important for many years and dictate a need for utilizing infection control procedures as much as possible, particularly in hospitals and institutions, so as to minimize spread. Efforts to develop specific vaccines are important as their use could prevent as well as reduce exposure of cancer patients to these viruses. Development of specific antivirals is important for use in immunocompromised patients as normal recovery mechanisms may be seriously impaired.

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Chapter 33
BK, JC, and Parvovirus Infections in Patients with Hematologic Malignancies

Véronique Erard and Michael Boeckh

Abstract The polyomaviruses, BK and JC virus, as well as parvoviruses are emerging infections in patients with hematologic malignancies and hematopoietic cell transplant recipients. BK virus has a predilection to the urinary tract and may cause hemorrhagic cystitis and nephritis. BK viremia appears to be an important marker and predictor for BK disease in immunocompromised patients. No well-established treatment options exist, but cidofovir has been used in addition to supportive care measures. JC virus is the cause of progressive multifocal leukoencephalopathy in immunosuppressed patients. The optimal treatment is not defined. There is increasing evidence that parvoviruses may also cause serious disease in immunocompromised patients, including anemia, pericarditis, myocarditis, hepatitis, pneumonitis, and neurologic disease. The frequency of these complications of parvoviruses is presently poorly defined. Treatment consists of intravenous immunoglobulin; no specific antiviral treatment exists. This chapter will review the epidemiology, disease manifestations, and diagnostic and management options for polyomaviruses and parvoviruses in patients with hematologic malignancies.

Keywords Polyomavirus • BKV • JC virus • Viremia • Progressive multifocal leukoencephalopathy • Immunosuppressed patients • Cancer • Stem cell transplantation • Hemorrhagic cystitis • Nephritis

BK Virus

Polyomavirus BK was first reported to be a human pathogen in 1971, when a renal transplant recipient, with initials BK, presented with ureteric stenosis [1]. Reports of the role of

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BK virus infection in clinical disease increased with the advent of more potent immunosuppressive medication. In the last decade, BK virus became an emerging pathogen in the setting of kidney transplantation by its propensity to cause severe nephritis in the allograft resulting in graft loss in up to 80% [2, 3]. In the bone marrow and stem cell transplant population, the association of BK virus infection and hemorrhagic cystitis (HC) was reported first in the mid-1980s [4, 5]. In this review, we will focus on BK-associated HC, the main manifestation of BK virus in patients with hematological malignancies and following hematopoietic stem cell transplantation (HCT), as well as on nephritis, which can also occasionally occur in these settings.

Virologic Aspects

BK virus is a small (diameter 40 nm) nonenveloped virus with a double-stranded DNA genome. It belongs to the Papovaviridae family together with JC virus and the simian virus (SV) 40. The viral icosahedric capsid is composed of three structural proteins, VP1, VP2, and VP3. The viral DNA is a supercoiled (like plasmid DNA), circular, double-stranded DNA of 5,300 base pairs and shares approximately 75% of homology with the JC virus and 69% with the SV40 [6]. The genome is organized in three regions (early, late, and regulatory region), each of which has specific functions. The early region encodes the large tumor antigen (TAg) and small tumor antigen (tAg); the late region encodes the viral capsid proteins VP1, VP2, and VP3 and the nonstructural agnoprotein; and the noncoding control region contains promoter elements for both the early and late regions and the origin of DNA replication [6]. Currently, there are four known seroptypes of BKV in the human population. Sequences variation within the VL1 gene accounts for the antigenic differences of the BKV genotypes [6].

The details of the many steps leading to productive BKV infection remain incompletely defined. At the cellular level, the entry of BK virus into the cells remains partially known and is described in recent reports [7–13]. After attachment

to the surface of the cell membrane, the virions induce the formation of vesicles called caveolae [10, 14] and are transported eventually to the nucleus. BK virus employs specific trafficking pathways, relying on various cellular components, to establish a productive infection [8]. However, the details of the many steps leading to productive BKV infection remain incompletely defined.

Transmission and Pathogenesis

The mode of transmission of BK virus is not yet well defined; however, the reports in the literature suggest the respiratory route as the main mechanism of transmission. BK virus seroprevalence is reported to reach up to 90% in adolescents and adults around the world [15]. Potential alternative modes of transmission include transplacental transmission [16–18], fecal–oral [19, 20], or organ transplantation [21, 22].

Primary infection with BK virus during childhood is generally asymptomatic or associated with fever and mild upper respiratory symptoms [23], and occasionally followed self-limited hemorrhagic cystitis [24]. Primary infection is followed by viral dissemination to the sites of persistent infection. The sites of latency are principally the cells of the kidney and urinary tract [25–27].

Intermittent replication may occur as evidenced by periodic excretion of BK virus in the urine in immunocompetent individuals and pregnant women [18, 28–30]. The control of persistent infection by the host innate, humoral, and cellular immunity is incompletely understood. Initial studies suggest a role of cell-mediated immunity [2].

BK Virus-Associated Disease

Polyomavirus replication is lytic, and hence, cytopathic. Depending on the state of the immune system, host cellular lysis may elicit nonspecific inflammatory response or specific cellular and humoral immune response. Thus, polyomavirus infections have been associated with diverse pattern according to the cytopathic, inflammatory, and immunologic features. The pathogenesis of tissue damage in BK virus-infected tissues is to date only partially understood and principally described in kidney transplant recipients. The preferential manifestation of BK virus nephropathy in the allograft kidney of renal transplants as compared to other allografts or to autologous kidneys of other organ transplants suggests that organ tissue and immunologic factors interplay [25, 31–33].

In cancer patients, BK virus has been mainly associated with hemorrhagic cystitis following HCT [34]. In recent years, cases of BK nephritis have been reported sporadically in HCT recipients and patients with leukemia [35–40].

Hemorrhagic Cystitis

Definition. HC is characterized by hemorrhagic inflammation of the bladder mucosa leading to painful micturation, urinary frequency, and urgency with hematuria. HC can be ranging from a mild and brief (Grade I) to a severe and life-threatening (Grade IV) complication [41, 42]. In the HCT setting, HC occurs early (before engraftment) or late (after engraftment) after transplantation. Early manifestation has been linked to the toxicity of the conditioning regimen containing high dose of cyclophosphamide, especially when administered in association with busulfan or irradiation [43–46]. The administration of 2-mercaptoethane sodium sulfonate (MESNA), polyuric diurese, bladder irrigation, and alkalization are the various protective measures in the prevention of hemorrhagic cystitis after allogeneic HCT [41, 47–50] (Table 33.1).

In the HCT settings, late onset of HC is attributed mainly to viral infection such as BK virus, adenovirus, and rarely, cytomegalovirus (CMV). Other factors that have been associated with late HC include myeloablative conditioning regimen, HLA mismatch, and graft versus host disease [43, 63–66].

BK virus-associated HC. The association of BK virus infection with HC was first reported two decades ago in the HCT population. These early studies reported a qualitative association between BK viruria and late HC [4, 41, 67]. BK viruria was often present in patients with HC and preceded the onset of disease. However, a significant percentage of patients presented with persistent BK viruria without hemorrhagic cystitis. Subsequent studies demonstrated a quantitative association between HC and BK viruria [68–70]. BK viremia has been shown to be a sensitive and specific indicator of BK virus nephritis in kidney transplant recipients [71]. An association of BK viremia with HC has also been observed [34, 46, 55, 71]. The association seems to be particularly strong with high viral load in plasma [46]. However, this observation was not found in all studies [72, 73]. A recent seroepidemiologic study has identified that patients who developed a higher peak of viruria and hence an increased risk of HC were more likely to have higher anti-BK virus antibody titers before HCT [70].

Given that BK viruria occurs frequently in HCT recipients who remained free of hemorrhagic cystitis, it is thought that other factors are likely to contribute to the development of BK virus-associated HC [72, 73]. Several theories of the pathogenesis of BK virus-associated HC have been proposed [2, 69]. First, chemotherapeutic agents and/or irradiation damage the uroepithelium providing a supportive environment

Table 33.1 Studies and Case reports of BK virus-associated disease in patients with hematologic malignancies

First authors, year	Study design	Study population	Disease	Incidence[a]
Leung, 2002 [44]	Prospective cohort s	HCT adults, $n=50$	Hemorrhagic cystitis (HC)	12%
Erard, 2004 [51]	Retrospective cohort	HCT adults/children, $n=132$	HC	14%
Gorczynska, 2005 [52]	Retrospective cohort	HCT children, $n=102$	HC	25%
Fioriti, 2005 [53]	Prospective cohort	HCT, $n=20$	HC	25%
Giraud, 2008 [54]	Prospective cohort	HCT adults/children, $n=175$	HC	12%
Cesaro, 2008 [55]	Prospective cohort	HCT children, $n=15$	HC	30%
Park, 2009 [56]	Retrospective cohort	HCT adults, $n=12$ (alemtuzumab); $N=18$ (ATG)	HC	42% (ALTZ) 6% (ATG)
Gaziev, 2010 [57]	Prospective cohort	HCT children, $n=117$	HC (with/without BK infection)	26% 58% (ATG) 17% (no ATG)
De Padua Silva, 2010 [58]	Prospective cohort	HCT adults, $n=209$	HC	12%
Strake, 2003 [59]	Case report	HCT adult, $n=1$	Nephritis	–
Lekakis, 2009 [37]	Case report	HCT adult, $n=1$	HC and nephritis	–
Verghese, 2009 [60]	Case report	HCT children, $n=2$	HC and nephritis	–
Galan, 2005 [61]	Case report	LLC adult, $n=1$[b]	Fatal pneumonia	–
Sandler, 1997 [62]	Case report	HCT child, $n=1$	Fatal pneumonia	–

HCT hematopoietic cell transplant, *ALTX* alemtuzumab, *ATG* antithymocyte globulin

[a]Incidence figures may refer to the overall rate of HC or that related to BK virus; see references for details

[b]Patient had received chemotherapy for chronic lymphatic leukemia

for BK virus replication, which proceeds in the absence of functional immunity. The restoration of immunity occurring at engraftment further increases the mucosal damage induced by the cytopathic effects of viral replication [2]. No animal model has yet verified the hypothesis of an immune reconstitution disease. Furthermore, the role of immune reconstitution in pathogenesis remains controversial, as late HC has been reported in patients with very low lymphocytes counts, occurs with antithymocyte globulin- and alemtuzumab-based conditioning regimens [56, 57], and does not appear to be modified by steroids administration [46, 56] (Table 33.1). A direct lytic effect of the virus on the urothelium is possible, as BK virus has been detected in tissue samples from patients with HC [74]. Thus, to date the exact pathogenic link between BK virus and hemorrhagic cystitis remains enigmatic, mainly because a gold standard for the diagnosis of BK virus-associated cystitis does not exist.

Diagnosis of BK virus-associated HC. The diagnosis of BK virus-associated HC is indirect in most situations by testing urine and blood. Definite diagnosis requires a bladder biopsy. Most cases of BK-associated HC occur after engraftment. Cytology of the urine can detect polyomavirus-infected cells, the decoy cells. These cells are characterized by an enlarged nucleus containing basophilic intranuclear inclusion easily seen by phase-contrast microscopy [75]. The limitations of cytology to diagnose BK virus disease include that adenovirus or JC virus infection will produce similar cytology [76–78]. Viral cultures are not useful for detection of BK virus replication because the growth of the virus in tissue culture may take several weeks [79]. Currently, the method of choice for detecting BK virus in urine is the detection of DNA by quantitative PCR. The primer selection is important for optimal sensitivity of the PCR assay [80]. However, BK viruria has a low BK virus disease specificity. Other characteristics of BK virus replication may be utilized to diagnose BK virus-associated HC. Indeed, high peak urine viral loads (10^9 to 10^{10} copies/ml), BK viruria increasing by more than 3 $\log_{10}$ from baseline, or the presence of BK viremia, particularly greater than 10^4 copies/ml of plasma, have all been linked to an increased risk of hemorrhagic cystitis [55]. Therefore, as suggested in a recent review [81], patients who develop late-onset HC should be tested for BK virus in the urine followed by blood if the urine is positive and other causes should be ruled out, i.e., adenovirus, and to a lesser degree, CMV [82, 83].

Treatment. The management of hemorrhagic cystitis depends on the severity of the disease. In the majority of the cases, the treatment is supportive including analgesia, hyperhydration, and forced diuresis, as well as continuous bladder irrigation in order to prevent clot formation. Furthermore, measures to control and alleviate bleeding, including platelet and red blood cell transfusions, may be required. In the case of urinary tract obstruction following severe bleeding, cystoscopy for clots removal and possible cautherization should be considered. In the extreme situation of intractable bleeding, a cystectomy may be the only alternative [45, 84].

Despite the emergence of BK virus-associated nephropathy in the kidney transplant population over the last decade, antiviral drugs with specific activity against BK virus have not been approved for treatment. However, several drugs, including cidofovir, leflunomide, fluoroquinolones, and intravenous immunoglobulins (IVIg), have been tested in

small clinical series involving kidney and HCT recipients [37, 52, 57, 85–91] (Table 33.2).

Cidofovir is a nucleotide analog of cytosine active against a large number of DNA viruses. Cidofovir has emerged as the most selective antipolyomavirus agent; however, its mechanism of antiviral action is uncertain [96]. The drug is licensed for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Nephrotoxicity and hematotoxicity can occur after multiple dosing (especially with higher doses) and limit routine use following HCT.

Leflunomide is an immunosuppressive agent, acting by the inhibition of several enzyme involved in the pyrimidine synthesis and lymphocytes signaling pathways [88]. It is licensed for the treatment of rheumatoid arthritis [97]. It has in vitro anti-CMV and anti-BK virus action [37, 86, 98, 99]. The mechanism of antiviral action is unknown.

Fluoroquinolones have been shown to inhibit the helicase, an essential enzyme for replication of SV40 in vitro [100].

Intravenous immunoglobulin (*IVIg*) has immunomodulatory properties and contains polyomavirus-reactive antibodies [101]. However, the role of antibody-mediated immunity in polyomavirus control remains unclear, as majority of patients with active BK virus infection have high level of specific antibodies.

Clinical results. A recent review of treatment for BK virus-associated nephropathy in kidney transplant recipients [102] reported 184 patients treated with cidofovir (0.25–1 mg/kg per dose, every 2–3 weeks). The clearance of viremia was 49% and the graft loss 23%. Other studies show no results of low-dose cidofovir [95]. Patients treated with leflunomide ($n=189$) had the same rate of viremia clearance, but a lower percentage of graft loss (12%). The authors stress that a high dose of leflunomide (~40 mg per day) is required to achieve a therapeutic effect. None of the patients treated with fluoroquinolones ($n=14$) achieved viremia clearance. Patients treated with IVIG ($n=29$) at a dose of 2 g/kg divided over 2–5 days had a 52% rate of viremia clearance and only 7% had allograft loss, but the majority of patients received concomitant treatment with leflunomide ($n=16$) or cidofovir ($n=1$). The results are difficult to interpret because of the lack of adequate controls.

In HCT settings, systemic administration of cidofovir has achieved some success to treat BK virus-associated HC; however, none of the studies were randomized or included a control group with multivariate modeling to evaluate the role of supportive care alone [57, 85, 91, 103]. Savona et al. reported clinical response in 84% of patients treated with weekly low dose of cidofovir; however, a decreased viral load in urine was observed in only 47% [91]. In a retrospective study, Cesaro et al. reported a complete clinical response in 67% of patients and among them a viral clearance in 81% and 20% of patients from blood and urine, respectively.

Cidofovir was given for a median number of doses of 4 (1–15) at a dose ranging from 0.5 to 5 mg/kg, with renal toxic effect observed in only a few patients [85]. A recent study by Gaziev et al. showed an increase of HC in children receiving ATG as part of their conditioning regimen and a response to cidofovir [57]; patients receiving supportive care alone also recovered; however, the treated and untreated patients differed in terms of disease severity making interpretation of the results difficult.

Intravesical administration of cidofovir leading to clinical improvement and reduction of viruria has been reported in few cases and has been suggested as an alternative to systemic therapy in patients with kidney dysfunction [93, 104, 105], 0.5–5 mg/kg, 1–15 doses) [85].

In HCT recipients, leflunomide has been used to treat refractory CMV infection with variable success [106, 107]. A recent report by Lekakis et al. describes the case of a HCT recipient with BK virus-associated cystitis and nephritis, treated by leflunomide in combination with *IVIg* [37]. Treatment was effective in reducing hemorrhagic cystitis symptoms and stabilizing kidney function [37]. Nevertheless, the requirement of high doses of leflunomide to achieve a therapeutic effect, the unpredictable relationship between drug dose and blood level, and the myelosuppressive and hepatotoxic properties of the drug limit its use in HCT population.

Leung et al. observed that ciprofloxacin decreases BK virus shedding in urine [92]; however, the clinical significance of fluoroquinolones in BK virus-associated HC was not convincing. Furthermore, based on the limited antiviral activity of fluoroquinolones observed in vitro, authors have suggested that fluoroquinolones may be more effective as prophylactic agents against BK virus-associated hemorrhagic cystitis rather than therapeutic agents [81, 108]. A single nonrandomized clinical study investigated the effect of prophylactic ciprofloxacin (500 mg orally/200 mg IV twice a day) on BK viruria and incidence of severity of postengraftment HC in adult HCT recipients [108]. In this trial, ciprofloxacin decreased the peak of BK viruria, but did not reduce the HC incidence. However, Rhandawa et al. demonstrated that ciprofloxacin had a modest antiviral activity and expressed a low selectivity index (defined as the ratio of the 50% in the host cell replication value to the 50% virus inhibitory concentration value) [109]. This observation let the author conclude that the drug may have a prophylactic effect, but its low selectivity index makes its efficacy very uncertain in a established disease characterized by high viral load. *IVIg* has been used in BK disease after kidney transplantation with variable success (Table 33.2); however, to date, there are no published data on the efficacy of *IVIg* for BK virus-associated disease in HCT setting.

Overall, to date no conclusive evidence from randomized trials or multivariate analyses of larger clinical cohorts exists

Table 33.2 Potential preventive and medical therapeutic interventions in BK virus-associated diseases

Interventions	References	Study design	Population	Disease	Controls	Key outcome	Comment
Prevention							
Ciprofloxacin	Leung, 2005 [92]	Prospective	Allogeneic HCT recipients	HC	Nonrandomized control: cephalosporines	Reduction in BK peak viral load in urine	Small sample size; nonrandomized; no effect on HC
MESNA versus hyperhydratation	Bedi, 1995 [41]	Prospective	Allogeneic HCT recipients	HC	Randomized	Both methods equally effective	Important trial
Continuous bladder irrigation	Hadjibabaie, 2008 [48]	Prospective	Allogeneic HCT recipients	HC	Nonrandomized control: no irrigation	Continuous irrigation was additive to MESNA, hydration, and alkalization	Relatively small sample size, nonrandomized
Therapeutic							
Cidofovir (high dose)	Gorczynska, 2005 [52]	Prospective	Allogeneic pediatric HCT recipients	HC	None	Clinical response in 15/19 children; eradication of viremia in all responders; one progression on cidofovir	Small series; no controls; no significant toxicities
Cidofovir (low-high dose)	Cesaro, 2009 [85]	Retrospective	Allogeneic HCT recipients	HC	None	Complete response in 67%; renal toxicity in 6/57; neutropenia 1/57	Larger series ($N=57$) but no controls
Cidofovir (high dose)	Gaziev, 2010 [57]	Prospective	Allogeneic HCT recipients (pediatric)	HC	Nonrandomized Untreated controls	Complete clinical response in treated and untreated patients	Small sample size; treated and untreated patients differed in severity of disease
Cidofovir (low dose)	Savona, 2007 [91]	Retrospective	Allogeneic HCT recipients	HC	None	Clinical response in 16/19; 14/19 no increase in serum creatinine	Small sample size, no controls
Cidofovir intravesical	Rao, 2009 [93]	Case series retrospective	Allogeneic HCT recipients	HC	None	Resolution of symptoms; no renal toxicity but mild pain	Small sample size, no controls
Cidofovir intravesical	Cesaro, 2009 [85]	Case series retrospective	Allogeneic HCT recipients	HC	None	Complete response in 3/6 patients; partial response in 1/6; bladder spasm 1/6	Small sample size; no controls; poorly tolerated in one patient
Leflunomide	Canivet, 2009 [30]	Pilot	Kidney transplant recipients	Nephritis	None	Clearance or reduction in viral load in 9/12 patients; one organ loss	Small sample size; no controls
Immunoglobulin	Sener, 2006 [94]	Case series	Kidney transplant recipients	Nephritis	None	Response in 7/8 patients	Small sample size; no controls
Immunoglobulin	Wadei, 2006 [95]	Case series	Kidney transplant recipients	Nephritis	Analysis of various treatments, including low-dose cidofovir	No clear effect on functional decline and viral clearance	Small sample size; no controls

MESNA 2-mercaptoethane sodium sulfonate, *HC* hemorrhagic cystitis, *HCT* hematopoietic cell transplant

demonstrating that treatment with cidofovir (at any dose) or any other therapeutic is superior to supportive care.

Others Manifestation of BK Virus Disease After HCT

BK virus nephritis. Over the past few years, BK virus-associated nephritis has been sporadically reported in the native kidneys of HCT recipients, not always accompanied by hemorrhagic cystitis [37–40, 42]. This complication was always severe, leading to permanent renal failure in all cases despite treatment. Therefore, any unexplained significant deteriorating kidney function should be evaluated for BK virus involvement. A rational diagnostic algorithm may include initial testing in urine and blood followed by a renal biopsy with immunostaining for BK virus. The optimal treatment of BK virus nephritis in HCT population is currently unknown. If feasible, a reduction of immunosuppression should be attempted. Correction of hypogammaglobulinemia, low-dose cidofovir (0.25–1 mg/kg up to twice a week) without probenecid, and/or use of leflunomide with careful monitoring for possible adverse events are available for treatment; however, none of these therapies have been systematically evaluated.

Other organ manifestations. Clinical manifestations of BK virus infection in hemato-oncologic patients (with or without AIDS) outside the genitourinary tract have been reported in selected cases, including disseminated disease, meningitis, encephalitis, and pneumonitis [39, 61, 62, 110, 111]. A systematic evaluation of the significance of BK virus in disease manifestations outside the urinary tract has not been performed.

JC Virus

JC virus is a nonenveloped DNA virus and also classified as polyomavirus. JC virus is the cause of progressive multifocal leukoencephalopathy in immunosuppressed patients. Several cases have been reported after HCT and in patients with hematologic malignancies [112–116]. Overall, the frequency of this complication seems to be very rare. PCR detection of JC virus in the cerebrospinal fluid is used for diagnosis [117]; however, its sensitivity is not 100%. Therefore, brain biopsies may be required; plasma PCR may also be useful [116]. The optimal treatment is not defined. Cidofovir has activity in vitro; however, little is known about its in vivo efficacy in HCT recipients [118]. A study in HIV-infected individuals failed to show a therapeutic effect of cidofovir. Other treatment options include IL-2, cytarabine, chlorpromazine, or the antipsychotic drugs ziprasidone, risperidone, and olanzapine

[116, 119]; however, only individual patients have been treated with these drugs, thus making an assessment of efficacy difficult [120]. CMX-001, an oral derivative of cidofovir, is highly active against JC virus in vitro [121]. The compound is presently undergoing clinical testing in immunosuppressed patients for BK virus and CMV disease.

Parvovirus B19

Parvoviruses are small, naked, single-stranded DNA viruses. Parvovirus B19 is the best-studied virus; however, other parvoviruses exist and may cause human disease. Human parvovirus can be isolated from asymptomatic blood donors and be detected by PCR, but transmission via blood products (especially when viral load is low) is uncommon [122]. Seroepidemiolocal studies showed evidence of past infection in approximately 60% of young adults. The virus is most likely spread by respiratory transmission or by blood. Parvovirus B19 can infect erythroid progenitor cells. Parvovirus B19 commonly is associated with aplastic crisis in patients with hemolytic anemia. It is also the cause of erythema infectiosum, a self-limited disease of childhood characterized by fever, fatigue, myalgias, a lace-like rash, and a "slapped-cheek" appearance. Parvovirus B19 has also been associated with some cases of rheumatoid arthritis.

Besides hematologic complications (anemia, thrombocytopenia, engraftment failure), clinical manifestations that have been associated with parvovirus immunocompromised patients include transient prolonged viremia pancytogenia, chronic anemia, pericarditis, myocarditis, hepatitis, pneumonitis, and neurologic disease [123–127]. Neurologic diseases, including encephalitis, meningitis, stroke, and peripheral neuropathy, have been reported to occur in both immunocompetent and immunosuppressed individuals [128]. The basis for these reports is the detection of parvovirus in patients with disease; however, more work is needed to conclusively establish parvovirus as a pathogen in these disease manifestations.

PCR is useful as a diagnostic tool [124]. These associations have been seen in case reports or small series. A more systematic evaluation of parvovirus as a cause of these clinical syndromes is needed for most of these manifestations.

IVIg is effective in treating parvovirus B19 symptomatic infection [129]. Prophylactic *IVIg* seems to have a protective effect against parvovirus B19, although this has not been established in a randomized study [130]. *IVIg* has also been used for treatment (e.g. 400 mg/kg for 5 days) and reduction of immunosuppression, if feasible, has been advocated [127], however, no systematic evaluation of these strategies is available. At this time, there is no antiviral drug treatment available for parvovirus infection.

Summary

BK virus has emerged as an important pathogen in the solid organ and hematopoietic cell transplant population. With the rising development of immunosuppressive drugs and the increasing population of immunocompromised patients, the incidence and diversity of BK virus manifestations are expected to increase. Although therapies for BK virus have been described, the quality of the evidence supporting their use is poor and randomized studies are urgently needed to determine the efficacy of the currently available antiviral drugs. Furthermore, the development of more effective and specific antiviral agents is needed. A candidate antiviral agent, HDP-cidofovir (CMX001), an oral derivative of cidofovir with significantly enhanced activity against BK virus, is presently undergoing clinical testing. Also, studies are needed to better understand the interaction of the virus with the host to answer unresolved questions in BK virus pathogenesis.

It should also be emphasized that besides hemorrhagic cystitis, nephritis appears to be of increasing importance in HCT recipients. The optimal management of this disease remains unknown; however, low dose of cidofovir, reduction of immunosuppression, correction of hypogammaglobulinemia, and perhaps leflunomide might be reasonable options. Regarding late-onset hemorrhagic cystitis, because of the transient nature of the condition in most cases and the toxicity of available antiviral drugs, optimal supportive treatment seems to be a nonnocere approach, especially for mild-to-moderate disease. Any further interventions for more severe disease would have to be considered on an individual basis for a given clinical scenario, balancing benefits and risks.

No proven treatment options exist for JC virus and the outcome of JC virus disease is often devastating. Agents under development (CMX001) are promising based on their in vitro susceptibility, but no clinical data exist at this point.

Parvoviruses have long been associated with hematologic complications. However, recent reports also occasionally implicate this virus in cardiac, lung, hepatic, and neurologic disease. More systematic evaluation to establish the role of parvovirus as a true pathogen is needed.

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Chapter 34
Antiviral Resistance and Implications for Prophylaxis

Robin K. Avery

Abstract Development of prophylactic, preemptive, and therapeutic strategies has reduced the morbidity and mortality of viral infections after HSCT. However, the future success of such strategies is threatened by the increasing emergence of antiviral-resistant virus strains. In some cases, resistance is common enough to warrant changes in recommendations for prophylaxis (e.g., influenza in the 2008–2009 season). In other cases (HSV, VZV, CMV, HBV), resistance has not yet altered the primary class of agent(s) utilized for prophylaxis or preemptive therapy at the majority of centers, but clinicians should have a heightened awareness of the possibility of antiviral resistance and a low threshold to alter therapy in the setting of high viral loads, unusual clinical presentations, or refractoriness to standard therapy. A detailed overview of the scope of this problem and strategies for managing patients with these difficult-to-treat infections is presented in this chapter.

Keywords Viral drug resistance • Influenza virus • CMV • Herpes simplex virus • Varicella-zoster virus • Hepatitis B virus

Background

Viruses, like bacteria and fungi, are becoming more resistant to standard antimicrobial agents over time. One of the cornerstones of successful infection prevention programs in HSCT recipients has been the use of antiviral agents, principally derivatives of acyclovir and ganciclovir for prevention or suppression of herpesvirus infections, including cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV) [1] (Table 34.1). Genotypic antiviral resistance appears to be increasing for all three of these

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viruses, but alternative agents such as foscarnet and cidofovir have potential adverse effects such as nephrotoxicity. Agents on the horizon include the investigational benzimidazole agent maribavir (for CMV and EBV); the rheumatoid arthritis drug leflunomide (for CMV, BK polyomavirus, and HSV); and the antimalarial drug artesunate (for CMV). One of the most rapidly changing viruses with respect to resistance is influenza A, which developed widespread oseltamivir resistance (in the seasonal H1N1 group) between the 2007–2008 and the 2008–2009 seasons, but then pandemic H1N1 influenza was almost entirely oseltamivir-sensitive. In addition, hepatitis B virus strains resistant to lamivudine are increasingly appearing, a development particularly affecting HSCT programs in areas endemic for HBV.

For the most part, with the exception of influenza A (H1N1) viruses [2], these trends toward more resistance have not as yet led to abandonment of one or more standard agents or other major changes in recommendations [1]. However, the transplant community should be aware that antiviral prophylaxis for the viruses mentioned above, as well as possibly others, may become less efficacious over time, and future guidelines may be altered accordingly. Increasing reliance on early detection, newer agents, and other strategies may result. Interventions to restore pathogen-specific immunity without precipitating graft-versus-host disease will be welcome developments.

Herpes Simplex Virus

Herpes simplex virus (HSV) is an important pathogen after HSCT, causing mucosal ulcerations of the oropharynx, esophagus, genital, and perianal areas, as well as at times, visceral infection such as hepatitis, pneumonitis, and meningoencephalitis. Prophylaxis against HSV is frequently administered to HSCT recipients in the form of acyclovir or ganciclovir derivatives (which have activity against acyclovir-sensitive HSV). The investigational drug maribavir lacks intrinsic activity against HSV and VZV, and in future,

Table 34.1 Viruses with genotypic resistance of importance in HSCT

Virus	Resistance mutation types[a]	Primary agent(s) that resistance affects	Therapy for antiviral-resistant viral infections
HSV	Thymidine kinase, DNA polymerase	Thymidine kinase: acyclovir, ganciclovir DNA polymerase: acyclovir, ganciclovir, foscarnet	Foscarnet, cidofovir ?Leflunomide
VZV	Thymidine kinase, DNA polymerase	Thymidine kinase: acyclovir, ganciclovir DNA polymerase: acyclovir, ganciclovir, foscarnet	Foscarnet, cidofovir
CMV	UL97 kinase UL54 DNA polymerase UL27	UL97: acyclovir, ganciclovir; maribavir (different loci) UL54: acyclovir, ganciclovir, foscarnet, cidofovir UL27: maribavir	Foscarnet, cidofovir ?Maribavir, ?Leflunomide, ?Artesunate
Influenza A	Adamantane resistance Neuraminidase	Adamantane resistance: amantadine, rimantadine Neuraminidase: oseltamivir (possibly zanamivir in future)	Zanamivir or rimantadine for H1N1 viruses; oseltamivir for H3N2 or influenza B; zanamivir or rimantadine/oseltamivir for unknown type
HBV	Precore, core promoter, YMDD	YMDD: lamivudine	Adefovir, entecavir, adefovir/lamivudine

[a]Resistance is not invariably conferred by mutations in these regions

patients who are receiving CMV prophylaxis with maribavir may need a coadministered agent with anti-HSV and VZV activity.

The activity of acyclovir depends upon phosphorylation by a viral thymidine kinase to acyclovir triphosphate, which in turn inhibits viral replication. In the early 1980s, acyclovir resistance due to a thymidine kinase-deficient strain was reported, producing reduced phosphorylation of acyclovir [3–5]; shortly thereafter, resistance at the level of viral DNA polymerase was described, conferring reduced affinity for acyclovir triphosphate [6]. The thymidine kinase pathway is the more common one and can occur by a variety of mechanisms including insertion and deletion of nucleotides and point mutations [7]. Resistance to acyclovir has been described primarily in HSCT recipients [5, 8–16] and in persons with AIDS [17–19]. Although initially it was thought that such viruses might be attenuated, soon descriptions emerged of clinically significant disease, such as severe mucocutaneous lesions of the anogenital region [17], progressively severe esophagitis [20], bilateral keratitis [21], and meningoencephalitis [22]. Surprisingly, an acyclovir-sensitive infection can follow an acyclovir-resistant one [9]. Often, development of acyclovir-resistant HSV has followed suppressive courses of acyclovir prophylaxis or therapy [3, 16]. Ljungman and colleagues described three HSCT recipients with severe pneumonia due to acyclovir-resistant HSV, after receiving prophylaxis and repeated courses of therapy with acyclovir for previously acyclovir-sensitive HSV [23]. Although most reports describe the emergence of resistance after transplant, there is one report of a pediatric HSCT recipient who had pretransplant acyclovir-resistant HSV that reactivated posttransplant and acquired resistance to foscarnet as well [24]. In another case report, a pediatric HSCT recipient developed HSV 11 days after transplantation and was found to have acyclovir-resistant HSV 8 days later [25].

HSCT clinicians should be alert to the possibility of acyclovir resistance even early after transplant.

Large single- and multicenter surveillance studies have shown concerning trends. In one study of 207 HSV isolates from a tertiary care center, resistance was detected in 7/148 isolates from immunocompromised patients (4.7%), but in none of the isolates from immunocompetent patients [26]. However, there are now reports of acyclovir resistance in the immunocompetent population [27, 28]. As early as 1996, 25% of European oncology centers reported acyclovir-resistant HSV [29]. In 2004, a network of 15 virology laboratories evaluated HSV isolates from 3,357 patients [30]. This study found acyclovir-resistant strains in 0.32% of immunocompetent and 3.5% of immunocompromised patients from whom HSV was isolated, with the highest incidence being in the HSCT population (10.9% of strains from this group) [30]. A study from the Netherlands assessed 542 isolates and also found a low incidence of resistance in immunocompetent patients (0.27%), but 7% resistance in strains from immunocompromised patients, and again, the highest incidence of acyclovir resistance in HSCT recipients (14.3% of isolates from this group) [31]. Multidrug resistance may be increasing; in one study of 196 HSCT recipients, 14 developed acyclovir-resistant HSV of whom seven also had foscarnet resistance (3 initially, and 4 developing on therapy) [10]. Although virologic cidofovir resistance was not seen in this study, clinical responses to cidofovir were noted in only three of seven patients [10].

Risk factors identified for development of resistant HSV include severe GVHD [32], T-cell depletion [12], and unrelated donor HSCT [10]. Regarding the length of acyclovir prophylaxis, Erard and colleagues performed a large retrospective study in three consecutive cohorts of HSCT recipients (total $n=2,049$); cohort 1 received acyclovir for 30 days, cohort 2 for 1 year, and cohort 3 for >1 year after HSCT [8].

The 2-year probability of HSV disease was 31.6%, 3.9%, and 0% in the three cohorts, respectively. Acyclovir resistance developed in ten patients in cohort 1 (1.3%), two patients in cohort 2 (0.2%), and no patients in cohort 3. The authors concluded that longer-term acyclovir suppression appears to prevent drug resistance in HSV [8]. Thus, although it might be thought that increasing exposure to acyclovir would predispose to development of resistance, it appears that effective suppression during the period of time of maximum immunosuppression can overcome this.

Diagnosis of acyclovir-resistant HSV with the rapidity required for clinical decision-making has been problematic, since phenotypic assays traditionally have been time-consuming, often requiring 7–10 days [33]. A colorimetric phenotypic assay has been developed that is easier to perform and is suitable for large-scale screening [34]. Most recently, development of genotypic assays has been facilitated by an increasing understanding of the types of mutations leading to resistance [15, 31, 33, 35]. Many are thymidine kinase rather than DNA polymerase mutations and can be characterized by sequencing of the thymidine kinase gene directly from clinical specimens [35].

Therapy of acyclovir-resistant HSV has usually been with foscarnet [10, 17, 18] or cidofovir [10, 36, 37], and considerable experience with these drugs has been derived from the treatment of patients with AIDS and CMV retinitis [18, 38, 39] as well as HSV [17, 36]. Vidarabine was used in some early reports [40], but a controlled trial of foscarnet versus vidarabine revealed that foscarnet was more efficacious and less toxic [41]. Vidarabine and trifluridine are available in topical ophthalmic preparations for herpes simplex keratitis [42], a clinical entity displaying increasing acyclovir resistance even in immunocompetent patients (6.4% in one study) [43].

As described above, foscarnet resistance can emerge during therapy [10]. A case report of cidofovir therapy treating both BKV-associated hemorrhagic cystitis and acyclovir-resistant HSV in an HSCT recipient has been described, illustrating the versatility of cidofovir's broad spectrum of antiviral activity [44].

Systemic toxicity of foscarnet makes long-term therapy with this drug challenging [38]. Adverse effects include nephrotoxicity, electrolyte disturbances (potassium, phosphate, magnesium), and genitourinary ulcerations. In addition, it is available only in intravenous form. Multiple daily doses as well as intravenous hydration make this a cumbersome agent to use for home intravenous therapy. Topical foscarnet has been reported to be useful in the treatment of mucocutaneous HSV lesions unresponsive to acyclovir [19], but this formulation of foscarnet is not currently licensed in the US or Europe.

Cidofovir is also potentially nephrotoxic, particularly in the higher dosing range used for CMV (3–5 mg/kg/dose), although less so in the dose range used for BK polyomavirus therapy (0.3–1.0 mg/kg/dose). It has a broad spectrum of antiviral activity and has been used for adenovirus therapy as well as herpesviruses and BK virus. Possible adverse effects also include cytopenias including neutropenia and ophthalmologic side effects including uveitis and a complete loss of ocular pressure. Currently, only the intravenous formulation is licensed in the US and Europe.

The rheumatoid arthritis drug leflunomide has been reported to have novel anti-HSV activity as well as activity against CMV and BK virus [45, 46], although controlled clinical trials are lacking. Leflunomide should be used with caution in HSCT recipients with abnormal liver function [45].

Recent intriguing in vitro studies have reported that hydroxyurea, a ribonucleotide reductase inhibitor, can increase the susceptibility of antiviral-resistant HSV strains to acyclovir and cidofovir [47, 48], but not foscarnet [48]. The possibility of inhibition of viral ribonucleotide reductases encoded by HSV was described as far back as 1985 [49]. A ribonucleotide reductase-null HSV mutant has been described with enhanced sensitivity to antivirals [50]. Further data on the clinical utility of hydroxyurea as a potentiator of antiviral activity in drug-resistant viral infections would be of interest. Adverse effects would have to be closely monitored because of the issue of bystander cytotoxicity [51]; in fact, HSV thymidine kinase plus ganciclovir is under evaluation as an antitumor strategy [52] and as a therapy for graft-versus-host disease (in which HSV thymidine kinase is introduced into donor lymphocytes via retroviral transfer before allogeneic transplantation, and then these cells can be removed by ganciclovir after transplantation) [53].

Varicella-Zoster Virus

As with HSV, resistance to acyclovir in VZV was described in the early 1980s. An in vitro study demonstrated that VZV could acquire resistance to acyclovir through serial passaging in culture media containing acyclovir; as with HSV, most of these mutants showed loss of virus-specific thymidine kinase activity, but less commonly viral DNA polymerase mutations were seen [54].

VZV lesions resistant to acyclovir have been described in a non-HIV positive leukemic infant [55]. In this patient, the lesions were atypical, becoming hyperkeratotic and verrucous after initially presenting as vesicular and necrotic [55]. The infant responded to foscarnet therapy. This underscores the importance of clinical suspicion of resistant VZV infection even when lesions are not typical and when the patient is on prophylaxis. Further reports have included persistent disseminated hyperkeratotic papules in four patients with AIDS who were receiving long-term acyclovir therapy [56]. VZV with altered or absent thymidine kinase was isolated from each of these [56]. A report of foscarnet therapy in five

AIDS patients with acyclovir-resistant VZV lesions noted complete healing in four, although foscarnet resistance developed in serial specimens from one patient [57]. Another study of 18 patients with acyclovir-resistant VZV reported responses to foscarnet in 10/13 patients, but later relapses in 5/10 of the foscarnet-treated patients [58]. On the other hand, not all apparently clinically refractory VZV infections are due to resistant strains. Of 11 AIDS patients with persistent VZV after 10 days of acyclovir therapy, only three were acyclovir-resistant on further testing [59].

Of concern was the development of acyclovir-resistant VZV meningoradiculoneuritis in an AIDS patient with recurrent multidermatomal zoster who received several courses of acyclovir; during the last episode, the VZV strain from cutaneous lesions was still sensitive to acyclovir, but the VZV from the CSF was subsequently found to be acyclovir-resistant [60]. There are two reports of pediatric oncology patients developing acyclovir-resistant VZV of the Oka strain after varicella vaccination [61]. Clinicians should maintain high suspicion for varicella-zoster infection with any persistent vesicular or atypical verrucous eruption and should consider testing for antiviral resistance when VZV lesions do not respond to acyclovir. Visceral VZV infection is more difficult to diagnose, particularly when rash is absent, but testing of CSF and other body fluids by PCR as in the case above can be useful. The possibility of resistance developing after several courses of therapy should always be considered, even when the initial VZV strain was sensitive to standard antivirals.

Cytomegalovirus

A tremendous amount of basic, clinical, and translational research has gone into defining the cellular and molecular basis, risk factors, outcome, and therapies for ganciclovir-resistant CMV (GCV-R CMV) infection. Ganciclovir has been the mainstay of CMV therapy, but its use can be limited by hematologic toxicity including neutropenia and thrombocytopenia. GCV-R CMV was described in the early 1990s in the setting of AIDS patients on long-term ganciclovir therapy for CMV retinitis [62]. Then, Limaye and colleagues reported GCV-R CMV in high-risk solid organ transplant recipients who were receiving oral ganciclovir prophylaxis [63]. The risk for GCV-R CMV appears to be a function of the viral load as well as exposure to incompletely suppressive levels of antivirals [64]. Although it has been claimed that preemptive therapy (as opposed to prophylaxis) would lessen the risk of resistance by decreasing exposure to antivirals [65], GCV resistance has been described in lung transplant patients receiving preemptive therapy as well [66]. Valganciclovir, an oral derivative of ganciclovir, was found to be associated with decreased risk for GCV resistance

when compared with oral ganciclovir in a randomized trial of 3 months of prophylaxis in high-risk solid organ recipients [67, 68]. However, GCV resistance after valganciclovir therapy has also been described (see below) [69].

Ganciclovir resistance occurs in relation to two different types of mutations: in the UL97 region (kinase) and the UL54 region (DNA polymerase) [70]. Mutations in the UL97 region, the most common sources of GCV resistance, affect the phosphorylation of ganciclovir to ganciclovir triphosphate; these affect only ganciclovir, acyclovir, and their derivatives and occur usually at codons 460, 520, or 591–596 [71]. By contrast, UL54 mutations affect the viral DNA polymerase and may confer resistance to foscarnet, cidofovir, or ganciclovir and its derivatives [72]. Multidrug resistance has been described [45, 73–76]. However, not all mutations in these regions are associated with antiviral resistance. The investigational drug maribavir, a benzimidazole agent which inhibits the UL97 kinase, is active at a different point of the virus's life cycle and is potentially active against CMV resistant to other agents [77]. However, maribavir resistance due to mutations in the UL27 and UL97 regions of CMV has already been described (with the UL97 mutations in a different region from those conferring ganciclovir resistance) [78, 79].

In hematopoietic stem cell transplantation, antiviral-resistant CMV poses an increasingly difficult problem. As early as 1996, a European survey found that 28% of HSCT centers reported GCV-R CMV [29]. It is important, however, to recognize that sustained, recurrent, or even increasing viral loads do not necessarily mean resistance in this context [80]. One report of three pediatric patients receiving T-cell depleted HSCT who developed GCV-R CMV (one also had resistance to foscarnet) emphasized that such infections do not necessarily have devastating outcomes [81]. On the other hand, these infections can be clinically severe, as in the description of two pediatric HSCT recipients who developed antiviral-resistant CMV, one with resistance to GCV and one to foscarnet, with a mutation conferring multidrug resistance [75]. In a case report by Hamprecht et al., an HSCT recipient developed CMV retinitis and fatal CMV encephalitis; several in vivo viral variants were noted, and the effect of oral ganciclovir therapy with a rapidly rising viral load in blood (10^6) serves as a cautionary reminder of the potential for mutation in the setting of exposure to antivirals that are not completely suppressive [82].

Although valganciclovir is associated with decreased risk for resistance as compared with oral ganciclovir prophylaxis in solid organ transplant recipients [68], Marfori and colleagues reported on two allogeneic HSCT recipients who developed rising CMV antigenemia after 4–5 months of preemptive therapy with valganciclovir, including one with fatal CMV pneumonia [69]. One recipient was found to have a newly described UL97 mutation; the other had a known UL97 mutation and a newly described UL54 mutation which conferred resistance to ganciclovir and cidofovir [69].

The availability of rapid genotyping assays [83] is an advance over previous phenotypic testing, which required growth of the virus in tissue culture prior to phenotype determinations (and could take weeks). A genotypic assay for resistance is helpful in the setting of tissue-invasive or high viral load CMV infection that is not clinically responding to ganciclovir. On the other hand, clinicians should also be alert for GCV-R CMV in the patient with multiple recurrences of CMV viremia with lower viral loads. Sending a rapid genotyping assay can allow for prompt changes in therapy, avoiding progression of CMV disease and the toxicity of continuing ganciclovir derivatives.

As discussed in the HSV section above, the principal alternatives to ganciclovir derivatives for therapy of active CMV are foscarnet and cidofovir, with the toxicities listed above, including nephrotoxicity (both) and electrolyte disturbances (foscarnet). The combination of foscarnet and cidofovir has also been used successfully for treatment of GCV-R CMV retinitis and encephalitis in an HSCT patient [84]. Maribavir, an investigational benzimidazole agent which is active against CMV and EBV (but not HSV and VZV), has recently been studied in a randomized trial of CMV prophylaxis [85]. In this study, 111 CMV seropositive HSCT recipients were randomized to receive maribavir at one of three dosing levels, or placebo. CMV infection as measured by plasma CMV DNA was decreased in the maribavir groups (7–19%) as compared with placebo (46%) [85]. CMV disease occurred in three patients receiving placebo, but none receiving maribavir [85]. Maribavir will likely be useful in the future due to its lack of hematologic toxicity, as compared with ganciclovir derivatives, with which neutropenia is common. It should be emphasized, however, that the study described above did not compare maribavir prophylaxis with ganciclovir derivatives, but rather with placebo. Further comparative studies will be of interest, as well as information on use of maribavir as therapy for active CMV, in addition to prophylaxis.

Other drugs with anti-CMV activity include the rheumatoid arthritis drug leflunomide, which has activity against CMV, HSV, and BK virus [45, 86–88]. One case report of an HSCT recipient with CMV refractory to ganciclovir, foscarnet, and leflunomide showed a marked reduction in viral load due to leflunomide, but subsequent worsening of liver function in the setting of preexisting GVHD of the liver [45]. Another report concerned a pediatric HSCT recipient who had CMV refractory to cidofovir, but who responded to a combination of foscarnet and leflunomide [89]. Although leflunomide may prove to be helpful in a subset of patients with complex CMV syndromes, its toxicities in HSCT recipients should be closely monitored (especially hepatic and hematologic), keeping in mind that leflunomide has a long half-life and may be detectable for weeks to months after discontinuation.

The most recent addition to the anti-CMV armamentarium is the antimalarial drug artesunate. Shapira et al. reported on an HSCT recipient with ganciclovir- and foscarnet-resistant CMV due to a DNA polymerase mutation, who responded to artesunate therapy with a 1.7–2.1 log decrease in viral load by day 7 [90]. This promising therapy warrants further study, but artesunate is not routinely available in the US at this time.

Strategies for preventing GCV resistance have also included use of antivirals other than ganciclovir derivatives for preemptive therapy. Such strategies have also been used during the neutropenic phase of HSCT when ganciclovir administration is problematic. Preemptive therapy with cidofovir has been studied in a pilot study, in which two of four HSCT patients treated with cidofovir developed CMV disease and one developed uveitis as a side effect of cidofovir [91]. On the other hand, in another study of cidofovir as second-line therapy in pediatric HSCT recipients who had already been treated with another agent, responses were seen in five of eight patients receiving cidofovir, with an acceptable toxicity profile [92]. Foscarnet has also been studied as a preemptive therapy agent, with less than expected toxicity in a 14-day course in a group of 15 HSCT patients monitored by CMV PCR [93]. In this group, electrolyte disturbances were common, but decreasing renal function requiring dose adjustment occurred in only two patients [93]. Neither foscarnet nor cidofovir has yet replaced ganciclovir derivatives as first-line preemptive therapy, and therapy for active disease, at most centers. However, if the incidence of GCV-R CMV increases, these strategies may become more widespread.

Influenza Viruses

Influenza viruses are classified into two main varieties, influenza A and influenza B, and are further categorized into subtypes according to their hemagglutinin type (H) and neuraminidase type (N). The influenza vaccine each year contains antigens corresponding to two influenza A types and one influenza B type. The composition of the vaccine is different each year because of changes in circulating strains from one year to the next.

Antiviral therapy for influenza in the past has consisted of the adamantanes (amantadine and rimantadine), which are effective only against influenza A, and the newer neuraminidase inhibitors oseltamivir and zanamivir, which are effective against both influenza A and B. For many years, the adamantanes were the only antiviral therapy available for influenza and were most frequently used for therapy of severely symptomatic disease, but sometimes also for chemoprophylaxis of an entire unit (e.g., a bone marrow transplant unit) in the setting of an outbreak. Resistance to the

adamantanes has limited their use in recent years; from January 2006 onward, only the neuraminidase inhibitors were recommended for therapy and chemoprophylaxis. Prolonged excretion of an amantadine-resistant virus for one month after cessation of antiviral therapy in an immunocompromised patient underscores the potential for antiviral-resistant viruses to spread within oncology and HSCT units [94].

Oseltamivir and zanamivir were welcomed when they were first introduced, both because of their therapeutic potential for influenza B and because of widespread resistance to amantadine and rimantadine. In particular, oseltamivir has been widely used, because zanamivir is available only in an inhaled formulation. In addition, oseltamivir was widely hailed as a possible therapy for avian influenza. During the 2008–2009 respiratory virus season, however, oseltamivir resistance became widespread among H1N1 influenza A viruses (standard, not pandemic flu). However, pandemic 2009 H1N1 influenza was oseltamivir-sensitive with rare exceptions; and in the 2010–2011 influenza season, circulating H1N1 influenza is almost all pandemic H1N1 and therefore oseltamivir-sensitive. The CDC has issued a set of recommendations regarding therapy and chemoprophylaxis 95. The two circulating strains of influenza A so far fall into the H1N1 subtype resistant to adamantanes but susceptible to oseltamivir or the H3N2 subtype (resistant to adamantanes but susceptible to oseltamivir); influenza B also remains susceptible to oseltamivir. If oseltamivir resistance is suspected due to clinical refractoriness or viral persistence on testing, however, zanamivir should be used. This would potentially apply to severely ill immunocompromised patients. It may be difficult to administer zanamivir in an intubated or critically ill patient, and it is not indicated for children under 7 years of age, persons with chronic airways disease, or others who cannot use the zanamivir inhalation device.

The underlying mechanisms responsible for rapid development of resistance to antiviral drugs have been elucidated [95, 96]. Although the majority of currently circulating H3N2 viruses are susceptible to oseltamivir, a novel mutation in the neuraminidase gene of an H3N2 virus has been described that confers resistance to oseltamivir [97]. Resistance to oseltamivir occurring while on therapy has been described, particularly in seasonal H1N1 viruses [96]. Newer antiviral drug development is urgently needed; there are neuraminidase inhibitors which are not yet clinically available, which have activity against influenza resistant to oseltamivir [98].

Diagnosis of influenza itself is not difficult as rapid PCR testing on nasopharyngeal swabs is now widely available. Testing to distinguish H1N1 from H3N2 viruses is being developed, so as to target therapy to the strain detected and to avoid use of agents to which the particular strain is not susceptible.

It is clear that therapy and chemoprophylaxis of influenza is not a static issue and the rapidity with which strains develop resistance will likely make each year's recommendations different. Clinicians are encouraged to consult the CDC's website, www.cdc.gov, for additional recommendations. Chemoprophylaxis is still encouraged in institutional outbreaks or when a person at high risk for influenza complications has recent household or close contact with a person with laboratory-confirmed influenza, but the specific nature of prophylaxis administered should be in accordance with the most recent guidelines. Use of vaccination remains extremely important. Meticulous attention to infection control guidelines, including the 2007 Guideline for Isolation Precautions [99], remains crucial in protecting the oncology ward or HSCT unit from hospital-associated spread of influenza and other infections.

Hepatitis B Virus

Hepatitis B virus infection in the HSCT recipient poses a risk for posttransplant reactivation which is sometimes fulminant. Patients who are hepatitis B surface antigen (HBsAg)-positive chronic carriers are at risk for reactivation with development of severe liver disease and cirrhosis [100], but even patients who are HBsAg-negative with serologic antibody evidence of past HBV can undergo "reverse seroconversion," in which previous antibodies to HBV are lost, in conjunction with the emergence of HBsAg positivity and sometimes clinical hepatitis [101]. In addition, in parts of the world where HBV is highly endemic, the donor pool may also have a high incidence of HBV carriage [102].

Prophylactic and therapeutic strategies have been developed which mostly center on the antiviral drug lamivudine, which is effective in many circumstances [103, 104]. For example, one study assessed patients who underwent HSCT from HBsAg+ donors with and without prophylaxis using lamivudine therapy for both donor and recipient and recipient vaccination posttransplant [102]. With this strategy, HBV-related hepatitis developed in only 6.9% of recipients, compared with 48% of those transplanted without prophylaxis, and death from HBV-related liver disease was 0% versus 24% [102]. This study also identified HBV DNA positivity in the donor as a risk factor for posttransplant HBV [102]. Occasionally, hepatitis B immune globulin (HBIg) has been combined with lamivudine for prevention of posttransplant HBV reactivation [105], but HBIg is costly. Duration of lamivudine therapy remains an issue, and severe hepatitis following lamivudine withdrawal has been described [104, 106].

Despite the success of lamivudine as described above, emergence of lamivudine-resistant mutants, particularly at the YMDD locus, is an increasing problem [107]. Other mutations have also been described. In 1994 and 1997, HBV infection due to precore mutants was described in HSCT recipients [108, 109], in one instance refractory to alpha-interferon [108], and in the other, causing fatal fibrosing cholestatic hepatitis after HSCT [109]. Lamivudine-resistant HBV due to a YMDD mutation was described in an HSCT recipient receiving lamivudine prophylaxis after transplant from an HBsAg-positive donor [110]. Fatal fulminant hepatitis refractory to lamivudine was described in a patient with reverse seroconversion who was found to have a mutation in the core promoter region [111]. A study comparing HSCT recipients with HBV with nontransplanted HBV carriers found an increased incidence of core promoter and precore mutations in the HSCT recipients as well as an increase in decompensated liver disease [112]. In one study of lamivudine prophylaxis before and after HSCT, in which patients received lamivudine for a median duration of 73 weeks, 10 of 16 patients (63%) developed lamivudine resistance mutations, although there were no cases of severe hepatitis or death due to HBV [113].

As yet there is a paucity of data regarding newer anti-HBV agents (e.g., adefovir, tenofovir, entecavir) in the setting of HSCT. However, there is a growing experience with these agents in the setting of liver transplantation, either for salvage therapy of patients with lamivudine-resistant HBV or for prophylaxis to prevent posttransplant reinfection [114–117]. In addition to monotherapy, combinations of anti-HBV drugs with or without HBIg are also options in the liver transplant setting [115]. It appears that adding adefovir to lamivudine for lamivudine-resistant HBV, rather than switching to adefovir as monotherapy, can delay the appearance of resistance to adefovir [118]. Lessons learned from liver transplantation will likely be applied to HSCT in the future. For now, if an HSCT candidate is known to be HBsAg+ with a lamivudine-resistant strain of HBV, posttransplant prophylaxis with another agent or combination of agents should be considered and close monitoring of HBV DNA, HBsAg, and liver function tests is indicated.

Vaccination of the donor against HBV (in case of a related donor) has been cited as an intervention for prevention of reactivation of HBV after transplant [119, 120], but should not be relied upon as the sole intervention [101]; development of HBV reactivation with a novel surface mutation despite donor vaccination has been described [107]. The role of donor viral load reduction pretransplant for HBsAg+ donors is being explored as part of combination prophylaxis [121]. Posttransplant HBV vaccination of the recipient with a 3-dose series after cessation of immunosuppression has also been reported to help prevent HBV reverse seroconversion after HSCT [122]. In an era of increasing resistance, more randomized trials of different prophylaxis strategies from HBV-endemic areas are anticipated.

Summary

Development of prophylactic, preemptive, and therapeutic strategies has reduced the morbidity and mortality of viral infections after HSCT. However, the future success of such strategies is threatened by the increasing emergence of antiviral-resistant virus strains. In some cases, resistance is common enough to warrant changes in recommendations for prophylaxis (e.g., influenza). In other cases (HSV, VZV, CMV, HBV), resistance has not yet altered the primary class of agent(s) utilized for prophylaxis or preemptive therapy at the majority of centers, but clinicians should have a heightened awareness of the possibility of antiviral resistance and a low threshold to alter therapy in the setting of high viral loads, unusual clinical presentations, or refractoriness to standard therapy. Patients at higher than average risk for reactivation of viruses posttransplant may benefit from close monitoring by a sensitive molecular detection method. More rapid technologies for performing genotyping for detection of resistance mutations are helping clinicians to make treatment decisions in a more timely fashion.

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Chapter 35
Management of Gram-Positive Bacterial Disease: *Staphylococcus aureus*, Streptococcal, Pneumococcal and Enterococcal Infections

Samuel Shelburne and Daniel M. Musher

Abstract Gram-positive bacteria are a diverse group of organisms that are a major source of morbidity and mortality in patients with cancer. The increasing use of long-term indwelling central catheters and cytotoxic chemotherapies has contributed to the emergence of Gram-positive bacteria as the leading cause of bacteremia in cancer patients. These organisms are also among the foremost causes of pneumonia, skin and soft-tissue infections, osteomyelitis, and central nervous system infections in cancer patients. Gram-positive organisms have a remarkable ability to develop resistance to many of the currently available antimicrobials, but the predilection to become antimicrobial resistant varies substantially for particular organisms and for individual antimicrobial agents. Therefore physicians treating cancer patients need to be familiar with the common clinical manifestations, complications, and treatment options for a wide variety of diseases caused by Gram-positive bacteria.

Keywords *Staphylococcus aureus* • Streptococcal, pneumococcal, and enterococcal Infections • Cancer • Antibiotic resistance

Historical Perspective

Historically, Gram-negative rods were the predominant bacterial pathogens causing invasive disease in patients with cancer [1, 2]. However, a major rise in the incidence of Gram-positive infections occurred in the mid- to late-1980s such that Gram-positive organisms now cause the majority of invasive bacterial disease in patients with cancer (Fig. 35.1) [3–13]. Reasons for the increase in Gram-positive infections include, but are not limited to, antimicrobial prophylaxis

strategies, increased use of long-term in-dwelling catheters, and advances in chemotherapeutic regimens [5, 14, 15]. Regardless of the causal factors for the escalation of Gram-positive infections, physicians caring for patients with cancer need to be familiar with the epidemiology and clinical manifestations of, and the treatment options for, infections due to Gram-positive bacteria. In this chapter, we will examine the major Gram-positive bacterial genera that cause invasive disease in cancer patients (Table 35.1).

Staphylococci

Staphylococci are the predominant Gram-positive pathogens causing serious infections in patients with cancer (Fig. 35.2) [16–19]. Staphylococci can be divided into two main classes depending on their ability to coagulate rabbit plasma, with *Staphylococcus aureus* being coagulase positive and the remainder of species grouped together as coagulase-negative staphylococci (CNS). *S. aureus* has the ability to cause a broad array of serious diseases, whereas CNS are plainly less virulent pathogens [20, 21].

Staphylococcus aureus

Epidemiology

S. aureus is a common commensal that can be isolated at any given time from 20 to 40% of humans [22, 23]. *S. aureus* is a leading cause of both community-onset and nosocomial infections and is commonly divided into methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) depending on sensitivity to β-lactam antimicrobials [24]. Prior to 2000, a reasonable rule of thumb was that MSSA caused disease in the community whereas MRSA caused nosocomial infections [25]. The rise of community-associated MRSA (CA-MRSA), however, in many parts of the world means that MRSA now causes the majority of *S. aureus* disease in

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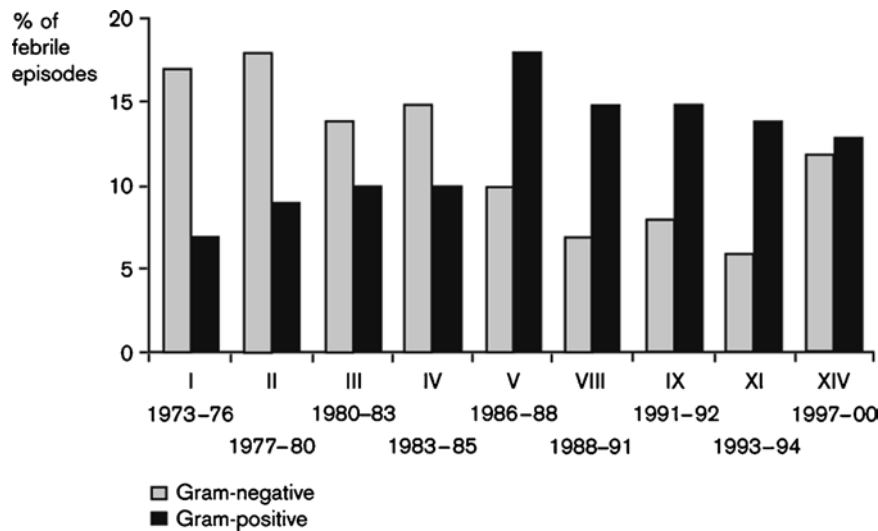
Fig. 35.1 Data demonstrating percent of infection in patients with neutropenia caused by Gram-negative (*gray bars*) and Gram-positive (*black bars*) bacteria. Note the increase in Gram-positive infection beginning in mid-1980s. Data graphs are single organism bacteremias in International Antimicrobial Therapy Group of the European Organization for Research and Treatment of Cancer trials of febrile neutropenia. Reprinted with permission from ref. [3]

Table 35.1 Summary of major Gram-positive pathogens causing invasive infections in patients with cancer

Bacteria	Risk factors	Typical infections	Treatment options	Comments
Staphylococcus aureus	Breaks in skin, mechanical ventilation, and indwelling venous catheters	Skin and soft-tissue infection, pneumonia, osteomyelitis, and catheter-related bacteremia	β-lactams vancomycin	Surgical intervention often necessary
Coagulase-negative staphylococci	Indwelling venous catheters and prosthetic devices	Catheter-related bacteremia and prosthetic device infection	Vancomycin	Generally cause healthcare related infections
Viridans group streptococci	Neutropenia and mucositis	Septicemia and pneumonia	β-lactams vancomycin	Cause of septic shock in neutropenic patients
β-hemolytic streptococci	Breaks in skin and chronic disease	Skin and soft-tissue infection, septic shock, and osteomyelitis	Penicillin	Surgical intervention needed for necrotizing soft tissue infections
Streptococcus pneumoniae	Chronic medical diseases, impaired immunoglobulin production	Pneumonia and meningitis	β-lactams, vancomycin, and fluoroquinolones	Consider vaccination
Enterococci	Broad-spectrum antimicrobials, surgery, and prolonged hospital stay	Catheter-related bacteremia and catheter-related urinary tract infections	β-lactams, vancomycin; Q/D,[a] and daptomycin for VRE[b]	Low virulence pathogens

[a]*Q/D* quinupristin/dalfopristin
[b]*VRE* vancomycin resistant enterococci

both the community and healthcare settings, including patients with cancer [26–28].

Most invasive *S. aureus* disease in patients with cancer occurs when mechanical defense barriers are breached, for example due to breaks in the skin resulting from catheter placement or bypassing of airway defenses by the insertion of an endotracheal tube [29]. Compared to the general population, patients with cancer have a nearly 13-fold increase of invasive disease due to *S. aureus* with major additional risk

factors including graft-versus-host disease, receipt of corticosteroids, surgery, mechanical ventilation, neutropenia, diabetes mellitus, and hemodialysis [29–31].

Clinical Manifestations/Diagnosis

Although many *S. aureus* infections are confined to the skin and soft-tissue, a considerable number of patients, especially
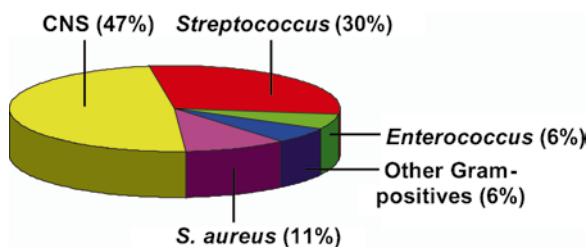
Fig. 35.2 Epidemiology of Gram-positive organisms causing bloodstream infections in patients with neutropenia. Data are from compiled from refs. [4, 6–8]. *CNS* coagulase-negative staphylococci

Fig. 35.3 Chest computerized tomography demonstrating cavitary pneumonia due to *S. aureus* that resulted from hematogenous seeding due to an infected Hickman catheter in a 30-year-old man with osteosarcoma

those who are immune-compromised, develop more invasive disease [4, 24]. *S. aureus* is a leading cause of catheter-related bacteremia, prosthetic joint infections, and postsurgical infections [21]. Among patients with cancer, suppurative complications such as infective endocarditis, bacteremic pneumonia, and osteomyelitis often result from *S. aureus* bacteremia [32, 33]. Necrotizing pneumonia due to *S. aureus* in patients with malignancy usually occurs in mechanically-ventilated patients, but can affect healthy patients in the community especially following an antecedent influenza infection or in patients with long-term in-dwelling catheters (Fig. 35.3) [34, 35]. The rise of CA-MRSA has been especially concerning given that CA-MRSA isolates can cause devastating invasive infection such as necrotizing fasciitis and necrotizing pneumonia even in otherwise healthy hosts and more so in patients with cancer [36]. *S. aureus* is commonly isolated from cancer patients with

pyomyositis, septic arthritis, and septic bursitis either as a result of contiguous infection or hematogenous seeding [32].

The diagnosis of *S. aureus* infection is relatively straightforward as the organism is hardy, grows well in the microbiology laboratory, and is easily identified. The isolation of *S. aureus* from a sterile site should almost always be taken as evidence of invasive disease with the exception that, on occasion, *S. aureus* may contaminate blood cultures [37]. In light of the propensity of *S. aureus* to colonize, the isolation of *S. aureus* from nonsterile samples such as an endotracheal aspirate does not, in and of itself, indicate an infectious process [38]. Serologic or antigen assays have not proven to be clinically helpful in the diagnosis of an *S. aureus* infection.

Treatment

Therapy of *S. aureus* disease consists of a combination approach involving antimicrobials and surgical drainage when indicated [39]. The importance of drainage of pus and/or surgical removal of dead tissue cannot be overemphasized as many patients will respond to surgery alone, whereas few patients will be cured with antimicrobials alone when pus is undrained or nonviable tissue is present [40, 41]. Similarly if foreign-material, such as an indwelling venous catheter or an infected prosthetic joint, remains in place, then therapeutic success rates are markedly reduced [42, 43].

Antibiotic treatment of *S. aureus* infection is complicated by extensive antimicrobial resistance. When the organism is sensitive, β-lactam antibiotics are the drugs of choice for *S. aureus* infections with typically used agents including nafcillin, oxacillin, and cefazolin [44–46]. Optimal treatment for invasive MRSA infections is an area of intense debate with the most experience having been accumulated with vancomycin [47]. Treatment of bacteremic MRSA infection with vancomycin is associated with a substantial failure rate – perhaps 15–20%, although overt vancomycin resistance is not responsible [48]. These failures have motivated a search for alternative anti-MRSA agents [49, 50] and, during the past decade, new drugs active against MRSA have been developed including quinupristin-dalfopristin, linezolid, tigecycline, and daptomycin [49–52]. Each of these agents has significant limitations and none has been proven superior to vancomycin in a clinical trial setting.

The duration of therapy for *S. aureus* infection is highly individualized, but a minimum of 2 weeks is typical given for uncomplicated catheter-related bacteremia [53]. Patients with complicated disease such as infective endocarditis, necrotizing pneumonia, septic arthritis, and osteomyelitis are generally treated with between 4 and 8 weeks of antimicrobials [54, 55]. The therapy is usually all intravenous for more serious infections whereas some portion of treatment may be oral for nonlife threatening infections such as lower

extremity osteomyelitis [56]. Regardless of treatment duration, complications, such as a new suppurative focus, may arise during therapy or for a significant period of time thereafter meaning that patients with serious *S. aureus* infections need to be closely monitored [57].

Coagulase Negative Staphylococci

Epidemiology

CNS are part of the normal flora of the human mucosa and skin with up to 90% of persons being colonized with CNS at any given time [58]. In contrast to patients without cancer, patients with cancer are especially vulnerable to CNS infection as a result of their damaged immune response, extensive contact with the healthcare system, and high frequency of use of medical devices [17, 18]. When species studies are performed, *Staphylococcus epidermidis* is generally the leading cause of invasive CNS in patients with cancer [59].

The major CNS diseases in cancer patients are bloodstream infections in patients with indwelling catheters and postsurgical infections (Fig. 35.2) [60, 61]. The pathogenesis of device-related CNS infection is thought to stem from their capacity to form biofilms on indwelling catheters [62]. CNS are also the leading cause of cerebrospinal fluid (CSF) shunt infections which are a significant issue for cancer patients with primary or metastatic central nervous system tumors [63].

Clinical Manifestations/Diagnosis

Catheter-related bacteremia due to CNS generally presents as fever without an apparent site of infection [64]. Infected catheters may have little to no evidence of purulence or surrounding erythema, and patients with CNS bacteremia may appear relatively asymptomatic [65]. Complications of CNS catheter-related bacteremia include infective endocarditis and hematogenous osteomyelitis among others, but complications of CNS-related bacteremia are rare compared to more virulent organisms such as *S. aureus* or Gram-negative rods [66]. CNS are the leading cause of prosthetic valve endocarditis, and endocarditis must be considered in all patients with a prosthetic valve and CNS bacteremia [67]. Prosthetic valve endocarditis due to CNS often presents with valve dysfunction or intracardiac abscess [68].

The clinical presentation of CNS infection of prosthetic devices other than venous catheters depends on the device involved and the level of the inflammatory response. For example, CNS infection of CSF shunt may present with overt meningitis, but often the presentation is more subtle with only low-grade temperature, alteration in mental function, or

shunt-malfunction [63]. Pleocytosis of the CSF may be mild or the cell count may even be normal. Similarly, CNS infection of prosthetic joints may present with symptoms ranging from mild pain or joint dysfunction to a prominent, localized inflammatory response [42].

The diagnosis of CNS infection relies on isolation of the organism from appropriately obtained specimens. Because CNS are present on the skin of patients and healthcare workers, false-positive cultures from blood and other sterile sites are exceedingly common and lead to substantial difficulty in physician interpretation [69]. Good data on the reliability of blood cultures come from studies of CNS catheter-related bacteremia [43]. If a catheter is the source of infection, then quantitative cultures generally show fourfold higher numbers of colony forming units for blood drawn through the catheter compared to peripheral blood [64]. Similarly, cultures of blood drawn through an affected catheter tends to turn positive in automated blood culture systems at least 2 h earlier compared to those obtained from peripheral blood [64, 70]. The diagnosis of CNS infection from sources other than blood needs to be considered on a patient-specific basis with full knowledge that CNS is both the most common culture contaminant and a leading cause of prosthetic device infection.

Treatment

Because of the propensity of CNS to adhere to foreign material, optimal treatment of CNS infection includes removal of the infected device when possible [71]. The vast majority of CNS causing healthcare-associated infections are resistant to β-lactams [72]. Vancomycin is the drug for which most experience is available for CNS infection [73]. Because rifampin is active against CNS in the biofilm state, rifampin may be added for serious CNS infections such as prosthetic valve endocarditis although there is no clear proof of its efficacy [68, 74]. CNS are usually susceptible to recently developed antimicrobials such as quinupristin/dalfopristin, linezolid, and daptomycin [60]. With the exceptions of prosthetic valve endocarditis and prosthetic joint infection, most CNS infections respond readily to antimicrobials especially when the infected device is removed [10, 75]. Guidelines suggest that 7 days is adequate treatment for uncomplicated CNS catheter-related bacteremia after catheter removal and relapse rates are generally lower than those observed for *S. aureus* [43].

Streptococci

The streptococci are a heterogeneous group of pathogens with a confusing and oft-changing nomenclature [76]. For the purposes of this chapter, we will follow the approach of

the clinical microbiology laboratory, stratifying streptococci into viridans group streptococci (VGS), β-hemolytic streptococci, and *Streptococcus pneumoniae*. Streptococci not classified into these groups rarely cause invasive disease in patients with cancer and thus will not be discussed further herein.

Viridans Group Streptococci

Epidemiology

VGS are a diverse group of bacteria that commonly colonize the human oropharynx, upper respiratory tract, gastrointestinal tract, and female genital tract [77]. Viridans, derived from Latin, *viridis*, means green and refers to the tendency of these organisms to break down hemoglobin in blood or chocolate agar plates (α-hemolysis) causing a greenish color to appear. Most clinical microbiology laboratories do not routinely speciate α-hemolytic streptococci beyond determining whether *S. pneumoniae* is present, with non-*S. pneumoniae* α-hemolytic streptococci being broadly labeled as VGS. The major VGS responsible for invasive disease in cancer patients belong to the *mitis* group and include *S. mitis*, *S. oralis*, *S. sanguis*, and *S. parasanguis* [78–80].

VGS are considered to have low intrinsic virulence and rarely cause disease other than endocarditis in immunocompetent individuals [81]. Similar to CNS, VGS are far more likely to cause disease in patients with cancer, and these organisms are consistently identified as among the leading if not the most common cause of bloodstream infection in neutropenic individuals (Fig. 35.2) [82–84]. VGS bacteremia occurs almost exclusively in patients receiving aggressive cytoreduction therapy for such conditions as acute leukemia or following bone marrow transplantation [85, 86]. It is believed that the development of mucositis allows for translocation of colonizing VGS from the oropharynx or gastrointestinal tract into the bloodstream [87]. VGS bacteremia has been correlated with the use of prophylactic antimicrobials that have limited anti-VGS activity such as trimethoprim-sulfamethoxazole and fluoroquinolones [88].

Clinical Presentation/Diagnosis

Most patients with invasive VGS disease present with fever in the setting of mucositis and profound neutropenia [89]. Approximately 25% of patients present with a fulminant septic shock syndrome characterized by hypotension, rash, and adult respiratory distress syndrome (Fig. 35.4); *S. mitis* is the VGS species most commonly isolated from these patients [78, 89, 90]. Whether the dramatic clinical presenta-
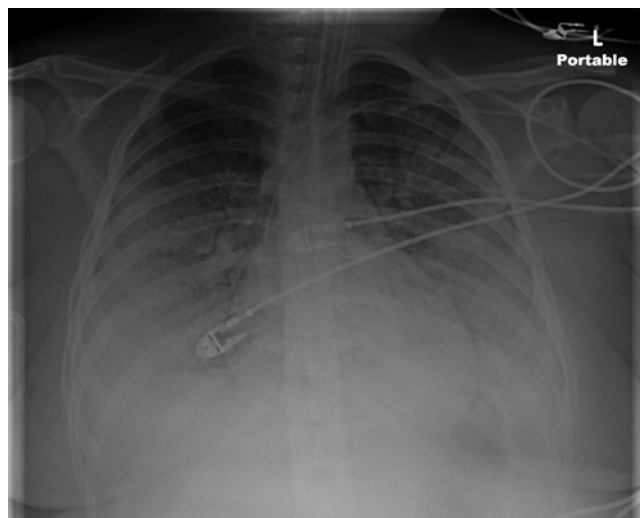
Fig. 35.4 Anterior-posterior chest X-ray demonstrating features consistent with adult respiratory distress syndrome (ARDS) that occurred following viridans group streptococcal bacteremia in a 23-year-old woman being treated for acute lymphoblastic leukemia

tion in such patients is due to host susceptibility, *S. mitis* toxin elaboration or a combination of both is not currently understood. VGS bacteremia only rarely leads to endocarditis in patients with neutropenia, perhaps because of concomitant thrombocytopenia [65, 81].

The diagnosis of VGS disease relies on culturing the organism from a sterile site, usually the bloodstream. Isolating VGS from the skin or mucosal sites has no diagnostic significance given that these organisms are common colonizers. VGS may contaminate blood cultures [91]. But should be considered true pathogens in the appropriate clinical setting, i.e. in patients with neutropenia, mucositis, and fever. Serologic or antigen tests have no utility in diagnosing invasive VGS disease.

Treatment

Therapy of VGS disease is hampered by increasing resistance to β-lactam antimicrobials [92, 93]. When isolated from patients with neutropenia, VGS susceptibility to penicillin may be as low as 40% [86]. β-lactams remain the drugs of choice for invasive VGS disease if the organisms are susceptible. VGS isolates are uniformly susceptible to vancomycin, and vancomycin is commonly prescribed when invasive VGS is suspected [94]. Isolates from VGS infections that develop in patients receiving fluoroquinolone prophylaxis are often fluoroquinolone resistant [88, 95]. VGS bacteremia is generally treated for 10–14 days with longer course reserved for complicated cases, such as endocarditis. Whether agents such as intravenous immunoglobulin would help patients with fulminant VGS sepsis is not known [96].

β-Hemolytic Streptococci

The β-hemolytic streptococci are so-called because of their ability to fully lyse red blood cells during growth on blood agar plates. Most cancer-related β-hemolytic streptococcal infections are caused by group A β-hemolytic streptococci (*S. pyogenes*), group B β-hemolytic streptococci (*S. agalactiae*), and groups C and G β-hemolytic streptococci (*S. dysgalactiae* subspecies *equisimilis*) [97–99]. For purpose of clarity, herein we will call these organisms GAS, GBS, GCS, and GGS for group A, B, C, and G *Streptococcus* respectively.

Epidemiology

β-hemolytic streptococci are ubiquitous colonizers of the human skin and mucous membranes and a major cause of invasive disease in patients with and without cancer [100]. The main sites of GAS colonization in humans are the oropharynx and skin [101, 102]. GBS commonly colonizes the perineal area, whereas GCS and GGS can be isolated from the throat and skin [103, 104]. The vast majority of infections due to these organisms have a community onset [64]. Having a malignancy markedly increases the risk of invasive disease due to β-hemolytic streptococci compared to the general population [105, 106]. The risk of cellulitis due to β-hemolytic streptococci is even further increased in patients with cancer who have had disruption of lymphatic drainage by, for example, a lymph node dissection [107]. Limited systematic studies have suggested that GBS is the most common of the invasive β-hemolytic streptococci isolated from persons with cancer followed by GAS, GCS, and GGS [108, 109]. The development of invasive GAS disease, however, carries an especially poor prognosis with mortality rates of >50% [110].

Clinical Manifestations/Diagnosis

Most β-hemolytic streptococcal infections in adult cancer patients are skin and soft-tissue related. Disease may range from relatively uncomplicated cellulitis to necrotizing fasciitis and toxic shock syndrome especially when the etiologic agent is GAS. Cellulitis due to β-hemolytic streptococci tends to develop rapidly, spread quickly, and be accompanied by systemic manifestations such as chills and fever [111]. Erysipelas is a form of cellulitis caused by β-hemolytic streptococci in which disease is restricted to the dermis. Lesions are raised above the level of the surrounding tissue, and there is a clear demarcation of involved from uninvolved tissue [112]. This infection tends to occur – and, importantly – to recur in areas of damaged lymphatic drainage, which explains the propensity for recurrent infection in the ipsilateral

arm after breast resection and lymph node dissection. Among children, GAS along with GCS and GGS are the leading bacterial causes of pharyngitis which is usually uncomplicated, although invasive disease, such as peritonsillar abscess and cervical lymphadentis, may occur [102].

Although less common than uncomplicated cellulitis or pharyngitis, infection of deeper tissues by β-hemolytic streptococci causes substantial morbidity and mortality in cancer patients [110]. Large skin lesions (>5 cm), pain out of proportion to abnormal findings on physical examination, systemic toxicity, skin discoloration, and the development of bullae all raise concern for deep tissue involvement and mandate consideration of invasive β-hemolytic infection [113]. Toxin elaboration by β-hemolytic streptococci, especially GAS, leads to profound tissue destruction and rapidly expanding disease. Streptococcal toxic shock syndrome has also been described among cancer patients with mortality rates exceeding 50% [109]. Hematogenous osteomyelitis is a common presentation of invasive GBS disease, especially among patients with diabetes mellitus [114].

Culture is the mainstay of diagnosis for β-hemolytic streptococcal infection. Rapid antigen tests when positive are reliable in diagnosing GAS pharyngitis when the ordered in patients with a high pretest probability of having the disease [115]. Recovery of β-hemolytic streptococci from a sterile site should be taken as indication of a true infection, whereas the isolation of β-hemolytic streptococci from mucous membranes and skin are often without clinical significance. An exception to this rule is toxic shock syndrome, which can occur in the absence of invasive disease; thus a diagnosis of GAS-related toxic shock syndrome can be supported by isolation of the organism from a mucosal site [116]. Serologic tests are not useful in the acute setting in diagnosing disease due to β-hemolytic streptococci. Acute and convalescent serum for antibodies to streptolysin O or DNase can be sent to determine whether an infection with GAS has occurred although these tests are rarely used in a clinical setting [117].

Treatment

β-hemolytic streptococci remain susceptible to penicillin and other β-lactam antibiotics, and these agents remain the drugs of choice for the treatment of infections due to β-hemolytic streptococci [118]. For patients who cannot receive β-lactams vancomycin is recommended although consideration should also be given to carbapenems if the penicillin allergy is not life threatening [119]. Macrolide and lincosamide resistance rates are highly variable, and these agents should not be used for serious infections without knowing strain susceptibility [120]. Many isolates are resistant to tetracyclines and trimethoprim-sulfamethoxazole [121, 122]. Experience with newer Gram-positive agents such as

daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline is limited although in vitro data are promising [123, 124]. In cases of serious soft tissue infection, especially toxic shock syndrome, clindamycin is added to reduce toxin production by slowly dying GAS [125]. Uncomplicated bacteremia due to β-hemolytic streptococci can be treated with a 10-day course of antibiotics whereas complicated disease mandates longer therapy. Surgical debridement of devitalized tissue is mandatory when these agents cause necrotizing soft-tissue infections [113].

Streptococcus pneumoniae

Epidemiology

Although genetically quite closely related to VGS, *S. pneumoniae* is generally considered distinct because of its prominent role as a major pathogen of both immunocompetent and immunocompromised humans. Pneumococci colonize the nasopharynx of 20–40% of children and 10–20% of healthy adults at any given time [126]. As indicated by its name, *S. pneumoniae* is among the leading causes of community-acquired pneumonia [127]. *S. pneumoniae* is the also the most common etiology of bacterial meningitis [128]. Risk factors for *S. pneumoniae* infection include extremes of age, comorbid illnesses such as chronic obstructive pulmonary disease and chronic kidney disease, and deficiencies in humoral immunity such as in patients with B cell neoplasms like chronic lymphocytic leukemia, non-Hodgkin's B cell lymphoma or multiple myeloma and following splenectomy or in patients with human immunodeficiency virus infection [129]. Malignancy itself is a risk factor for invasive disease due to *S. pneumoniae* with persons with leukemia or lymphoma, those having undergone a hematopoietic stem cell transplant, and those receiving corticosteroids being at highest risk [130–132]. *S. pneumoniae* causes high rates of invasive disease in children less than 5 years of age so young children with cancer have a particularly increased chance of being infected [133].

Clinical Presentations/Diagnosis

S. pneumoniae is a major cause of infection in all parts of the respiratory tract and contiguous structures including the middle ear, sinuses, bronchi, and lungs [134]. Community-acquired pneumonia is the most common serious pneumococcal infection among patients with malignancy and generally presents with cough, fatigue, fever, chills, and shortness of breath [135]. Patients with pneumococcal meningitis may or may not have concomitant pneumonia and tend to present with fever, headache, stiff neck, and altered sensorium or obtundation.
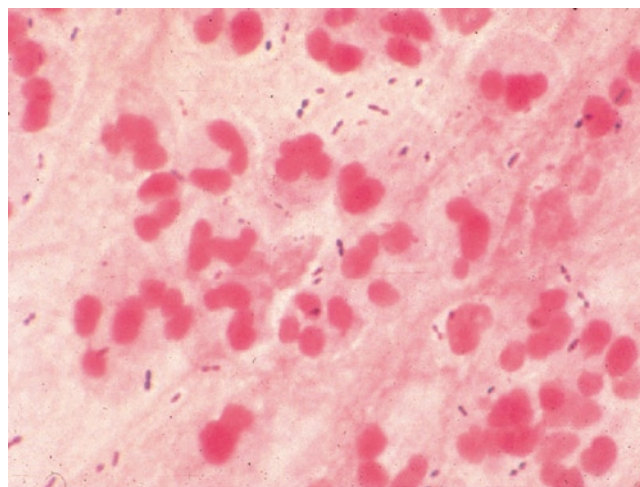
Fig. 35.5 Gram stain of sputum sample from patient with pneumococcal pneumonia. Note diploid organisms surrounded by polymorphonuclear cell infiltrate

Unlike staphylococci or even other streptococci, *S. pneumoniae* can be difficult to identify by sputum culture, and the value of diagnostic cultures is significantly reduced with prior antibiotic administration [136]. When a valid sputum sample can be obtained (this is possible in about two-thirds of pneumonia patients) and the patient has not received prior antibiotics, there is an 85% likelihood of identifying pneumococci in a Gram-stained specimen (Fig. 35.5) and a 90% likelihood of identifying the organism by culture. A subset of patients will have bacteremia along with pneumonia, but blood cultures are positive in only approximately 20% of pneumococcal pneumonia [134]. Serologic studies are not helpful acutely in making a diagnosis of invasive disease due to *S. pneumoniae*. A recently described test (BINAX-NOW) that detects C-polysaccharide in the urine is positive in 75–85% of adult patients with bacteremia pneumococcal pneumonia and a lower proportion of non-bacteremia cases; This test in adults is almost never falsely positive [137]. Patients with pneumococcal meningitis have a leukocytosis with polymorphonuclear predominance, low glucose, and high protein in the CSF. CSF Gram-stain and culture establish the diagnosis in nearly all patients who have not received antibiotics [134].

Treatment

The definition of penicillin susceptibility of *S. pneumoniae* has recently been redefined to include consideration of the site of infection and the route by which antibiotics are being delivered [138]. *S. pneumoniae* causing an infection that does not involve the central nervous system and will be treated with intravenous penicillin is considered susceptible if it is inhibited by ≤2 μg/mL penicillin; in the United States at the present time, about 95% of all pneumococci are susceptible by this definition [138]. In a case of meningitis,

inhibition by <0.06 µg/mL penicillin defines susceptibility; an MIC of ≥0.12 µg/mL is defined as resistance with about 75% of pneumococcal isolates causing meningitis in the USA being susceptible by these criteria [138]. Pneumococcal isolates are universally susceptible to vancomycin and usually susceptible to quinolones for which there is extensive experience in treating most *S. pneumoniae* infections, except for meningitis [139]. *S. pneumoniae* resistance to macrolides, clindamycin, trimethoprim-sulfamethoxazole and tetracyclines ranges from 20 to 40% in the USA, and these drugs should not be used in treating cancer patients who have invasive pneumococcal disease [140] unless susceptibility has been proven by in vitro testing. There are increasing data indicating that linezolid is effective for *S. pneumoniae* infections whereas daptomycin is not used to treat pneumonia because it is inactivated by pulmonary surfactant [141]. Although mortality for invasive pneumococcal disease remains around 15% for the first 7 days after admission, most infections respond to relatively short course of antimicrobials with longer courses reserved for meningitis, empyema, and complicated bacteremia [134].

Of all the pathogens discussed in this chapter, *S. pneumoniae* is the only one for which a vaccine is available. A vaccine consisting of capsular polysaccharides from 23 serologic types of pneumococcus is licensed for use in adults [142]. Vaccination is indicated in all adults ≥65 years of age and at any age for patients with malignancy who have an increased risk of pneumococcal disease such as those with lymphoma, multiple myeloma, transplant recipients, and those receiving chronic glucocorticoids [143]. Unfortunately, it is these very adults who are least likely to respond to such vaccination [144]. In the past decade a protein-conjugated vaccine that includes capsular polysaccharides from seven pneumococcal types has been licensed for use in children. Widespread use of this vaccine in infants and toddlers has reduced the incidence of pneumococcal disease in the entire population; however, replacement by other pneumococcal types has eroded vaccine efficacy in the population at large [129].

Enterococcus

Epidemiology

Similar to CNS and viridans group streptococci, enterococci cause a disproportionate amount of disease in patients with cancer compared to the general population [145]. The two main species causing disease in humans are *Enterococcus faecalis* and *Enterococcus faecium* [146]. As their name implies, enterococci are common colonizers of the gastrointestinal tract. The vast majority of enterococcal infections are nosocomial in origin [146]. The major risk factors for

serious enterococcal disease include general debilitation, a prolonged hospital stay, recent surgery, neutropenia, presence of indwelling catheters, and receipt of broad-spectrum antimicrobials [147, 148]. Patients with malignancy appear to have especially high risk for infection with vancomycin resistant enterococci (VRE) perhaps because of broad use of vancomycin and agents with anti-anaerobic activity in this patient population [147].

Clinical Presentation/Diagnosis

Enterococci may cause catheter-related urinary tract infection, bacteremia (either catheter-related or from a gastrointestinal source), intra-abdominal infections, wound infections, and meningitis in patients with in-dwelling CSF catheters [149]. Enterococci are considered to be low virulence pathogens, and enterococcal infections often have a minimal inflammatory component [150]. Fever may or may not be present even in cases of bacteremia [151]. Culture is the mainstay of diagnosis with serologic or antigen tests being of no value. The isolation of enterococci from nonsterile specimens such as urine, sputum, or draining wounds usually represents colonization or subclinical infection rather than infection that requires treatment. Prescribing antibiotics in this situation generally fails to eradicate the organism while promoting the development of antimicrobial resistance and exposing the patient to potentially serious side effects [152]. Even when isolated from sterile sites, such as the abdominal cavity, enterococci are usually present along with one or more other organisms [153], and treatment of more virulent pathogens has been shown to cure such infections even in the absence of targeted enterococcal therapy [151]. This concept is illustrated by the highly effective nature of cephalosporins in treating intra-abdominal infections despite having no anti-enterococcal activity [154].

Treatment

Treatment of enterococcal infection is complicated by some unusual antimicrobial resistance. Most *E. faecalis* isolates remain relatively susceptible to penicillins, specifically penicillin, ampicillin, amoxicillin, and piperacillin (not nafcillin) and carbapenems (for example, imipenem), but are intrinsically resistant to cephalosporins [155]. In contrast, penicillin resistance among *E. faecium* isolates exceeds 50% [155]. Enterococci are generally resistant to macrolides, trimethoprim-sulfamethoxazole, and fluoroquinolones [156]. Vancomycin has been the drug of choice for treating enterococci resistant to β-lactam agents, but rates of VRE have increased dramatically over the past 20 years [152]. Enterococci are tolerant to β-lactam antibiotics, meaning that they are

inhibited but not killed by them; this becomes clinically meaningful in treating endocarditis and, perhaps, infections in neutropenic patients, as well [152]. A bactericidal effect may be achieved against some isolates by the addition of an aminoglycoside. Because, in this instance, the killing is attributable to the aminoglycosides, no synergy occurs against strains that are highly resistant to aminoglycosides, and such resistance has been increasing [157]. The emergence of VRE has left physicians with relatively few treatment options. Linezolid and quinupristin/dalfopristin are the only drugs approved by the United States Food and Drug Administration for treatment of infections due to VRE, although both drugs have significant limitations such as a lack of efficacy of quinupristin/dalfopristin against *E. faecalis* [158]. In vitro data with daptomycin and tigecycline are encouraging although emergence of resistance and reports of clinical failures are concerning [159]. The lack of clear clinical data regarding VRE treatment has recently led the Infectious Diseases Society of America to declare that determining optimal VRE treatment strategies is an area of paramount importance [160].

The Effect of the Emergence of Gram-Positive Infections on Empiric Antimicrobial Therapy for Patients with Malignancy

For many years empiric antimicrobial treatment of cancer patients with possible bacterial infections focused on Gram-negative pathogens, because bacteremic infection with these organisms was associated with a high risk of death [75]. The increased rates of isolation of Gram-positive pathogens has led many physicians to add an anti-Gram-positive antimicrobial, such as vancomycin or linezolid, when treating cancer patients with suspected infection [161], even though the same risk for death has not been documented for Gram-positive compared with Gram-negative bacteremia [66, 162]. In fact, clinical trials demonstrate no clinical benefit for the addition of targeted anti-Gram positive antimicrobials in empiric treatment regimens [94, 163, 164]. Widespread use of vancomycin and other targeted anti-Gram-positive agents is a major factor contributing to the emergence of such multidrug resistant organisms as VRE [165]. Nonetheless, the practice of adding vancomycin or other targeted Gram-positive antimicrobials empirically in neutropenic patients with fever and, by extension, in many other cancer patients who are not neutropenic, remains pervasive [166]. Taken together, these factors have led to specific recommendations against adding empiric anti-Gram-positive treatment in patients with cancer and suspected infection [94]. Institutional attempts to limit additional empiric anti-Gram-positive antimicrobial treatment to patients with specific risk factors

have had limited success to date, but provide some hope for minimizing the overuse of antimicrobial agents [4]. Historically, a broad array of Gram-positive pathogens have shown the remarkable ability to overcome any widely prescribed antimicrobial, and thus antimicrobial conservation may play a pivotal role in the long-term control of these prevalent organisms [167].

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Chapter 36
Infections Caused by Aerobic and Anaerobic Gram-Negative Bacilli

Kenneth V.I. Rolston, David E. Greenberg, and Amar Safdar

Abstract Many cancer treatment centers have documented a decline in the proportion of bacterial infections caused by aerobic Gram-negative bacilli in the past 2 decades. Nevertheless, these organisms still cause a wide spectrum of infection (from benign colonization to disseminated disease) and are associated with substantial morbidity and mortality in patients with cancer, particularly during episodes of neutropenia. The most significant problem developed in the recent years has been the emergence of resistance among most Gram-negative pathogens, with some organisms acquiring multiple resistance mechanisms, which render them multi-drug-resistant. Exacerbating this problem is the fact that the pipeline for new drug development is relatively dry. This has led to the increased use of combination regimens and the revival of older agents such as colistin. Greater emphasis needs to be placed on antimicrobial stewardship and on strict adherence to infection control policies, in order to reduce the frequency of and limit the spread of these organisms. Bacteroides and other anaerobic Gram-negative bacteria may lead to life-threatening infections, presence of refractory hypotension, high-grade fever, acute intravascular hemolysis and disseminated coagulation, and early onset of tissue necrosis are the hallmark of this devastating disease. A high level of suspicion and prompt systemic therapy coupled with surgical excision of devitalized tissue when possible may improve outcomes.

Keywords Cancer • Pseudomonas • Stenotrophomonas • Drug-resistance • Antimicrobial therapy • *E. coli*

Introduction

Aerobic Gram-negative bacilli account for 15–20% of documented bacterial infections in neutropenic patients [1]. Furthermore, ~80% of polymicrobial infections have a Gram-negative component [2]. Since polymicrobial infections now account for 25–30% of documented bacterial infections (a proportion that has been increasing over the last 2 decades), Gram-negative bacilli are isolated from ~50% of bacterial infections in this patient population. This occurs despite the use of antimicrobial prophylaxis directed primarily against Gram-negative bacilli in high-risk neutropenic patients. The majority of Gram-negative pathogens are residents of the human intestinal tract, although some are acquired from environmental or other sources. In general, Gram-negative, and polymicrobial infections are associated with greater morbidity and mortality than Gram-positive infections. Consequently, the prompt administration of empiric, broad-spectrum, parenteral, antimicrobial therapy is the standard of care for most febrile neutropenic patients [3]. Unfortunately, neutropenic episodes occur often, and the frequent use of antimicrobial agents for prophylaxis and therapy has led to the emergence of resistant organisms [4–6]. Some organisms acquire multiple resistance mechanisms that render them multi-drug-resistant (MDR) – defined as resistance to at least three different classes of antimicrobial agents that are expected to be active against a particular pathogen. MDR Gram-negative pathogens pose a significant problem, especially since the pipeline for new drug development is relatively dry, as outlined by several recent publications from the Infectious Diseases Society of America [7, 8]. This chapter will deal with Gram-negative infections overall, and with specific Gram-negative organisms of particular importance.

Current Spectrum of Gram-Negative Organisms

Most cancer treatment centers have documented a decline in the proportion of bacterial infections caused by aerobic Gram-negative bacilli over the past 2–3 decades, with a corresponding increase in Gram-positive infections [1, 9, 10]. Of late, some centers are reporting a shift back toward a predominance of Gram-negative infections [11, 12]. Unfortunately, most epidemiologic studies focus primarily

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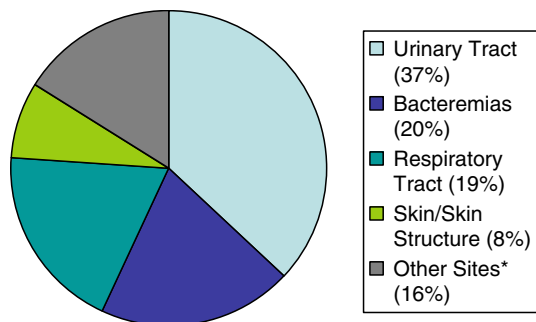
Fig. 36.1 Most common sites for Gram-negative infection in cancer patients

Fig. 36.2 Proportion of various Gram-negative bacilli causing infection in cancer patients

on single-organism (monomicrobial) bacteremias, and fail to provide data on polymicrobial infections and on sites of infection other than the bloodstream (e.g., urinary tract, respiratory tract, skin/skin structure, intestinal/hepato-biliary tract). Since bacteremias account for only 15–25% of infections in such patients, these data paint an incomplete picture. Whereas Gram-positive organisms predominate as the cause of bacteremias (up to 80% in some reports), Gram-negative organisms predominate at most other sites of infection [10, 13]. Additionally, ~80% of polymicrobial infections have a Gram-negative component, and 30–35% are caused by multiple Gram-negative species [2, 14]. Consequently, when all sites of infection, and polymicrobial infections are taken into account, a substantially different epidemiologic picture, with a greater proportion of infections being caused by Gram-negative organisms, emerges. The most common sites of infection are depicted in Fig. 36.1. These include urinary tract infections (37%), bacteremias (20%), respiratory tract infections (19%), and skin/skin structure infections (8%). Other, less common but important sites include the hepato-biliary tract, pleural fluid, peritoneal fluid, and cerebrospinal fluid. It is also commonly accepted that many cancer patients with clinically documented infections (e.g., pneumonia, neutropenic enterocolitis) and with episodes of unexplained fever have undocumented Gram-negative infections, especially if they are receiving prophylactic antibiotics.

Studies from various parts of the globe consistently show that *Escherichia coli*, Klebsiella species, and *Psuedomonas aeurginosa* are the three most common Gram-negative organisms isolated from cancer patients [1, 9, 10, 13, 15–17]. Other Enterobacteriaceae, Acinetobacter species, *Stenotrophomonas maltophilia*, and non-aeruginosa Pseudomonas species are less common but important pathogens that often develop multiple mechanisms of resistance to commonly used antibiotics. Local and interinstitutional differences do occur. It is therefore important to conduct periodic epidemiologic/surveillance studies in order to determine the most current spectrum of infections and susceptibility/resistance patterns. In our most recent survey, isolates from 903 consecutive,
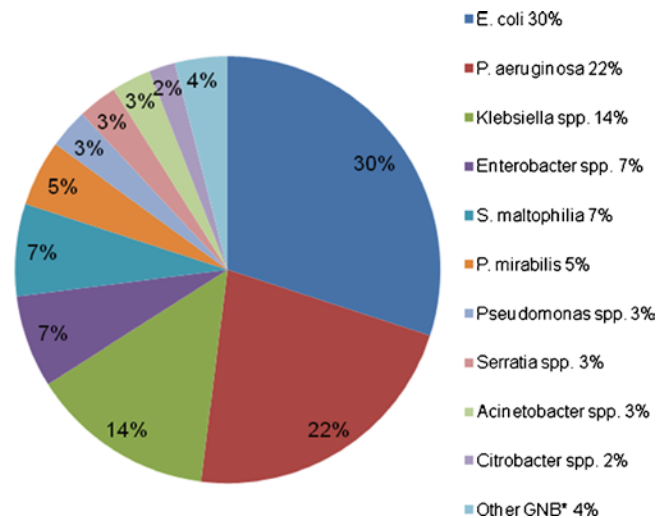
monomicrobial Gram-negative infections were collected for susceptibility testing. The most frequently isolated Gram-negative species were *E. coli* (268 – 30%), *P. aeruginosa* (200 – 20%), Klebsiella spp. (122 – 14%), Enterobacter spp. (62 – 7%), and *S. maltophilia* (61 – 7%) (Fig. 36.2). This spectrum is virtually identical to previous surveys we have conducted with the exception of a substantial increase in the proportion of infections caused by *S. maltophilia* from 3% in 1993 to 7% in the latest survey [18, 19]. *S. maltophilia* is isolated even more frequently from patients treated in our intensive care unit – being the third most common Gram-negative pathogen in that setting (unpublished data from the MDACC antimicrobial stewardship program). The remainder of this chapter will focus on individual Gram-negative pathogens.

The Enterobacteriaceae

Bacteria from the family Enterobacteriaceae are among the most common human pathogens, affecting all populations (immunosuppressed and immunocompetent). They cause syndromes ranging in severity from simple cystitis to widely disseminated infection. The Enterobacteriaceae are part of the normal intestinal flora. They are, however, opportunistic pathogens with infection usually being spread by fecal-oral contact routes. In cancer patients receiving chemotherapy, translocation of bacteria from the intestinal lumen to the bloodstream is common across damaged mucosal surfaces. This has led to the practice of administering antimicrobial prophylaxis to high-risk patients.

E. coli is the most frequent Gram-negative pathogen isolated from cancer patients. Infections frequently caused by *E. coli* include urinary tract infection, bacteremias, neutropenic
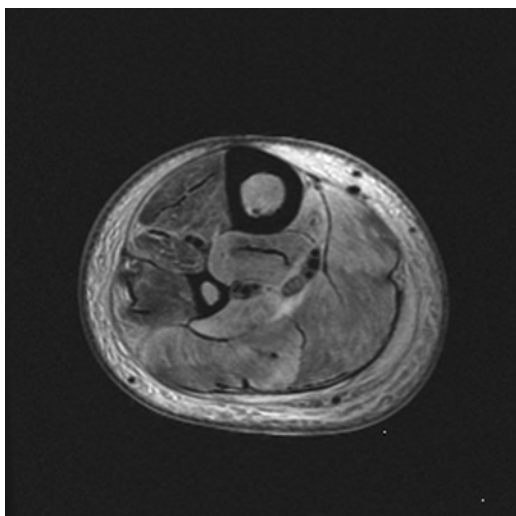
Fig. 36.3 Magnetic resonance image showing massive edema of leg muscles associated with *E. coli* pyomyositis

Table 36.1 Spectrum of infections caused by Gram-negative bacilli

Bacteremia – primary and catheter related
Pneumonia
Urinary tract infections – primary and catheter related
Enterocolitis/typhlitis/perirectal infection
Meningitis/brain abscess
Wound infection
Cholangitis/biliary tract infection
Abdominal/pelvic/hepatic abscess
Otitis externa/mastoiditis
Keratitis/endophthalmitis
Empyema
Prostatic infection
Osteomyelitis/device-related infection
Septic arthritis
Skin/ecthyma gangrenosum

enterocolitis, perirectal infections, and infections of the hepato-biliary tract. Investigators at The University of M.D. Anderson Cancer Center have recently described several cases of pyomositis caused by *E. coli* [20, 21]. All patients who developed pyomositis were receiving chemotherapy for hematologic malignancies and had profound neutropenia. The areas most often involved were the muscles of the calves and thighs. Septic shock (50%) was common. Magnetic resonance imaging showed diffuse abnormality of the musculature including edema, consistent with pyomositis (Fig. 36.3). Frank abscesses were present in 50% of these patients, and *E. coli* was the only pathogen isolated from these abscesses. All these isolates were resistant to fluoroquinolones and 55% produced extended spectrum beta-lactamases. The mortality was 33%, higher than in patients with other *E. coli* infections.

Klebsiella species have consistently been the second most frequent Gram-negative organisms isolated from cancer patients. The two most frequent pathogens are *Klebsiella pneumoniae* and Klebsiella oxytoca. The spectrum of infections caused by these organisms is similar to that caused by *E. coli* and other Gram-negatives (Table 36.1). Other, less frequent Enterobacteriaceae causing infections in cancer patients include Enterobacter species, Citrobacter species, and Serratia species. Collectively, they cause ~60% of monomicrobial Gram-negative infections in this patient population. *Serratia marcescens* has been the source of many healthcare-associated outbreaks, generally as the result of contamination of products such as medical devices, disinfectants, hand soaps, and medication vials. The last such incident was a 9-state outbreak of 162 cases of *S. marcescens* bacteremia associated with prefilled heparin and/or saline syringes made by a specific manufacturer [22]. Cultures of unopened prefilled heparin and saline syringes from this source grew

S. marcescens during the subsequent investigation of the outbreak. Of the 83 *S. marcescens* blood culture isolates from patients in this outbreak, 84% were genetically related to the strain isolated from the prefilled syringe. A US Food and Drug Administration inspection revealed that the manufacturer was not in compliance with quality systems regulations. A voluntary, national recall of the prefilled syringes led to termination of the outbreak. This incident shows the importance of clinical vigilance and cooperation among multiple agencies entrusted with investigating such outbreaks.

Historically, bacteria from the family Enterobacteriaceae have been susceptible to a wide range of antimicrobial agents. During the past 2 decades however, multidrug resistance has become widespread. Resistance is mediated primarily via acquired genes that code for extended-spectrum-beta-lactamases (ESBLs) [23]. The ESBLs confer resistance to penicillins, cephalosporins, and aztreonam. However, these isolates typically remain susceptible to the carbapenems (imipenem, meropenem, ertapenem), and these agents are considered the drugs of choice for treating infections due to ESBL-producing bacteria. Data from our institution, the only comprehensive cancer center to participate in the Meropenem Yearly Susceptibility Testing Information Collection (MYSTIC) study, have shown that the proportion of ESBL producing *E. coli* rose from 4.5% in 1999 to 19.4% in 2008 [6]. This increase was disproportionate when compared to other participating institutions.

E. coli isolates have generally also been susceptible to most agents used for prophylaxis in cancer patients [18, 24–26]. With the widespread and increasing use of fluoroquinolones for antimicrobial prophylaxis in neutropenic patients, the emergence of *E. coli* strains that are resistant to the fluoroquinolones and other frontline agents has become commonplace [4–6, 20]. This is not only true for patients with hematological malignances but also for those with solid tumors as well [27, 28]. Most individual studies of fluoroquinolone prophylaxis failed to demonstrate reduced mortality

as a result of this strategy [29, 30]. However, one recent meta-analysis of several studies suggests that the use of fluoroquinolones prophylaxis reduces mortality in neutropenic patients [31, 32]. The potential benefits of prophylaxis need to be weighed against the substantial risk of the development of resistance, not only among *E. coli* but also many other important Gram-negative species such as *P. aeurginosa*. Most guidelines caution against the routine use of quinolone prophylaxis for all neutropenic patients, and recommend this strategy only for high-risk patients with prolonged neutropenia [3, 33]. Fortunately, many quinolone-resistant isolates remain susceptible to the aminoglycosides, broad-spectrum beta-lactam agents, and tigecycline.

The most alarming recent development has been the emergence of carbapenem-resistant Enterobacteriaceae [34, 35]. In 1996, a carbapenem-resistant *K. pneumoniae* was recovered from a patient in North Carolina. This isolate produced a class A beta-lactamase which hydrolyzes penicillins, cephalosporins, aztreonam, and carbapenems and is named *Klebsiella pneumoniae* carbapenemase (KPC). Since then, many other KPC producing Enterobacteriaceae have been isolated from various sources. Some of these organisms produce metallo-β-lactamase VIM enzymes as well, which also confer carbapenem resistance [36–38]. The gene coding for these enzymes is carried by plasmids that often carry other resistance factors, resulting in extensively-drug-resistance (XDR) organisms, severely limiting our capability to treat them effectively.

Nonfermentative Gram-Negative Bacilli

Despite an overall decline in the frequency of Gram-negative infections in cancer patients, there has been an increase in the proportion of such infections caused by nonfermentative Gram-negative bacilli (NFGNB) [39]. Collectively, NFGNB cause ~36% of documented Gram negative infections in this patient population (Table 36.2). *P. aeruginosa* is the most frequently isolated and most important pathogenic NFGNB. Non-aeruginosa pseudomonas species are less common and are associated with lower morbidity and mortality. The frequency

Table 36.2 Increasing the frequency of infections caused by NFGNB[a] in cancer patients

References,[b]	Year	Total Gram-negative isolates – n	NFGNB,[a] n (%)
Bodey et al. [24]	1985	941	245 (26)
Bodey et al. [24]	1986	851	220 (26)
Rolston et al. [25]	1993	679	159 (23)
Jacobson et al. [26]	1996	758	225 (30)
Rolston et al. [18]	2002	903	329 (36)

[a]*NFGNB* nonfermentative Gram-negative bacilli
[b]Data from epidemiologic/surveillance studies conducted at The University of Texas M.D. Anderson Cancer Center

of infections caused by *S. maltophilia* has risen dramatically over the past 2 decades and may be related to the widespread use of the carbapenems as monotherapy in febrile neutropenic patients [40]. Acinetobacter species are still relatively uncommon but are often MDR, and difficult to treat. These pathogens will be discussed in greater detail below.

Pseudomonas aeruginosa

P. aeruginosa emerged as a common cause of bacterial infection in neutropenic cancer patients during the 1960s, and before the availability of agents such as carbenicillin, was associated with mortality rates in excess of 90%. Since then, the availability of potent antipseudomonal agents along with significant improvements in critical and supportive care has reduced the mortality to approximately 25–30%. Substantial regional and institutional differences in the frequency of infections caused by *P. aeruginosa* have been documented [19]. Consequently, knowledge of local epidemiology and susceptibility/resistance patterns is important.

A recent large review of *P. aeruginosa* infection in cancer patients identified several risk factors [41]. Most patients (54%) had an underlying hematologic malignancy – usually a variant of acute leukemia. *P. aeruginosa* bacteremia was 27 times more common in patients with acute leukemia than in patients with solid tumors. During the 2 weeks prior to documentation of *P. aeruginosa* bacteremia, 89% of patients received some form of antineoplastic therapy (mostly chemotherapy), and 43% underwent an invasive procedure or placement of a medical device (urinary or intravascular catheters, or Ommaya reservoir). Additionally, during the 7 days preceding the onset of *P. aeruginosa* bacteremia, 36% of patients had received antibiotics for presumed or proven infections. The practice of administering intensive chemotherapy in the outpatient setting has had an impact on Pseudomonas infections. In the study cited above, 50% of patients with *P. aeruginosa* were not hospitalized. However, 9% had been discharged from the hospital during the preceding 3 days and, 25% had been discharged during the preceding week.

P. aeruginosa has the potential for developing resistance to antimicrobial agents by multiple resistance mechanisms. A recent study demonstrated that the risk factors associated with multidrug-resistant *P. aeruginosa* infection were the use of a carbapenem for ≥7 days, a history of *P. aeruginosa* infection during the preceding year, and a history of chronic obstructive pulmonary disease [42].

As mentioned, these infections are more common in patients with hematologic malignancies, and are often polymicrobial. While pseudomonal infections are documented less frequently in patients with solid tumors, a much wider spectrum is seen [43]. This is because most of these infections are associated with catheters or other foreign medical

devices, surgical procedures, and the presence of obstructive lesions or devitalized tissues caused by the presence of large and rapidly growing tumors. Specific infections depend on the location of the tumor or foreign device. *P. aeruginosa* is often isolated from surgical wounds. Patients who have obstructive pulmonary lesions due to primary or metastatic tumors develop postobstructive necrotizing pneumonias, lung abscess, broncho-pleural fistula, or empyema. *P. aeruginosa* is a common pathogen in these settings, especially in patients requiring prolonged hospitalization, broad-spectrum antibiotics, or mechanical ventilation. Patients with hepato-biliary, gastro-intestinal, and gynecological malignancies develop localized infections such as abdominal, pelvic, or hepatic abscesses, and ascending cholangitis. These infections are predominantly polymicrobial with *P. aeruginosa* being among the most common isolates [2]. Genito-urinary infections including prostatitis are common in patients with prostate cancer and other tumors causing local obstruction. Finally, with the increased use of vascular access devices, urinary and other catheters, stents, and a variety of other foreign medical devices, an increasing number of pseudomonal infections are being documented.

Stenotrophomonas maltophilia

S. maltophilia colonization/infection rates in patients with cancer have substantially increased over the past 2 decades. Surveillance studies conducted at the University of Texas M.D. Anderson Cancer Center in Houston have documented an increase in the proportion of *S. maltophilia* from 2% of all Gram-negative bacilli isolated in 1986 to 7% in 2002 [18]. During this time, *S. maltophilia* increased from being the ninth most common Gram-negative isolate, to the fifth most common. Patients with prolonged neutropenia, exposure to broad spectrum antibiotics, particularly the carbapenems, and those requiring mechanical ventilation have a higher risk of infection [44–46]. However, these infections are being documented more often even in patients without these risk factors [47]. Some of these infections appear to be community acquired as they are being documented in patients not previously exposed to the healthcare system.

The most common clinical manifestation of *S. maltophilia* infection include bacteremia, which is often catheter-related, respiratory tract infection, skin and skin structure infection, and complicated urinary tract infection usually in the presence of obstruction of foreign medical devices. Furthermore, at our institution a significant increase (13%) in moderate to high-grade bacteremia (>100 cfu/mL) caused by *S. maltophilia* has occurred, and may reflect the increasing severity of these infections (Table 36.3).

Recovery of the *S. maltophilia* does not always indicate the presence of infection. Skin and intestinal colonization

Table 36.3 Frequency of moderate-to-high-grade bacteremia[a] in cancer patients at MDACC[b]

Organisms	Moderate to high-grade bacteremia	
	No. (%) of isolates	
	1998	2004
Gram-negative isolates	111 (39)[c]	78 (42)[d]
S. maltophilia	4 (4)	13 (17)
P. aeruginosa	14 (13)	8 (10)
Acinetobacter spp.	7 (6)	8 (10)

[a] Moderate: 101–500 CFU/mL; high-grade: >500 CFU/mL
[b] *MDACC* M.D. Anderson Cancer Center
[c] From a total of 284 Gram-negative bacilli
[d] From a total of 186 Gram-negative bacilli

occur most often. Intestinal colonization may occur after fluoroquinolone prophylaxis. In a recent surveillance study, *S. maltophilia* colonization was demonstrated in 10% of hospitalized neutropenic patients [48]. *S. maltophilia* respiratory tract colonization occurs frequently in patients with (a) prolonged stay in an intensive care unit, (b) presence of a tracheostomy, and (c) prolonged exposure to broad-spectrum antibiotics, and often precedes infection.

Trimethoprim/sulfamethoxazole (TMP/SMX) has had the most potent and reliable in vitro activity against *S. maltophilia*, but resistance rates appear to be increasing [49]. Several beta-lactams have been reported to have variable activity (ranging from 35 to 70%) against *S. maltophilia* including ceftazidime, cefepime, ticarcillin/clavulanate, and piperacillin/tazobactam [50]. The aminoglycosides have poor activity against these organisms. The quinolones have variable activity, with the newer agents such as moxifloxacin being more active than older ones such as ciprofloxacin [51]. Minocycline and the novel glycecycline agent tigecycline are also active against most *S. maltophilia* isolates [52].

Acinetobacter baumannii

Acinetobacter baumannii is being increasingly recognized worldwide as a significant cause of morbidity and mortality. *A. baumannii* usually causes infections in those who are immunosuppressed, with cancer patients being one of the groups who are most at risk [53]. Centers from around the world have reported high rates of *Acinetobacter* isolation. In one Brazilian cancer hospital, *A. baumannii* represented 9.3% of bloodstream infections among solid organ cancer patients during a 2-year study period [28]. This rate slightly surpassed that of *P. aeruginosa*. At the National Cancer Institute in Cairo, Egypt, *Acinetobacter* species comprised 6.9% of over 770 isolates from patients with either hematologic malignancies or solid tumors [54]. *Acinetobacter* is also seen in the pediatric population. In one study of 92 bloodstream isolates of *Acinetobacter* spp. over a 5-year

period, ~50% of cases were in children with malignancies (both solid and hematologic) or transplants (solid organ and bone marrow). In a multivariate analysis, having a solid organ malignancy was associated with a greater risk of developing *Acinetobacter* infection [55].

The clinical manifestations of *Acinetobacter* infections are similar to those seen with other Gram-negative bacilli. Frequently seen infections include bacteremia, pneumonia, wound, and urine infections [56]. Although having cancer is an important risk factor for *Acinetobacter* infections, it is not clear if patients with cancer have higher attributable mortality due to *Acinetobacter* infections than those without cancer.

The increasing levels of antibiotic resistance that have been seen with other Gram-negative bacilli are also being seen in *Acinetobacter* isolates. In one large European study of antimicrobial susceptibility of bacterial isolates between 2004 and 2007, ~16% of all the *A. baumannii* isolates were considered multidrug resistant [57]. Due to the development of multidrug-resistant Gram-negative organisms, including *Acinetobacter* pp., older drugs such as colistin, which had been used infrequently due to toxicities, are now making a comeback. However, resistance to colistin has developed as well. In a recent study looking at colistin resistance among *A. baumannii* strains from across the world, 23% were found to be colistin heteroresistant [58]. In another recent study, the in vitro activity of tigecycline, minocycline, and colistin-tigecycline combination against clinical *A. baumannii* isolates including colistin-resistant isolates was evaluated [59]. Tigecycline showed better activity than minocycline even against pan-drug resistant strains.

Approximately, 4% of all Gram-negative infections are caused by other, less common, but important NFGNB including Achromobacter and Alcaligenes species, Chryseobacterium species, Burkholderia species, and non-aeruginosa Pseudomonas species [18]. Achromobacter and Alcaligenes species are ubiquitous organisms, and most infections can be traced to a common source such as contaminated dialysis fluid, deionized water, chlorhexidine solution, mechanical ventilators, and incubators [60]. Patients with cancer, those undergoing hematopoietic or solid organ transplantation, HIV/AIDS and other immunocompromised patients are at increased risk, and these infections can present as life-threatening events in such individuals. Primary uncomplicated bacteremia represents the most common clinical manifestation although infected indwelling catheters, pneumonia, and meningitis have also been reported. These organisms are uniformly resistant to the fluoroquinolones, and the impact of widespread fluoroquinolone prophylaxis on the frequency of these infections needs to be investigated. Most isolates are susceptible to TMP/SMX and the carbapenems [61]. Some combinations have been shown to be synergistic in vitro and may be preferred for therapy in neutropenic patients with sepsis and multiorgan dysfunction [62].

Chryseobacterium species (*C. indologenes* and *C. meningosepticum*) are rare pathogens but can cause life-threatening infections such as bacteremia and meningitis, especially in immunocompromised individuals [63–65]. *C. meningosepticun* is a waterborne saprophytic organism, ubiquitous in the natural and hospital environment. *C. indologenes* is also widely distributed in nature (plants, water, and soil). Antimicrobial susceptibility is variable with most isolates being resistant to the aminoglycosides, and many beta-lactams [66, 67]. The organisms may be susceptible to minocycline, TMP/SMX, rifampin, piperacillin/tazobactam, cefoperazone/sulbactam, and vancomycin. Combination therapy may be prudent in most cases. Burkholderia cepacia complex (BCC) is opportunistic pathogens that occasionally cause outbreaks in patients with cancer, which are generally traced to contaminated intravenous solutions, disinfectants such as chlorhexidine and povidone-iodine solution, ultrasound gel, mouthwashes, and aerosols [68–70]. They are often susceptible to TMP/SMX, the carbapenems, the quinolones, and extended spectrum cephalosporin and penicillins.

Pseudomonas fluorescens and Pseudomonas putida are members of the fluorescent pseudomonad group. Unlike *P. aeruginosa*, these organisms have low levels of virulence. They do colonize the skin in some individuals and can cause pseudobacteremia or procedure-related infections. The association between *P. fluorescens* and contaminated blood products has been well described [71–73]. They are also present in commercial bottled water, which can be a source of infection in neutropenic patients [74]. Catheter-related bacteremia and pneumonia are the most common clinical manifestations [75–77]. The carbapenems have the most reliable activity against these organisms. The activity of other beta-lactams and the quinolones is variable. The overall mortality associated with these organisms is low. Many patients respond to removal of the offending catheter alone, and most respond to appropriate antimicrobial therapy.

Treatment and Outcome

The treatment of Gram-negative infections in neutropenic patients, especially those caused by *P. aeruginosa*, has been the subject of considerable debate. There are two schools of thought. One school advocates the administration of combination therapy (preferably a synergistic combination) in all patients with documented Gram-negative infections, while the other considers treatment with a single, bactericidal, broad-spectrum agent with antipseudomonal activity to be adequate [78, 79]. It is likely that different approaches may be applicable for initial empiric therapy and for the treatment of documented Gram-negative infections [3, 80].

Empiric Therapy

Antipseudomonal coverage is an essential component of empiric therapy in neutropenic cancer patients [3]. This can be achieved using either combination antibiotic regimens or broad spectrum agents alone, as monotherapy. Traditionally, combination regimens have included an aminoglycoside and an antipseudomonal beta-lactam. Agents commonly used as monotherapy include the cephalosporins, ceftazidime, and cefepime; the carbapenems, imipenem, and meropenem; and piperacillin/tazobactam [3]. Several randomized trials in this setting have found monotherapy to be as effective as combination therapy, while some studies have hinted at the superiority of combination regimens [81–86]. A recent meta-analysis concluded that several broad-spectrum agents (ceftazidime, piperacillin/tazobactam, imipenem, and meropenem) were suitable as monotherapy in this setting [87]. Unfortunately, the number of documented pseudomonal infections in these trials was too small to draw firm conclusions regarding the treatment of this specific organism. Some authors have cautioned against the use of cefepime as monotherapy apparently due to an increase in all cause mortality associated with this agent compared to other beta-lactams, as published in a recent systemic review and meta-analysis [88]. Other authors have questioned the methods used to arrive at this conclusion [89, 90]. The FDA has conducted its own analysis which did not confirm this association, and deemed cefepime to be a suitable agent for monotherapy [91]. Monotherapy using an aminoglycoside is suboptimal in neutropenic patients whether used empirically or for the treatment of documented Gram-negative infections shown to be aminoglycoside susceptible in vitro [92].

Therapy of Documented Infections

As mentioned previously, the main debate regarding the treatment of documented Gram-negative infections is whether or not one needs to always use combination regimens, particularly for infections caused by *P. aeruginosa*. Two large studies collectively evaluating 665 episodes of *P. aeruginosa* bacteremia have been published from the M.D. Anderson Cancer Center [41, 93]. Both demonstrated that there was no significant difference in response rates between patients receiving monotherapy with an antipseudomonal beta-lactam and those receiving combination therapy. The overall response rate in the more recent study was 80%, a significant improvement over the 62% response rate in the earlier study. This probably reflects the availability of more potent antipseudomonal agents and advances in supportive care in recent years. Factors associated with an unfavorable outcome included (a) delay in the administration of appropriate therapy, (b) persistent and severe neutropenia, (c) severe sepsis including septic shock,

and (d) the presence of tissue-based infections (pneumonia, enterocolitis/typhlitis, perirectal infections). The response rate was 97% in patients whose neutrophil count increased above 0.10×10^4/L during treatment compared to 62% if the neutrophil count persisted below this level. Patients with persistent neutropenia might benefit from the administration of hematopoietic growth factors (G-CSF, GM-CSF) or white blood cell transfusions although clear guidelines for the use of these modalities have not been established.

In a large study (covering 2 decades of experience) of the outcomes of bacteremia in neutropenic cancer patients, Elting et al. characterized bacteremia as simple and complex [94]. Simple bacteremias included those without any tissue site or those associated with minor infections such as cystitis, cellulitis, or bronchitis. Complex bacteremias were those that had sites of infection in major organs (lung, liver, spleen, colon, bones, joints, meninges) and extensive soft-tissue infections (>5 cc in size or with necrosis). The cure rate for simple bacteremia was 95% compared to 50% for complex bacteremias. Although the overall mortality was not significantly increased when patients with bacteremia due to Gram-negative organisms initially received monotherapy, this strategy increased the duration of therapy by 25%. These researchers also demonstrated that certain regimens considered therapeutically equivalent based on conventional response rates associated with them may differ drastically when time to clinical response is taken into consideration [95].

Clearly, there is no uniform strategy to treat Gram-negative infections in patients with or without neutropenia. One of the biggest problems in prospectively evaluating different therapeutic approaches has been the small number of documented Gram-negative infections even in large trials. Organizations such as the IDSA and NCCN have published guidelines for antimicrobial usage in neutropenic patients [3, 33]. Both sets of guidelines consider empiric monotherapy to be as effective as combination therapy. Opinion regarding the treatment of documented *P. aeruginosa* infection remains divided [96]. Although monotherapy might be effective for simple pseudomonal infections, most clinicians are more comfortable using combination regimens for complex pseudomonal infections [3, 33, 96]. In addition to increased efficacy as a result of synergy, other potential advantages of combination therapy might be a reduction in the emergence of resistance, and a quicker time to defervescence [3, 94, 95].

Antimicrobial Stewardship

Increasing rates of antimicrobial resistance among Gram-negative pathogens have been documented at most cancer centers [1, 3, 9, 10]. One method of combating this problem has been the development of novel agents that have activity against these resistant pathogens. Currently, however, the

Table 36.4 Antimicrobial stewardship strategies

- Create Multidisciplinary Antimicrobial Stewardship Team (MAST)
- Determine real time institutional epidemiology and susceptibility resistance patterns
- Know institutional formulary make up and prescribing habits
- Limit chemoprophylaxis to high-risk patients
- Encourage targeted therapy (not always feasible in neutropenic patients)
- Conduct prospective audits of antimicrobial usage
- Provide feedback (positive and/or negative) to prescribers
- Consider formulary restriction and/or preauthorization of certain agents
- Create institutional guidelines and pathways
- Consider antimicrobial heterogeneity
- Streamline (de-escalate) initial broad-spectrum regimen (when possible)
- Dose optimization and appropriate duration of therapy
- Education activities
- Strict adherence to infection control policies

Adapted from refs. [97–99]

pipeline for novel agents with potent activity against resistant Gram-negatives is relatively dry [7, 8]. Consequently, the judicious use of currently available antimicrobial agents (antimicrobial stewardship) to prevent the emergence of resistant organisms and strict adherence to infection control practices to reduce the spread of resistant organisms have become important strategies in the overall management of high-risk patients. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have published joint guidelines for developing institutional antimicrobial stewardship programs [96]. Collecting baseline data at the onset of a stewardship program is necessary as institutional differences do exist. These data include local epidemiologic and susceptibility/resistance patterns, and knowledge of hospital formulary and institutional prescribing habits. Armed with these data, several strategies can be implemented, Table 36.4. These include limiting the use of antibacterial prophylaxis, dose optimization, targeted therapy when possible, de-escalation or streamlining of the initial broad spectrum regimen, antibiotic heterogeneity, and educational/prospective feedback sessions. These strategies already have been implemented with considerable success at several cancer centers [97, 98].

Anaerobic Bacterial Infections

The majority of anaerobic Gram-Negative bacilli belong to *Bacteroides fragilis* group. Infections mostly originate from orointestinal tract. Adults with systemic Bacteroides infections often have hematologic malignancy, such as refractory leukemia, myelodysplastic syndrome, aplastic anemia, or

have recently undergone surgery for bowel or gynecologic cancer [100, 101]. Presence of intestinal obstruction, poorly controlled diabetes mellitus, and intestinal epithelial damage due to cytotoxic drug or radiation therapy also increases risk for systemic GN anaerobic bacterial infection. Patients receiving high-dose systemic corticosteroids and those with high-grade graft-versus-host disease following allogeneic stem cell transplantation are also among the high-risk group [102]. Direct inoculation of a surgical wound is another well-recognized source of anaerobic wound and deep tissue infections [100]. Central venous catheter is an uncommon source of anaerobic bacteremia. Patients with neutropenic enterocolitis with a hematologic malignancy may also have a higher risk for anaerobic bacteremia [102].

Bacteroides and other anaerobic Gram-negative bacteria may lead to life-threatening infections, presence of refractory hypotension, high-grade fever, acute intravascular hemolysis and disseminated coagulation, and early onset of tissue necrosis are the hallmark of this devastating disease [100]. A dusk pallor tissue that is cold to touch heralds severe underlying tissue damage; crepitus on palpation may not be evident in patients with deep tissue involvement are most frequently seen in patients with clostridial myonecrosis. Muscle necrosis accompanies loss of arterial supply and sensation to the distal tissue in patients with proximal limb infection. In these patients, infection may have originated from the lower intestinal tract and spread via retroperitoneal facial planes. A high level of suspicion and prompt systemic therapy coupled with urgent surgical excision of devitalized tissue when possible improves outcomes. In select cases, adjuvant treatment with intravenous hyperimmunoglobulin and ribosomal active antimicrobials for arresting exotoxin production may also be attempted. In severely neutropenic patients with refractory neutropenia, recombinant myeloid growth factors and G-CSF primed donor-derived granulocyte transfusions need further evaluation and are presently used as salvage therapy. However, it is critical to emphasize that this disease progresses with lightening speed; therefore, any ameliorative measures and antimicrobial therapy require to be administered in most urgent manner.

Summary

Aerobic Gram-negative bacilli continue to be important pathogens in cancer patients with and without neutropenia, and are still associated with substantial morbidity and mortality despite significant advances in supportive care. Although the overall frequency of infections caused by these organisms has declined, the spectrum of organisms causing infection has expanded. The most important development impacting the treatment of Gram-negative bacterial infections

has been the emergence of antimicrobial resistance. Some organisms such as Acinetobacter species, Klebsiella species, *P. aeruginosa*, and *S. maltophilia* have developed multiple mechanisms of resistance leaving very limited treatment options when they are isolated. This problem will continue to challenge clinicians for the foreseeable future, despite the implementation of antimicrobial stewardship and infection control programs. Bacteroides and other anaerobic Gram-negative bacteria may lead to life-threatening infections, presence of refractory hypotension, high-grade fever, acute intravascular hemolysis and disseminated coagulation, and early onset of tissue necrosis are the hallmark of this devastating disease. A high level of suspicion and prompt systemic therapy coupled with surgical excision of devitalized tissue when possible may improve outcomes.

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Chapter 37
Listeriosis and Nocardiosis

Heather E. Clauss and Bennett Lorber

Abstract The bacterium *Listeria monocytogenes* infrequently causes illness in the general population. In some groups, however, including pregnant women, newborns, elderly persons, and those with impaired cell-mediated immunity, including many cancer patients, it is an important cause of invasive disease, particularly bacteremia, meningitis, encephalitis, and brain abscess. *Nocardia* species are aerobic, Gram-positive, branching, filamentous, bacterial rods, which are most often found in the environment in soil, water, and vegetable matter. The key host defense against developing nocardiosis is cell-mediated immunity; the humoral immune response offers little protection. These organisms are considered opportunistic pathogens, causing infection in patients with impaired cell-mediated immune response, including patients with lymphoreticular neoplasia, organ transplantation, HIV/AIDS, diabetes mellitus, and alcoholism. In particular, there is a well-documented association between nocardiosis and chronic granulomatous disease (CGD). In this chapter, we present a detailed review of epidemiology, clinical presentation, and management of these opportunistic infections in immunosuppressed patients with cancer.

Keywords Listeriosis • Nocardiosis • Brain abscess • Meningitis • Bacteremia • Antibiotic therapy • Refractory disease

Listeriosis

Introduction

The bacterium *Listeria monocytogenes* infrequently causes illness in the general population. In some groups, however, including pregnant women, newborns, elderly persons, and

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those with impaired cell-mediated immunity, including many cancer patients, it is an important cause of invasive disease, particularly bacteremia, meningitis, encephalitis, and brain abscess [1–3]. Additionally, listeriae may cause other clinical syndromes, including in utero infection typically resulting in miscarriage or stillbirth, as well as focal infections of the eye, skin, heart valves, joints, liver, and spleen, and a self-limited febrile gastroenteritis [4].

L. monocytogenes is a small, Gram-positive rod that is facultatively anaerobic, nonsporulating, and grows readily on blood agar where it produces incomplete beta-hemolysis [5]. The bacterium exhibits characteristic tumbling motility at room temperature and, unlike most bacteria, grows well at refrigerator temperatures (4–10°C). In clinical specimens, the organisms may be gram-variable and may look like diphtheroids, cocci, or diplococci leading to misdiagnosis. The isolation of a "diphtheroid" from blood or CSF should always alert one to the possibility that the organism is really *L. monocytogenes*.

Pathogenesis

Human-to-human transmission of *L. monocytogenes* has not been reported aside from vertical transmission between mother and child and sporadic cross contamination in neonatal nurseries [6]. Most commonly, listeriae are transmitted via the ingestion of contaminated food. In mammals $\geq 10^9$ organisms are required for infection [7]. Alkalinization of the stomach with antacids, H_2 blockers, proton pump inhibitors, or the achlorhydria associated with advanced age may promote infection [8]. The incubation period for invasive disease (bacteremia, meningitis) is not well established, but evidence from cases related to specific ingestions points to a range from 11 to 70 days (mean 31 days) [9].

Once inside an enterocyte or macrophage, *L. monocytogenes* uses its major virulence factor, listeriolysin O, to escape from the phagosome [10]. Through other novel mechanisms, it then can move from cell to cell without entering the extracellular space, thus avoiding contact with

complement, antibodies, and neutrophils [11]. There is no increased frequency of listeriosis in those with deficiencies in neutrophil numbers or function, splenectomy, complement deficiency, or immunoglobulin disorders, the latter not surprising given that *L. monocytogenes* can be passed from cell to cell without being exposed to antibody.

Listeriae have a particular predilection for the central nervous system (CNS). Experimental data indicate that *L. monocytogenes* can use several different mechanisms to invade the CNS: (a) transportation of bacteria to the CNS within circulating leukocytes in a phagocyte-facilitated (Trojan horse) mechanism as described above, (b) via direct invasion of endothelial cells of the blood–brain barrier by blood-borne bacteria, or (c) via a neural route whereby bacteria are inoculated into oral tissues when abrasive food is chewed, followed by tissue macrophage phagocytosis of the bacteria making possible the invasion of cranial nerves [12]. In the latter case, bacteria move in a retrograde direction through the nerve axons, eventually reaching the CNS where they continue to spread intercellularly to the parenchyma.

Another important virulence factor for *L. monocytogenes* is the ability to scavenge iron. In vitro, iron enhances organism growth [13]. In animal models of listeria infection, iron overload is associated with enhanced susceptibility to infection and iron supplementation with enhanced lethality, whereas prolonged survival results from iron depletion [14]. Iron overload states are risk factors for listerial infection, and clinical correlates include outbreaks of listerial infection in patients receiving hemodialysis who have transfusion-induced iron overload and patients with hemochromatosis [9].

Epidemiology

L. monocytogenes is readily isolated from soil and decaying vegetation and has been found to be present in the feces of many mammals [15]. The organism has been isolated from the stool of ~5% of healthy adults [16]. Many foods are contaminated with *L. monocytogenes*; recovery rates of 15–70% have been found from raw vegetables, unpasteurized milk, fish, poultry, and meats [17]. Ingestion of listeriae must be a common occurrence. Numerous foodborne outbreaks have occurred with vehicles including unpasteurized soft cheeses, hot dogs, and deli-style ready-to-eat sliced poultry products. In October 2002, *L. monocytogenes* was found in sliced deli-style turkey meat, the ingestion of which produced illness in 54 patients in 9 states, resulting in the largest recall of meat ever in the United States (more than 30 million pounds of food products) [18].

The highest infection rates of invasive listeriosis are seen in adults >60 years of age and in infants <1 month old [19]. The rate of infection declines sharply between the ages of 1 and 11 months. Pregnant women account for approximately 27% of all cases of listerial bacteremia and 60% of cases in the 10–40-year age group. It is noteworthy, that although pregnancy is a clear risk factor for bacteremia, for unknown reasons, listerial meningitis is exceedingly rare during pregnancy unless a second risk factor, such as corticosteroid therapy, is present. Sixty-nine percent of nonperinatal infections occur in patients with impairments in cell-mediated immunity. Seemingly, normal persons may develop invasive disease, particularly those older than age 60.

The major risk factor for listeriosis is impaired cell-mediated immunity whether due to a specific disease or due to immunosuppressive therapy. Specific risk factors for developing listeriosis include corticosteroid treatment, organ transplantation, hematologic malignancy, AIDS, pregnancy, liver failure, solid malignancy, diabetes, and age >60 [20]. Reports continue to be published on *L. monocytogenes* meningitis presenting as an opportunistic infection in AIDS [21] and as a complication of solid organ transplantation [22]. One new risk factor for listerial infection is the use of antitumor necrosis factor alpha (TNF-α) agents. Case reports describe listerial meningitis complicating infliximab treatment for Crohn's disease [23] as well as etanercept treatment for Still's disease [24]. An interesting basic science correlate of these clinical events is the observation that, in a murine model, TNF was found to play a crucial role in the intracerebral control of *L. monocytogenes* infection [25].

Major Clinical Syndromes

The species name derives from the fact that an extract of the *L. monocytogenes* cell membrane has potent monocytosis-producing activity in rabbits [26], but monocytosis is a very rare feature of human infection.

Infection in Pregnancy and the Neonatal Period

Pregnant women are prone to develop listerial bacteremia with an estimated 17-fold increase in risk [27]. Listeriae proliferate in the placenta in areas that appear to be unreachable by usual defense mechanisms [28], and cell-to-cell spread facilitates maternal–fetal transmission [29]. For unexplained reasons, CNS infection, a commonly recognized form of listeriosis in other groups, is extremely rare during pregnancy in the absence of other risk factors [27, 30]. Bacteremia is manifested clinically as an acute febrile illness, often accompanied by myalgias, arthralgias, headache, and backache. Twenty-two percent of human perinatal infections result in stillbirth or neonatal death; spontaneous abortion is common. Untreated bacteremia is generally self-limited, although if there is a

complicating amnionitis, fever in the mother may persist until the fetus is spontaneously or therapeutically aborted. Among women who have listeriosis during pregnancy, two thirds of surviving infants develop clinical neonatal listeriosis. Early diagnosis and antimicrobial treatment of the infected woman can result in the birth of a healthy infant [9, 27].

Similar to disease due to Group B streptococcus, neonatal infections manifest as early-onset sepsis with disseminated infection, typically in premature infants, or late-onset meningitis, typically in term infants who were healthy at birth.

Bacteremia

Bacteremia without an evident focus is the most common manifestation of listeriosis after the neonatal period [20]. Clinical manifestations are similar to those seen in bacteremia with other causes and typically include fever and myalgias; a prodromal illness with diarrhea and nausea may occur [9].

Central Nervous System Infection

The organisms that cause bacterial meningitis most frequently (*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae*) rarely cause parenchymal brain infections such as cerebritis and brain abscess. By contrast, *L. monocytogenes* has tropism for the brain itself, particularly the brain stem, as well as for the meninges [2, 3, 31]. Many patients with meningitis have altered consciousness, seizures, or movement disorders, or all of these, and truly have a meningoencephalitis.

Meningitis

In an active meningitis surveillance study [32], *L. monocytogenes* accounted for 20% of cases in neonates and 20% in those older than 60 years. Worldwide, *L. monocytogenes* is one of the three major causes of neonatal meningitis; is second only to pneumococcus as a cause of bacterial meningitis in adults older than 50 years; and is the most common cause of bacterial meningitis in patients with lymphomas [33], organ transplant recipients, or those receiving corticosteroid immunosuppression for any reason [9].

Clinically, meningitis caused by *L. monocytogenes* is usually similar to that due to more common causes [34, 35]; features particular to listerial meningitis are summarized in Table 37.1. Despite the name "monocytogenes," the CSF pleocytosis is more often neutrophilic than monocytic.

The first prospective study of meningitis due to *L. monocytogenes* recently was reported from the Netherlands [36]. In this nationwide cohort study of 30 adults, notable clinical

Table 37.1 Features particular to listerial meningitis as compared to more common bacterial etiologie.s (adapted from refs. [9, 34, 36])

Feature	Frequency (%)
Presentation can be subacute >24 h[a]	~60
Absense of stiff neck is more common	25
Movement disorders (ataxia, tremors, myoclonus) are more common	15–20
Seizures are more common	10–25
Fluctuating mental status is more common	~75
Focal neurologic findings are more common	35–40
Positive blood culture is more common	50–75
Cerebrospinal fluid (CSF)	
Positive Gram stain is less common	30–40
Normal CSF glucose is more common	>60
Mononuclear cell predominance is more common	~30

[a]May be several days or more and mimic tuberculous meningitis in ~10–30%

features of listerial meningitis included headache in 88%, nausea in 83%, and fever in 90%; but only 75% of patients had a stiff neck at the time of presentation. A focal neurologic deficit was present in 37% (many patients with meningitis have simultaneous infection of the brain parenchyma and truly have a meningoencephalitis). Only 43% had the classic meningitis triad of fever, neck stiffness, and change in mental status. At the time of presentation, 19 out of 30 patients had symptoms persisting for greater than 24 h, and 8 had symptoms for ≥4 days. Remarkable CSF findings included a median white blood cell count of 620 (range 24–16,003) and protein of 2.52 g/L. Spinal fluid Gram stain revealed a Gram-positive rod in only 28% of patients while blood cultures were positive for *L. monocytogenes* in 46% of patients. These data illustrate how difficult it can be to make a definitive diagnosis of listerial meningitis at initial presentation.

Mortality from listerial meningitis has variously been reported at 15% in a CDC active surveillance study [32], 27% in the Massachusetts General Hospital review [34], and 17% in the prospective study from the Netherlands [36]. In the last report, all deaths occurred within 3 days of being admitted to the hospital. Mortality is low (0–13%) for adults without serious underlying disease or immunosuppressive treatment [31].

Brain Stem Encephalitis (Rhombencephalitis)

An unusual form of listerial encephalitis involves the brain stem [37]. In contrast to other listerial CNS infections, this illness usually occurs in healthy adults. The typical clinical picture is one of a biphasic illness with a prodrome of fever, headache, nausea, and vomiting lasting about 4 days followed by the abrupt onset of asymmetric cranial nerve deficits, cerebellar signs, and hemiparesis or hemisensory deficits, or both. About 40% of patients develop respiratory failure. Nuchal

rigidity is present in about one half, and CSF findings are only mildly abnormal with a positive CSF culture in about one third. Almost two-thirds of patients are bacteremic. Magnetic resonance imaging is superior to computed tomography for demonstrating brain stem encephalitis [38]. Mortality is high, and serious sequelae are common in survivors.

Brain Abscess

Macroscopic brain abscesses account for about 10% of CNS listerial infections. Bacteremia is almost always present, and concomitant meningitis with isolation of *L. monocytogenes* from the CSF is found in 25–40%; both these features are rare in other forms of bacterial brain abscess [39]. Most cases occur in known risk groups for listerial infection [40]. Subcortical abscesses located in the thalamus, pons, and medulla are common; these sites are exceedingly rare when abscesses are caused by other bacteria. Mortality is high, and survivors usually have serious sequelae.

Listeriosis in Cancer Patients

Louria, in 1967 [41], was the first to point out the strong association between opportunistic listerial infection and malignancies, particularly Hodgkins disease being treated with corticosteroids. He described 18 cases of invasive listerial infection, 16 of which had underlying hematologic malignances. Twelve of the 18 cases were receiving corticosteroids at the time of diagnosis.

L. monocytogenes infection occurred in 94 patients during 1955–1997 at Memorial Sloan-Kettering Cancer Center; the incidence was 0.5 (1955–1966), 0.96 (1970–1979), and 0.14 (1985–1997) cases per 1,000 new admissions [33]. Eighty-five of ninety-four (90%) patients had listerial bacteremia, and 34/94 (36%) had evidence of intracranial infection. Listeriosis in these patients with cancer occurred most often in individuals receiving antineoplastic therapy for advanced or relapsed malignancy (77%), and systemic corticosteroids (68%). In another study, combined treatment with fludarabine and prednisone in patients with chronic lymphocytic leukemia decreased their CD4+ T-lymphocyte counts and increased their incidence of listeriosis; fludarabine alone was not associated with listeriosis [42].

In a comprehensive review [34] of 33 years experience at Massachusetts General Hospital with CNS listeriosis outside of the neonatal period and pregnancy, including a case series of 41 patients and 776 episodes from the literature, the most common predisposing factor for developing listerial meningitis was malignancy (both solid tumor and hematologic), occurring in 24% of patients.

At another institution, from 1990 to 2001, 34 cancer patients with listeriosis were reviewed and 20 (59%) had an underlying hematologic malignancy [43]. In 11 patients, listeriosis complicated bone marrow transplantation (BMT). Twenty-six patients received prior corticosteroids. Here again, bacteremia was the most common presentation of listeriosis (74%), followed by meningoencephalitis (21%). The rate of response to antimicrobial therapy was 79%, and no relapses were identified. Listeriosis contributed to death in 9 (75%) of the 12 patients who died. In the Memorial Sloan-Kettering study [33], 37 (39%) of the 94 patients died of listeriosis; in more than one third of deaths occurred within the first 48 h after *L. monocytogenes* cultures were obtained.

Another interesting relationship exists between listeriosis and cancer. Listerial endocarditis, not bacteremia per se, in an otherwise healthy person, may be an indicator of underlying gastrointestinal tract pathology, including colon cancer [44].

Diagnosis

The key to making a diagnosis of listerial infection and initiating early, appropriate treatment is knowing when it should be considered. CNS listeriosis should be a major consideration as part of the differential diagnosis in the following clinical settings:

1. Meningitis or parenchymal brain infection in:

   - Patients with hematologic malignancy, AIDS, organ transplantation, corticosteroid immunosuppression, or those receiving anti-TNF agents
   - Patients with a subacute presentation of meningitis
   - Neonates and adults >50 years of age
   - Those in whom CSF shows Gram-positive rods or is reported to have "diphtheroids" on Gram stain or culture

2. Simultaneous infection of the meninges and brain parenchyma.
3. Subcortical brain abscess.
4. Spinal symptoms in the setting of acute bacterial meningitis of uncertain etiology.
5. Fever during pregnancy, particularly in the third trimester.
6. Blood, CSF, or other normally sterile specimen reported to have "diphtheroids" on Gram stain or culture.
7. Foodborne outbreak of febrile gastroenteritis when routine cultures fail to identify a pathogen.

Diagnosis requires isolation of *L. monocytogenes* from a normally sterile site such as blood or CSF and identification through standard microbiologic techniques. Antibodies to listeriolysin O have proved useful during investigation of outbreaks of febrile gastroenteritis [45] but have not proved useful in invasive disease [46]. *L. monocytogenes* DNA in

CSF and tissue can be detected specifically by polymerase chain reaction (PCR) assays, though these have not proved to be useful clinically to diagnose invasive disease [47]. MRI is superior to CT for demonstrating parenchymal brain involvement, especially in the brainstem [37, 38].

Treatment

Many antimicrobials show in vitro activity against listerial isolates, but only a few agents have been proved clinically efficacious. Ampicillin has been the most widely used agent in the treatment of *L. monocytogenes* infections and generally is considered the preferred agent [2, 35]. Synergy has been demonstrated both in vitro and in animal models when an aminoglycoside is added to ampicillin or penicillin, and many authorities recommend the addition of an aminoglycoside to ampicillin for at least in the first week of treatment of CNS infection [9].

In the absence of a positive CSF Gram stain, initial therapy for bacterial meningitis in adults older than age 50 should include an antilisterial agent (either ampicillin or trimethoprim-sulfamethoxazole [TMP-SMX]). Due to the high affinity of *L. monocytogenes* for the CNS, meningitis doses of the chosen antibiotic should be used for all bacteremic patients, even in the absence of CNS findings, until the CSF is examined. An exception is bacteremia in pregnancy without another risk factor, since, in this group, CNS infection is almost never present. Relapses are reported in those with meningitis treated for less than 2 weeks; therefore, treatment for 3 weeks is recommended for all cases of listerial meningitis. Bacteremic patients with normal CSF may be treated for 2 weeks. Patients with brain abscess, cerebritis, or rhombencephalitis should be treated for at least 6 weeks and followed with repeated brain imaging studies. In cases of listerial brain abscess, surgical intervention may not be necessary; numerous case reports describe successful treatment with antimicrobial therapy alone.

In those with penicillin hypersensitivity, TMP-SMX is the treatment of choice and appears to be bactericidal and as effective as the combination of ampicillin and gentamicin. Cephalosporins have limited activity against listeriae. Many reports document treatment failures with cephalosporins, and patients have developed listerial meningitis while receiving cephalosporins for other reasons. Chloramphenicol has also been shown to have unacceptable failure and relapse rates and should not be used. Erythromycin and tetracycline have been reported to be effective, but are unreliable therapeutic options and should be avoided. Vancomycin has been successfully used in penicillin-allergic patients, but listerial meningitis has developed in patients being treated with vancomycin. Both imipenem and meropenem have also been used successfully to treat cases of listeriosis, but caution is advised because both drugs lower the seizure threshold, imipenem was less effective than ampicillin in a mouse model [48], and meropenem clinical failure has been documented [49].

In an animal model of listerial meningitis, the addition of rifampin to ampicillin was no better than ampicillin alone. While some newer quinolones and linezolid show good in vitro activity, clinical experience is mixed [50–52], and, to date, too limited to support recommending these antimicrobials.

Although adjunctive corticosteroids have become the standard of care in the initial management of bacterial meningitis, their value in listerial infection remains unknown. Listeriae use iron as a virulence factor; therefore, in patients with iron deficiency, it seems prudent to withhold iron replacement until treatment of infection is completed.

Prevention

Cancer patients with hematological malignancies and/or those on corticosteroids should be advised to avoid certain foods. People at high risk for listeriosis may choose to avoid soft cheeses. It is best to avoid foods from deli counters, such as prepared salads, meats, and cheeses. Those at risk who choose to eat these high-risk foods should be instructed to thoroughly cook them, avoid cross-contamination, and only refrigerate cooked perishable foods for short periods of time [53].

Except from infected mother to fetus, human-to-human transmission of listeriosis does not occur; therefore, patients do not need to be isolated.

Listerial infections are effectively prevented by TMP-SMX given as *Pneumocystis* prophylaxis to those on long-term corticosteroids [54].

Nocardiosis

Introduction

Nocardia species are aerobic, Gram-positive, branching, filamentous, bacterial rods, which are beaded appearing and stain variably with the modified acid-fast Kinyoun stain. They fragment into pleomorphic, rod-shaped, or coccoid pieces. Their relatively slow growth can result in the cultures being discarded before the colonies can be seen. Nocardia are found most often in the environment in soil, water, and vegetable matter.

The key host defense against developing nocardiosis is cell-mediated immunity; the humoral immune response offers little protection. These organisms are considered opportunistic pathogens, causing infection in patients with

impaired cell-mediated immune response, including patients with lymphoreticular neoplasia, organ transplantation, HIV/AIDS, diabetes mellitus, and alcoholism. In particular, there is a well-documented association between nocardiosis and chronic granulomatous disease (CGD) [55]. *Nocardia asteroides, N. farcinica, N. nova,* and *N. brasiliensis* are the most important causes of human infection.

Clinical Syndromes

Clinical syndromes caused by *Nocardia* species include nodular lymphangitis, systemic disease, pulmonary masses, nodules, infiltrates and cavities, and brain abscesses. Primary infection occurs via inhalation or direct inoculation of skin and soft tissues. Then, bloodstream dissemination can cause metastatic infection throughout the body, most commonly to the CNS. Sites of metastasis can include virtually any other anatomic site.

The most important site of primary infection is the lung. Common clinical symptoms include a subacute course (over days to weeks) of fever, cough, purulent sputum production, malaise, and dyspnea on exertion. Oxygenation is usually preserved at rest until disease has advanced. Chest radiograph findings can include focal or multifocal disease, nodules, or consolidations that can progress to cavities [56]. In one study from Spain, predisposing conditions for 31 pulmonary nocardiosis patients were transplantation (29%), HIV infection (19%), and treatment with steroids (64.5%) [57]. In this study, the median time to diagnosis was 42 days, and the mortality rate for pulmonary nocardiosis was 41 and 64% for disseminated nocardiosis.

In all cases of pulmonary nocardiosis, an MRI of the brain should be performed to evaluate for CNS infection. Like *L. monocytogenes*, *Nocardia* species have a particular tropism for the brain and spinal cord. CNS involvement is seen in 44% of cases of disseminated nocardiosis [58]. These lesions can be seen throughout the brain, and there may be meningitis with or without involvement of other portions of the brain. Clinical presentation is usually subacute to chronic, as with the pulmonary infection. One should consider brain biopsy for diagnosis in an immunosuppressed patient with a CNS lesion.

Nocardiosis in Cancer Patients

At M.D. Anderson Cancer Center between 1988 and 2001, 42 cancer patients were diagnosed with nocardiosis [59]. Twenty-seven patients (64%) had hematologic malignancies, and in 13 patients, nocardiosis complicated BMT. Patients had received steroids in 25 (58%) episodes of nocardiosis and had received chemotherapy within 30 days before the onset of nocardiosis in 10 (23%) episodes. Pulmonary nocardiosis was diagnosed in 30 of 43 cases (70%), while only one (2%) patient developed CNS nocardial infection. The mortality rate in this study was 60%.

In bone marrow transplant patients at one institution, the rate of nocardiosis was 1/554 (0.2%) among autologous BMT recipients and 5/302 (1.7%) in allogeneic BMT recipients from 1980 to 1994 [60]. Interestingly, three of the patients developed nocardiosis despite taking TMP-SMX for *Pneumocystis* prophylaxis. In a retrospective study of 27 patients with nocardiosis, 40% had taken TMP-SMX regularly prior to developing nocardiosis [61]. In another study of *Nocardia* infection in organ transplant recipients, 69% (24/35) of the case patients developed their infection while on TMP-SMX [62]. Clearly TMP-SMX is not protective against nocardial infections in patients the same way it is protective against listerial infections in the HIV positive population.

Diagnosis

The mainstay of diagnosing nocardiosis is to inform the laboratory that this diagnosis is being considered. The organism must be isolated from a clinical specimen, noting that *Nocardia* species are not common lab contaminants or oral flora. However, some patients with chronic lung disease can have transient nocardial carriage, which must be interpreted with caution. Often this diagnosis requires an invasive procedure such as a lung biopsy, skin biopsy, or brain biopsy. All biopsies should be evaluated by Gram stain, modified acid fast staining, culture, and pathology. Blood cultures for *Nocardia* species require prolonged incubation. The organism usually grows in 3–5 days.

Treatment

The mainstay of treatment of nocardiosis is TMP-SMX. High doses are used for patients with high disease burden or CNS disease. Second line therapy includes the combination of imipenem/cilastin and amikacin. Common recommendations for treatment include 3–6 weeks of intravenous therapy, followed by several months of oral therapy (1–3 months for nonimmunosuppressed and 6 months for immunosuppressed). In patients with CNS infection, a minimum of 12–15 months would be appropriate [63]. A recent report describes six cases of nocardiosis successfully treated with linezolid [64].

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Chapter 38
Antibacterial Distribution and Drug–Drug Interactions in Cancer Patients

Ursula Theuretzbacher and Markus Zeitlinger

Abstract Cancer as such does not impact distribution of antimicrobials; however, various pathophysiological changes in cancer patients may do so. Neutropenia, cachexia, hypoproteinemia, and effusions are common situations in cancer patients that may change the concentrations of antibiotics in blood and tissues. Such changes should be taken into account and dosage regimens adapted accordingly. As the therapeutic management of cancer patients becomes more complex, drug–drug interactions in oncology are of particular importance. Commonly used antibiotics that are most likely involved in drug–drug interactions are rifampin and its derivates, the macrolides erythromycin and clarithromycin, the fluoroquinolone ciprofloxacin, and trimethoprim/sulfonamide combinations. Knowing the interaction profiles of individual agents and potential outcomes of the interaction allows healthcare providers to minimize the risk.

Keywords Pharmacokinetics • Pharmacodynamics • Distribution • Antibiotics • Interaction • Cancer

Infections are a frequent complication of patients suffering from cancer. Cancer can affect all age groups and may, due to its often progressive character, transform a person with intact organ functions into a critically ill patient. Therefore, the cancer patient requiring antimicrobial therapy might have normal physiology or, in the later stage of the disease, may suffer from severe impairment of body functions including organ dysfunction, sepsis, and shock. In its first part, the present chapter reviews the basic concepts of pharmacokinetics of antibiotics applicable to all patients and then focuses on specific alterations frequently observed in cancer patients.

As patients suffering from cancer often receive a wide range of concomitant medication coincident with their need for antimicrobial therapy, the second part of the chapter will discuss relevant drug–drug interactions in cancer patients requiring antibiotic treatment.

Introduction to Pharmacokinetics

Pharmacokinetics describes the concentration-time profile of a drug within the organism. Its main determinants are dose, absorption, distribution, metabolism, and elimination. Absorption, distribution, metabolism, and elimination (ADME) in turn are influenced by the chemical properties of a drug and by the demographic and physiological characteristics of the organism, resulting in complex organism–drug interactions. Pharmacokinetic profiles can be characterized by a range of pharmacokinetic parameters like bioavailability, plasma protein binding, maximum concentration, area under the concentration-time curve, elimination half life, clearance, and volume of distribution.

- Bioavailability (BA, %): describes the percentage of a drug which becomes systemically available when the drug is not given intravenously.
- Plasma protein binding (PPB, %): is the percentage of a drug which is bound to circulating proteins in plasma. Only the free, unbound fraction (f) of an antibiotic is microbiologically active [1, 2].
- Maximum concentration (C_{max}, g/liter): highest drug concentration achieved during the dosing interval.
- Area under the concentration-time curve (AUC, g·hour/liter): describes the exposure of an organism toward a drug over time.
- Volume of distribution (Vd, liter): represents an approximate value for the distribution of a drug within the organism. As the volume of distribution is calculated only by use of the concentration-time profile in plasma, it is often referred to as "apparent" volume of distribution. This "apparent" volume of distribution can exceed the total volume of the body considerably, indicating accumulation of a drug outside the blood stream. Although volume of distribution can help to describe the penetration

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of a drug from the central compartment (blood) into tissues, the volume of distribution cannot be used to define exact concentrations in individual organs, tissues or tissue compartments.

- Elimination half life ($t_{1/2}$, hour): amount of time during which the concentration in plasma has decreased by 50%.
- Clearance (cl, liter/hour): volume of the body which is totally cleared from drug in a given time. It is an estimation of the potency of the body to eliminate a certain drug from the body. The pharmacological clearance is the sum of renal and extrarenal (mainly hepatic, transdermal and pulmonal) clearance.

Pharmacokinetic/Pharmacokodynamic Indices for Anti-Infective Therapy

Physicians are interested in clinical success or side effects of an antimicrobial agent rather than in its pharmacokinetic profile. In order to predict outcome of an antibacterial treatment by pharmacokinetic parameters they have to be related to pharmacodynamic action by use of pharmacokinetic/pharmacodynamic (PK/PD) indices. The pharmacodynamic action of an antimicrobial is commonly described by the minimal inhibitory concentration (MIC), i.e., the concentration of an antimicrobial drug at which no visible growth of a given bacterial strain can be observed after 24 h of incubation in a growth medium.

fC_{max} and $fAUC_{0-24}$ (free drug AUC over 24 h) to MIC-ratio (fC_{max}/MIC, $fAUC_{0-24}$/MIC) as well as the time (t) the free concentration of the antibiotic exceeds the MIC (ft>MIC) are considered as most important PK/PD indices [3–7]. The relevance of each of these indices for predicting antimicrobial and clinical outcome varies for different antimicrobial classes. For instance, beta-lactam-antibiotics, display a "time-dependent" pattern of activity and ft>MIC is considered most predictive for outcome. For these antibiotics frequent doses, sometimes even continuous infusions lead to best clinical results with lowest side effect rates [8]. In contrast, for antibiotics, such as aminoglycosides, fluoroquinolones, and most other antibiotics, the free drug AUC_{0-24}/MIC-ratio is a good predictive index and determines the antimicrobial efficacy. To achieve fast bacterial eradication, these antibiotics should be given infrequently in high doses as long as this is not precluded by toxicity. However, for aminoglycosides high doses administered once daily not only improves efficacy but also reduces side effects, as aminoglycoside uptake into body cells is saturable and its vestibulotoxicity and nephrotoxicity is higher with a more fractionated dose than with a single bolus [9]. Therefore, PK/PD considerations
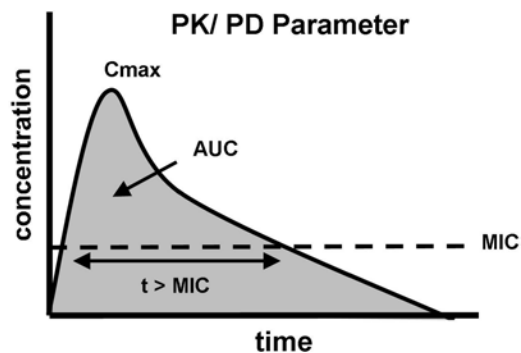
Fig. 38.1 PK/PD Parameters of antimicrobial therapy. Area under the concentration- time curve (AUC) and maximal concentration (C_{max}) divided by the minimal inhibitory concentration (MIC, C_{max}/MIC, AUC/MIC) as well as the time period during which the concentration of the antibiotic exceeds the MIC (t>MIC) of a pathogen are considered the most important PK/PD parameters. The unbound concentration of the drug should be used

provide good tools for optimizing the dosage of antibiotics by minimizing toxicity, maximizing activity, and limiting resistance development. Figure 38.1 depicts PK/PD indices for antimicrobial therapy.

Impact of Cancer on Pharmacokinetics of Antimicrobial Agents

Impairment of organs that are responsible for elimination of drugs like kidney or liver impacts the pharmacokinetics of drugs. Although this is also the case for patients suffering from cancer, information on dosing in case of renal or hepatic impairment can be obtained from the approved label of each antibiotic and will not be further discussed here. Nevertheless, it should be noted that, as a general rule, antibiotics with narrow therapeutic index should be used cautiously after cytotoxic chemotherapy has been employed, e.g., aminoglycoside therapy after treatment with cisplatin [10].

Usually, antimicrobial breakpoints are based on pharmacokinetic parameters obtained from blood of healthy subjects during early phases of drug development. However, it is known that disease may alter pharmacokinetics of antibiotics. A wide range of data is available regarding the change of pharmacokinetics of antibiotics in sepsis and septic shock, a disease which alters various functions of the human body [11–13]. Therefore, regulatory authorities like EMA (European Medicines Agency) and FDA (Food and Drug Administration) recommend evaluating pharmacokinetics of antimicrobials in the target population rather than in healthy volunteers [14, 15]. If available, concentrations obtained from the target site of infection should be considered as basis for PK/PD models in order to predict efficacy

of antimicrobial therapy in the relevant clinical population [16].

Cancer as such does not impact pharmacokinetics of antimicrobials; however, various pathophysiological changes in cancer patients may do so. For instance, underexposure to an antibiotic might occur because of increased volume of distribution due to oedema, ascites or pleural effusion [17, 18]. In this case ascites or other pathological compartments with high content of water can be considered part of the central compartment when effects of distribution for hydrophilic agents like beta-lactams or aminoglycosides are studied [19, 20]. Another case type is effusions with high protein content. These may bind antibiotics followed by slow back distribution into systemic circulation and prolongation of overall elimination half life [21].

Neutropenia and Neutropenic Fever

Neutropenia is a typical complication of cytostatic chemotherapy. Patients with neutrophil count below 1,000 cells per µl have an increased susceptibility to infection [22]. Antibiotics are frequently prescribed both for treatment of neutropenic fever and prophylactically to reduce the risk of infection.

Beta-lactams show important changes in pharmacokinetics associated with neutropenia [22]. A substantially shorter elimination half life and decreased AUCs of ceftazidime were found in patients with neutropenia compared to healthy elderly patients [23]. Similarly, cefpirome, imipenem, and meropenem showed marked increase in the volume of distribution in patients with neutropenia compared with controls [24, 25]. Due to these pharmacokinetic changes, continuous administration preceded by a loading dose was advocated for beta-lactams in this indication [22].

Various aminoglycoside pharmacokinetic changes have been reported in patients with neutropenia. Amikacin, gentamicin, and tobramycin all showed increased volume of distribution and faster clearance compared to healthy volunteers resulting in reduced average peak concentrations [26–28]. In order to maintain therapeutic drug concentrations, dose adjustment was necessary in some cases [29]. Similar to other indications, once daily administration seems to be comparable or even superior to more frequent dosing of aminoglycosides. An increase of serum creatinine was delayed and less pronounced when amikacin was given once daily compared to once every 8 h [30]. Likewise, higher efficacy and lower toxicity was observed for once vs. thrice daily administration of tobramycin to neutropenic children [31]. Nowadays, the once daily administration of aminoglycoside in neutropenic patients is an accepted dosage regime.

Similar to other antimicrobial classes, increased volume of distribution and clearance was observed for vancomycin and partially also for teicoplanin in neutropenic patients [22, 32, 33]. For vancomycin, substantially reduced elimination half life was reported. Careful monitoring of serum trough concentration is recommended for glycopeptides.

Daptomycin, measured after a standard dose of 6 mg/kg, achieved mean AUC levels in patients with neutropenic fever that where modestly below those observed for healthy volunteers (521 vs. 730 µg×h/mL) [34, 35]. However, high interindividual differences among patients (SD 524 µg×h/mL) seem to be clinically more important. Therefore, in case of a poor clinical response of an individual patient despite in vitro antimicrobial activity of an antibiotic, changed pharmacokinetics should be considered and appropriate modification of the antimicrobial regime initiated.

In contrast, the pharmacokinetics of linezolid in patients with neutropenia did not differ from the overall compassionate use population [36]. We have only insufficient data regarding fluoroquinolones for this indication.

Surgery

Another typical indication for antimicrobial treatment in cancer patients is surgical antimicrobial prophylaxes in elective tumor surgery. Similar to sepsis postsurgical conditions, especially after major interventions, might negatively impact penetration of antibiotics into tissue as demonstrated for piperacillin or levofloxacin [37, 38]. Thus, antibiotics with wide therapeutic index in high doses should be preferred in surgical indications.

Oral bioavailability of ciprofloxacin was reduced in surgery patients on the first days after the intervention. Therefore, intravenous administration of ciprofloxacin in the early period after elective surgery is required [39].

Cachexia

Cachexia may have significant impact on pharmacokinetics of antibiotics [40]. While descriptive pharmacokinetic data are in line with the well documented difficulties for correct dosing of cytostatic chemotherapy in cachectic patients [41, 42], the pathophysiological mechanism is still speculative. Possible changes may include:

- Cachexia and the frequently associated parenteral nutrition may influence the fluid and electrolyte status of the patient [43]. For gentamicin and amikacin, parenteral nutrition resulted in enhanced volume of distribution and reduced peak serum concentration, possibly impacting

effectiveness of these "concentration dependent" antibiotics [26, 43, 44]. Due to the high interindividual differences of aminoglycoside pharmacokinetics, serum concentrations should be frequently measured and the dosing regimen individualized as quickly as possible [26].

- Impact on the absorption process of orally administered drugs: bioavailability of cefuroxime in a cachexia rat model was lower than in animals with normal diet, possibly due to changes in the small intestine [40]. As bioavailability always might be impacted by severe disease, cancer patients with life-threatening infections should get parenteral antibiotics.
- Impaired protein status in malnourished or cachectic patients may lead to higher volume of distribution and modified pharmacodynamic action as unbound drug may more readily diffuse into tissues and interact with targets. In addition, low protein binding might also lead to enhanced renal clearance. As previously discussed, oedema, ascites, and pleural effusion may result in retention of drug in these pathological compartments.
- On the other hand, severely malnourished patients may exhibit decreased oxidative metabolism and reduced glomerular filtration rate leading to higher concentrations in plasma than expected from healthy subjects [42, 45].

These to some extend contradictory mechanisms might explain why cachexia may result both in increase of plasma levels as observed for metronidazole and tetracycline [45, 46] or reduction of AUC as demonstrated for cefuroxime and aminoglycosides [40, 43, 44]. Severity of cachexia, as well as the class of antibiotic influences the pharmacokinetics of the antimicrobial agent.

Hypoproteinemia

Independent of cachexia, changes in protein binding might affect the pharmacokinetics of antibiotics. Numerous conditions such as age (e.g., in neonates), body temperature, plasma pH or a variety of diseases like uremia, hepatitis, hypoalbuminemia, acute viral hepatitis, cirrhosis, nephrotic syndrome, and epilepsy may lead to significant decreases in protein binding [47]. Albumin has the highest binding capacity of all human serum proteins for drugs including antimicrobials [48, 49]. Other proteins which might bind antibiotics include transferrin, lactoferrin, and alpha-1-acid Glycoprotein [50].

Particularly in cases of highly bound antibiotics, pharmacokinetics might be modified by hypoalbuminuriaemia. For ceftriaxone, a cephalosporin that binds strongly to albumin, a significant increase of volume of distribution was detected in steady state conditions. AUC values for free ceftriaxone in these patients were twice as high as for healthy volunteers suggesting favorable antimicrobial activity in these patients.

Table 38.1 Protein binding of selected antimicrobials[a]

Quinolones	Ciprofloxacin: 20–30%
	Levofloxacin: 30–40%
	Moxifloxacin: 40%
Glycopeptides/lipopeptides	Vancomycin: 55%
	Teicoplanin: 90–95%
	Daptomycin: 90%
Aminoglycosides	Gentamicin: <10%
	Amikacin: <10%
	Tobramycin: <10%
Cephalosporins	Cefuroxime: 50%
	Cefotaxime: 25–40%
	Ceftazidime: 10%
	Ceftriaxone: 85–95%
	Cefepime: 19%
Penicillins	Amoxicillin: 17–20%
	Ampicillin: 15%
	Piperacillin: 30%
Carbapenems	Imipenem: 20%
	Meropenem: 2%
	Ertapenem: 92–95%
	Doripenem: 8%
Tetracyclines	Doxycycline: 82%
	Tigecycline: 71–89%
Other	Fosfomycin: 0%
	Linezolid: 31%

[a] Obtained by the respective approved label

On the other hand, for drugs with a narrower therapeutic range but high degree of protein binding (>80%), hypoproteinemia can increase toxicity.

Even in case of antibiotics with low protein binding like amikacin, decreased protein concentration in serum might have a clinical impact. Hypoalbuminemia has been identified as an independent risk factor for aminoglycoside nephrotoxicity [51]. In patients with serum albumin below 3.0 g/dL, amikacin obtained higher peak concentrations and produced significantly more episodes of nephrotoxicity than in patients with albumin level above 3.0 g/dL [51]. However, hypoproteinemia doesn't influence pharmacokinetics or toxicity of all antibiotics as has been shown via experiments in sheep with artificial hypoproteinemia when dosed with minocycline, a tetracycline with moderate protein binding [52]. Table 38.1 provides a list of percentage of protein binding for important parenteral antibiotics.

Tissue Infections

Although the majority of PK/PD models are based on plasma concentrations, many infections do not occur in blood but in tissues. Antimicrobial agents need to reach appropriate target site concentrations to exert their antimicrobial effect. The site

of tissue infections, i.e., the location of the bacteria, and thereby the target site of antimicrobial action is represented by the interstitial fluid of tissues and other body fluids such as pleural fluid, bronchial fluid, epithelial lining fluid, middle ear fluid, and cerebrospinal fluid [53]. Homogenized whole tissue samples do not represent the site of infection because bacteria and antibiotics are not distributed evenly in the distinct pharmacological compartments of a tissue. The concentrations of antimicrobials vary in the compartments of complex organs like lung or brain [54, 55] due to the anatomy and the histological structure of the organ and to the physicochemical properties of the drug. For example in case of respiratory tract infections, concentrations may be measured by sampling of sputum, respiratory secretions, pleural fluid, and surgical collection of whole lung tissue and bronchial mucosa, each yielding concentrations for different compartments of the respiratory system and yet none of these may provide adequate information about the site of infection [55, 56]. As for pneumonia, bacteria indeed may be located in the epithelial lining fluid, bronchial mucosa, the interstitial fluid of lung, and in rare cases even within cells. Depending on the pathogen and its location, concentrations of antibiotics should be determined at this infection site and correlated to the pharmacodynamic parameter (usually MIC). In case of pneumonia the site of infection due to extracellular pathogens (pneumococci and most other clinically relevant microorganisms) is the intraalveolar space (epithelial lining fluid) and in later phases, the interstitial fluid of the lung tissue. If intracellular pathogens (Mycobacterium tuberculous, Chlamydia pneumonia) are involved, an additional infection site is represented by alveolar macrophages [55, 57]. The measurement of target site concentrations remains an ongoing challenge, due to methodological obstacles and ethical limitations.

It has been shown that interstitial tissue fluid to plasma equilibration of antimicrobial agents may significantly differ between healthy volunteers and critically ill patients [11, 12, 38]. In addition, high interindividual differences in interstitial tissue fluid penetration should be expected among septic patients, since hemodynamics and treatment strategies substantially vary within this patient group [58, 59]. These high interindividual differences in interstitial tissue fluid penetration might explain the observation that antimicrobial therapy lacks efficiency in some patients, despite documented in vitro susceptibility of the causative pathogen showing that the same pathogen is eradicated in patients with more favorable penetration to the site of infection. Strategies to identify patients with a high risk of not reaching sufficient levels at the site of infection are necessary steps in the successful antimicrobial therapy of critically ill patients [60]. In several in vitro and animal studies, inappropriate target site concentrations have been associated with the development of bacterial resistance [3, 61, 62].

Malignant effusions as a potential factor influencing systemic pharmacokinetics of antimicrobials were discussed above. However, in cancer patients malignant effusions frequently also manifest as a site of potential infections and thus a target site of antimicrobial therapy. Ascites and pleural effusions will be briefly discussed as two important representatives of artificial compartments susceptible to infections.

Pleural effusion usually impacts systemic pharmacokinetics less than ascites due to its smaller amount of fluid. For example, plasma pharmacokinetics of cefoxitin, a cephalosporin used as prophylaxis in surgery, was not impacted by pleural effusion [63]. Although accumulation outside the blood stream is not typical for hydrophilic antimicrobials like cephalosporins, concentrations in pleural fluid for cefuroxime and cefoxitin were comparable or even higher than in systemic circulation [20, 63]. For ascites, maximum concentrations of cefuroxime, a cephalosporin with moderate protein binding, clearly exceeded corresponding concentrations in plasma [20]. In contrast, in pleural effusion fluid concentrations of the highly protein bound ceftriaxone were below than those observed in plasma throughout the dosing interval [21, 64].

Thus, high protein binding seems to prevent sufficient penetration of antibiotics into ascites or pleural fluid. The high amount of protein frequently present in malignant ascites or pleural effusions may additionally reduce the antimicrobial activity at this site. Use of antibiotics with moderate protein binding (below 50%) seems more advisable in this indication.

Drug–Drug Interactions in Cancer Patients

As the therapeutic management of cancer patients becomes more complex, drug interactions in oncology are of particular importance [65]. Unrecognized interactions can lead to overdosing, undertreatment, or potentiation of side effects, each with severe clinical consequences. In addition to cytotoxic chemotherapy, most patients receive supportive care agents such as pain, emesis, depression, seizures, and anti-infective medications. Older oncology patients with multiple comorbidities require medications for comorbid conditions such as cardiovascular, gastrointestinal, and rheumatological diseases and are, thus, at even higher risk of drug–drug interactions [66, 67]. Such medications are most commonly implicated in interactions in cancer patients [68]. According to a study in older oncology outpatients with an average of three comorbid conditions and an average of nine prescription and nonprescription drugs, cardiovascular drugs were the most common medications [69]. Increased availability of over-the-counter (OTC) medication and herbal supplements for self-treatment can all contribute to polypharmacy in this

population and is often unknown to the healthcare team [70]. Hanigan et al. reported that 96% of patients took prescription drugs within 3 days prior to chemotherapy, 71% reported taking OTCs, and 69% reported supplement use. On average, patients took 9.6 concomitant medications 3 days prior to chemotherapy. Many of these concomitant medications alter drug metabolism and/or disposition [71]. Additionally, some patients are also exposed to duplicate medications, most often corticosteroids, proton pump inhibitors, or benzodiazepines [68].

Concerning polypharmacy and the chronic use of multiple drugs in patients with cancer and polymorbidities, very limited data exist on their frequency and clinical consequences [72]. To quantify the frequency of potential drug interactions unrelated to chemotherapy in cancer patients and to define risk factors for such interactions, Riechelmann et al. analyzed patient charts [73]. In this study population, 63% of screened patients were at risk for at least one potential drug interaction during their stay and only 25% of these potential interactions were rated as minor. According to this study, the most frequent combinations encountered with potential for interaction were opioids with benzodiazepines, Selective Serotonin Reuptake Inhibitors (SSRI) with opioids, Non-Steroidal Anti-Inflammatory Drugs (NSAID) with low-molecular-weight heparin, dexamethasone with phenytoin, and omeprazole with benzodiazepines. However, not all potential interactions resulted in clinically significant effects [73]. As expected, the potential interactions were found to be more likely to occur in patients with longer hospital stays, those receiving a higher number of medications, and those with risk factors that are more likely to be encountered among older patients with cancer.

For drugs in clinical development, the potential for interactions is usually assessed early on using suitable in vitro probes and careful selection of interacting drugs for early in vivo studies [74]. However, the interaction profile of a drug may not be fully understood until several years after it is introduced onto the market. Given the reality of polypharmacy and the number of clinical problems faced by patients with cancer, a proportion of cancer patients with drug interactions are likely to have serious complications. In addition to case reports, clinical data needs to be generated to raise awareness of this increasingly common problem that may further reduce quality of life of cancer patients.

Management of Potential Drug Interactions

Potential harmful consequences of polypharmacy can only be averted if the mechanism and principles of drug interactions are understood and recognized in advance. As there are

rarely well designed clinical studies available, prediction of potential drug interactions must be made based on what is known about the interactive properties of drugs. Being aware of the potential for interactions allows healthcare providers to minimize risk by applying the following principles:

- Avoiding unnecessary polypharmacy including OTC, food additives, and herbs.
- Identifying patients at high risk for developing interactions (i.e., narrow therapeutic range of the medication, decreased hepatic and/or renal function).
- Knowing the interaction profiles of individual agents and potential outcomes of the interaction: Decreased effects may mean a loss of therapeutic effect. Increased effects may mean increased effectiveness, or increased side effects.
- Weighing the risk of the interaction against the benefits of concurrent therapy to the patient.
- Determining if the interaction applies to all drugs within the same class or just a subset.
- Selecting an alternative agent with less interaction potential.
- Actively managing potential interactions by alteration of administration schedules, dosage adjustments, additional patient monitoring.

Usually, antibiotics are used empirically for therapy of acute signs of infections but also used prophylactically for reducing the risk of febrile neutropenia. In general, antibacterial agents – with the exception of rifamycin derivates (rifampin, rifabutin, rifapentine), macrolides (erythromycin and clarithromycin), fluoroquinolones (ciprofloxacin), and trimethoprim/sulfonamide – are rarely implicated in major clinically relevant drug interaction problems. In patients without concurrent tuberculous or other mycobacterial infections, rifamycin derivates and macrolides usually can be avoided. Ciprofloxacin is commonly prescribed for cancer outpatients [75]. The risk of interactions in patients who receive multiple medications needs to be considered including additional monitoring that should be followed if ciprofloxacin can't be avoided. Cotrimoxazole (trimethoprim/sulfamethoxazole) can usually be substituted with other antibiotics for treatment of common bacterial infections.

Principles of Drug Interactions

Drug interactions can be pharmaceutical (in vitro inactivation), pharmacokinetic, or pharmacodynamic. Pharmacodynamic drug interactions may increase or decrease the clinical effects of drugs even without altered drug concentrations. The risk of side effects also may greatly increase.

Drug interactions may have wanted or unwanted effects. The following review will focus on unwanted pharmacokinetic

interactions between antibiotics and other drugs that are commonly used in cancer patients. The most important and most common pharmacokinetic drug interactions involving antibiotics are altered drug absorption, inhibition or induction of metabolism, and inhibition of renal excretion. Transporter-based interactions have been increasingly documented such as the inhibition or induction of transport proteins, such as P-glycoprotein (P-gp) by erythromycin [76]. Overlapping substrate specificities with cytochrome P450 enzymes result in complex and sometimes perplexing pharmacokinetic profiles of multidrug regimens [77]. The effects of an interaction may take from several hours to several days to become clinically significant and may last beyond the time period of concurrent administration.

Interactions Affecting Drug Absorption

A number of mechanisms can affect drug absorption including a change in gastric pH, chelation, ion exchange, change in gastric motility, alteration in gut flora, modulation of transport proteins, or inhibition of intestinal enzymes. Indeed bioavailability may be reduced by as much as 90%. Examples in the field of antibiotics include chelation of tetracyclines and quinolones with di-and trivalent cations such as the aluminum or magnesium in antacids, calcium in dairy products, highly buffered drugs, ferrous sulfate in iron replacement agents, and multivitamin preparations with zinc. To prevent chelation of intravenous formulations, quinolones should not be coadministered in the same IV line with a multivalent cation, e.g., magnesium. Even if the impaired absorption and reduced concentration of oral quinolones as a consequence of this absorption interaction is not clinically apparent, it may influence the development of resistance. In a study with over 3,000 patients who received a course of oral levofloxacin, coadministration of divalent, or trivalent cation-containing compounds was significantly associated with subsequent identification of a levofloxacin-resistant isolate [78].

Many absorption interactions can be managed by adjusting the administration schedule to avoid the loss of drug activity. The recommended separation time required between the quinolones and chelating agents varies from two (ciprofloxacin, levofloxacin) to 4 h (moxifloxacin) with antibiotics administered first.

Interactions Based on Drug Metabolism and Transporters

The majority of reported drug interactions are due to drug metabolism inhibition. Cytochrome P450 enzymes are essential for the metabolism of many medications. Although this class has more than 50 enzymes, six of them metabolize 90% of drugs, with the two most significant enzymes being CYP3A4 and CYP2D6 [79]. Individual isoforms are capable of interacting with a wide range of diverse substrates and some CYPs have overlapping substrate specificities. In general, drugs that are metabolized via the cytochrome P450 system should alert clinicians and demand special considerations. Clinicians are encouraged to have a sound knowledge on drugs that behave as substrates, inhibitors, or inducers of CYP3A4, and take proper cautions and close monitoring for potential drug interactions when using such drugs [80, 81].

- P-glycoprotein is a transmembrane protein that controls concentrations of endogenous and exogenous substances across cell membranes by functioning as cellular efflux pumps [82]. Genetic variability in the expression and production of P-gp has a significant effect on the bioavailability and site distribution of many drugs. Both CYP3A4/CYP3A5 and the transporter P-gp are frequently coexpressed in the same cells and share a large number of substrates and modulators. The disposition of such drugs is thus affected by both metabolism and transport.

- A cytochrome P450 inhibitor is any drug that inhibits the metabolism of a cytochrome P450 substrate. Such inhibition may cause reduced metabolism of the substrate and thus increased concentrations with the potential of toxic effects. Clinically, the most important CYP3A4 inhibitors include:

  - HIV protease inhibitors (e.g., ritonavir)
  - Macrolide antibiotics (e.g., erythromycin, clarithromycin)
  - Antidepressants (e.g., fluoxetine and fluvoxamine)
  - Calcium channel blockers (e.g., verapamil, and diltiazem)
  - Antifungals (e.g., ketoconazole, itraconazole)
  - H_2-receptor antagonists (e.g., cimetidine)
  - Steroids and their modulators (e.g., gestodene and mifepristone)
  - Several herbal and dietary components (e.g., grapefruit juice)

- A cytochrome P450 inducer increases the amount of P450 enzyme and may accelerate clearance of a substrate which causes decreased and potentially ineffective concentrations. Typical potent inducers are rifampin, phenytoin, phenobarbital, and ritonavir. St John's Wort induces the expression of P-gp and decreases concentrations of P-gp substrates [83]. The effect of a cytochrome P450 inducer can occur within 24 h up to 1 week after administration [84]. Induction persists for several days.

- A cytochrome P450 substrate is any drug that is metabolized by one or more of the P450 isoenzymes (Table 38.2). A drug that is metabolized by cytochrome P450 isoenzymes becomes vulnerable to interference by other drugs that are either inhibiting or inducing the enzyme system.

Table 38.2 Selected substrates of cytochrome P450 isoenzymes (modified from [76, 77, 79, 80, 84, 107–109])

CYP 3A4 substrates	*CYP 2C8 substrates*
Antiarrhythmics, benzodiazepines, immune modulators, HIV protease inhibitors, antihistamines, calcium channel blockers, statins, macrolides, itraconazole and ketoconazole	NSAIDs, oral antidiabetic drugs, warfarin, statins, paclitaxel, digoxin, amiodarone, verapamil, zopiclone, voriconazole
CYP2C9 substrates	*CYP2C19 substrates*
NSAIDs, oral hypoglycemic agents, angiotensin II blockers, celecoxib, fluvastatin, naproxen, phenytoin, sulfamethoxazole, tamoxifen, torsemide, warfarin	Proton pump inhibitors, antiepileptics, amitrptyline, clomipramine, clopidogrel, cyclosphosphamide, progesterone, voriconazole
2B6 substrates	
Bupropion, cyclophosphamide, ifosfamide	

Table 38.3 Influence of antibiotics on Cytochrome P450 isoenzymes and P-gp [76, 105, 108–110]

Drug	Inhibitor	Substrate	Inducer
Rifampin/Rifabutin			3A4, 2C8, 2C9, 2C19, 2B6, P-gp
Erythromycin/Clarithromycin[a]	3A4, P-gp	3A4	
Ciprofloxacin[b]	1A2		
Trimethoprim	2C8		
Sulfamethoxazole	2C9		

[a]Simultaneous reversible and irreversible inhibition effects should be taken into account in a reaction mixture of substrate and multiple inhibitors of CYP3A4 [111]. Azithromycin is not an inhibitor of CYP450 and may be used as substitute if clinically warranted

[b]Levofloxacin and moxifloxacin are weak or no inhibitors of CYP1A2 and may be used as substitute if clinically warranted

Sex differences in cytochrome P450 activity have been reported with increased CYP3A4 activity in women compared with men and CYP1A2 activity being lower in women than in men [85]. Differences in the expression of these enzymes may directly produce interindividual differences in susceptibility to compounds whose toxicity is modulated by these enzymes [86]. Genetic variations can cause a patient to metabolize drugs abnormally fast, abnormally slow, or not at all. Genetic polymorphism is the most common cause of the interindividual differences in metabolism of CYP2D6 substrates. CYP2C9 shows high interethnic and intraethnic variability.

In actual clinical situations with patients taking multiple drugs, clinicians should always consider that metabolic inhibitory effects may be additive and they should be aware that the extent of drug interactions is difficult to predict based on pharmacokinetic studies only examining two drugs [87].

Commonly used antibiotics that are most likely involved in cytochrome P450 mediated drug interactions are: rifampin and its derivates, the macrolides erythromycin and clarithromycin, the fluoroquinolone ciprofloxacin, and trimethoprim/sulfonamide combinations (Table 38.3).

Significant Interactions by Drug Class

Rifamycin Derivates

Rifampin (=Rifampicin) has numerous well documented clinically significant drug interactions associated with its use and new interactions continue to be found. Whenever clinicians prescribe therapy with either rifampin or rifabutin, it is prudent to screen for drug interactions and adjust dosages carefully [87]. Rifampin is indicated as component of a three-drug regimen for treatment of tuberculous and for the treatment of asymptomatic carriers of Neisseria meningitidis and Staphylococcus aureus (not approved in the U.S.). Among the group of antibiotics, rifampin is the most potent inducer of the CYP450 isoenzymes and may cause severe drug interactions if these enzyme induction properties are not considered. The three commercially available rifamycin derivatives – rifampin, rifabutin, and rifapentine – have different CYP3A induction potencies. In vitro data demonstrate that rifampin is the most potent, followed by rifapentine and rifabutin [88]. Although rifabutin interactions are generally less dramatic than rifampin interactions, many are clinically relevant. Rifamycins are essential drugs for the treatment of active tuberculous. In HIV-TB coinfected patients, rifamycins are associated with significant drug interactions with protease inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, maraviroc, and raltegravir. Consultation with an HIV expert is recommended [89].

Rifampin induces the isoenzymes CYP3A4, 2C8, 2C9, 2C19, 2B6 and the transporter P-gp [90]. When coadministered with drugs that are substrates of the same enzymes, their metabolism may be accelerated resulting in lower concentrations and less efficacy. The enzyme induction effect is only gradually reduced over a 1–2-week period, and sometimes longer, when rifampin is discontinued. Important CYP 3A4 substrates are listed in Table 38.2. A possible drug interaction between linezolid and rifampin was described by Gephart et al., which resulted in decreased serum linezolid levels, probably caused by increased P-gp expression [91].

Erythromycin/Clarithromycin

Erythromycin and clarithromycin, commonly used macrolides, are known to be substrates and inhibiters of CYP3A4 and P-gp. Complex interactions with potentially serious toxic consequences are known to be caused by this group of antibiotics when combined with CYP 3A4 substrates (Table 38.2). Concurrent administration of clarithromycin and rifabutin has been observed to cause an increased risk of side effects due to elevated rifabutin concentrations [92]. Also, rifampin reduces clarithromycin concentrations. If alternatives are available, erythromycin, and clarithromycin should not be prescribed as part of complex drug regimes.

Ciprofloxacin

The fluoroquinolone ciprofloxacin is an inhibitor of CYP1A2. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (e.g., theophylline, caffeine, tizanidine, clozapine) results in increased plasma concentrations of the coadministered drug (or coffee) and could lead to clinically significant side effects from the coadministered drug [93].

Other quinolones, such as levofloxacin or moxifloxacin, do not show inhibition of CYP1A2 and, thus, don't interfere with theophylline metabolism [94]. Levofloxacin and ciprofloxacin have shown weak inhibition of CYP2C9 in vitro [95], but clinical consequences are not clear.

Ciprofloxacin has been implicated in adverse drug interaction with methotrexate by mechanisms other than CYP450 metabolism [96]. Potential changes of the absorption of ciprofloxacin when extensive mucositis is present have been suspected. Ciprofloxacin also has been shown to interact with phenytoin, sulfonylurea glyburide, cyclosporine, warfarin, and NSAIs [93].

Moxifloxacin and Other Quinolones

Iron and antacids reduce the bioavailability of moxifloxacin (s. above).

Linezolid

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase with interaction potential with adrenergic and serotonergic agents as well as with large amounts of foods or beverages with high tyramine content [97]. It has been well documented in the literature that the combination of linezolid and serotonergic antidepressants such as fluoxetine may cause serotonin syndrome [98, 99].

Aminoglycosides

Due to the ototoxic and/or nephrotoxic potential of aminoglycosides, the concurrent or serial use of other ototoxic or nephrotoxic agents such as vancomycin, amphotericin B, colistin, viomycin, or, cisplatin should be avoided because of the potential for additive effects. They also should not be given concurrently with potent diuretics, such as ethacrynic acid and furosemide as they may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Vancomycin

Similar to aminoglycosides, the concurrent administration of potentially neurotoxic and/or nephrotoxic drugs should be avoided or carefully monitored. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions.

Beta-Lactam Antibiotics

Probenecid inhibits the renal excretion of beta-lactam antibiotics that are mainly eliminated by renal tubular secretion and its use may result in increased and prolonged concentrations.

- Amoxicillin/Clavulanate: The incidence of rashes increases substantially when given with concurrent allopurinol.
- Piperacillin/Tazobactam: The prolongation of the neuromuscular blockade of vecuronium when used concomitantly with piperacillin is not considered clinically important [100]. Case reports suggest that coadministration of methotrexate and piperacillin may reduce the clearance of methotrexate and cause significant increased concentrations of methotrexate [101, 102].
- Carbapenems: Limited data indicates that meropenem may reduce serum levels of valproic acid resulting in impaired seizure control [103]. Concomitant administration of ganciclovir during imipenem therapy should be avoided because of increased risk of seizure.

Metronidazole

Limited or modest interactions with ethanol have been reported for drugs such as metronidazole. Although the possible disulfiram-like reaction (also suggested to be a toxic serotonin syndrome) when metronidazole is combined with alcohol is rare, patients should still be informed about this potential interaction [104].

Trimethoprim-Sulfamethoxazole

Trimethoprim inhibits CYP2C8 and may increase concentrations of CYP2C8 substrates such as NSAIDs, oral antidiabetic drugs, warfarin, statins, paclitaxel, digoxin, amiodarone, verapamil, and zopiclone [105]. Sulfamethoxazole inhibits CYP2C9 and may increase concentrations of CYP2C9 substrates such as warfarin, oral antidiabetic drugs, phenytoin, NSAIDs, angiotensin II receptor blockers [105].

Tigecycline

Tigecycline is not metabolized by the cytochrome P450 system. Nevertheless, concomitant administration with warfarin increases the concentrations of warfarin and monitoring of prothrombin time is advisable [106].

In conclusion, in most cases, significant interactions with antibiotics that are included in complex therapeutic regimes for cancer patients can be avoided by prudent use of antibiotics, substituting rifampin, erythromycin, clarithromycin, ciprofloxacin, and cotrimoxazol by similar antibiotics or by carefully monitoring patients when potential interactions are anticipated.

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Chapter 39
Mycobacterium tuberculous Infection

Michael Glickman

Abstract This chapter will outline various aspects of the diagnosis and treatment of Tuberculous in the cancer patient. We provide a general framework to understand the relationship between immunosuppressive cancer therapy and TB risk. We also review information about the risk of TB with specific malignancies and their treatment. It is our intention that this chapter will provide a cancer-specific supplement the information contained in national guidelines about TB therapy.

Keywords Cancer • Tuberculous • Disseminated disease • Cellular immune defect • Immunotherapy • Chemotherapy • Lymohoma • Solid tumors • Purin analog • Alemtuzumab • Graft versus host disease • T-cell defect

Introduction

In this chapter, we will review Tuberculous in cancer patients. Rather than reviewing basic tenets of Tuberculous diagnosis and therapy, which have been extensively reviewed and codified in national guidelines [1–3], we will focus on aspects of Tuberculous specific to cancer patients. In many cases, specific clinical data about TB in cancer patients is lacking. Therefore, clinical decisions about TB risk, prevention, and therapy in the cancer patient must be made based on extrapolation from data in HIV infected patients, assessment of cancer related immunosuppression, and drug interactions specific to cancer patients. Modern therapy of cancer is in rapid evolution and therapies that suppress immune function are myriad and constantly evolving. We hope to provide a clinical framework to manage Tuberculous in cancer patients that draw on presently available clinical data and can also adapt to the evolution

of cancer therapy over time. To understand the epidemiology of TB in cancer patients, it is necessary to examine both the underlying immune response to TB infection and the impact of various cancers and their therapies on the immune system.

Basic Biology of *M. tuberculous* Infection

Mycobacterium tuberculous is rod shaped bacterium that is acid fast when stained with carbol fuschin and decolorized with acid alcohol. *M. tuberculous* and other slow growing pathogenic mycobacteria have a remarkably slow doubling time in vitro, 18–24 h under optimal conditions. *M. tuberculous* is an obligate human pathogen that passes from person to person by inhalation of aerosolized droplets containing viable bacteria. There is no known environmental reservoir or fomite transmission. Upon deposition in the lung through inhalation, *M. tuberculous* replicates inside host macrophages and can disseminate to almost any organ during early infection. This primary infection is usually asymptomatic in an immunocompetent adult. With the onset of antigen specific immunity and associated granuloma formation, *M. tuberculous* replication is controlled such that bacterial numbers are reduced to uncultivatable levels. The detectable remnants of this primary infection are a delayed type hypersensitivity reaction to *M. tuberculous* antigens, assayed as Tuberculin reactivity or positive Interferon gamma release assay. Some patients will also develop pulmonary scarring and/or lymph node calcification which can be detected on chest radiography but is not specific for TB infection.

The hallmark of *M. tuberculous* infection of humans is latency. Although human immunity is highly effective at controlling *M. tuberculous* during primary infection, in many patients viable bacteria resist complete elimination and persist in a state of clinical and microbiologic dormancy. Latent infection can reactivate to cause active disease, sometimes after decades of latency, but often within the first 5 years after primary infection. In most adult

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patients, reactivation of latent *M. tuberculous* infection does not occur with a defined defect in immunologic function, although defects in cellular immunity clearly raise the risk of reactivation (discussed further below). Clinical tuberculous in adults is usually the result of reactivation of latent infection and many of our efforts to control Tuberculous in the general population and in cancer patients is based on the detection of latent infection, its elimination by preventative therapy, and surveillance for reactivation in those at risk.

States of Susceptibility to Tuberculous Infection

Control of mycobacterial infection depends on CD4 T cells and cytokines typical of Th1 polarization. This conclusion is based on findings in both humans and mice that establish the critical importance of Interferon gamma, Interleukin 12, and Tumor Necrosis Alpha in defense against mycobacterial infection.

Much of the world receives BCG vaccination at birth. The BCG vaccine is a live, attenuated strain of *Mycobacterium bovis* that is the world's most widely administered vaccine. Although BCG is generally well tolerated, its wide administration has revealed a small subset of the population with inherited susceptibility to mycobacterial infection, manifest by disseminated or progressive localized BCG infection after vaccination. This syndrome, called Mendelian Susceptibility to Mycobacterial disease (MSMD), also confers susceptibility to severe infection with other mycobacteria of low virulence. Characterization of patients with MSMD has defined pathways of antimycobacterial immunity. The mutations that cause MSMD are in either of the two interferon gamma receptors, the signal transduction cascade downstream of the IFN-gamma receptor, the IL-12 cytokine gene, or its receptor [4, 5]. These patients confirm that Th1 immunity is critically important for defense against mycobacterial infection. Experiments using mice deficient in Interferon gamma, TNF, and CD4 T cells confirm these conclusions [6]. Further support for the importance of CD4 T cells and their cytokines on mycobacterial immunity comes from HIV infected patients, who have dramatically elevated rates of reactivation Tuberculous compared to immunocompetent controls [7–9]. Further evidence for the importance of TNF in human antimycobacterial immunity comes from the high rates of Tuberculous in patients receiving therapeutic antibodies that neutralize TNF. In contrast, deficiency of humoral immunity does not seem to predispose patients to Tuberculous.

Cancer and Its Therapy that Produce Deficiencies in Antimycobacterial Immunity

This background provides a framework for understanding the risk of Tuberculous in patients with cancer. Cancer, or cancer therapies, differ widely in the degree and type of immunosuppression that they produce. These differences have significant implications for predicting TB risk. Cancer or its therapy that depletes functional CD4 T cells or impairs their function should confer increased higher risk for TB reactivation than cancers or therapies that deplete only neutrophils or antibodies. For this reason, hematologic malignancies, which impair T cell immunity, should be associated with a higher risk of reactivation Tuberculous than solid tumors that do not specifically impair T cell immunity in the absence of therapy. Similarly, therapeutic interventions that specifically impair T cell function should confer the greatest risk of Tuberculous. Since there is no environmental reservoir of *M. tuberculous*, the chance of either reactivation TB or progressive primary TB after exposure is proportional to the incidence of Tuberculous in the community. In fact, abundant observational data demonstrates that TB rates with cancer or its therapy are proportional to TB prevalence in the surrounding population.

Risk of Tuberculous with Specific Cancers and Cancer Therapies

Several observational studies have examined rates of Tuberculous in cancer patients. The most recent such series examined all cases of Tuberculous at Memorial Sloan Kettering Cancer Center from 1980 to 2004 [10]. The overall rate of microbiologically confirmed Tuberculous was 55/100,000 persons, a rate somewhat higher than the rate recorded in New York City over the same time period. When stratified according to cancer type, hematologic malignancy conferred the highest risk (Hodgkins disease 204/100,000, acute leukemia 120, Non-Hodgkins lymphoma 231) with a lower rate in solid tumors. Among solid tumors, the highest rate of TB was seen in head and neck cancer (135/100,000), a finding that is consistent with earlier studies from MD Anderson and MSKCC [11, 12]. Importantly, when compared to TB rates in the general population, the rate of TB for solid tumor patients born in the US, excluding head and neck cancer, was not higher than rate of the surrounding population. Similar conclusions can be drawn from a review of 30 cancer patients with TB over 10 years from MD Anderson cancer center. Of the 30 TB cases, 19 had hematologic malignancy. Of the 11 solid tumor patients, 4 had head and neck cancer [13].

The impact of birth origin on TB in cancer patients is significant, paralleling the epidemiology of Tuberculous in the United States. Across all tumor types, foreign born cancer patients have TB rates 3–7-fold higher than US born patients[10]. Taken together, these studies indicate that among cancer patients, hematologic malignancy confers the greatest risk of Tuberculous, followed by Head and Neck cancer, and then other solid tumors. It is unclear from this data whether risk of TB is associated with the tumor itself or its treatment.

Bone Marrow Transplantation

Both autologous and allogeneic bone marrow transplantation confer substantial immunosuppression and are often complicated by a wide variety of infections. Allogeneic BMT generally confers a more lasting defect in T-cell function due to measures used to prevent Graft versus host disease (T-cell depletion, pharmacologic immunosuppression) or GVHD itself. Multiple studies have examined rates of Tuberculous following BMT. In a questionnaire based review of mycobacterial infection at European transplant centers, the rate of Tuberculous was 0.09% for autologous and 1.05% for allogeneic transplants [14]. In a series of 8,013 BMTs in Spain, a country with one of the highest rates of Tuberculous in Western Europe (30/100,000), the rate of TB was 101 cases/100,000 patients per year with the rate in allogeneic transplants twice that of autologous transplants. Compared to the rate of the general population, TB was not more common in autologous transplant patients, but occurred in allogeneic patients 3 times as frequently [15]. In both of these European studies, Tuberculous was a late infectious complication, occurring a median of 181 [14] and 324 [15] days after transplant with 8/20 [14] and 4/20 [15] cases presenting with extrapulmonary disease. In a series of 304 allogeneic transplants from India, a high TB incidence country, there were 9 TB cases (2.3%). All of these patients were receiving glucocorticoids for GVHD and five of these cases had disseminated Tuberculous [16]. In a series of 577 allogeneic transplants at Memorial Sloan Kettering Cancer Center, 4 (0.69%) developed Tuberculous, all of whom were foreign born [17]. These studies indicate that Tuberculous is more common in allogeneic transplant patients than autologous patients and that the rate in allogeneic transplants often exceeds the rate in the general population. It is reasonable to conclude that allogeneic BMT patients have an elevated risk of TB, though the risk may vary among regions, and could be considered for screening and prophylaxis (discussed below).

Pharmacologic Cancer Therapy and TB Risk

An increasingly broad array of small molecule and biologic agents are used in the therapy of human malignancy. Many of these agents suppress T cell function or deplete T cell numbers, thereby placing patients at increased risk for infections that require intact T cell function for protection, including Tuberculous. In this section, we will review the risk of Tuberculous that is conferred by these agents.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that binds CD52. Alemtuzumab is FDA approved for salvage therapy of chronic lymphocytic leukemia (CLL), but is also used for therapy of refractory autoimmune disease and to prevent GVHD in allogeneic bone marrow transplantation. CD52 is a surface protein expressed on a wide variety of leukocytes including T cells, B cells, monocytes, and NK cells. As such, Alemtuzumab causes broad immunosuppression that includes T cell depletion that can last 6 months to 1 year after administration. Alemtuzumab has been associated with scattered cases of active Tuberculous when used for bone marrow transplant, hematologic malignancy, and solid organ transplantation. In most reports in the literature, the rates of Tuberculous are low and it is not clear that the incidence is increased by Alemtuzumab compared with alternative therapies or the malignancy itself [18–21]. The highest documented incidence of Tuberculous after Alemtuzumab therapy comes from a series of 27 patients in Hong Kong [22], a high incidence TB area. Seven (26%) developed tuberculous, all but one within 4 months of therapy with Alemtuzumab. In contrast, a British study found only 3/357 cases of TB in Alemtuzumab treated leukemia patients [23], a rate not clearly different from the underlying rate in the hematologic malignancy population. Although these observations are not controlled, they suggest that the risk of TB after Alemtuzumab may depend upon the incidence of latent tuberculous in the treated population and targeted screening and treatment may be reasonable in higher risk patients.

Purine Analogs

Purine nucleoside analogs such as Fludarabine and 2-Chlordeoxyadenosine are commonly used as therapy for CLL, hairy cell leukemia, and in conditioning regimens for allogeneic bone marrow transplantation. The agents

produce myelosuppression, including lymphopenia, which can last 1 year from the last administration. In addition to depleting T cell numbers, Fludarabine may also cause functional T cell dysfunction by depleting STAT-1 protein [24], which is required for signal transduction downstream of the Interferon gamma receptor. Thus, purine analogs produce both CD4 T cell depletion and dysfunction. Accordingly, a wide variety of infections have been reported after purine analog therapy including Pneumocystosis, Listeriosis, and reactivation herpesvirus infections, all of which require an intact T cell arm for defense [25]. In a review of 917 patients with hematologic malignancies in Brazil, there were 24 cases of TB. Multivariate analysis of risk factors for development of active Tuberculous included malnutrition, corticosteroids (OR 5.32), and Fludarabine (OR 6.08) [26]. In contrast, in a retrospective review of 18 patients with hairy cell leukemia in Hong Kong, 12 of whom received 2-CDA, there were three cases of Tuberculous. Only one of these cases was in a 2-CDA treated patient [27]. In summary, purine analogs are potent T cell immunosuppressants. The limited clinical data available indicates that they may increase risk for Tuberculous, although the data are not definitive.

Temozolamide

Temozolamide is an oral alkylating agents used in the therapy of glioblastoma and melanoma. This agent produces prolonged and severe CD4 T cell depletion that confers risk of infection. For example, when given to melanoma patients at a dose of 75 mg/m^2, CD4 counts progressively dropped below 200 cells by week 16–20. After two cycles, 64% had CD4<200 [28, 29]. Although such severe CD4 depletion would be predicted to increase rates of TB reactivation, there is only a single case report of TB in a Temozolamide treated patient [30].

TNF Inhibitors

Biologic agents that neutralize Tumor Necrosis Factor confer significant risk of reactivation Tuberculous [31]. Although these agents have not found wide use in cancer therapy, they may find a future role as adjunctive therapy of graft versus host diseases in allogeneic bone marrow transplantation. Early trial of these agents for this purpose have shown some activity [32] and, if they become more widely used, surveillance for reactivation Tuberculous will be warranted as the incidence of active TB after these agents is elevated 4–90-fold depending on comparator group [33, 34].

Diagnosis of Latent Tuberculous in Patients with Cancer

Present strategies for prevention of Tuberculous are based on the identification of people at increased risk, screening for latent TB infection (LTBI) in these populations, and administration of preventative therapy. Having reviewed the risk of TB in different populations of cancer patients, we will now review the use of newer diagnostic tests for LTBI in the cancer population. Recently, assays have become available that use antigen stimulated interferon gamma release (IGRA) from lymphocytes to detect LTBI. These assays use the *M. tuberculous* antigens ESAT-6 and CFP-10 to stimulate peripheral blood lymphocytes to produce Interferon gamma, which is detected by ELISA. Since ESAT-6 and CFP-10 are encoded by genes present in the RD-1 region of the *M. bovis* and *M. tuberculous* chromosomes, which is deleted in BCG, BCG vaccinated patients have negative IGRAs in the absence of true exposure to *M. tuberculous*. As such, these assays are clearly more specific than tuberculin skin testing in BCG vaccinated patients and are potentially useful to determine whether LTBI is present in a PPD positive, BCG vaccinated individual [35]. Their sensitivity for detecting LTBI is likely similar to tuberculin skin testing, although this conclusion is difficult in the absence of a gold standard test to detect LTBI [35]. In contrast to the well validated clinical risk of reactivation conferred by PPD conversion, the risk of active Tuberculous in IGRA positive patients has not been determined. The IGRA marketed under the tradename Quantiferon gold detects soluble Interferon gamma by ELISA. T-spot TB, a similar test that detects IFN-gamma release by ELISPOT, used previously in Europe, was approved for use in the United States in 2008. IGRAs have been recommended by the CDC as a suitable replacement for the PPD in all situations where the PPD is used to diagnose LTBI [36]. As with PPD testing, IGRA positivity is likely to be affected by immune status. Limited clinical data is available about the performance of IGRA in immunosuppressed patients [35, 36]. Additionally, limited clinical data is available about the use of IGRA in cancer patients to diagnose LTBI. The most likely use of these at present would be to screen for LTBI in a cancer patient at high risk for LTBI and reactivation (discussed above) who is PPD positive and BCG vaccinated. A positive IGRA in this circumstance would prove LTBI and make the patient a candidate for preventative therapy. The test is unlikely to be useful in the assessment of a patient with undiagnosed progressive pulmonary infiltrates requiring hospitalization, just as a PPD test is not useful in this setting. A negative IGRA would not be helpful as the sensitivity of these assays in this patient population is unknown [36]. The role of IGRAs in the diagnosis of LTBI is in rapid evolution and more data about their performance in the cancer population will hopefully be forthcoming.

Guidelines for TB Prophylaxis in Cancer Patients

A basic tenet of Tuberculous control is to detect latent infection by tuberculin skin testing in patients at increased risk for reactivation and to administer preventative therapy. This approach is based on large clinical trials demonstrating increased risk of active Tuberculous in patients with positive PPD or radiographic evidence of old TB and reduction of this risk by Isoniazid preventative therapy [37, 38]. As discussed above, many risk factors for reactivation of latent disease have been identified, most prominently HIV infection, gastrectomy, and end-stage renal disease. This paradigm has been extended to apply to certain malignancies that carry an increased risk of Tuberculous. Table 39.1 presents a compilation of relative risk of Tuberculous according to various malignant and nonmalignant risk factors. As presented above, US born solid tumor patients (except head and neck cancer) do not appear to have an increased risk of TB compared to the general population. Patients with hematologic malignancy and head and neck cancer do carry an elevated risk, which is greater in foreign born cancer patients. As a result, the 2000 CDC guidelines for targeted tuberculin testing only identify head and neck cancer and leukemia/lymphoma [2] among cancers as conditions conferring an increased risk of TB. This data supports the CDC recommended screening strategy for LTBI in these populations with a cutoff of 10 mm for Leukemia/Lymphoma/Head and neck cancer [2], although some authors have recommended a cutoff of 5 mm [10]. The PPD positivity cutoff for hematopoietic stem cell transplant patients is 5 mm with prophylactic therapy recommended for HSCT patients either exposed to a source case or with a positive tuberculin skin test [3]. There is also data to suggest that administration of Alemtuzumab, Purine analogs, and Temozolamide would increase a patient's risk of reactivation Tuberculous from known latency. Increased surveillance for reactivation disease and administration of preventative therapy in these patients for PPD positivity is a reasonable strategy.

Table 39.1 Relative risk of TB by clinical condition

Clinical risk factor	Relative risk	PPD cutoff (mm)	Reference
HIV	35–162	5	[2, 7–9]
ESRD	10–25	10	[2]
Gastrectomy	2–5	10	[2]
Hematologic malignancy	8–72	5	[10, 44]
Autologous BMT	1	5	[15]
Allogeneic BMT	3	5	[15]
Head and neck cancer	5–22	10	[10, 44]
Solid tumor US born	Approximately 1	15	[10]

Therapy of Tuberculous in Cancer Patients

The antimicrobial agents used for preventative therapy of latent Tuberculous or treatment of active disease do not differ between cancer and noncancer patients. We will not reiterate these regimens as they are the subject of multiple national guidelines. Several aspects of TB therapy in the cancer patient deserve special emphasis. No controlled clinical trials have been performed specifically in cancer patients with Tuberculous. However, recommendations for HIV patients do differ from immunocompetent TB patients, providing some guidance for management of the immunosuppressed cancer patient. These differences are in the regimens used for the continuation phase of therapy due to concerns about emerging drug resistance and treatment failure. For example, in noncavitary pulmonary disease with a negative sputum smear after the 2 month induction phase, once weekly Isoniazid/Rifapentine can be given to immunocompetent patients to complete 6 months of therapy[1]. This regimen is not recommended in HIV infected patients due to high rates of Rifamycin resistant TB in patients who relapse [39]. Similarly, in HIV patients with CD4 < 100, twice weekly regimens are not recommended due to rifamycin resistance in relapsed patients [40]. Extrapolating this data to the cancer population, it is reasonable to avoid once weekly and twice weekly continuation regimens in cancer patients whose immunosuppression affects CD4 T cells, such those which hematologic malignancies, Allogeneic BMT, or pharmacologic agents that reduce T cell function or number. In these patients, the regimen for the continuation phase should be either 3× per week or daily INH/Rifampin. For Solid tumor patients, standard continuation phase regimens can be used, based on susceptibility testing. For all patients, including cancer patients, the induction regimen does not change and initially includes four drugs (INH, Rifampin, PZA, Ethambutol) until susceptibilities are known.

Important Drug Interactions Relevant to Cancer Patients

Rifampin is a cornerstone of chemotherapy for active tuberculous and therapy of active tuberculous in cancer patient is likely to include this agent. Rifamycins have many significant drug interactions, some of which potentially impact drugs likely to be encountered in the cancer patient. Rifampin induces the metabolism of opiates and therefore lowers the effective levels of opiates. As such, initiation of Rifampin therapy can precipitate painful crises in cancer patients receiving opiates for pain. Careful attention to pain control is necessary when Rifampin is initiated. Rifampin also induces

the metabolism of cyclosporin, leading to diminished immunosuppressive effect and elevated risk of GVHD when used in Allogeneic bone marrow transplant. Judgment about the use of Rifampin in the treatment of tuberculous in patients who require one of these medications must be made in conjunction with the patient's oncologist. If dose adjustment in the interacting agent is possible and levels can be monitored (i.e., cyclosporine, Tacrolimus) then Rifampin therapy may be possible. Rifabutin offers a suitable therapeutic alternative to Rifampin [41, 42] and may offer more favorable drug interaction profile for some agents, as has been recommended in therapy of Tuberculous in HIV patients taking protease inhibitors (CDC HIV). If no drug monitoring is available and alternative cancer agents are not available or indicated, a nonrifampin containing TB regimen may be used. This decision has major therapeutic consequences as regimens without rifampin require extension of therapy to 12–18 months, as recommended by national guidelines [43].

Summary

Diagnosis and treatment of TB in the cancer patient is likely to undergo substantial changes in the future. Tuberculous infection remains a significant worldwide health problem with a large reservoir of latent disease. As the array of immunosuppressive cancer therapies expands and are administered to populations with high rates of LTBI, the chance of active Tuberculous in cancer patients is likely to increase. Controlled trials are badly needed to assess the relative risk of TB and its optimal management in the cancer population. As is the case for Tuberculous across all patient groups, new antimicrobials that will allow shortening of TB regimens to less than 6 months are badly needed.

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Chapter 40
Nontuberculous Mycobacterial Infections

Amar Safdar

Abstract The spectrum of nontuberculous mycobacterial infections has changed. Improved understanding of the immunopathogenesis of slow growing mycobacerial disease has been accompanied by a higher number of cases in patients with or without cancer. In recent years, difficult-to-treat infections due to rapidly growing mycobacteria are on the rise, this may in part reflect newer molecular identification methods; however, rise in susceptible immunosuppressed patient population and frequently used indwelling prosthetic devices are also important contributors in this trend. Despite resistance to a number of available antimicrobials, newer agents may provide the much-needed treatment options for high-risk cancer patients with nontuberculous mycobacterial infection-disease.

Keywords Rapidly growing mycobacteria • Slow growing mycobacteria • Lady Windermere syndrome • Interferon gamma defect • *Mycobacterium avium* intracellulare

Antimycobacterial Immune Defense

Intact reticuloendothelial system provides the bases of innate immune defense against the invading virulent *Mycobacterium tuberculous* as well as most nonvirulent environmental mycobacterial species other than *M. tuberculous.* However, it is the adaptive cellular immune response that provides effective containment and elimination of intracellular mycobacteria residing within the mononuclear cells [1]. All components of T-lymphocytes including $\gamma\delta$ cells play a role, although CD4 cells are the dominant $\alpha\beta$ lymphocytes that provide the backbone of host's immune response against mycobacterial infections [2, 3]. Interferon gamma (IFN-γ) is the most important proinflammatory cytokine secreted by primed T-helper type-1 (T$_H$1) lymphocytes, which activates fixed tissue macrophages, recruits peripheral mononuclear cells to the site of infection, and sets in the stage for granuloma formation [4]. The granuloma serves as (a) physical barriers for mycobacterial propagation, (b) promotes unfavorable oxygen and micronutrient deficient environment, and (c) most importantly, creates a milieu in which various components of the immune cells and extracellular cytokines and chemokines interact to enhance effector cell-mediated mycobacterial cell death [5, 6].

The delayed-type hypersensitivity reaction against the invading mycobacterial infection on one hand is critical in effective containment of infection and on the other, via calcification of granulomas, large quantities of caseation necrosis and formation of pulmonary cavities paradoxically enables the intracellular mycobacteria to evade host's immune surveillance [7]. The cytokine that plays important role in antimycobacterial immune defense cascade other than IFN-γ includes interleukin 12, T-cell-derived tumor necrosis factor alpha, and the expending family of TNF-related immunoactive peptides [8–10].

Immunologic Susceptibility to NTM Disease

The host's immune defects in the light of earlier discussion, mostly involve dysregulation of cellular adaptive immune response. A complicated cascade of events is set into effect following exposure to mycobacterial antigens, and organism-specific antigen primed T-cell at the infection site orchestrates events leading to cell death of these intracellular pathogens.

Defects in the protagonist T$_H$1 cytokine, IFN-γ may either present as deficiency in cytokine production, or dysfunctional cytokine (IFN-γ) specific receptor have been shown to increase difficult-to-treat systemic mycobacteriosis [11–14]. Furthermore, defects in postreceptor cytoplasmic signaling pathways such as signal transducer and activator of transcription 1 (STAT1), signal transducing molecule, nuclear factor (NF)$_\kappa\beta$ essential modulator (NEMO), ancillary cytokines including interleukin-12, interlukine-18, and tumor necrosis factor-α can also lead to enhanced risk of severe disseminated infection due to otherwise nonvirulent mycobacteria [1, 4, 8].

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At present, the consensus to undertake an immunologic work is warranted in only non-HIV-infected patients who present with refractory mycobacterial infections or those with recurring pulmonary nontuberculous mycobacteriosis (NTM) with no known underlying predisposing conditions. The NTM even though is due to organisms with low-disease causing potential, is often in the setting of immunologically intact host, and an extensive immunologic work up at present may not yield clinically relevant information. Although in a select group of patients with unresponsive mycobacterial infection, immunologic investigation may be undertaken in consultation with infectious diseases.

Clinical Characteristics

The scope of mycobacterial infections due to species other than *M. tuberculous* has expanded near-exponentially in the recent past. In part this increase is attributed to the widespread availability of newer molecular identification methods [15]. Most nontuberculous mycobacteria are ubiquitous in nature, and unlike *M. tuberculous* person-to-person spread is not a significant means of transmission of infection. Isolation of these low-virulence mycobacteria is not uncommon and in immunologically intact, nonsusceptible individual they frequently represent either laboratory/environmental contaminant or nondisease-associated colonization of respiratory, orointestinal or genitourinary tracts. In patients with severe adaptive cellular immune defects, these mycobacteria may pose a serious threat.

Another feature that distinguishes these organisms from *M. tuberculous* is that they exhibit variable antimicrobial susceptibility profiles and often not susceptible to the first line antituberculous agents. The NTM is discussed under two broad headings based on the time needed for them to grow in laboratory. Slow-growing mycobacteria (SGM) are somewhat similar to *M. tuberculous* and take between 4 and 8 weeks to grow in enriched culture medium, whereas in case of rapidly growing mycobacteria (RGM) growth becomes evident within 7 days.

Slow-Growing Mycobacteria

Mycobacterium avium-Intracellular

Mycobacterium avium and *Mycobacterium intracellular* were originally differentiated on the bases of virulence to chickens and rabbits, respectively. Human infections were reported in 1943, and during 1980 and 1990s increased appreciation of diseases associated with MAC has been attributed in part due to HIV epidemic, although a higher number of non-HIV-infected patients have also been described as having infectious diseases due to these NTMs.

Pulmonary infections are most common, and isolation of MAC in respiratory tract samples including tracheal aspirate or bronchial samples by itself is not diagnostic of pulmonary MAC infection. Diagnosis requires the presence of a radiographic and clinical disease that is compatible with MAC infection. The radiographic feature suggestive of pulmonary NTM includes small, multicentric nodules, tree-in-bud appearances, and/or small thin-walled cavitary lesions. Cough is the most prominent symptoms, sputum production is relative minimal, except in patients with severe cystic bronchiectasis. Chronic lung disease is a well-recognized predisposing factor in the nonimmunosuppressed patients; these include patients with silicosis, chronic bronchitis, emphysema, and cystic fibrosis. Patients with healed fibrocavitary tuberculous remain at risk for secondary *M. avium-M. intracellular* infection.

Since 1980s, an increasing number of MAC-associated pulmonary NTM cases have been noted in the middle-aged and elderly women with no obvious immune defects. The most common feature of this illness is chronic cough, fatigue, inability to gain weight, depression, and in advance cases multicentric, cystic bronchiectatic pulmonary lesions; fever and night sweats are often not present. The author have described an underlying defect in interferon-gamma production in these patients who were initially mischaracterized as having Lady Windermere syndrome [11, 12]. This defect in the critical cytokine pathway has led the otherwise healthy patients to develop indolent, locally destructive pulmonary lesions due to environmental mycobacteria with low disease-causing potential in otherwise healthy individuals.

MAC infections are difficult to treat due to resistance to several antimicrobial agents; therapeutic regimen comprises of 3–4 drugs to which clinical isolates are susceptible; rifampin, ethambutol, macrolide derivatives such as azithromycin and clarithromycin plus a fluoroquinolone, like ciprofloxacin, moxifloxacin are often used. Clofazimine-based regimens are not suggested due to unacceptable drug toxicity and high mortality seen in HIV seropositive patients with disseminated MAC. The duration of therapy is longer than that for patients with pulmonary tuberculous. Most patients are treated for 18–24 months; in those with extra-pulmonary disease, duration may be extended to 36 months.

Mycobacterium kansasii

Mycobacterium kansasii is antigenically related to *M. tuberculous* and may be associated with false positive PPD

due to antigenic cross-reactivity. Most infections in the United States are seen in urban centers situated in the Southeast and Midwestern part of the country. As animal studies suggest, presence of dust by unexplained mechanisms enhances disease-causing potential of *M. kansasii* [16], it is not surprising that patients with pneumoconiosis are more susceptible to *M. kansasii* lung infection compared with general population; infections are fourfold higher in men compared to women. Similarly, infections tend to be common with certain occupations that involve chronic exposure to dust, these include miners, welders, sandblasters, and painters.

Pulmonary infections are slowly progressive although unlike MAC, *M. kansasii* leads to lung involvement difficult to distinguish from tuberculous. Infections frequently involve the upper lung lobes, and thin-wall cavities are seen routinely in patients with *M. kansasii* pulmonary NTM. Treatment is rifampin-based, although rifampin-resistant strains are on the rise, especially in patients with HIV-associated AIDS receiving rifampin prophylaxis [17, 18]. *Mycobacterium kansasii* is intrinsically resistant to pyrazinamide [19], and a large study has shown that isoniazid can be excluded for antimicrobial regimen [20]. Clarithromycin is often added with rifampin plus ethambutol, while awaiting rifampin susceptibility results [21]. Duration of therapy is 12–18 months.

Other Slow-Growing Mycobacteria

Mycobacterium ulcerans, *Mycobacterium marinum*, *Mycobacterium genavense Mycobacterium haemophilum*, *Mycobacterium simiae* are occasionally associated with infection in human.

M. haemophilum was almost exclusively seen in patients with severe immune dysfunction either due to HIV-associated AIDS [22] or in recipients of hematopoietic stem cell transplantation [23]. Disseminated infections were common, and predilection for tendon sheaths, bone, and joints was similar to infection seen with RGM.

M. simiae complex includes *M. simiae*, *Mycobacterium lentiflavum*, and *Mycobacterium triplex*; like *M. kansasii* these SGM lead to pulmonary disease that is difficult to distinguish from tuberculous. However, nearly 3/4th of clinical isolates may be associated with no discernable disease [24, 25]. In certain regions of the United States, it has become the second most frequent NTM [25]. Infections tend to be more refractory to antimicrobial therapy, and high-frequency of drug resistance further complicates options for effective drug regimen. Clarithromycin, quinolones, ethambutol, cycloserine, and ethionamide show favorable in vitro activity [26].

Rapidly Growing Mycobacteria

These organisms exhibit prominent growth on solid culture medium within 7 days after incubation. The most recent distribution of pathogenic species includes *Mycobacterium fortuitum* complex, which besides *M. fortuitum*, *Mycobacterium mucogenicum*, and *Mycobacterium septicum*, now also incorporates formerly known species of *Mycobacterium chelonae* complex (*M. chelonae* and *Mycobacterium abscessus*). *Mycobacterium smegmatis* forms the newly described second group, including *M. smegmatis*, *Mycobacterium wolinskyi*, and *Mycobacterium goodii* [27].

Pneumonia. In patients with pulmonary NTM in the United States, RGM are the third common cause of NTM after MAC and *M. kansasii*, respectively. *M. abscessus* is associated with most pulmonary infection in RGM group, whereas infections due to *M. fortuitum*, sub. sp. *fortuitum*, *M. smegmatis* sub. sp. *smegmatis*, and *M. goodii* are less frequent [28]. *M. goodii* has been mostly isolated in patients with aspiration lipoid pneumonia. Similar to SGM, isolation of RGM from respiratory tract samples is not sufficient to make diagnosis of RGM infection; as in most cases, these organisms may represent either colonization or environmental contamination.

To establish RGM's link to pulmonary disease, microbiologic isolation should be accompanied with radiographic and clinically compatible disease [29]. Clinical symptoms of pulmonary NTM, which at best are nonspecific of mycobacterial infection, include chronic, minimally productive cough, low-grade fever, weight loss, and in severe cases hemoptysis may occur [29].

Clinical and microbiological response to antimicrobial therapy for RGM pulmonary mycobacteriosis is less encouraging compared to treatment response in patients with SGM infections [30]. Drug combination including clarithromycin, high-dose cefoxitin plus amikacin has been associated with good clinical response, albeit microbiologically refractory *M. abscessus* infections are not uncommon.

Skin and soft-tissue infection. *M. fortuitum* is the most common RGM that is often associated with skin and soft-tissue infection in immunologically competent patients; most infections occur due to accidental inoculation such as stepping on a nail. Whereas, most infections due to *M. chelonae* are seen in patients with a underlying predisposing condition such as chronic corticosteroid use, rheumatoid arthritis, lupus, and cancer [29, 31].

Health-related infections occur sporadically and have been seen in patients after deep intramuscular injection, sternal wound infection following cardiac surgery, and after a variety of reconstructive and plastic surgical procedures including augmentation mammoplasty, chest wall reconstruction after tumor resection [32].

Catheter-related infections. These infections have become the most common healthcare-related infections due RGM, most infections involve patients with long-term indwelling

intravascular catheters, and often catheter-insertion sites are involved. In cancer patients, *M. chelonae* and *M. abscessus* are by far the most common in this setting [33]. Recently identified RGM species are increasingly reported in patients with cancer with catheter-related infection, they include *M. smegmatis* [34], *Mycobacterium neoaurum* [35], *Mycobacterium aurum* [36], *Mycobacterium lacticola* [37], and *Mycobacterium brumae* [38].

It is important to emphasize the fact that the RGM are frequently isolated in hospital and laboratory water supplies, and number pseudo-outbreaks involving contaminated blood culture materials, fiberoptic bronchoscope sterilizing machine contamination have been described [39, 40]. Therefore, strict criteria must be instituted before attributing to these low-virulence ubiquitous nontuberculous mycobacteria as a cause of catheter infection [41]. Treatment includes prompt removal of infected devices, and systemic combination antimicrobial therapy for 6–12 weeks. Selection of antimicrobials depends on RGM species, as a general rule RGM are resistant to most antituberculous agents with the exception of ethambutol. In patients with *M. chelonae-M. abscessus* infections, selection of appropriate drug therapy is even more limited due to high-level of intrinsic drug resistance. Clarithromycin-based regimen is currently recommended, although newer fluoroquinolones, such as gatifloxacin, and moxifloxacin; linezolid in vitro profile also appears promising, albeit further clinical experience is needed before such treatment is recommended. Other agents under investigation include tigecycline, a new glycycline that shows promising activity against most clinical isolates of *M. abscessus* [42].

Summary

The spectrum of nontuberculous mycobacteria is changing rapidly, as immunopathogenesis of SGM continues to improve. In recent years, difficult-to-treat infections due to RGM are on the rise, this may in part reflect newer molecular identification methods; however, rise in susceptible immunosuppressed patient population and frequently used indwelling prosthetic devices are also important contributors in this trend. Despite resistance to a number of available antimicrobials, newer agents may provide the much-needed treatment options for high-risk cancer patients with nontuberculous mycobacterial infection-disease.

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Chapter 41
Parasitic Infections in Cancer Patients: Toxoplasmosis, Strongyloidiasis, and Other Parasites

Brian G. Blackburn and José G. Montoya

Abstract The most important parasitic infections in cancer patients are *Toxoplasma gondii* and *Strongyloides stercoralis*. Both can cause life-threatening disease in immunocompromised patients, where *T. gondii* can present as encephalitis, pneumonia, fever of unknown origin, myocarditis, hepatitis, and chorioretinitis, and *S. stercoralis* as the disseminated hyperinfection syndrome. Effective therapies are available for both, but high case-fatality rates result if these syndromes are not recognized and treated promptly. Excellent preventative measures are available for both parasites, including prophylactic anti-*Toxoplasma* therapy or ivermectin treatment for strongyloidiasis in properly selected patients. Identifying cancer patients at risk for these syndromes is therefore critical, so that these measures can be instituted before life-threatening disease develops.

Keywords Toxoplasmosis • *Strongyloides stercoralis* • *Toxoplasma gondii* • Myocarditis • Hepatitis • Chorioretinitis • Disseminated hyperinfection syndrome

Toxoplasmosis

Introduction

Toxoplasma gondii is a ubiquitous intracellular parasite that infects over one billion people worldwide. In cancer patients, *T. gondii* infection (most commonly reactivation of latent infection) can result in major morbidity and life-threatening syndromes if left untreated. Reactivation of this parasite is usually the result of significantly impaired T-cell mediated immunity. Cancer patients with defects in this arm of the immune system (e.g., lymphoma, acute lymphoblastic leukemia) or who undergo treatments that cause such a

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defect (e.g., hematopoietic stem cell transplant [HSCT] or alemtuzumab) are at higher risk. Because the organism is so difficult to isolate, laboratory diagnosis is primarily based upon the use of serological, DNA amplification, and immunohistochemical methods. Following early diagnosis, treatment can reverse the initial clinical manifestations of toxoplasmosis, and decrease mortality in immunocompromised patients. Toxoplasmosis in cancer patients should be suspected in patients with fever, pneumonia, hepatitis, myositis, myocarditis or encephalitis, as well as in those with lymphadenopathy, chorioretinitis, and brain abscesses.

Life Cycle and Epidemiology

T. gondii exists in nature primarily in three forms, the tachyzoite, tissue cyst, and oocyst. The *tachyzoite* has a "banana" or "bow" shape, measures 2–3 μm by 5–7 μm, and its presence is pathognomonic for acute or reactivated infection (Fig. 41.1a). Thus, the visualization of tachyzoites in fluids or tissues, using hematoxylin and eosin, Wright-Giemsa, or immunoperoxidase stains, is indicative that a patient's symptoms and signs can be attributed to toxoplasmosis.

Tissue cysts are present in asymptomatic and chronically infected individuals or animals, contain the dormant form called "bradyzoites," and can measure up to 100 μm (Fig. 41.1b). After acute infection, individuals remain infected with *T. gondii* indefinitely, as these tissue cysts persist for life. Tissue cysts in meat are rendered nonviable by γ-irradiation, heating to 67°C (153°F), or freezing for 24 h at ≤−20°C (−4°F). The finding of a tissue cyst in a pathology specimen does not necessarily indicate that a patient's syndrome can be attributed to toxoplasmosis unless a heavy inflammatory reaction and a large number of cysts are also present in the tissue.

Oocysts are present in the gut (and feces) of infected felids (including housecats), contain sporozoites, and measure 10 × 12 μm (Fig. 41.1c). Ten million oocysts per day can be shed by an infected cat, and may remain viable for up to 18 months in moist soil; it takes 1–5 days after excretion into
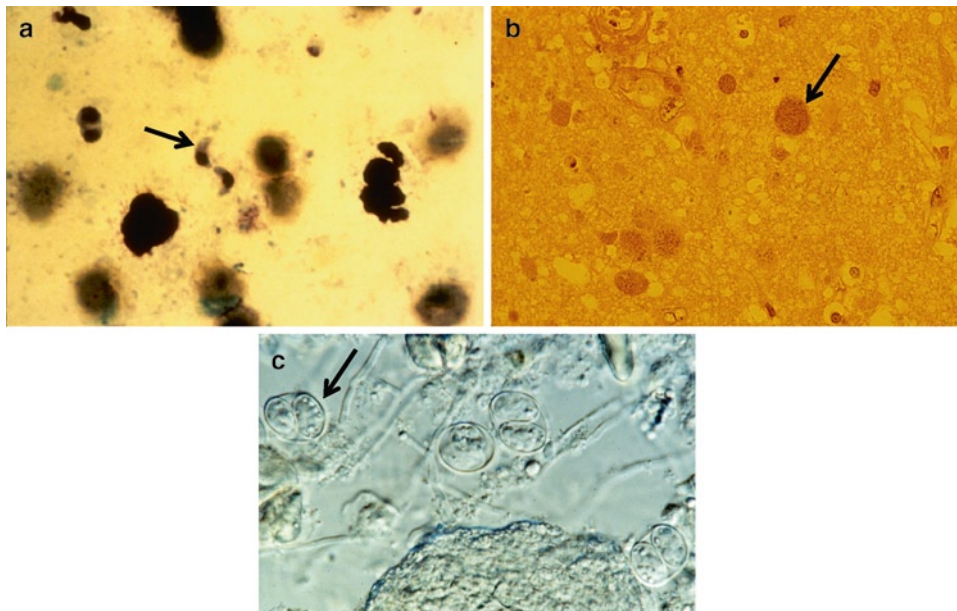
Fig. 41.1 (**a**–**c**) Main forms of *T. gondii* found in nature (see *arrows*). Tachyzoites (**a**), tissue cysts (**b**) containing bradyzoites, and oocysts (**c**) containing sporozoites

the environment for oocysts to become infective. Felids are the definitive host for *T. gondii*, and it is only in them that the reproductive cycle can be completed and the parasite amplified. Cats shed oocysts for only 1–2 weeks after initial infection with *T. gondii*.

Humans are infected with *T. gondii* primarily via the oral route, either by consuming tissue cysts in meat, or oocysts spread in the environment by cat feces. Although consumption of undercooked or raw infected meat or contact with infected cat feces are the classically recognized sources of infection, more than 50% of recently infected patients do not report either risk factor [1]. Most individuals thus become infected with *T. gondii* in ways less traditionally associated with toxoplasmosis. Therefore, the decision to test patients for *T. gondii* should not be based solely on a history of cat ownership or ingestion of undercooked or raw meat. A recent study performed by the Centers for Disease Control and Prevention (CDC) and the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory (PAMF-TSL) identified the ingestion of raw oysters, clams, and mussels as a novel risk factor for recent *T. gondii* infection in the United States [2]. Other studies have shown consumption of contaminated water to be an important means of transmission [3–5]. In the U.S., the prevalence of the infection appears to be declining; a recent study demonstrated that the age-adjusted *T. gondii* seroprevalence among persons 6–49 years old was about 11%, significantly decreased from a previous survey [6]. *T. gondii* prevalence increases with age; within the U.S., the seroprevalence also varies widely by geographic locale and by ethnicity; in some cohorts, the prevalence can be as high as 50%. In many countries, persons in lower socioeconomic

strata have higher *T. gondii* prevalence rates than their wealthier counterparts [7]. Many countries have much higher *T. gondii* prevalence rates than the U.S., including countries in the developing world and Europe. In certain countries it appears that the prevalence has been sustained for decades or is increasing [7].

The epidemiology, virulence, and clinical manifestations of the parasite may vary by geographical area. It is believed that *T. gondii* has evolved to a few clonal strains (termed types I, II, and III) that are distributed unequally worldwide. The more aggressive type I/III strains appear to be more common in South America, the less virulent type II strain predominates in Europe, and the USA has a mixture of the strains [8].

Clinical Manifestations

Acute *T. gondii* Infection

Most individuals do not experience illness when exposed to *T. gondii* for the first time. When clinical manifestations are present, painless and nonsuppurative lymphadenopathy is the most common presentation in Europe and the U.S. However, recent data indicate that even immunocompetent patients with acute toxoplasmosis in other latitudes (e.g., South America) may present with additional symptoms (e.g., high fever, constitutional symptoms, life-threatening pneumonia) [9]. Thus, cancer patients who travel should be advised regarding prevention and early recognition of toxoplasmosis outside the USA and Europe.

Recent data suggest that chorioretinitis as a result of acute, postnatally acquired *T. gondii* infection occurs more frequently in the USA and Europe than previously thought, particularly in patients older than 50 years of age; older data had suggested that most ocular toxoplasmosis was due to reactivation of congenital infection [5, 10]. Ocular toxoplasmosis causes a retinochoroiditis, and can result in blurred vision, eye pain, decreased visual acuity, floaters, scotoma, photophobia, or epiphora. Other less common but well-documented syndromes have been associated with the acute infection including hepatitis, myositis, and myocarditis.

Toxoplasmosis as a Result of Reactivation of Chronic Infection

Patients who acquire *T. gondii* remain latently infected indefinitely. In patients with cancer, immunosuppressive drugs or stem cell transplants greatly increase the risk of reactivation in latently infected persons. Clinically apparent toxoplasmosis in such patients usually results from reactivation of latent infection rather than from acute infection. In patients with allogeneic stem cell transplants, the presence of graft versus host disease (GVHD) increases the risk for toxoplasmosis, and most of the disease presents between days 31 and 100 (64% of cases) post-transplantation [11].

Several syndromes have been associated with reactivation of the parasite in these patients including encephalitis, chorioretinitis, fever of unknown origin, pneumonia, myocarditis, hepatosplenomegaly, lymphadenopathy, and rash. Brain abscesses can result, causing headache, altered mental status, seizures, coma, and focal neurologic changes (Fig. 41.2). Diffuse encephalitis can also occur, without focal neuroimaging findings, and is associated with a poor prognosis. Meningitis alone is rarely a manifestation of toxoplasmosis. Chorioretinitis can be the sole manifestation of toxoplasmosis in immunocompromised patients and may present with similar symptoms as in acute infections. Other well-documented syndromes occur with toxoplasmosis and are often overlooked. Fever with pneumonia can be the sole manifestation of toxoplasmosis in immunocompromised patients. Toxoplasmic pneumonitis can present with cough, dyspnea, hypoxia, and diffuse bilateral infiltrates. Fever alone has been well described in patients with allogeneic stem cell transplants.

Laboratory Diagnosis

Laboratory diagnosis of *T. gondii* infection and toxoplasmosis can be established by serological methods, polymerase chain reaction (PCR), or immunohistochemistry [12].
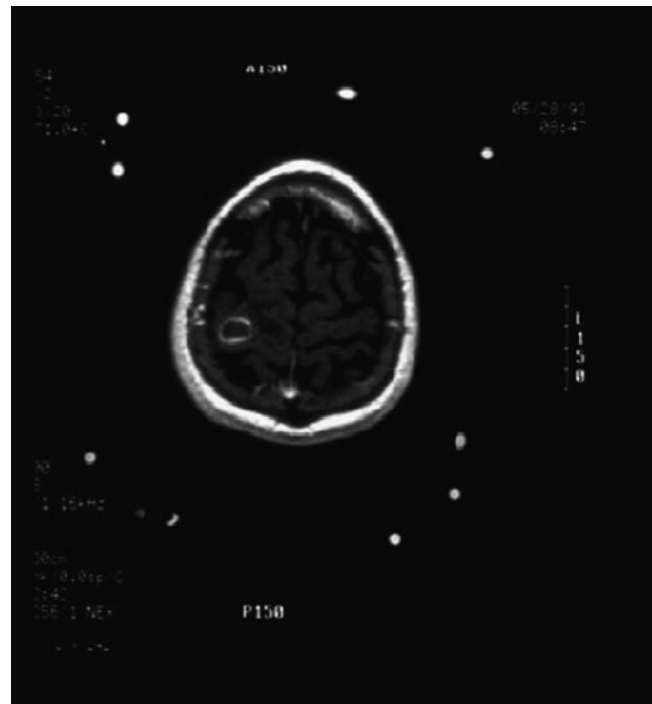
Fig. 41.2 Brain MRI depicting ring-enhancing brain lesion in immunocompromised patient. *T. gondii*-specific immunoperoxidase staining of brain biopsy tissue was diagnostic of toxoplasmic encephalitis

Serological Tests

Initial serological testing for *T. gondii* can be accomplished at nonreference or commercial laboratories, where *Toxoplasma* IgG testing tends to be reliable. IgM results, when negative, are also usually accurate. Positive IgM results, however, should be viewed with caution. Many nonreference laboratories have a high rate of false-positive IgM results when compared against reference *Toxoplasma* laboratories; positive IgM test results should therefore be confirmed at a reference laboratory (see below).

Negative IgG and IgM test results establish that the patient has not been exposed to the parasite (assuming that the patient is capable of producing normal immunoglobulin levels). Positive IgG with negative IgM test results establish that the patient has been infected with the parasite in the past, and is at risk for reactivation. Positive IgM test results (with either positive or negative IgG test results) should raise the suspicion for a recent infection. However, a positive IgM result may indicate not only an acute infection, but also can be observed in the setting of a chronic infection, or may be a false positive result. Positive IgM test results should be confirmed at a reference laboratory (e.g., at PAMF-TSL, http://www.pamf.org/serology/; telephone (650) 853-4828; e-mail, toxolab@pamf.org) [13]. At PAMF-TSL, confirmatory tests include the use of a more specific IgM ELISA (using the "double-sandwich"

method invented by Dr. Jack S. Remington), differential agglutination (or AC/HS), IgG avidity testing, IgA ELISA, and IgE ELISA [12].

Because patients chronically infected with *T. gondii* are at risk of reactivating the parasite and toxoplasmosis can be life-threatening, serological testing for toxoplasmosis should be performed in all high risk immunocompromised patients (the more profound the T-cell mediated defect, the higher the risk). The diagnosis of chronic infection is established by a positive IgG test result and a negative IgM test result (additionally, some patients with chronic infection may have a positive IgG and IgM result). Once it has been established that the patient is IgG positive for *Toxoplasma* and that the patient has a chronic infection, there is little or no utility in repeating or performing additional serological testing. Serological testing does not have any role in the diagnosis of toxoplasmosis due to reactivation of a latent infection, and is not useful for following response to therapy. PCR and histological methods are best used in this setting.

Polymerase Chain Reaction

In immunocompromised individuals, PCR of body fluids or tissues is of great value in diagnosing toxoplasmosis. PCR can be performed on almost any body fluid, including cerebrospinal fluid (CSF), bronchoalveolar lavage, vitreous fluid, aqueous humor, and peripheral blood. Positive results usually establish the diagnosis of toxoplasmic encephalitis, pneumonia, chorioretinitis, or disseminated disease, respectively. If feasible and safe, a lumbar puncture should be performed in patients suspected to have toxoplasmic encephalitis. Although the sensitivity of the CSF by PCR has been variable, specificity approaches 100% [14]. Although positive CSF IgM test results have been reported in congenitally infected infants, serological testing of CSF should be discouraged in adults, and PCR testing should be the priority. PCR testing for *T. gondii* is available at PAMF-TSL and other laboratories.

Histological Methods

Tachyzoites and tissue cysts can be demonstrated by the use of Wright-Giemsa staining or immunohistochemistry. Almost any tissue can be examined with the *T. gondii*-specific immunoperoxidase method; this technique has been useful for the diagnosis of toxoplasmic encephalitis. The histological diagnosis of toxoplasmosis requires the demonstration of tachyzoites or multiple tissue cysts near an inflammatory necrotic lesion.

Management

All cancer patients with significant T-cell mediated immunity defects should have *Toxoplasma* serological testing performed and if possible, testing should be done before significant immunosuppressive therapy is begun (e.g., HSCT or immunosuppressive drugs). In patients chronically infected with toxoplasmosis, primary prophylaxis should be considered to prevent reactivation disease, and a low threshold for testing clinically indicated body fluids and tissues for toxoplasmosis (by PCR and immunohistochemistry) should be used when patients fall ill.

Invasive Procedures

Invasive diagnostic procedures should be considered in patients in whom toxoplasmosis is suspected, especially those with fever, pneumonia, myocarditis, brain lesions, encephalitis, chorioretinitis, or rash. Bronchoalveolar lavage or myocardial, brain, vitreous, or skin biopsies should be considered early during the illness and specimens tested by PCR and specialized stains. The empiric use of anti-*Toxoplasma* drugs in patients with multiple brain lesions who are seropositive for *T. gondii* (prior to examining the CSF by PCR or performing a brain biopsy) has not been validated in non-AIDS immunocompromised patients, and if feasible, should be avoided in this patient population. Rather, early consideration should be given to a brain biopsy.

Drugs

Toxoplasmosis should always be treated with combination therapy, and higher doses are indicated for immunocompromised patients (Table 41.1). Pyrimethamine is the most effective agent against *T. gondii* and should be part of the drug regimen if possible. The combination of pyrimethamine/sulfadiazine (with folinic acid to minimize the toxicity of pyrimethamine) is considered the first-line regimen for toxoplasmosis. Limited supply and the lack of an IV formulation have been major barriers for more widespread use. Recent data suggest that trimethoprim/sulfamethoxazole (TMP/SMX) has similar efficacy to pyrimethamine/sulfadiazine in the setting of both toxoplasmic encephalitis and chorioretinitis [15, 16]. TMP/SMX has the additional advantage of being available intravenously. Another effective regimen is pyrimethamine plus clindamycin. Alternatively, pyrimethamine can be used with atovaquone. In extreme cases, when none of the above drugs can be used, clarithromycin, dapsone, or azithromycin can be substituted.

Table 41.1 Recommended drug regimens for immunocompromised patients with toxoplasmosis[a] (primary therapy)

Pyrimethamine (PO)	200 mg loading dose followed by 50 mg (<60 kg) to 75 mg (>60 kg/day)
Folinic acid[b] (PO)	10–20 mg daily (up to 50 mg/day) (during and 1 week after therapy with pyrimethamine)
plus	
Sulfadiazine (PO)	1,000 (<60 kg) to 1,500 mg (>60 kg) every 6 h
or	
Clindamycin (PO or IV)	600 mg every 6 h (up to 1,200 mg every 6 h)
or	
Atovaquone (PO)	1,500 mg orally twice daily
Trimethoprim/sulfamethoxazole (PO or IV)	10 mg/kg/day (trimethoprim component) divided in 2–3 doses (doses as high as 15–20 mg/kg/day have been used)
Pyrimethamine/folinic acid	Same doses as above
plus	
Clarithromycin (PO)	500 mg every 12 h
or	
Dapsone (PO)	100 mg/day
or	
Azithromycin (PO)	900–1,200 mg/day

Preferred combinations: pyrimethamine/sulfadiazine/folinic acid or trimethoprim/sulfamethoxazole

[a]Assistance is available for the diagnosis and management of patients with toxoplasmosis at the Palo Alto Medical Foundation *Toxoplasma* Serology Laboratory, telephone number (650) 853 4828

[b]Folinic acid = leucovorin; folic acid should not be used as a substitute for folinic acid

After the successful use of a combination regimen during the acute/primary therapy phase, same agents at half-does are usually used for maintenance or secondary prophylaxis

Prevention

Seronegative (*Toxoplasma* IgG negative) immunocompromised patients should be advised to avoid exposure to the parasite (http://www.cdc.gov/toxoplasmosis/prevent.html). In addition to the recommendations presented at this website, these patients should also be warned about the possibility of acquiring *T. gondii* by ingesting raw oysters, clams, and mussels.

Seropositive immunocompromised patients should be considered candidates for primary prophylaxis. The most successful agent for this indication has been TMP/SMX (e.g., one double strength [or single strength] tablet daily [assuming normal renal function]). Alternatively, atovaquone can be used (1,500 mg/day) or any of the other drugs listed above, but at half the treatment dose.

Strongyloidiasis

Strongyloidiasis is caused by the intestinal nematode, *Strongyloides stercoralis*. Primarily transmitted in tropical areas, *S. stercoralis* usually causes a chronic gastrointestinal syndrome or can remain asymptomatic for decades [17]. The primary medical importance of this parasite in the developed world lies in its potential to cause the hyperinfection syndrome in immunocompromised patients, wherein larvae may disseminate throughout the body, with mortality rates of up to 70–80% [18–20].

The Organism

The life cycle of *S. stercoralis* is complex, alternating between free-living and parasitic cycles, and includes adult worms, two different larval stages, and eggs. These cycles form the basis for autoinfection and multiplication within the host, features relatively unique among helminths to *Strongyloides* [21, 22].

Soil-living adult worms produce eggs, which give rise to noninfective *rhabditiform larvae*. These either continue the free-living cycle by maturing into adults, or become infective *filariform larvae*. Filariform larvae can penetrate intact human skin, after which they migrate to the lungs. From there, they are expectorated, swallowed, and reach the small intestine; this journey takes about 3–4 weeks. In the intestine, *S. stercoralis* matures into adult worms, which are semi-translucent and about two millimeters long. These produce eggs, which hatch and become rhabditiform larvae. Although most of these larvae exit the gastrointestinal tract via the stool and subsequently develop into adult worms in the soil, a small number directly become infective (filariform) larvae within the gut and penetrate the intestinal mucosa or perianal skin, completing the life cycle without leaving the host. This is termed *autoinfection*, and differentiates *S. stercoralis* from nearly all other helminths in several ways, including indefinite persistence in a host (in the absence of treatment), multiplication in the absence of exogenous re-infection, and potential person-to-person transmission [23].

Epidemiology

Global estimates of strongyloidiasis prevalence vary widely, from 3 to 100 million infected [20, 21, 24]. *S. stercoralis* is less common than other major intestinal nematodes such as *Ascaris*, *Trichuris*, and hookworms [17]. Strongyloidiasis is found throughout the tropics and subtropics and in limited foci of the USA (e.g., Appalachia) and Europe [24]. Because transmission occurs via skin contact with fecally-contaminated soil, transmission is favored where poor hygienic conditions are combined with a warm, moist climate. Primary prevention involves better hygiene and footware use in endemic areas.

Studies based on stool examination in the 1960s and 1970s showed prevalence rates of 0.5–4.0% in differing US cohorts, mostly in the Southeast and Appalachia [21, 24]. Although prevalence has subsequently decreased, infections are still seen in patients from those areas, especially patients who are older than 50 years, institutionalized, of low socioeconomic status, or who have lived in rural areas [24]. In cohorts in developing countries, strongyloidiasis prevalence rates can be striking, for example 25% in Thailand and Nigeria, 28% in Brazil, and 40% in Colombia [21, 24]. Because of the superior sensitivity of serology for diagnosis, seroepidemiology studies generally report higher prevalence rates; in one Peruvian cohort, 9% tested positive by stool examination for *S. stercoralis*, while 72% were seropositive [25]. Prevalence rates in resettled US refugees can be high, with one recent study reporting 46% *S. stercoralis* seroprevalence in a group of resettled Sudanese refugees [26]. Another study found that 39% of asymptomatic refugees in Boston with eosinophilia were *S. stercoralis* seropositive [27]. Given the high prevalence in many tropical and subtropical areas and the lifelong persistence of this parasite in the absence of treatment, physicians should consider strongyloidiasis both in persons with recent exposure to endemic areas, and immigrant or refugee patients in developed countries even if they immigrated decades earlier.

Pathogenesis, Immunity, and the Hyperinfection Syndrome

Strongyloides infection is sustained over time in a given host by a small, stable number of intestinal adult worms. Although these die after a finite lifespan, autoinfection ensures the constant production of new worms, perpetuating the cycle even in the absence of reinfection [28]. In patients with chronic strongyloidiasis, autoinfection is normally well controlled by cell-mediated immunity, and the number of adult worms remains low and stable. With immunosuppression, more autoinfective larvae complete the cycle, and the population of parasitic adult worms increases, causing *hyperinfection* [28]. The large numbers of migrating larvae can disseminate, often associated with polymicrobial sepsis, bronchopneumonia, and meningitis. Untreated, disseminated strongyloidiasis is usually fatal, and even with treatment mortality approaches 25–30% [19, 29].

Both parasite and host factors affect regulation of this cycle. The population size of *S. stercoralis* in a host depends in part on secreted parasite hormones that regulate autoinfection [22, 30]. When the immune response is impaired, larger numbers of autoinfective parasites can develop, as reported in patients with hematologic malignancies, solid organ transplant and HSCT, hypogammaglobulinemia, and severe malnutrition [31–33]. Interestingly, there has been little association between cyclosporine use and hyperinfection syndrome; some evidence suggests cyclosporine may have an antihelminthic effect on *S. stercoralis* [34].

Among HTLV-infected patients, there is a strong association with increased susceptibility to infection with *Strongyloides*, the hyperinfection syndrome, and poor response to treatment. Control of *S. stercoralis* in vivo is most dependent on the Th2 immune response, but the predominant immune response in HTLV-infected patients shifts from Th2 to Th1 [35–37]. There is some suggestion that *S. stercoralis* may hasten the development of leukemia among HTLV co-infected patients [38]. In contrast, there have been surprisingly few reports of hyperinfection among *S. stercoralis*-infected patients with AIDS. Although disseminated strongyloidiasis does occasionally occur in AIDS patients, this disease was removed from the list of AIDS-defining illness by the CDC in 1987 [39, 40].

Corticosteroid use carries a disproportionately high risk for disseminated strongyloidiasis compared to other forms of immunosuppression [41, 42]. Corticosteroids may upregulate growth of *S. stercoralis*, and allow the parasite to develop preferentially into autoinfective filariform larvae, in addition to suppressing immunity [22, 43, 44]. They may also allow nonreproductive adult worms to regain reproductivity [30, 45]. Patients have developed hyperinfection after only a few days of corticosteroid administration [46].

Clinical Findings

Most patients infected with *S. stercoralis* are asymptomatic, or have only mild symptoms. Shortly after infection, some patients develop a localized, erythematous, pruritic rash [29, 47–49]. Pulmonary symptoms and eosinophilia may appear several days later; diarrhea and abdominal pain may follow. Blood is occasionally detected in the stool, but over 50% are asymptomatic. Chronic strongyloidiasis is not generally associated with pulmonary symptoms. Although

about 75% of chronically infected patients have eosinophilia, it is usually low-grade (5–15% of the WBC differential) [21, 50]. Migrating larvae may produce *larva currens*, a serpiginous, erythematous, track-like rash. Some chronically infected patients note epigastric pain, nausea, diarrhea, blood loss, and possibly malabsorption. Rarely, heavy infections can cause bowel obstruction. The majority of chronically infected patients are asymptomatic [41]. There has been an association between *S. stercoralis* infection and biliary cancer, but this observation requires confirmation [51].

With hyperinfection, the intestines and lungs harbor many larvae, and diarrhea is common (Fig. 41.3). When dissemination occurs, larvae are found widely, sometimes involving the central nervous system (CNS). Eosinophilia is often absent during hyperinfection. Other gastrointestinal manifestations are common, including abdominal pain, vomiting, and intestinal obstruction. Hemorrhage, peritonitis, or bacteremia can occur. Pneumonitis is common, with cough, respiratory failure, and diffuse interstitial infiltrates or consolidation on radiographs; respiratory secretions often contain the parasite (Fig. 41.4a, b). CNS invasion may cause meningitis and brain abscesses, with larvae in the CSF or tissue. An association with SIADH has been reported [52, 53].
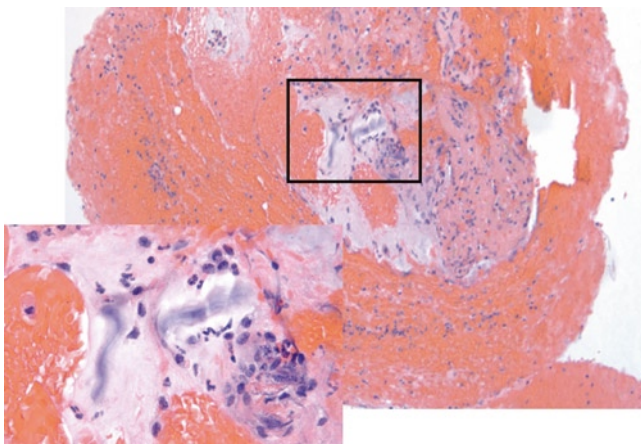
Diagnosis

Uncomplicated strongyloidiasis is diagnosed by finding rhabditiform larvae in microscopic stool examination; it is uncommon to find eggs in the stool. Because few larvae are shed, the sensitivity of a single stool examination is only about 30%; multiple samples should therefore be examined (with concentration techniques). Examination of up to seven stool samples can significantly increase sensitivity [21, 54]. Sampling duodenal fluid or small bowel biopsy can increase sensitivity, but practical issues limit usefulness [55]. Placing stool samples on agar plates to observe tracks left by the motile larvae may be the most sensitive method among the stool examination techniques [56–58].

Because of the difficulty with microscopic diagnosis, serologic tests (which are more sensitive) are often favored, such as the enzyme-linked immunoassay offered by CDC (Atlanta, GA). This is about 95% sensitive in stool-positive patients, although specificity is lower because of cross-reactivity with other helminths [25, 50]. The titer of *Strongyloides* antibodies in infected patients generally begins to decline 6–12 months after cure, as does the peripheral

Fig. 41.3 Bronchoscopic biopsy in patient with *Strongyloides* hyperinfection syndrome. Courtesy Chandra Krishnan, MD, Stanford University, Department of Pathology
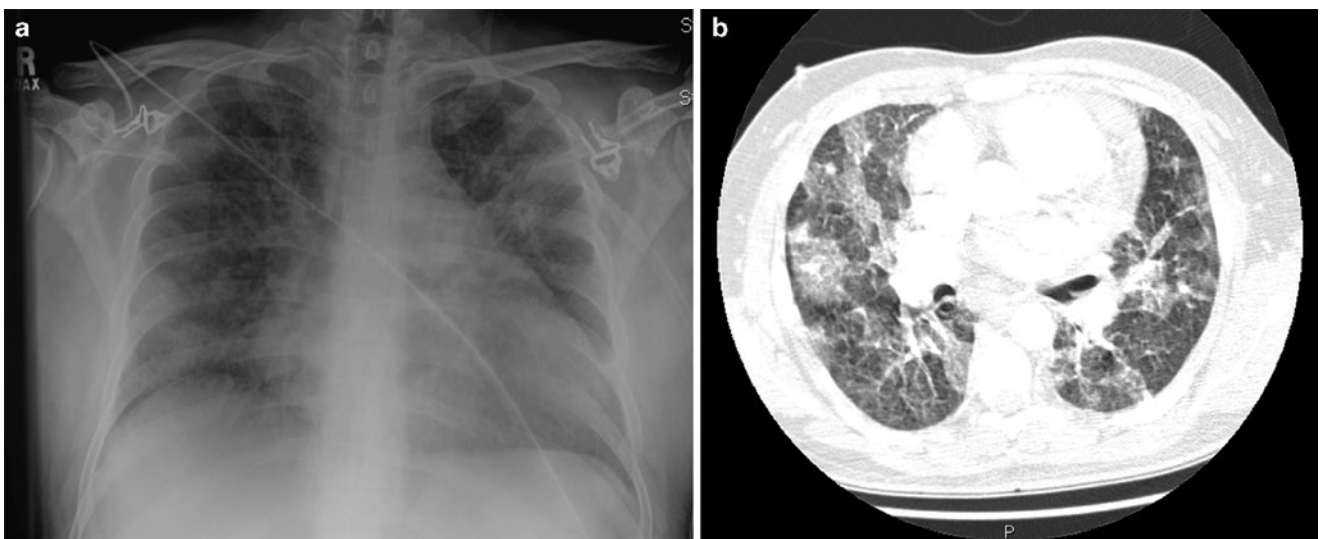
Fig. 41.4 (**a**) Chest radiograph in patient with *Strongyloides* hyperinfection syndrome. (**b**) Chest computed tomographic examination in patient with *Strongyloides* hyperinfection syndrome
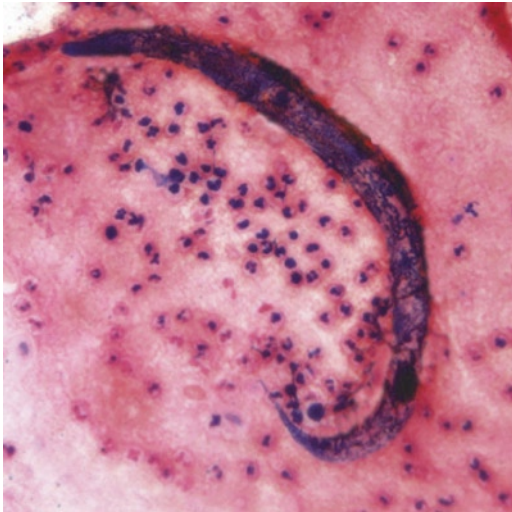
Fig. 41.5 Sputum sample from patient with *Strongyloides* hyperinfection syndrome. Courtesy Stanford University, Microbiology Laboratory
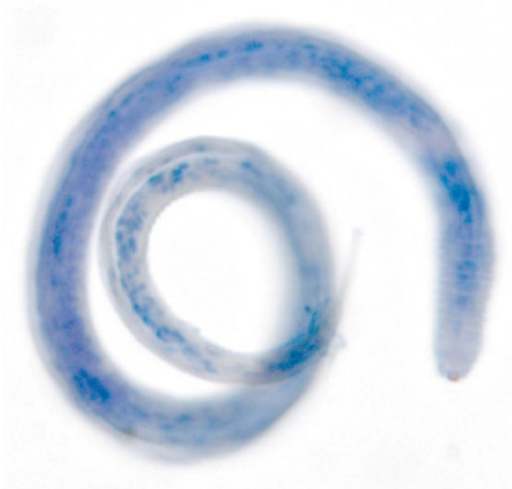
Fig. 41.6 Bronchoalveolar lavage sample showing filariform *S. stercoralis* larvae in patient with hyperinfection syndrome. Courtesy Chandra Krishnan, MD, Stanford University, Department of Pathology

eosinophil count [50, 59, 60]. In contrast to chronic strongyloidiasis, hyperinfection and disseminated strongyloidiasis are easily diagnosed by microscopic stool examination (or other samples, such as sputum), which typically contain many filariform larvae (Figs. 41.5 and 41.6).

Strongyloidiasis in Cancer Patients

Given the risk of hyperinfection syndrome, identifying strongyloidiasis in cancer patients is critical. This is paramount in endemic areas, as evidenced by a Brazilian cohort of gastrointestinal cancer patients, of whom 24% were infected with *S. stercoralis* [61]. It is also important in nonendemic areas, given the global increase in travel and immigration. One retrospective review at a US cancer center found 2.0 *S. stercoralis* infections per 10,000 leukemia patients, and 0.8 infections per 10,000 cancer patients overall; however, systematic screening was not done, so these are likely underestimates. Among the infected patients, 48% had received systemic corticosteroids, and 36% antineoplastic therapy. Fifty-seven percent had diarrhea, 48% eosinophilia, and 24% developed the hyperinfection syndrome. Both of the patients with hyperinfection syndrome who had received HSCTs died despite appropriate therapy [62].

Although most chemotherapeutic agents have been associated with hyperinfection, the association seems particularly strong for vinca alkaloids [41]. These exert a toxic effect on myenteric neurons, decreasing intestinal motility and increasing larval transit time, perhaps allowing more to become autoinfective filariform larvae.

Treatment

All persons infected with *S. stercoralis* should be treated. The drug of choice for uncomplicated strongyloidiasis is oral ivermectin, 200 μg/kg/day for 2 days, which cures 70–85% of chronically infected patients. One study demonstrated a higher cure rate with two-dose ivermectin regimens compared to previously used single-dose regimens [63, 64]. Alternatives include thiabendazole or albendazole for 3–7 days, although ivermectin appears more effective; thiabendazole is poorly tolerated, and albendazole has the lowest cure rate among these drugs [64–68]. Ivermectin is also preferred for hyperinfection/disseminated strongyloidiasis. It should be administered daily until symptoms have resolved and larvae have not been detected for at least 2 weeks [20, 41]. Several patients with disseminated strongyloidiasis have received veterinary formulations of subcutaneous ivermectin. Although still experimental, this is an alternative for patients poorly tolerant of oral therapy and for those with severe infection [69–72]. Some patients have received a combination of ivermectin and albendazole with success [73]. If possible, immunosuppressive therapy should be stopped (particularly corticosteroids). Some recommend monthly treatment subsequently for patients who require continued immunosuppression [18–20].

Follow-up stool examinations should be repeated frequently to document cure. For long-term follow-up, serology and eosinophil counts may offer stronger evidence of treatment efficacy. These findings generally begin to normalize 6–12 months after cure [50, 59].

Prevention of Hyperinfection

For all patients who are (or will soon become) immunosuppressed, examination of stool and serologic specimens for *S. stercoralis* should be considered for those who have lived in an endemic area or had other possible exposure to *S. stercoralis* at any time in their life (particularly those infected with HTLV-1 or receiving corticosteroids) [74]. Though most important for persons from highly endemic developing countries, this is also a consideration for residents of the southeastern USA, especially older persons who lived there during childhood. Such screening would be particularly important for those with clinical strongyloidiasis (e.g., eosinophilia, larva currens, abdominal pain). All infected patients should be treated promptly, preferably prior to initiation of immunosuppressive therapy. If a patient's condition requires immunosuppression before *S. stercoralis* diagnostics are available, the risks of empiric antiparasitic therapy for strongyloidiasis must be weighed against the risks of disseminated infection [75].

Other Parasitic Infections of Importance in Cancer Patients

Although *T. gondii* and *S. stercoralis* are the most clinically important parasitic infections in cancer patients, many others also warrant discussion. The clinical relevance of these parasites stems from either (1) increased risk of severe disease in immunocompromised hosts, or (2) association between infection and subsequent malignancy.

Opportunistic Parasites

Trypanosoma cruzi (Chagas' Disease)

Trypanosoma cruzi, a protozoan endemic only to the Americas (mostly limited to the tropics), is transmitted primarily by bloodsucking Triatomine insects [76]. A minority of patients suffer symptoms in the weeks after infection including fever, myocarditis, and meningoencephalitis; although occasionally severe, most patients recover and enter an asymptomatic *indeterminate phase* of infection. *T. cruzi* then persists indefinitely, causing end-organ disease in 20–30%, years-to-decades later [76]. Heart disease is most common (e.g., conduction disease and heart failure) among symptomatic patients, with gastrointestinal disease (megaesophagus or megacolon) also seen; patients with achalasia are at increased risk for esophageal cancer [77]. Diagnosis of chronic infection can be made serologically.

Acute Chagas disease is rarely seen in the USA, but immunocompromised hosts chronically infected with *T. cruzi* are at increased risk for reactivation; this syndrome resembles acute infection, but can be more severe. Atypical manifestations are seen, including *T. cruzi* brain abscesses, skin lesions, and mucosal involvement [78, 79]. Treatment is with either benznidazole or nifurtimox; in the USA, these drugs are available only through CDC. No consensus exists regarding approach to *T. cruzi* infection in oncology patients, but serologic screening should be considered for patients (or HSCT donors) who have lived in endemic areas. Many centers use a presumptive treatment approach in infected, immunocompromised patients, initiating antiparasitic therapy if parasitemia becomes detectable by culture or PCR [80, 81]. Others recommend prophylactic therapy in all infected patients who are currently, or will imminently be, immunosuppressed [82].

Acanthamoeba and Balamuthia

Acanthamoeba spp. and *Balamuthia mandrillaris* are free-living, ubiquitous environmental amebae. Although clinically apparent human infection with these organisms is rare, a meningoencephalitis-like syndrome (often with CNS mass lesions) can occur, largely in immunocompromised patients [83]. Disseminated disease can involve the skin, lungs, liver, and bones; typical progression is over weeks to months [84]. Diagnosis typically requires biopsy, although serologic tests exist. Case-fatality rates are high, even with multiple antimicrobials; no consensus treatment regimen exists, but effective antimicrobials include pentamidine, azoles, sulfonamides, macrolides, and flucytosine.

Visceral Leishmaniasis

Leishmania spp. are intracellular protozoans transmitted by sandflies. Most cases of visceral leishmaniasis (VL) are acquired in South Asia, East Africa, or Brazil, although some transmission also occurs in the Mediterranean littoral. A wide clinical spectrum exists for patients, with most infections subclinical. Although immunocompetent patients can progress to symptomatic disease, immunosuppression (such as cancer chemotherapy or HSCT) is an established precipitant of this [85–87]. For patients who become symptomatic, clinical disease can present months or years after initial infection. VL causes protean manifestations, including fever, hepatosplenomegaly, weight loss, skin changes, cytopenias, and hyperglobulinemia. Diagnosis is by biopsy and microscopic examination or culture of involved tissues, although serology can be an adjunct; untreated, progressive VL is usually fatal.

Treatment options include liposomal amphotericin, pentavalent antimony compounds, miltefosine, and paromomycin.

Intestinal Protozoa

Intestinal protozoa such as *Cryptosporidium* spp., *Isospora belli*, and *Cyclospora cayetanensis* can cause severe diarrhea in immunocompromised patients. Recent data suggest *Cryptosporidium* in particular may be a common cause of diarrhea in some oncology cohorts [88, 89]. Diarrhea is generally watery, and diagnosis is by stool studies; all three parasites can be detected through modified acid fast stains, and *Cryptosporidium* can also be detected through sensitive stool immunoassays. Treatment of *Cryptosporidium* is with nitazoxanide, while *Isospora* and *Cyclospora* are treated with trimethoprim-sulfamethoxazole [90].

Microsporida can cause diarrheal disease in immunocompromised patients; they can also disseminate, with involvement of the CNS, lungs, or other organs [91]. Diagnosis is by trichrome staining of the stool, and treatment is with albendazole or fumagillin, depending on the species [90].

Parasites Associated with Carcinogenesis

Liver Flukes

The liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini* are helminths that are acquired by ingestion of undercooked fish. *C. sinensis* is endemic mostly to East Asia and *O. viverrini* to Southeast Asia [92]. These parasites can cause chronic biliary disease, and epidemiologic evidence links infection to the development of cholangiocarcinoma, usually years later. Evidence is best for *O. viverrini*, but is also emerging for *C. sinensis*; a related species, *Opisthorchis felineus*, has been less well studied. Infected persons have a 5–15-fold higher risk of developing cholangiocarcinoma than uninfected persons in endemic areas, depending on the parasite burden and region studied [93, 94]. Diagnosis is generally via stool examination; serologic tests exist, but are not widely available outside endemic areas. Treatment with praziquantel is usually curative, but once cholangiocarcinoma has developed, antiparasitic treatment does not generally affect the course of the malignancy.

Schistosomiasis

Schistosoma spp. are blood flukes acquired through skin contact with infested freshwater. Although several species cause gastrointestinal and hepatic disease, *Schistosoma haematobium* (endemic to Africa and parts of the Middle East),

causes primarily genitourinary disease. Chronic infection causes hematuria and urinary obstruction. Infection over many years has been linked epidemiologically with the development of squamous cell bladder carcinoma, an otherwise uncommon malignancy [95]. Diagnosis is classically through stool or urine examinations, but serologic assays are more sensitive. Treatment with praziquantel is usually curative, but does not generally affect the course of the cancer once established.

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Chapter 42
Zoonoses in Cancer Patients

Donald Armstrong

Abstract Prevention of zoonoses in cancer patients is the theme of this chapter and it is hoped that it will encourage and help doctors caring for such patients to educate them to avoid the infections. Avoidance need not include separation from a pet or occupation or recreation, but the use of caution conditioned by knowledge of the sources of infection and the ways we contact them should lead to effective prevention.

Keywords Zoonoses • Immunocompromised cancer patients • Prevention • Epidemiology • Hygiene • Veterinarians

Zoonoses are defined as infectious diseases, which are transmitted from nonhuman animals to man. According To one study [1] there are 1,415 organisms that infect man and of these 868 (61%) can cause zoonoses. A number of these have a predilection for infecting and for being especially severe in the immunocompromised host [2–4]. Because of this, prevention is extremely important for patients with neoplastic disease and immune defects associated with the neoplasm or its therapy. Immune defects can be categorized as indicated in Table 1.1 [5] and they are discussed extensively in other chapters. This chapter will stress the prevention of zoonoses in patients with neoplastic disease including those who appear to have intact immune responses for that may change with progression of disease or future chemotherapy or irradiation. It must be stressed that pets are extremely important to most humans and often especially to those who are ill. They provide companionship or they can be the objects of biological interest and study. Nonhuman animals provide occupations for large numbers of humans. Contact with various species can result in infections, however, and these can be especially severe in patients with immune defects. There are far too many examples to be included in this chapter, thus the most common will be discussed along with some of the

rarer examples, which may be emerging infections and therefore of particular interest. The aim of this chapter is to encourage doctors to educate their patients so that they are aware of these dangers and how best to avoid them.

Unusual contact such as kissing, nuzzling, and even touching [6–8], in an uncontrolled setting, pets and other animals should be discouraged. And, of course, simple hygiene such as hand washing should be stressed. In addition, patient and at times medical doctor contacts with veterinarians is important so that non human animals will receive preventive care as well as care for apparent illnesses.

In addition, in some difficult situations such as a question of whether to initiate rabies vaccine, departments of public health, city or state or the Centers for Disease Control can be very helpful.

Epidemiology

On June 1, 1778, Edward Jenner introduced his paper on vaccination with cowpox to protect against smallpox with the following words [9]. "The deviation of man from the state in which he was placed by nature seems to have proven to him a prolific source of diseases. From the love of splendor, from the indulgences of luxury and from his fondness for amusement, he has familiarized himself with a great number of animals, which may not originally have been intended for his associates. The wolf disarmed of ferocity is now pillowed in the lady's lap. The cat, the little tiger of our island, whose natural home is the forest, is equally domesticated and caressed." I assume Dr. Jenner would be amazed, if not appalled at the number and variety of pets owned by people on his island and world wide – and how pets, wild animals that have contact with pets and people travel, meet and exchange microorganisms. In evaluating the epidemiology of zoonoses there are four major factors to take into account; Geography, the Home, Occupation and together, Habits and Hobbies. Transmission of infections from humans to nonhuman pets has been observed with associated illness. It should be considered especially when either host could be

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a carrier with reinfection occurring ("ping-pong infections"). Two other methods of exposure, Bioterrorism and xenotransplantation, will not be discussed in this chapter.

Geography

World travel of both people and pets has allowed and continues to present opportunities for spread of zoonoses. Not only people or pets can carry microorganisms but vectors such as mosquitoes can travel by plane and introduce new organisms to a new environment. An example of this is West Nile Virus that came from the Middle East to New York City and then moved across the continent to the west coast of the United States. It has been postulated that the trip across the Atlantic was via mosquitoes on a plane and that the transcontinental trip was by infected crows or humans or other birds. In addition, wild birds migrating over thousands of miles may bring organisms from and to domesticated or wild avian species and thus to humans.

A history of travel of a human should be routinely obtained and should include exposures to pets belonging to the patients and also belonging to friends or neighbors. A pet travel history can be equally important in revealing zoonotic exposures. Vacation plans should be discussed and patients educated about avoiding endemic areas for zoonoses such as the southwestern USA (plague) or babesiosis on islands off the northeastern coast.

Home

Our homes may be shared with mice, rats, and bats among others, each carrying microorganisms that can infect humans and may be lethal particularly in immunocompromised individuals. Some may choose these animals for "pets" including bats by putting out nesting "bat boxes," others may find them as unwelcome "guests." They are difficult to exclude or evict from a home, but it is wise to do so and professional exterminators may be necessary in some instances. Raccoons may make themselves "at home" especially when food may be available in uncovered garbage. Raccoons may bite when they feel cornered or threatened. They may carry rabies. Young raccoons may carry a roundworm parasite, *Baylis ascaris* procyonis that human toddlers may ingest from raccoon feces that can result in brain abscesses.

Occupations

Veterinarians in practice are constantly exposed to pets and farm animals and in some cases to zoo animals. They should be vaccinated against rabies. In the southwestern USA veterinarians

have contracted the plague from treating infected cats which are especially prone to be infected or carry fleas from wild rodents. In addition to veterinarians, butchers, abattoir workers, farmers, ranchers, biologists, zoo workers and animal breeders are all liable to be exposed to zoonoses in their daily work. Animal husbandry can expose farmers to three *Brucella* species and Q fever from birth products of cows, goats, and pigs. Microbiologists have been infected with a number of organisms especially *Brucella* spp. and *Mycobacterium tuberculous*.

Habits and Hobbies

Some people are more regularly exposed to the microflora of pets by sleeping with them or kissing them while the pet licks the humans' mouths. Changing cat litter exposes people to toxoplasmosis. In addition sandboxes can be used by neighbors' or feral cats and serve as a source for *Toxoplasma gondii* to infect children. Changing papers from bird cages (as well as handling and kissing birds) may expose owners to ornithosis, salmonellosis, or cryptococcosis, the latter two being well recognized opportunistic pathogens. Hunting and dressing prey can include exposure to tularemia, or brucellosis and even horse back riding can include exposure to mice and rats living with the horses in the stables and shedding their organisms. In addition, *Rhodococcus equi*, is an opportunistic pathogen which has been associated with horse contact

Since dogs, cats, and birds are the most common pets and live closest to their human owners, they will receive the most attention.

Dogs (Table 42.1)

Dog bites frequently result in infections just as human bites do and the mouth flora bacteria causing infection are similar with the exception of *Pasteurella multocida* and *Capnocytophaga canimorsus*, which are more commonly found in dog bites. Both the organisms are sensitive to beta lactams and augmentin. The most important feature of bites, however, is that anaerobes may flourish in the presence of dead tissue so that drainage is all important. Prevention is dependent on education of children and adults about caution with strange dogs and with their own pet dogs, which may bite because of fear often combined with surprise such as stumbling on the pet. Other infections from dogs may be from organisms carried in their gastrointestinal tracts and hygienic measures must be stressed in all potential hosts, but especially those who are immunocompromised. Particular care should be taken with dogs with loose stools. Dog saliva or sputum may carry *Bordetella bronchiseptica*, an opportunistic

Table 42.1 Dogs-associated zoonoses in cancer patients

Organisms	Exposures	Prevention	Diagnosis	Treatment
Bacteria				
Mixed mouth flora including *Streptococcus pyogenes* MSSA or MRSA	Bites	Avoid	Smear and culture	Augmentin, usually empiric, drain when necessary
Pasteurella multocida	Bites	Avoid	Smear and culture	Augmentin, usually empiric, drain when necessary
Capnocytophaga canimorsus	Bites	Avoid	Smear and culture	Augmentin, usually empiric, drain when necessary
Brucella canis	Urine and birth products	Avoid	Smear and blood culture	Tetracycline
Bordetella bronchoseptica[a]	Saliva or sputum	Avoid	Serology, culture and smear	Tetracycline
Salmonella spp. (except *Salmonella typhosa*)[a]	Feces	Avoid	Culture stool and blood	Quinolone, susceptibility prn
Campylobacter spp.[a]	Feces	Avoid	Culture stool and blood	Quinolone or macrolide susceptibility prn
Yersinia pestis[a]	Fleas, sputum	Flea powder	Culture blood and lymph node, sputum	Gentamicin ± quinolone empiric prn
Francisella tularensis	Ticks, skincuts	Carefully remove	Culture blood and skin lesion	Quinolone or aminoglycoside
Leptospira spp.	Urine	Avoid	Serology, PCR	Penicillin, tetracycline
Borrelia burgdorferi	Ticks	Avoid, remove immediately (within 24 h)	Serology	Penicillin
Anaplasma phagocytophilum	Ticks	Avoid, remove immediately	Blood smear, culture PCR	Tetracycline
Ehrlichia spp.	Ticks	Avoid, remove immediately	Blood smear, culture PCR	Tetracycline
Rickettsia rickettsii	Ticks	Avoid, remove immediately	Serology, PCR, skin biopsy	Tetracycline
Fungi				
Blastomyces dermatitidis	Sylvan soil on pets	Keep clean	Smear and culture	Amphotericin B
Microsporon spp.	Hair or lesions	Keep clean and treat	Smear and culture	Topical azole
Trychophyton spp	Hair or lesions	Keep clean and treat	Smear and culture	Topical azole
Parasites				
Giardia lamblia	Feces	Avoid	Stool exam	Metronidazole
Babesia species[a]	Ticks	Remove, tick powder	Blood smear serology	Clindamycin + quinine, atovaquone + azithromycin
Toxocara canis	Feces	Avoid	Smear	Mebendazole or thiabendazole
Dipylidium caninum	Feces, fleas	Avoid feces and fleas	Smear	Niclosamide
Dirofilaria immitis	Mosquitoes	Treat dogs	Serology, lung biopsy	Extirpation
Ecchinococcus granulosus	Feces	Avoid	Smear or biopsy	Albendazole or extirpation
Ancylostoma caninum	Feces	Avoid	Smear or biopsy	Albendazole
Cryptosporidium spp.[a]	Feces	Avoid	Smear	Paramomycin, nitazoxanide, azithromycin
Viruses				
Rabies virus	Bites, saliva	Avoid, vaccine	PM on dog	Presumptive vaccine therapy
LCM virus[a]	Urine	Avoid	Serology, PCR	Supportive
Influenza virus[a]	Respiratory secretions	Avoid, vaccine	Sputum smear serology, PCR	Oseltamivir, zanamavir
Mumps virus	Respiratory secretions	Avoid, vaccine	Saliva	Supportive

[a] Opportunistic pathogen

pathogen, which can produce a whooping cough-like illness in the immunocompromised patient. Dog saliva can also be colonized with *Yersinia pestis*. *Leptospira* spp. can be passed onto humans from dog urine producing leptospirosis. An increase in incidence of this infection has been reported in humans in suburban areas. Dog fleas and ticks should be controlled as indicated in Table 42.1 as part of routine veterinary care and if found should be removed immediately using tweezers or gloves and dropped in alcohol, a toilet or a campfire.

Among the fungi, *Blastomyces dermatiditis* has been associated with dog contact, but it maybe the soil with which both human and dog have contact, which is the vector.

Dermatophytes may cause severe skin infections in patients with T-cell defects and when seen in a dog should be cared for promptly.

Parasites are usually passed from dogs to humans via feces. *Dipylidium caninum*, the dog tapeworm, however, is transmitted by infected fleas, usually ingested by children. *Dirofilaria immitis*, the dog heartworm is transmitted via mosquitoes and can be prevented by prophylaxis of the dog as directed by a veterinarian.

Viruses can be transmitted by various routes, usually respiratory or by saliva. The frequency of spread of influenza viruses to humans is unclear, but should be prevented by immunization of humans. An immunosuppressed patient may not show a normal antibody response, but some protection may result. In the event of a novel influenza virus such as H1N1, when a vaccine is not available, respiratory precautions should be used. Rabies should be considered in any dog bite. If rabies cannot be ruled out in the dog, prophylactic vaccine should be administered to the patient. The regimen should include five inoculations in an immunocompromised host rather than the four now recommended for the normal host [10].

Cats (Table 42.2)

Most infections we get from cats (with the possible exception of bites) are from free roaming cats, which acquire the zoonotic infection from other animals in the wild. Cats carry many of the same organisms as dogs and bites result in the same types of infections. The bites are usually associated with stepping on the cat, startling it in some other fashion or holding it against its will. Cleansing and draining are important just as for dog bites,

Cat scratch disease due to *Bartonella henseleae* has been associated with cat scratches of minimal size as well as larger and sometimes none are apparent at all. Kittens are often the carriers, especially those which roam outside. Feral cats are much more likely to be infected than house cats [11].

Q fever due to *Coxiella burnetii* usually follows exposure to farm animals, but cats – especially farm cats can carry it and pass it to humans through exposure to birth products.

The Plague due to *Y. pestis* can be transmitted to humans by cat fleas or if the cat is sick with pneumonia the organism can be carried in the saliva or sputum. The cats contract the infection or fleas from rodents. The organism is endemic to the USA southwest, but can also be found worldwide. Tularemia due to *Francisella tularensis* can be contracted from direct contact with rabbits or from ticks from cats as well as dogs and is endemic to the southern USA.

The ubiquitous gastrointestinal pathogens *Campylobacter* spp. and *Salmonella* spp. can be transmitted through cat feces.

Among the fungi, *Cryptococcus neoformans* or *Cryptococcus gattii* may be carried by cats especially in nasopharyngeal granulomas. How often they may be passed to humans is uncertain, but nuzzling cats when immunosuppressed should be avoided.

Table 42.2 Cats associated zoonoses in cancer patients

Organisms	Exposures	Prevention	Diagnosis	Treatment
Bacteria				
Mixed mouth flora including *S. pyogenes* and MSSA or MRSA	Bites	Avoid	Smear and culture	Drain prn augmentin
Pasteurella multocida	Bites	Avoid	Smear and culture	Drain prn augmentin
Capnocytophaga spp.	Bites	Avoid	Smear and culture	Drain prn augmentin
Bartonella henselae[a]	Bites scratches	Avoid	Smear and culture serology	Drain prn azithromycin or beta lactam
Coxiella burnetii	Exposure to birth products	Avoid	Blood, lymph node biopsy culture	Tetracycline
Yersinia pestis[a]	Saliva/sputum fleas	Avoid, flea powder	Smear and culture serology	Gentamicin ± quinolone, empiric prn
Francisella tularensis	Ticks, sores, cuts	Remove, tick powder	Smear and culture	Quinolone or aminoglycoside
Campylobacter spp.[a]	Feces	Avoid	Culture feces ± blood	Quinolone or macrolide
Salmonella spp.[a]	Feces	Avoid	Culture feces ± blood	Beta lactam or quinolone
Fungi				
Cryptococcus neoformans[a]	Nasal secretions	See DVM avoid	Smear and culture antigen detection	Amphotericin B + 5FC fluconazole
Dermatophytes	Skin lesions	See DVM avoid	Smear, culture	Topical azoles
Parasites				
Toxoplasma gondii[a]	Feces	Avoid	Serology biopsy	Sulfa pyrimethamine
Ancyclostoma caninum	Feces	Avoid	Stool exam	Albendazole
Echinococcus multilocularis	Feces	Avoid	Stool exam	Albendazole
Viruses				
Rabies virus	Bites, saliva	Avoid, vaccine	Biopsy of contact	Vaccine
Cowpox virus[a]	Skin lesions	Avoid	Smear, culture	Supportive

[a] Opportunistic pathogen

Just as with dogs, cat dermatophytes should be controlled in consultation with a veterinarian.

T. gondii is the most significant opportunistic parasite carried by cats, which takes advantage of T-cell defects. It is widespread in nature, found in mice and other rodents which transmit it to cats, which can then pass it to humans through their feces. In the normal host most infections are asymptomatic or mild, but severe disease including brain abscess may be seen in highly susceptible patients. Since many of the disseminated infections are due to unpredictable reactivation of latent infections it is impractical to use antimicrobial prophylaxis for all patients with antibody indicating previous infection. Very low T cells (<200 cells/μL) should be a consideration for prophylaxis. It is prudent to advise all patients at risk to avoid cat feces and specifically not to empty "kitty litter" boxes. Somebody else in the household should that.

Ancylostma caninum and *Echinococcus multilocularis* can be contracted from cat feces as well as from dogs

Among the viruses, cats can transmit rabies and should be vaccinated and kept up to date just as with dogs.

Cowpox virus can be transmitted to humans from exposure to infected cats [12]. Infections can be severe and persistent in humans and especially in those in the habit of nuzzling the cat's nose where the virus may be carried with or without evident lesions. In humans, the lesions can be destructive locally or in the immunocompromised, disseminate. It is possible that an apparent increase in these infections in Europe is associated with lose of immunity among the general population due to cessation of smallpox vaccinations with vaccinia virus (cowpox) vaccine.

Birds (Table 42.3)

It is not easy to avoid bird feces, especially if the birds are kept as pets. Some one has to clean the cages and it should not be an immunocompromised host. The best known organism is *Chlamydia psittaci*, the cause of parrot fever or psittacosis, which should be called ornithosis because any bird can be a carrier not just psitticine or parrot-like birds. Most birds purchased in pet shops have been quarantined before sale and thus should be cleared of the danger of carrying *C. psittaci*, but regularly birds are sold without this precaution, especially by unauthorized dealers.

Birds may also carry *Campylobacter* and *Salmonella* species.

Very rarely members of the parrot family have carried *M. tuberculous* and infected humans [13]. Such birds are usually symptomatic exhibiting weight loss, ruffled feathers, hoarseness and lymphadenopathy.

Histoplasma capsulatum find the feces of birds a rich source of nourishment and colonize their gastrointestinal tracts as well as the feces. The fungus grows in abundance particularly in the feces of chickens and "blackbirds" including swallows and starlings. Chicken farms and coops, chimneys, blackbird roosts in belfries, or copses should be avoided by the immunocompromised host.

C. neoformans is classically known to flourish in pigeon feces, but also has been isolated from a patient with cryptococcal meningitis and his parakeet with genetically identical fungi [14].

Table 42.3 Birds associated zoonoses in cancer patients

Organisms	Exposures	Prevention	Diagnosis	Treatment
Bacteria				
Chalmydia psittaci	All birds	Avoid feces	Sputum smear, culture	Tetracycline, erythromycin
Salmonella spp.[a]	All birds	Avoid feces	Stool culture	Beta lactam, fluoroquinolone
Campylobacter spp.[a]	All birds	Avoid feces	Stool culture	Azithromycin, fluoroquinolone
Mycobacterium tuberculous[a]	Parrot family	Avoid respiratory secretions	Smear, culture, PCR	Quadruple therapy
Fungi				
Histoplasma capsulatum[a]	Blackbirds, chickens	Avoid feces	Smear, culture, sputum urine antigen	Azoles or amphotericin B
Cryptococcus neoformans[a]	Pigeons, psitticines	Avoid feces	Antigen in CSF or serum smear, culture	Azoles or amphotericin B ± 5FC
Parasites				
Cryptosporidium spp.[a]	Wild or caged birds	Avoid feces	Stool smear	Nitazoxanide
Giardia lamblia[a]	Wild or caged birds	Avoid feces	Stool smear	Metranidazole
Viruses				
Influenza viruses[a]	Ducks, chickens, migrating birds	Vaccine, avoid feces	Sputum smear, culture, PCR	Smear, culture, PCR
Alphaviruses	Migrating birds	Avoid mosquotes	Culture, serology	Supportive care
Flavoviruses	Migrating birds	Avoid mosquotes	Culture, serology	Supportive care
West Nile virus[a]	Migrating birds	Avoid mosquotes	Culture, serology	Supportive care

[a] Opportunistic pathogen

Among the parasites, Cryptosporidia species have been isolated from wild or caged birds and implicated in infecting humans. A rare occurrence has been the finding of *Giardia lamblia* causing diarrheal disease in a patient and his love birds.

Farm birds such as chickens, turkeys, ducks, geese and others, and wild migrating birds of all sorts have proven to be a rich source of viral infection for humans. Many of these infections such as influenza are spread through the feces and others are the result of mosquitoes carrying the virus from birds to humans. These include alphaviruses and flaviviruses causing encephalitis. An excellent example is the West Nile virus, which so readily crossed the North American continent with migrating birds and mosquitoes infecting horses as well as humans.

Less Common Pets or Contacts (Table 42.4)

Mammals

Rodents: The usual pathogens passed from rodents to humans are mouth flora from bites usually including *P. multocida*, and fecal spread of *Campylobacter* spp. and *Salmonella* spp. Mice in the southwestern USA carry Hanta virus, which regularly causes a fatal pneumonia. Mice and hamsters may carry lymphocytic choriomeningitis virus and mice may also harbor mites that carry *Rickettsia akari*, which cause rickettsialpox.

Praire dogs (some people keep as pets) along with other wild rodents may carry plague or tularemia (especially rabbits), and ferrets may carry influenza. Racoons, in addition to

Table 42.4 Less common pets or contacts

Mammals
  Rodents: mice, rats, hamsters, gerbils, guinea pigs, rabbits, ferrets, and raccoons
  Beasts of burden: horses, mules, donkeys, oxen, camels, and water buffalo
  Farm animals: cattle, pigs, sheep, goats, and Yaks
  Nonhuman primates: chimps, rhesus, cynomologus macaques, lemurs, and marmosets
  Bats: all species
Birds
  Canaries, finches, parakeets, parrots, and lovebirds
  Chickens, ducks, geese, and turkeys
  Wild birds – at feeders, in shelters, and shot by hunters
Reptiles
  Snakes, lizards, turtles, alligators, and horned toads
Amphibians
  Frogs, toads, salamanders, and newts
Fish
  Aquarium fish, caught, commercial or sport fish, and farmed fish
Note: see text for discussion

rabies, may carry a parasite, *B. ascaris* whose eggs maybe ingested from stools especially by infants playing in dirt, resulting in encephalitis. Pet rats may carry *Streptobacillus moniliformis* [15, 16] resulting in endocarditis in owners.

Bats are the most common carriers of rabies in the USA. They are to be avoided. Fruit bats have been implicated in Australia and Indonesia in transmitting encephalitis viruses that infect horses and humans in the former and pigs and humans in the latter. Bats are also carriers of the SARS corona virus in addition to civet cats and raccoon dogs in Asia.

Beasts of burden: Horses can transmit rabies. They also serve as an intermediate host for encephalitides (Eastern, Western and Venezuelan Equine, and West Nile virus) via mosquitoes to humans. Horse associated *R. equi* can cause severe disease, which manifests by skin and pulmonary lesions in patients with T-cell defects.

Farm animals: Brucellosis can be acquired from cows, pigs, and goats. They are popular in petting zoos and should be handled with special precautions by the zoo keepers and visitors. It is best not to pet them. This includes sheep which may infect humans with orf virus, which cause large pustular skin lesions. Cows may excrete *Escherichia coli* 0157:H4, which can cause lethal disease in humans. Bovine tuberculous due to *Mycobacterium bovis* can cause invasive infection in the immunosuppressed patient. Water buffalo urine can be a rich source of *Leptospira* spp. for human infections.

Nonhuman primates: Even in the immunocompetent, human Herpes simiae infection is close to 100% lethal due to encephalitis. Rhesus, cynomolgus or vervet monkeys should not be kept as pets. They can be asymptomatic carriers of this potentially fatal herpes virus. Animal handlers should be trained to work with monkeys, which should be free from infection before contact. Even so, trained animal handlers have died due to this infection.

The highly lethal Marburg and Ebola viruses can also be transmitted from monkey to man.

Monkey pox virus can cause local lesions in man and even disseminate causing a smallpox like disease. A recent outbreak in the USA was caused by a Gambian rat, which developed monkey pox lesions after arriving in a pet store where the infection was transmitted to American praire dogs, which were sold as pets and resulted in multiple cases in humans. Physicians and public health officials included small pox in the differential diagnosis causing quite a stir in several communities [17].

Chimpanzees have been kept as pets and can infect humans with *M. tuberculous* or carry human malaria. They have become infected with measles, hepatitis A virus, or influenza virus along with *Streptococcus pneumoniae* and *Staphylococcus aureus*. Intestinal pathogens such as giardia and Strongyloides can be excreted by chimpanzees.

Birds

In addition to commonly kept birds, chickens, ducks, turkeys, and geese can carry *C. psittaci* and strains of influenza. The avian flu strain, H3N1 has been isolated from many different birds, but chickens appear to be the primary source of the cases first described. Wild migrating birds often mix with flocks of farmed birds and can carry an organism thousands of miles. Humans who keep bird feeders filled are regularly exposed to bird excreta, which may carry organisms listed in Table 42.3 or in addition to those adenoviruses.

Reptiles

Snakes, lizards, turtles, alligators, or horned toads may all carry enteric pathogens and excrete them into terrarium soil or water sources.

Amphibians

Frogs, Toads, salamanders, or newts may carry the same organisms as reptiles and excrete them into their water or soil.

Fish

Aquarium fish may carry and excrete into their water *Mycobacterium marinum*, which can cause nodular skin lesions or disseminate in immunosuppressed patients. Farmed fish may carry *Vibrio*, vulnificus which causes especially severe gastroenteritis in the presence of immune defects. People handling fish commercially or in home preparation may be exposed to *Streptococcus iniae* or *Erysipelothrix rhusiopathiae*, both of which may cause local skin lesions or disseminate.

Foot Note

For detailed instructions on prevention of infections, which can apply to cancer patients, the CDC has published two compendia [18, 19] on the subject in HIV infected people. These can be applied to children and adults with T-Cell mediated immune defects and these are the patients most likely to develop opportunistic zoonotic infections. These are excellent reference documents.

Summary

Prevention of zoonoses in cancer patients is the theme of this chapter and it is hoped that it will encourage and help doctors caring for such patients in educating them to avoid such infections. Avoidance need not include separation from a pet, or occupation, or recreation, but the use of caution conditioned by knowledge of the sources of infection and the way we may contract them should lead to effective prevention.

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Part IV
Management of Antimicrobial Therapy

Chapter 43
Antimicrobial Stewardship: Considerations for a Cancer Center

Coralia N. Mihu, Alla Paskovaty, and Susan K. Seo

Abstract Since the discovery of penicillin, unbridled enthusiasm for antibiotics has led to their extensive application in medicine, animal care, and agriculture. Injudicious antimicrobial use has also contributed to the emergence and spread of multidrug-resistant bacteria, creating a situation in which there are few or no treatment options for infections due to these organisms. There is increasing awareness that antimicrobial resistance adversely impacts patient safety and public health. In essence, effective antimicrobial stewardship entails the optimal selection, dose, and duration of an antibiotic, resulting in the cure of an infection with minimal toxicity to the patient and minimal impact on selective pressure. A detailed discussion on this important issue is presented in this chapter.

Keywords Multidrug-resistant bacteria • Injudicious antimicrobial use • Optimal antibiotic selection • Duration of antibiotic therapy • Reduced drug toxicity

Introduction

Since the discovery of penicillin, unbridled enthusiasm for antibiotics has led to their extensive application in medicine, animal care, and agriculture [1]. However, representative studies from around the world have shown inappropriate antimicrobial usage in humans between a range of 20 and 50% [2–5]. One unintended outcome has been the selection of pathogenic organisms. An example is *Clostridium difficile*. Although earlier studies showed the value of restricting a specific drug (e.g., clindamycin) to reduce *C. difficile* infection (CDI) and control outbreaks [6–8], the popularity of fluoroquinolones as prescribed agents has been associated with more recent epidemics of

CDI [9, 10]. Increased fluoroquinolone resistance among epidemic (i.e., restriction-endonuclease analysis group BI/North American PFGE type I strains) and some nonepidemic strains of *C. difficile* has been described [11].

Injudicious antimicrobial use has also contributed to the emergence and spread of multidrug-resistant bacteria, creating a situation in which there are few or no treatment options for infections due to these organisms. The introduction of newer therapies is not immune to the phenomenon of resistance development, as in the case of tigecycline and *Acinetobacter baumanii* [12] or linezolid and vancomycin-resistant *Enterococcus faecium* (VRE) [13]. Despite a critical need for novel antibacterial agents, there are indications that such drug development programs are declining [14–16]. Emerging resistance is not limited to bacteria since resistant viral, fungal, and parasitic pathogens have also been recognized [17–22].

There is an increasing awareness that antimicrobial resistance adversely impacts patient safety and public health. Resistance can lead to a delay in administering microbiologically effective therapy [23, 24]. In case-control studies, infections due to resistant organisms have been associated with higher rates of mortality, longer hospital stays, and increased medical care costs [24–28]. In 1998, the Institute of Medicine estimated that the annual cost of infections caused by antibiotic-resistant bacteria was $4–5 billion [29]. Finally, drug-associated toxicity is an underappreciated but significant consequence of antimicrobial use. A recent study estimated that >142,000 visits were made annually to United States (US) emergency departments for antibiotic-related adverse events, of which four-fifths were allergic reactions [30]. These findings highlight the tremendous need for judicious use of antimicrobial agents.

In essence, effective antimicrobial stewardship entails the optimal selection, dose, and duration of an antibiotic, resulting in the cure of an infection with minimal toxicity to the patient and minimal impact on selective pressure [31, 32]. While several published surveys demonstrate an increased acceptance on the part of healthcare institutions to establish programs for rational antimicrobial use, it is clear that practices vary considerably and that there is room for improvement

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in both the US and Europe [33–37]. In 2007, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) jointly published a statement that outlined the rationale and provided guidelines for development of a formal antimicrobial stewardship program (ASP) by healthcare institutions [38]. How an ASP is implemented will vary from institution to institution, but a comprehensive approach with a full-time dedicated multidisciplinary team appears to be capable of yielding sustained and favorable clinical and economic outcomes [39]. Ideally, each institution should also have an active surveillance system to monitor resistant organisms and an infection control program to minimize secondary transmission of these pathogens [31].

The cancer center represents a distinctive entity, and formation of an ASP should take into account issues that are unique to the cancer center, such as local susceptibility patterns and the complexities of managing infectious complications in patients with varying immunocompromised states. Infection, a common cause of morbidity and mortality in patients with cancer, can result not only from the direct effect of the tumor, but also from the use of foreign devices (e.g., intravascular catheters) to aid in disease management and from cancer treatment (e.g., surgery, chemotherapy, radiation, or combination therapy). Current cancer therapies including tumor necrosis factor antagonists, antimetabolites, and monoclonal antilymphocyte antibodies have become increasingly sophisticated, and their use can add to profound immunosuppression [40–42]. These and other cancer therapies can also influence antimicrobial choice by virtue of their side effect profile (e.g., hepatic or renal toxicity) and potential drug–drug interaction. Another interesting dilemma is the recent influx of new and costly anti-infectives (e.g., mold-active agents like voriconazole and posaconazole, antiviral agents like cidofovir) that may be an incentive to develop an ASP for meaningful cost-containment [39]. The purpose of this chapter is to explore several aspects of coordinating an ASP at a cancer center, including formation of a multidisciplinary team, stewardship strategies, and barriers/challenges.

Implementation of ASPs

Effective ASPs can reduce antimicrobial use, improve patient care, and be financially self-supporting in both large academic institutions and small community hospitals [43–47]. Furthermore, the promotion of appropriate antimicrobial use by ASPs is in alignment with a growing emphasis on patient safety and quality assurance [48]. The support of hospital administration, medical staff leadership, and local providers is essential not only for the development of an institutional

Table 43.1 Creating a multidisciplinary antimicrobial stewardship program

1. Obtain baseline information
   a. Determine institutional antimicrobial usage and expenditures
   b. Know institutional susceptibilities
   c. Identify problems
2. Select strategies by which to execute antimicrobial stewardship
3. Determine team members and their roles and responsibilities
4. Establish support of hospital administration
5. Build constructive relations with other hospital services and clinicians
6. Devise a fail-safe mechanism for problem-solving
7. Provide feedback to prescribers
8. Conduct audits to monitor effectiveness of program activities

ASP but also for its maintenance [38]. From a practical standpoint, creation of an ASP should involve understanding institutional patterns of antibiotic usage, expenditures, and resistance. Such baseline knowledge is a key to setting goals and quantifying benefits of program activities. Other aims include selecting strategies by which antimicrobial stewardship will be executed in the hospital, determining personnel and means of financial support for the program, and constructing positive relations with the hospital-at-large. The ASP should also provide feedback to prescribers and conduct regular audits to validate the effectiveness of program activities (Table 43.1) [31, 49].

A computer-based infrastructure facilitates stewardship efforts. Utilization of healthcare information technology (IT) in the form of electronic medical records (EMR), computer order entry (COE), and clinical decision-support has the potential to improve prescribing and reduce medication errors as demonstrated by LDS Hospital in Salt Lake City, Utah [50–53]. While the computer surveillance and decision-support system of LDS Hospital is the ideal, conformation of such technology to individual institutions on a broader scale is not yet feasible. Depending on the IT resources available, institutional ASPs can still find ways to efficiently follow local susceptibilities, monitor antimicrobial use, and target antimicrobial interventions [38].

The Multidisciplinary Antimicrobial Stewardship Team

The core members of a multidisciplinary ASP are the Infectious Diseases (ID) physician and one or more clinical pharmacists. These members generally have dedicated time precisely for the purpose of antibiotic management and are compensated accordingly. Since antimicrobial stewardship relates to patient safety and is considered to be a medical staff function, the program is usually directed by the ID specialist or codirected by an ID physician and a clinical pharmacist with ID training [38].

Because of the specialized nature of oncologic care, a cancer center is well suited for a multidisciplinary team approach. One of the benefits of collaboration is the ability to develop and disseminate center-wide or malignancy-specific protocols for managing infectious diseases. The ASP team can work with medical and surgical oncologists as well as other allied healthcare specialists (e.g., clinical chemistry and hematology laboratories, microbiology, nursing, pathology, pharmacy, radiation oncology, radiology) as needed to build consensus, educate, monitor implementation, assess compliance and outcomes, and update ID management strategies. Another joint effort would be to work with the hospital pharmacy and therapeutics (P&T) committee to review and modify the formulary, keeping in mind that certain anti-infective classes such as mold-active antifungal agents may be used in high volume for a particular cancer patient population (e.g., patients with acute leukemia) rather than hospital-wide.

Specific to a cancer center, the ID physician with ASP responsibilities should have a broad and deep understanding of the immune defects associated with the underlying malignancy or cancer therapies, the pathogens known to cause infections in the immunocompromised host, and strategies for diagnosis and treatment. Similarly, ASP pharmacists at a cancer center can provide information regarding new or existing chemotherapeutic or antimicrobial agents and their associated pharmacokinetics, dosing schedules, drug–drug interactions, and toxicities. They can also serve as a liaison to hospital pharmacy by providing education to their pharmacy colleagues, monitoring formulary and nonformulary use, and ensuring appropriate antimicrobial selection and dosing.

Although microbiologists and hospital epidemiologists may not be directly involved in the day-to-day activities of the multidisciplinary ASP, they are integral to the functioning of the team. The microbiology laboratory ensures the timely identification of pathogens and the selective reporting of susceptibilities [38, 54]. One trend, however, is the outsourcing of infrequently ordered microbiologic tests to outside reference laboratories as part of cost-containment and quality control efforts [55]. This practice may affect clinical decision-making in high-risk patients, such as those with hematologic malignancies or allogeneic hematopoietic stem cell transplant (HSCT) recipients in whom such tests may be disproportionately ordered. Tracking resistance patterns in the hospital on an annual basis is another important task. Of note, cancer center- or unit-specific antibiograms should be formulated as patterns of antimicrobial use and thus susceptibilities of pathogenic bacteria may differ from the rest of the hospital [56, 57]. If possible, antifungal susceptibilities of *Candida* species should be tabulated, particularly in light of azole prophylaxis in certain cancer patient groups (e.g., allogeneic and autologous HSCT recipients) [58, 59].

Hospital epidemiologists create policies to contain the transmission of resistant pathogens, and they can provide assistance with analyzing the relationship between patterns of antibiotic use and trends in bacterial resistance. Infection control personnel are also well placed to provide continuing education programs to hospital staff [38, 54].

Stewardship Strategies

In general, the ASP team should understand their hospital culture in terms of prescribing practice and choose stewardship strategies that fit within the institutional framework. While there are no randomized, controlled trials in this field, two primary, proactive strategies exist: prior approval (also referred to as preauthorization) and postprescribing review (also called prospective audit with feedback). These are not mutually exclusive, and either approach can be enhanced with supplemental strategies.

The first core strategy links prior approval to a restricted formulary. Most hospitals have a P&T committee that evaluates whether a drug would be suitable for inclusion on the formulary on the basis of therapeutic efficacy, side effect profile, and cost. A well-structured antimicrobial formulary reflects local susceptibilities, minimizes the number of agents available for effective therapy, and avoids duplication [60, 61]. Furthermore, restriction of certain agents with the condition that prescribers call an ID physician or clinical pharmacist for approval has been reported to be effective in reducing inappropriate use and expenditures without detriment to patient care [62–65]. An interesting study performed at the Hospital of the University of Pennsylvania (HUP) in Philadelphia found that recommendations made by the multidisciplinary ASP team were more likely to be in accordance with prescribing guidelines (87 vs. 47%, $p<0.001$) and to result in clinical cure (64 vs. 42%, $p=0.007$) compared with those generated by ID fellows [44]. These findings highlight the need for scheduled time to engage thoughtfully in the approval process as well as staffing by practitioners who are viewed as having expertise in using antibiotics. This system, however, may be viewed as "policing," and clinicians anxious to maintain good relations with their colleagues circumventing it. In addition, prior approval generally only affects initial choice for empiric therapy. This strategy has little influence on duration or modification of therapy once microbiologic and radiographic evidence becomes available.

In postprescribing review, patients already on empiric therapy are identified by computer-generated screening and targeted for evaluation. When an intervention is deemed necessary, the ASP team communicates with the primary service, either verbally or via nonpermanent notes left in the medical record. Examples of interventions include ensuring appropriate

dosing, narrowing coverage (also called streamlining or de-escalation), modifying duration, or stopping antibiotics altogether if there is no evidence for infection.

The report by Schentag et al. was one of the earliest to show that clinical pharmacy specialists in conjunction with ID support could effectively handle streamlining and intravenous (IV)-to-oral conversion. By linking the pharmacy and microbiology computer systems, patients could be screened for inappropriate dosing as well as for mismatches between pathogens and drugs. No adverse outcomes were noted in patients whose regimens were modified or stopped, and antibiotic expenditures declined from 31% of the total pharmacy budget to 21.5% in the first year of operation [66]. Improvements in antimicrobial use with associated cost-savings have also been reported by other centers [43, 45]. Moreover, Carling et al. noted concomitant decreased rates of nosocomial infections due to *C. difficile* or resistant Enterobacteriaceae [45]. A significant impact can even be demonstrated at hospitals where daily review is not feasible due to limited resources. At a small community hospital in West Monroe, Louisiana, postprescribing review over a 1-year period by an ID physician and a clinical pharmacist 3 days a week led to a 19% reduction in antimicrobial expenditures [46]. This same report also revealed a potential shortcoming of postprescribing review in that only 69% of 488 suggested interventions were accepted and implemented. By the same token, success or failure of this system rests on the ability and availability of the ASP team members to educate prescribers during the intervention process [67].

Supplemental stewardship strategies include, but are not limited to, education, clinical pathways, streamlining, and IV-to-oral conversion. Depending on the personnel and available institutional resources, an ASP can combine one or more of these with the core stewardship strategy to augment program activities. A full, detailed explanation of these and other supplemental strategies is beyond the scope of this chapter but can be found in other published reviews and guidelines [38, 39, 68].

Briefly, education is the most basic strategy by which to influence clinicians to adopt and maintain good prescribing practices. Initiatives range from one-on-one instruction and formalized educational programs (e.g., lectures, mailings, internet-based learning activities) to utilization review with feedback. Although education is the cornerstone of any ASP, its effectiveness is dependent on the motivation of the clinician to make a behavioral change [69, 70]. Without incorporation of active intervention, education alone is marginally effective and has not demonstrated a sustained impact on prescribing practices [71–73].

Clinical pathways involve the development of peer-reviewed guidelines for commonly encountered infectious diseases. By limiting choice, the process of antibiotic selection for prophylaxis or treatment of an infection is simplified. Examples of national guidelines that would be of

relevance to a cancer center include empiric treatment for fever and neutropenia [74], prevention of opportunistic infections in HSCT recipients [75, 76], treatment of aspergillosis [77], treatment of candidiasis [78], and surgical prophylaxis [79, 80]. Standardized antimicrobial order forms, automatic stop orders, and computerized systems can ease the implementation of guidelines [51, 68].

Streamlining is a process that ensures that antimicrobial therapy is matched to culture and susceptibility data within 48–72 h after initiation of treatment. In doing so, prolonged, excessively broad treatment can be avoided. As seen in the management of ventilator-associated pneumonia (VAP), antimicrobial therapy may be shortened [81] or even stopped based on clinical criteria and negative culture results [82, 83]. Singh et al. also found that the rate of subsequent antibiotic-resistant infections was lower in the group receiving short-course treatment for suspected VAP compared to those receiving standard duration (15 vs. 35%, $p = 0.017$) [82]. An economic benefit has also been derived from this strategy. In one report, recommendations for streamlining occurred in 54% of antibiotic courses over 7 months, resulting in a projected annual savings of $107,637 [84]. In another report, a pharmacist-based intervention to discontinue unnecessary agents was successful in 134 (98%) of 137 episodes. Potential drug cost-savings and reduction in redundant antibiotic combination days were $10,800 and 584 days, respectively [85].

Finally, a systematic plan for IV-to-oral conversion can decrease hospital length-of-stay (LOS) and healthcare costs. The excellent oral bioavailability of several antimicrobial classes, including the fluoroquinolones, azoles, and oxazolidinones, makes this approach quite feasible. In contrast to oral formulations, IV medications are generally more expensive and can be associated with adverse events like phlebitis and catheter-related infections. Patients also benefit since oral treatment is convenient and easy [86]. This strategy, however, is reserved for those who are hemodynamically stable, have improved clinically within 48 h of prior IV therapy, and have functioning gastrointestinal tracts. Individuals with severe immunodeficiency states or infections like meningitis and endocarditis are not candidates [86, 87]. Representative studies report a positive experience with IV-to-oral conversion in terms of clinical effectiveness and cost savings [88–91].

Barriers and Challenges

A survey of ID physicians conducted by the IDSA Emerging Infections Network (EIN) has identified potential barriers to participation in antimicrobial stewardship [92]. The first barrier is the time and effort needed to develop and maintain an ASP. In 1987, Woodward et al. estimated that more than 100 h per month of combined personnel time were needed to

handle telephone requests and antibiotic reviews for just three restricted antibiotic classes at their institution [62]. Nowadays, one can imagine the difficulties in pursing program activities if ASP team members, namely clinical pharmacists, are pulled for assignments elsewhere in the hospital.

Another barrier is recruiting personnel with necessary ID expertise. Hopefully, the growing need for ID-trained pharmacy specialists can be met by encouraging pharmacy schools to support residency training and by training additional preceptors to oversee the instruction of pharmacy residents interested in ID [93]. With respect to the ID physician community, lack of compensation for added work responsibilities and insufficient support by hospital administration are not insignificant issues. In the aforementioned IDSA EIN survey, only 46 (18%) of 250 respondents reported receiving direct remuneration for their participation in antimicrobial stewardship [92]. However, the increasing reluctance of public and private payers to reimburse for healthcare-associated infections (e.g., catheter-related infections) coupled with published data supporting the value of ID specialists in directing institutional antimicrobial stewardship or infection control programs can provide a framework to negotiate appropriate compensation by the hospital [94]. There is also a perception that a particular stewardship strategy, prior approval, may antagonize colleagues in other specialties and potentially lead to lost income due to fewer requests for consultations [92]. This sensitive issue may be of particular concern at nonteaching institutions, but alternative stewardship strategies (e.g., postprescribing review) that do not affect prescribing autonomy can be employed instead [95].

Finally, measuring the full impact of an ASP on clinical outcomes, economics, and resistance is challenging. While a successful ASP can be financially self-supporting, evaluating the true economic benefits can be tough since direct and indirect (i.e., dispensing, administering, monitoring) drug costs represent a fraction of what is affected by optimizing antimicrobial use. One needs to also factor potential cost-savings from avoided adverse drug events, shortened hospital LOS, and decelerated resistance development. While financial savings are typically greatest in the early phases of an ASP, achieving other desirable outcomes such as decreased inappropriate antimicrobial usage and reduced hospital LOS requires continued vigilance [94]. Evaluating the impact of a multidisciplinary ASP on curbing antibiotic resistance is more complicated due to the multifactorial nature of the problem. Theoretically, it is thought that optimizing antibiotic use will minimize selective pressure and maintain or improve bacterial susceptibilities. It is also assumed that this will be accompanied by improvement in survival. Data to support this second notion are sparse, particularly as there are numerous confounders [68, 96]. A more detailed discussion is forthcoming in the next chapter.

Summary

The emergence and spread of multidrug-resistant pathogens coupled with a drying-up antimicrobial pipeline have led to the realization that optimization of currently available agents is an important priority. This has prompted national ID professional societies to advocate for the creation of ASPs by healthcare institutions. Although developing an ASP at a cancer center may seem counterintuitive, cancer patients generally receive multifaceted oncologic care, and a multidisciplinary approach to managing anti-infective therapy is thus complementary. Regardless of the setting, maintenance of an ASP requires processes that are both sustainable and adaptable to the evolving needs of the institution. Frequent assessment of program design is essential to its continued success, and collaboration with other local ASPs is crucial for the benefit of the community-at-large. Joint educational programs are an excellent way to disseminate vital information and promote acceptance of ASP efforts. As more and more hospitals document reductions in unnecessary antimicrobial use, cost-savings, and improvements in patient care, implementation of multidisciplinary ASPs will become more widespread.

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Chapter 44
Controversies in Antimicrobial Stewardship

Graeme N. Forrest

Abstract Antimicrobial stewardship programs are recommended by the Infectious Diseases Society of America as a method to control antimicrobial costs and resistance. These programs are usually implemented hospital wide, but there is little evidence on their effects in oncology units. Three controversial areas of antimicrobial stewardship in oncology units include whether these programs decrease antimicrobial resistance when antimicrobial restriction is implemented, the role of antimicrobial cycling on Gram-negative resistance and that these programs rarely control outpatient antimicrobial therapy. This review will discuss these controversial areas with regard to the evidence, strength of trial design, and the generalizability of their outcomes.

Keywords Antimicrobial management • Antimicrobial resistance • Antibiotic cycling • Outpatient antibiotic therapy • VRE • *Clostridium difficile*

Introduction

The preceding chapter discussed the benefits and scope of antimicrobial stewardship in the cancer center. With the costs of prolonged antimicrobial use in patients, especially antifungals and the emergence of multidrug resistant (MDR) bacteria as a threat to patient care, there appears to be a greater urgency to improve antibiotic utilization by controlling their use at an institutional level as a means to control these problems. At present there is very little data on the impact of these programs in cancer centers, with most information based on hospital wide strategies.

As described, establishing an antimicrobial stewardship program is complicated by competing interests all looking for different outcomes. The hospital administration wants to save money through shorter length of stay, decreased pharmacy costs, and lower resistance; infection control is looking for decrease in emergence of resistance in bacteria; pharmacy wants to save money by reducing antimicrobial therapy; microbiology wants to perform less surveillance screening and less susceptibility testing to save money; and lastly infectious disease is expected to develop guidelines, provide staff, and enforcement of the guidelines while getting little in return from the hospital. All these groups have interests in different outcomes, and all these outcomes are usually different from the oncologists who are ultimately responsible for managing the patient and the last thing they want is a patient to die from infection that either was due to ineffective antimicrobial therapy because of either antimicrobial restriction or antimicrobial resistance. It is this conflict of interests that is the basis for the controversies in antimicrobial stewardship.

Fortunately, These conflicts are mitigated in many centers by using a team of specialists to care for oncology patients. This team usually consists of the oncologist, physician assistants or nurse practitioners, infectious disease physician, clinical pharmacists, and the nurses. Subsequently, the group develop guidelines based on evidence when possible and is implemented as a group effort; however there are still areas of controversy that arise even within these guidelines. Several of the controversies to be discussed in this chapter are the impact on antimicrobial resistance by stewardship programs, antimicrobial preauthorization, antibiotic cycling and de-escalation strategies, and outpatient antibiotic management.

Does Antimicrobial Stewardship Impact Antimicrobial Resistance?

From the first combination, antibiotic study in febrile neutropenia [1] followed later by the initiation of empiric antifungal therapy [2] have all contributed to lowering mortality from infection in oncology patients. There are many guidelines for the antimicrobial management of febrile

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neutropenia in oncology patients in the literature [3–6]. However, antibiotic proliferation within the cancer center has resulted in the emergence of antimicrobial drug resistant organisms, especially vancomycin resistant enterococci (VRE), extended spectrum beta lactamases (ESBL), and of more concern *Klebsiella pneumoniae* carbapenemases (KPC) [7–10]. Therein lies the conundrum; oncology patients need antibiotics often for prolonged periods of time due to their neutropenia [11], but this antibiotic pressure results in the emergence of resistant isolates. If a cancer center does have antimicrobial resistant organisms, this will impact on empiric antimicrobial therapy and result in the selection of either more expensive or more toxic or multiple combinations of antibiotics to ensure adequate coverage [12]. Is there enough evidence that a well-structured antimicrobial program can reduce antimicrobial resistance in a cancer center? This depends on whether the aim of the antimicrobial stewardship program is to arrest an outbreak of a multidrug resistant organism or to have a sustained effect on prevention of resistance [13].

In the oncology setting, the only data supporting antibiotic stewardship programs have been to control outbreaks of multidrug resistant organisms. In particular, the two most common organisms that are targeted are VRE and *Clostridium difficile* [8, 14, 15].

VRE is one of the most common causes of nosocomial blood stream infection in the cancer center, affecting centers worldwide [8, 14, 16–18]. In a cohort study of adult stem cell transplant (ASCT) recipients from the Mayo Clinic, VRE colonization was shown to be associated with increased mortality regardless of other factors at 100 days [19]. Also, Zaas et al. identified vancomycin usage (relative risk [RR] 1.98, Confidence intervals [CI] 1.25–3.14) as a significant risk factor for VRE bloodstream infection in patients with cancer [20]. In recent studies, the risk factors in the cancer center have been identified as aminoglycoside usage within the previous 30 days, while the use of a carbapenem was significantly associated with VR *E. faecium* bacteremia, which had poor outcomes [8]. Prior studies have demonstrated an association with vancomycin either alone or with third generation cephalosporins and sometimes with metronidazole [20–22].

The data supporting the role of vancomycin restriction and reduced acquisition of VRE is unclear. The largest study suggesting that vancomycin was the most significant modifiable risk factor, was performed at 20 hospitals and 50 intensive care units (ICU) where data was adjusted for MRSA colonization. Those ICU's using a directed quality improvement on vancomycin use resulted in a 7.5% reduction in VRE compared to a mean increase of 5.7% ($P < 0.001$) in those that did not [23]. As patients with hematologic malignancy due to their illness may be admitted to the ICU, reducing the risk of acquisition in this setting may be very important [24]. Overall,

most studies investigating vancomycin usage on VRE colonization and infection have been heterogeneous [25].

All vancomycin intervention studies have been quasi-experimental, pre-post intervention Type A designs at the lowest level of strength of study design as described by Harris et al., and have significant heterogeneity in their study populations [25, 26]. Reflecting their design, many were performed at a single center, lacked a control group, and none removed and reintroduced the interventions [15, 23, 27–35]. Definitions on VRE endemicity versus outbreak are lacking in these studies and most state that VRE have been prevalent for several years [15, 23, 25, 27–35]. Three studies were performed in a cancer center setting [15, 29, 33]. Shaikh et al. interventions were a multifaceted approach at the M.D. Anderson Cancer Center, where they implemented a "vancomycin order form" to decrease empiric vancomycin usage. Simultaneously they implemented infection control policies including hand washing, routine isolation, screening, disposable and dedicated equipment, thorough cleaning of nondisposable equipment, and cohorting [33]. Their interventions over 3 years showed a reduction of total VRE infections from 0.437/1,000 patient days in 1997 to 0.229/1,000 patient days in 1999 ($P = 0.008$) and a similar reduction in VRE bloodstream infections and a reduction in vancomycin from 416 g/1,000 patient days to 208 g/1,000 patient days [33]. Montecalvo et al. also performed a multifaceted approach in a cancer center to reduce VRE, reporting a 1-year result, with reduced length of stay and an estimated $189,000 saved with implementing a program [15]. None of the studies looked at mortality reduction, and there has been no long-term follow up to see if these interventions have had long-lasting effects [15, 29, 33].

The rest of the studies on vancomycin use and reduction of VRE were performed in noncancer settings, most commonly ICU's [27, 28, 30–32, 34–36]. All studies demonstrate a reduction in vancomycin usage, either hospital or unit specific. Seven [15, 23, 29–31, 33, 35] of these studies showed statistically significant reductions in VRE infections and colonization ranging from 46 to 83% [25, 29, 33]. The rest [28, 32, 34, 36] were a wash in VRE reduction. The main limitations of these studies is that none controlled for random variables and severity of illness and the main intervention may take time to have an impact on VRE acquisition and similarly the efficacy of the interventions may wane over time [25, 26]. Over the last decade, antibiotics other than vancomycin implicated in causing VRE outbreaks (i.e., ceftazidime, antianaerobic agents) which [27, 30, 37, 38] have changed and reflects that good infection control policies at an institution are important for control of VRE. As good policy though, control of vancomycin usage is as important as good infection control practices in controlling VRE. What are needed are larger multicenter controlled trials to see the true benefit of vancomycin restriction on VRE.

Clostridium difficile associated diarrhea (CDAD) is associated with considerable morbidity in oncology patients [39, 40]. With the emergence of more hypervirulent strains (group B1 toxin) which have a higher mortality, are quinolone resistant, and fail metronidazole therapy more, prevention of this infection has become more imperative [41–43]. The same limitations of the VRE studies inherent in the CDAD data. Although recognized that the importance of antibiotic control, in particular cephalosporins, quinolones, and clindamycin, infection control procedures are just as important, including hand washing, patient isolation, and room disinfection [40, 44–46]. Muto et al. showed how an infection control bundle, which included antibiotic control, especially quinolone use could reduce CDAD with the hypervirulent strain [44, 47]. The greatest importance of preventing this strain is that with the high metronidazole failure, there is increased oral vancomycin usage, which increases costs and may lead to more VRE colonization [42, 48].

The benefit of antimicrobial control appears to be in conjunction with other infection control measures. There appears to be little evidence that either one alone will offer a benefit due to a lack of appropriately controlled studies. Despite this, it just seems prudent that in this era of emerging resistance that all possible measures be implemented to reduce resistant organisms which impact the mortality of cancer patients.

Antibiotic Cycling

There is increasing resistance of Gram-negative (GN) organisms to antibiotics within hospitals, especially within the ICU and cancer center [11, 49–55]. However, there have not been any new classes of antibiotics for the treatment of these MDR GN organisms for many years and there is few if any in the pipeline [56].

Despite the shift towards Gram-postitive organisms causing infections in oncology patients, *Pseudomonas aeruginosa* remains the most common GN infection and is associated with higher mortality [57–59]. The increasing antimicrobial resistance within the GN organisms greatly impacts the selection of empirical antimicrobial therapy in the neutropenic host, which may affect mortality [60–62]. The emergence of carbapenem resistant *P. aeruginosa* and *Acinetobacter* infections means the use of more toxic and less effective antibiotics such as colistin and tigecycline [58, 62, 63].

A method that has developed in the ICU setting is to "cycle" the GN antibiotics, which is the scheduled rotation of antibiotics after an exclusive use for a preset period of 6 or 12 months, as a means to prevent resistance [55]. This was first suggested by Gerding et al., who demonstrated that by rotating gentamicin/tobramycin with amikacin they could increase the susceptibility of GN organisms to all the aminoglycosides, despite the rotation being within the same class of antibiotics [64]. It was this approach that has exciting potential to improve antimicrobial susceptibility and preserve for longer the use of classes of antibiotic agents against GN organisms. However, this approach also is controversial and has not been compared to "antibiotic heterogeneity," which is the use of multiple classes of antibiotics as outlined by the choices in the IDSA febrile neutropenia guidelines [4, 55].

Antibiotic cycling or rotation involves substituting an antibiotic from one class with one or more from different classes, as opposed to replacing with one from the same class [65]. This practice is complicated by the fact that antibiotics that belong to one class may select resistance to one or more unrelated classes as a result of genetic linkages [65]. For example quinolone usage can lead to emergence of imipenem resistant *Pseudomonas* [66, 67].

There have been four studies of antibiotic cycling in a cancer center setting, with three looking at general outcomes and one on VRE [68–71]. A summary of their outcomes is in Table 44.1.

Bradley et al. investigated the impact of cycling antibiotic on hyperendemic VRE in a hematological malignancy unit, which had a baseline prevalence of 50% [71]. They performed a 3 phase study in which phase 1 was a 4 month observational period, phase 2 they substituted ceftazidime for piperacillin/tazobactam (PT), and then phase 3 returned to ceftazidime. In phase 2 they also performed hand-hygiene and infection control actions, which was continued through phase 3. They demonstrated that in phase 1 there was a 57% acquisition of VRE in 6 weeks from admission, compared to 19% in phase 2, and 1% in phase 3, however there was an increase in VRE colonization when ceftazidime was restarted, while vancomycin policy was not changed throughout the study [71]. As described previously, was the effect the cycling or the infection control measures and since there was no randomization, it is difficult to establish causality.

In contrast, Dominguez et al. performed a randomized study of neutropenic patients to one of four regimens cycled over a 2-year period. Of concern from this study, were that only 42% of patients were able to complete their assigned regimen, with 14% having breakthrough bacteremia, and a marked increase in enterococcal infections, but no increase in resistance [70]. A major flaw in this study that is not addressed is that 55% of patients (148/271 evaluable patients) failed their primary regimen and 117 of the 148 (75%) required changing of their antibiotic therapy [70]. The authors importantly do not address what the antibiotic regimens were changed to when deemed a failure, whether there was a crossover of salvage antibiotics into a prior or future regimen or a new antibiotic class altogether, and how long

Table 44.1 Summary of antibiotic cycling studies in oncology centers

Year	H/B	IC	Cycle description	Outcomes
1999 [71]	H	Y	Ceftazadime 4 months – observational	Reduced VRE Phase 2 > 3 > 1
			Piperacillin/tazobactam 4 months – +IC	No change in glycopeptide use
			Ceftazadime 4 months +IC	No gram-negative resistance data
2000 [70]	H	N	1. Ceftazidime and vancomycin – 6 months	No difference between groups, however 55% failed regimen and required antibiotic change
			2. Imipenem – 4 months	
			3. Aztreonam and cefazolin – 5 months	Increased Enterococci
			4. ciprofloxacin and clindamycin – 4 months	
2007 [68]	B	N	Cefepime – 3 months	No change in gram-negative resistance
			Piperacillin/tazobactam 3 months	Increased VRE
			For 4 years	Comparison group not cycled
2007 [69]	B	N	All received levofloxacin prophylaxis	Reduced gram-negative bacteremia compared to retrospective cohort
			Imipenem – 8 months	
			Cefepime + tobramycin – 8 months	Increased VRE
			Piperacillin/tazobactam + tobramycin – 8 months	

H hematological unit; *B* stem cell transplant unit; *Y* yes; *N* no; *IC* infection control policies implemented; *VRE* vancomycin resistant Enterococci

after starting therapy was the antibiotic change required. With over 50% of patients changing their antibiotic in a cycling study occurring within the cycle, it is most likely we are seeing antibiotic heterogeneity with this study and probably why there was no difference between the groups.

Cadena et al. have the longest time experience of cycling antibiotic therapy in a hematologic unit [68]. They rotated every 3 months PT and cefepime for a 5-year period and compared their profile to a solid organ transplant group. They noted that over this time period there was no increase in GN resistance to either antibiotics and were significant lower than the solid organ transplant group, however VRE increased [68]. Their study is limited as the comparison groups are not similar populations and that the increasing VRE rate again suggests that infection control is just as important issue. Craig et al. also did not see an increase in GN resistance with antibiotic cycling while using levofloxacin prophylaxis, however likewise saw increases in VRE in their unit [69]. Except for Bradley [71], none of the studies implemented infection control practices with the cycling and all studies lack an adequate control group to determine if these outcomes would not have occurred without cycling.

There are many problems that are concerning from these studies. Many patients with hematologic malignancies receive several courses of chemotherapy and require several admissions over their consolidation chemotherapy. No one addresses whether these patients are cycled to different antibiotics from a prior admission, as they could receive the same antibiotic over time and select a resistant organism. The same problem occurs if the patient is transferred to an ICU or to another institution where they may cycle onto a previously seen antibiotic and lastly all these studies demonstrate increases in VRE infections, something that has been

shown to increase mortality and costs in the cancer center [8, 19]. At present antibiotic cycling does not appear to worsen GN resistance, but may increase VRE rates and this appears consistent with ICU studies [72]. Importantly, larger better controlled studies are needed to show a true benefit over antibiotic heterogeneity. Unfortunately with the lack of new drug development, strategies are needed to preserve our ability to use antibiotics in oncology patients.

Outpatient Antibiotics: Avoiding the Restriction Process

The previous two sections have focused on controversial inpatient aspects of antimicrobial stewardship programs. Therefore, stewardship programs focus most of their attention on inpatient antibiotic usage as this is where most of them put the time and effort to demonstrate cost-savings, reduced antimicrobial usage, and sometimes resistance. However, since the middle of the 1990s, oncology practices are increasingly using oral antibiotics for febrile neutropenia prevention and infusion centers to give intravenous antibiotics, thereby effectively bypassing antimicrobial stewardship programs [55].

The move to outpatient antibiotic therapy has grown with more guidelines using a risk-based assessment to determine inpatient versus outpatient management [4, 73].

The observation that some patients are at lower risk with febrile neutropenia for serious infection has allowed for more home therapy. This initially was performed using intravenous antibiotics by Talcott et al. and then confirmed in pilot study of 30 patients which showed nine patients required

readmission, but unenrolled patients had over 44% higher costs [74, 75]. Due to the cost of either home infusion or even outpatient infusion, the next logical step was to determine if there was a low-risk group of patients that oral antibiotic therapy could be effective in febrile neutropenia. Subsequently, Freifeld et al. performed a randomized, double blind, placebo-controlled study in low-risk patients with fever and neutropenia with duration of less than 10 days [76]. Patients were randomized to either receive oral ciprofloxacin and amoxicillin/clavulinic acid or ceftazidime intravenously and the results demonstrated that the oral regimen was as effective as the intravenous regimen ($P = 0.48$) and there were no deaths, but increased intolerance of the oral regimen [76]. There have been many strategies utilized since then, as long as there is careful patient selection and this approach offers decreased hospital costs, risk of acquiring nosocomial infections, and improved patient comfort [73, 77].

With the increased use of outpatient oral antibiotics and intravenous infusions, there is little oversight from antimicrobial stewardship program. While the obvious benefits of home antibiotics for low risk patients have been described, more patients with hematologic malignancies and prolonged neutropenia are being managed as outpatients [77]. The impact on antimicrobial resistance and selection of resistance organisms is unknown, with very little data. Most is extrapolated from inpatient use. Kern et al. showed that a hematology unit at one hospital with high consumption of fluoroquinolones had higher rates of resistant E. coli compared to the low user hospital, but there was no difference in activity to P. aeruginosa [78].

Fluoroquinolones are the most widely used antibiotic for outpatient febrile neutropenia and for prevention of GN sepsis in leukemia patients. Despite their widespread use in this population, there is little documented resistance and development of carbapenemases [79, 80]. Kern et al. showed over a 6-years period an increase of fluoroquinolone resistant E. coli bloodstream isolates to over 50% from patients in their cancer center. They performed a 6-month fluoroquinolone prophylaxis discontinuation trial which showed that the rates of GN bacteremia increased from 8 to 20% in their acute leukemia patients. When they reinitiated the prophylaxis, the rates decreased to 9% again, however E. coli resistance returned to 50% again. The benefit appeared to outweigh the risks of resistance, however the inpatient service should be aware of this so that inpatient quinolones are not selected as empiric therapy for sepsis [80]. Fluoroquinolones can select for dual resistance to ciprofloxacin and imipenem in P. aeruginosa in vitro via a regulatory gene which can turn on an outer porin [79]. Mueller et al. performed a nested case control study in P. aeruginosa isolates with combined imipenem and fluoroquinolone resistance and found that imipenem resistance was strongly associated with imipenem use and not ciprofloxacin use [79]. This is important as carbapenems are frequently used in oncology centers as frontline therapy for sepsis.

The concern of widespread fluoroquinolone usage in the outpatient setting is inadequate empiric antimicrobial therapy especially if the patient presents to an outside hospital where their prior antibiotic therapy may not be known. The emergence of quinolone resistance in E. coli and Klebsiella pneumonia species is increasing and has been associated with increased mortality [50]. Even in a cohort study by Thom et al., inadequate antimicrobial therapy for these organisms was significantly associated with mortality [81].

The emergence of carbapenem resistant P. aeruginosa has not been a major problem from the outpatient setting, however with the presence of ESBL organisms increasing, the use of carbapenems is increasing and this likelihood will increase over time [82, 83]. Although colistin has shown in a single center retrospective review to be effective against MDR P. aeruginosa, its long-term toxicity has not been fully addressed in this population [58].

Presently, there is very little information on antimicrobial stewardship with outpatient oncology patients, however despite some reports of increasing GN resistance, the benefits appear to outweigh the risks. Also, most oncology patients receiving outpatient intravenous antibiotics would most likely have been initiated or assessed by an infectious disease specialist who works closely with the oncologists. Awareness of outpatient antimicrobials is important for initiating appropriate antimicrobial therapy when there is a suspicion of sepsis.

Summary

There is very little information on the role of antimicrobial stewardship programs in oncology services, with most data from implementation in general hospital programs. The goals and order of these programs may differ from the aims of the oncology group. Most antibiotic restriction programs in the oncology center are implemented because of an endemic resistance problem or after an outbreak of a resistant organism or Clostridium difficile. The supporting data are usually single center quasi-experimental designs without a control group and no ability to determine the washout of their intervention. There is no supporting data that antimicrobial restriction without good infection control practices reduces resistance.

Also, antimicrobial cycling has the same limitations, however has not shown to worsen GN resistance, but has increased VRE in units that have started them.

Lastly, outpatient antibiotic therapy for low-risk patients frequently circumvents antimicrobial programs, but the

benefits outweigh the risks, however there is little data on the outcomes of these patients if they present to a treatment center that is not their primary base requiring antimicrobial therapy and whether they receive appropriate therapy.

Despite these controversies and limitations, the hypothetical benefits of monitoring antimicrobial therapy would appear to outweigh the lack of evidence presently available, but larger multicenter trials with a control group would strengthen the data.

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Chapter 45
Prevention of Antimicrobial Resistance: Current and Future Strategies

Cesar A. Arias and Adolf W. Karchmer

Abstract Antibiotic-resistant organisms are now commonly found in centers dedicated to the care of cancer patients, but most worrisome, have been increasingly reported as a cause of serious infections in community settings, even in healthy individuals with no apparent contacts with the health system. The discovery and development of antimicrobial agents is one of the most significant advances in the history of clinical medicine. The delivery of aggressive invasive and immuno-suppressive medical care, as occurs with cutting edge therapies today, will not be possible in the absence of effective antimicrobial agents. This concept is particularly crucial in the care of cancer patients who receive complex chemotherapeutic regimens that damage their immune system. The emergence of increasingly multidrug resistance bacteria is a limiting challenge to successful cancer therapy and is accentuated by the absent development of new antimicrobials that are active against the most recalcitrant bacterial species. A concerted and integrated effort among clinicians, hospital epidemiologists, academic medical centers, pharmaceutical companies and government agencies is essential if the "tide" of antimicrobial resistant microorganisms that threaten the future of modern medical care is to be arrested.

Keywords Antibiotic resistance • Multidrug resistant gram negative bacteria • Carbapenemases • *E. faecium* • *MRSA* • *Enterobacteriaceae* • Mathematical models • Prevention of antibiotic resistance

The Emerging Threat of Antimicrobial Resistance

It is certainly difficult to imagine the care of a cancer patient in the absence of antimicrobial compounds since the therapies directed to destroy and eradicate cancer cells often have important effects in the immune system predisposing these patients to acquire a variety of infections. The success achieved in cancer chemotherapy relies in part on the capability to prevent and treat infectious complications during the course of therapy, an ability that has now been seriously threatened by the emergence of antibiotic resistance in both Gram-positive and Gram-negative bacteria. Antibiotic-resistant organisms are now commonly found in centers dedicated to the care of cancer patients, but most worrisome, have been increasingly reported as a cause of serious infections in community settings, even in healthy individuals with no apparent contacts with the health system [1].

Among the Gram-positive bacteria, infections produced by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE) are by far the most critical clinical challenges in hospitalized patients (Table 45.1). Recent data from the National Health Care Safety Network from the Centers of Diseases Control and Prevention (CDC) indicate that *S. aureus* is the second most common nosocomial pathogen isolated in the USA (after coagulase-negative *Staphylococcus* spp.) and the number one cause of ventilator-associated pneumonias and skin and soft tissue infection in US hospitals (2006–2007) [2]. In the same study, 56.2% of *S. aureus* nosocomial isolates were resistant to oxacillin (e.g., MRSA), indicating that the frequency of MRSA isolation in the USA continues to be very high. Also, MRSA organisms are now increasingly being reported as the cause of severe infections in patients with no contact with healthcare institutions (community-associated [CA] MRSA). A single clone of CA-MRSA (designated USA300) is responsible for the vast majority of skin and soft-tissue infections seen in US emergency rooms [3] and now appears to be replacing hospital-associated clones in hospitals all over the world [1, 3–8].

E. faecium is another example of the evolution of a nosocomial pathogen; considered initially as an organism of low virulence and the cause of sporadic infections, *E. faecium* has been able to evolve and become a major clinical problem (Table 45.1). These organisms are now one of the most

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Table 45.1 Selected multiresistant bacterial organisms causing major clinical problems and prevalence

Organism	Antibiotic resistance	Common mechanism of resistance	Antimicrobial resistance percentages in US hospitals [a]
S. aureus	Oxacillin (MRSA)	Acquisition of the *mecA* gene encoding penicillin binding protein (PBP)	56.2
	Vancomycin		–
	VISA	Thickening of the cell wall (not fully elucidated)	
	VRSA	Change in the last amino acid of peptidoglycan precursors	
	Daptomycin	Associated with changes in cell wall and cell membrane (not fully elucidated)	–
	Linezolid	Mutations in the 23S rRNA genes	–
		Acquisition of a methyl transferase gene (*cfr*)	–
Enterococcus faecium	Vancomycin	Change in the last amino acid of peptidoglycan precursors	80
	Ampicillin (common)	Mutation and over-expression of *pbp5*	90.4
	HLR to aminoglycosides	Acquisition of aminoglycoside modifying enzymes	–
	Linezolid	Mutations in the 23S rRNA genes	–
	Daptomycin	Unknown	–
	Q/D	Enzymes that inactivate Q/D, target modification	
Klebsiella pneumoniae/ Escherichia coli	Oxyimino cephalosporins	Extended-spectrum β-lactamase	27.1/8.1 [b]
	Carbapenems	Carbapenemases, decreased permeability	10.8/0.9 [b]
Acinetobacter spp.	Carbapenems	Decreased permeability, efflux, and carbapenemases	29.2 [b]
Pseudomonas aeruginosa	Carbapenems	Decreased permeability, efflux, and carbapenemases	23 [b]

VISA S. aureus with intermediate susceptibility to vancomycin; *VRSA* vancomycin-resistant *S. aureus*; *HLR* high-level resistance; *VR* vancomycin-resistant; *Q/D* quinupristin/dalfopristin; *HD* high-dose

[a] Data from Hidron et al., 2008 [2]

[b] Percentages relate to central-line-associated bloodstream infections as reported by Hidron et al. [2]

Modified from Arias CA & Murray BE [1]

common bacterial species isolated from nosocomial infections in 2006–2007 and, more worrisome, greater than 80% of *E. faecium* in the US hospitals are resistant to vancomycin and ampicillin, two of the most important antienterococcal antibiotics. This phenomenon has been attributed to the ability of a genetic lineage of *E. faecium* (often designated clonal cluster 17) to acquire virulence, colonization, and antibiotic resistance determinants that increase their ability to cause disease in the hospital setting [9, 10].

The situation with Gram-negative organisms is even more dire since therapeutic options for these bacteria are more limited and new compounds appear to be far in the horizon of clinical development. Members of the *Enterobacteriaceae* family are the most common Gram-negative pathogens in humans, but *Pseudomonas aeruginosa* and *Acinetobacter* have a prominent role as infectious agents in cancer patients [11] (Table 45.1). Until recently, clinically important multidrug resistance in Gram-negative organisms was mainly mediated by the presence of acquired genes encoding extended-spectrum β-lactamase enzymes (ESBLs) and β-lactamases mediated by chromosomal genes. These β-lactamases precluded the use of penicillin derivatives and potent cephalosporins, and substantially limited the therapeutic options for treatment of infections caused by the resistance Gram-negative organisms. The ESBL-producing enterobacteria have been increasingly reported in hospitals (e.g., 27% of *Klebsiella pneumoniae* associated with central-line bloodstream infections in the US are likely to harbor ESBLs [2]) and are now present in community settings [12]. However, most concerning, is the emergence and dissemination of carbapenemases in members of the *Enterobacteriaceae* family, *Pseudomonas aeruginosa* and *Acinetobacter* spp [12]. The genes coding for the carbapenemase enzymes (which effectively hydrolyze all the available carbapenems) are usually carried on transferable plasmids that often harbor other resistance factors as well. As a result, no reliable treatment is currently available for many of these organisms. Since members of the *Enterobacteriaceae* family are part of the normal human intestinal flora, the potential of spread of these enzymes by the fecal-oral route is enormous; moreover, bacteria carrying carbapenamases can persist for years. These genes could also spread to the healthy population in the community following the pattern we are currently seeing with the ESBLs [12, 13].

Clinicians taking care of cancer patients are now facing this gloomy picture and are challenged with "nonstandardized" decisions, particularly in treating certain infections caused by multidrug-resistance *E. faecium*, *Pseudomonas aeruginosa*,

and *Acinetobacter* spp. The problem is exacerbated by the absence from pharmaceutical pipeline of new antimicrobials with reliable bactericidal activity against the latter microorganims. Also, the costs of treating infections caused by antibiotic resistant bacteria place additional stresses on the health-care system. A recent estimate indicated that an important number of invasive infections were caused by MRSA in 2005, and that their treatment cost billions of dollars [14]; similarly, in 1998, an estimated 4.5 billion dollars were spent in treating nosocomial infections [15, 16]. In this dire scenario, prevention and control of the spread of antibiotic resistant bacteria in clinical settings, particularly those dealing with highly complex and vulnerable cancer patients, becomes of paramount importance. We will discuss some theoretical and practical strategies to counteract the emergence of antibiotic-resistant organisms in hospital settings. We will not include any comment on strategies directed to control the use of antibiotics in hospitals such as antibiotic restriction and stewardship programs since these topics will be discussed extensively in other chapters of this book.

Strategies to Prevent Antibiotic Resistance

Mathematical Models and Prevention of Antibiotic Resistance

Modeling of infectious diseases has become an important tool of public-health decision making including HIV/AIDS, pandemic influenza and, more recently, antibiotic resistance [17, 18]. These mathematical models have been constructed to attempt the identification of critical factors responsible for the increasing trends of antimicrobial resistance in nosocomial pathogens. The rationale for the use of these models is that they can potentially predict the factors that contribute to the emergence and dissemination of drug resistance and may help in designing and implementing strategies to control these factors [16, 19]. More than 60 modeling articles have been published on bacterial resistance to antibiotics since 2003 [20] and a detailed description of these models is beyond the scope of this chapter, although a few examples are worth mentioning. In 2000, a mathematical model was designed to evaluate the transmission dynamics of any one of several species of antibiotic-resistant bacteria which are usually commensals of the gastro-intestinal or respiratory tracts or the skin of humans [19]. This model assumes that bacteria are transmitted in hospitals via direct contact between patients, through contamination of the hospital environment or via human "vectors" (mostly health-care workers) [19]. Based on numerical assumptions related to the dynamics of

transmission and the effect of the use of antimicrobials, several conclusions were drawn: (1) inferences related to individual risk factors for the development of resistance to one particular antibiotic may be completely different for a different antibiotic; (2) nonspecific interventions that reduce transmission of all bacteria in the hospital would also reduce the prevalence of colonization by resistant bacteria, and (3) changes in the epidemiology of resistant bacteria in a given hospital after a successful intervention may occur over weeks to months but would be faster than in the community [19]. This model emphasizes that the introduction of antibiotic resistant bacteria into the community will potentially cause an influx of these bacterial species into the hospital until an "equilibrium" is reached with the net final result being the replacement of the hospital flora by CA antibiotic-resistant bacteria. A mathematical model using MRSA as an example has predicted that the CA-MRSA USA300 strain will replace hospital-associated clones and that this highly virulent organism will become the predominant clone in hospitals across the USA [21]; in fact, some studies suggest this process is occurring [4–8].

More recently, another model was designed to study the epidemiology of antibiotic-resistant bacteria in hospitals. The key elements in hospital-acquired infections caused by resistant bacteria were quantified and presented in a two-level analysis [22]. The model offered an ecological view of the evolution of antibiotic resistance by correlating the interaction of these two levels of bacterial populations [22]. This mathematical approach shows that the endemicity of antibiotic-resistant bacteria depends on the balance of bacterial populations with and without the corresponding resistance trait and that the rates of infection with multidrug resistant bacteria are proportional to the total bacterial load of each resistant strain [22]. Thus, controlling the number of infected patients and bacterial loads in the hospital setting appear to be the best strategies to curtail transmission.

Subsequently, and based on the above conclusions, the same group developed a different model designed to assess the effectiveness of interventions to control the emergence and spread of bacterial resistance in the hospital and included several key additional factors contributing to resistance, including the effects of the immune system, acquisition of resistance genes, and antimicrobial exposure [16]. The findings suggested the following: (1) shorter lengths of antibiotic therapy and early interruption appear to provide an advantage for the resistant strains, (2) early initiation of antibiotics is the most important strategy that prevents the emergence of resistant strains and (3) combination therapy with two antibiotics prevents the emergence of resistance strains in contrast to adding sequentially new antimicrobials.

The use of combination therapy to prevent the emergence of bacterial resistance has also been supported by a different model, which numerically evaluated different treatment

protocols [23] and similarly concluded that when more than one antibiotic is used, sequential use of different antibiotics in the population is always inferior to treatments where equal fractions of the population receive different antimicrobials simultaneously [23].

Although approaches defined by modeling have gained acceptance in recent years, they have elicited heavy criticism due to the fact that sometimes the calculations are based on simplistic assumptions whereas the dynamics of actual events are more complex [17, 24, 25]. Nonetheless, mathematical modeling is a useful resource with which to examine a public health problem whose inherent variability is difficult to standardize for clinical studies and the conclusions generated by models may suggest hypotheses that can be tested in well-designed clinical trials.

Infection Control Strategies

The "Search and Destroy" Approach

In the Netherlands and Scandinavian countries, a strategy designated "search and destroy" has been used successfully to control the spread of MRSA. This approach involves actively screening patients and health-care workers for MRSA and is complemented by strict isolation policies of known and suspected carriers and treatment of infection in high-risk patients with antimicrobials effective against MRSA until cultures results are available [26]. This program was established in 1980 and has managed to maintain the prevalence of MRSA in hospitals at very low levels compared to other parts of the world, including neighboring countries in Europe [27]. To control the spread of MRSA with the "search and destroy" strategy, the hospital population is divided in four groups: (1) the higher risk group include known carriers of MRSA (patients and health-care workers) or those who have a positive culture after screening; (2) patients who have been transferred to a Dutch or Scandinavian hospital from other countries, patients who shared a room with known carriers or were hospitalized in wards known to have a higher transmission of MRSA (including nursing homes and long-term care facilities, among others); (3) health-care workers involved in the management of known MRSA carriers, hospital staff who have worked in hospitals abroad, and dialysis patients who received treatment abroad, and (4) individuals who have no known risk factors [27]. Individuals in group (1) are always isolated with strict contact precautions and health-care workers are excluded from patient contact until their cultures are negative. Groups (2) and (3) are isolated until their MRSA status is confirmed and individuals in group (4) are cultured but not isolated preemptively [27]. The effectiveness of the "search

and destroy" strategy has been validated in epidemiological studies [27] and mathematical models [28] support this kind of intervention. However, this approach has been questioned due to the costs associated with the implementation of this policy [29]; for example, in a 700 bed hospital in the Netherlands, the yearly cost of the "search and destroy" policy between 1999 and 2001 was € 280,000 [30]. By 2004, a Dutch hospital reported spending € 1,383,200 to search for MRSA (search component) and € 2,736,762 for isolation and eradication (destroy component) [27]. Additionally, quality of patient care may be reduced [31] by the strict limitations and regulations applied to hospital staff and also the availability of hospital beds could be limited by the isolation of patients in single rooms and the need to close wards temporarily [28]. Moreover, this policy assumes the availability and use of rapid diagnostic tests to detect the resistant microorganisms to avoid unnecessary isolation. Although rapid diagnostic tests are available for MRSA, their use is also limited by costs. Interestingly, in a screening study using routine microbiological tests to detect MRSA in the Netherlands, 95% of patients were unnecessarily isolated for an average of 5 days [32].

The Centers for Disease Control and Prevention (CDC) Campaign to Prevent Antimicrobial Resistance

In 2002, the CDC developed an integrated campaign using evidence – based guidelines with the aim of preventing the emergence of antimicrobial resistance in nosocomial settings [33, 34]. The strategy included a 12-step approach (Table 45.2)

Table 45.2 Twelve steps to prevent antimicrobial resistance among hospitalized patients

Prevent infection
1. Vaccinate
2. Get the catheters out
Diagnose and treat infection effectively
3. Target the pathogen
4. Access the experts
Use antimicrobials wisely
5. Practice antimicrobial control
6. Use local data
7. Treat infection, NOT contamination
8. Treat infection NOT colonization
9. Know when to say "no" to vancomycin
10. Stop treatment when infection is cured or unlikely
Prevent transmission
11. Isolate the pathogen
12. Break the chain of control

Adapted from Centers for Disease Control and Prevention, campaign to prevent antimicrobial resistance [34]

which encompasses four main objectives: (1) prevent infections, (2) optimize the diagnostic tools and treat infections effectively, (3) use the appropriate antibiotics, and (4) prevent transmission of antibiotic-resistant organisms. This strategy has been evaluated and shown to be successful [35, 36] since the key elements can be easily tailored to fit the needs of any institution, regardless of size, affiliation or specialty. Additionally, the approach is flexible and can be implemented as a single step, as a broad strategy with multiple steps or as a "package" with the introduction of all 12 steps [35].

The CDC also released guidelines for the prevention of intravascular catheter-related infections and hand hygiene [37, 38]. The prevention of catheter related infection guidelines emphasize training in the proper insertion and maintenance of catheters using full barrier methods, preference for chlorhexidine skin preparation and selection of patients for the insertion of central venous lines [37]. Antiseptic or antibiotic impregnated central venous catheters were recommended if rates of catheter-related infections were high in an institution [37]. The catheter management is an important part of the 12-step campaign encouraging physicians to remove catheters as soon as they are not needed, avoid culturing catheter tips, and treat catheter-related bacteremia and not colonization [34]. In this regard, a collaborative cohort study performed in intensive care units assessed the effectiveness of implementing evidence-based interventions to decrease the rates of catheter-associated bloodstream infections [39]. The study showed that the implementation of such interventions (e.g., sustained education to health-care personnel, availability of a central-line cart, use of a checklist and feedback sessions on quality of practice, among others) resulted in a large and sustained reduction in rates of catheter-associated bacteremia during the study period (18 months) [39].

Another important component is hand hygiene procedures which encompass a core element of the CDC campaign and, in general, of efforts to prevent nosocomial infections and the dissemination of antibiotic-resistant organisms. Nonetheless, many health-care workers are noncompliant with optimal hand hygiene and it is performed in less than 50% of patient encounters [40–42]. Reasons for this behavior have been thoroughly investigated and include forgetfulness, fear of skin damage, time limitations due to other priorities in patient care, and lack of adequate access to hand-rub sanitizers or sinks [42–44]. To address this problem, the World Health Organization (WHO Global Safety Challenge "Clean Care is Safer") and the University of Geneva Hospitals developed a user-centered approach, which incorporates strategies of cognitive behavior, social marketing and human factors engineering, followed by an iterative prototype test phase within a target population [42]. This program, designated "my five moments for hand hygiene," systematically engages the moments of contact between health-care workers and patients and evokes ownership and commitment

to the hand hygiene process through a complete understanding of the dynamics of transmission [42, 45]. The model defines two specific areas, (1) a patient's zone, defined as the patient's intact skin and the immediate surroundings colonized by the patient's own flora, and (2) the health-care's zone, which contains all other surfaces [42]. Each moment is defined according to the interaction of the health-care worker and a zone: the *first* moment occurs between the last hand-to-surface contact with an object belonging to the health-care zone and the first within the patient zone; in other words, the moment crossing the virtual line between the two zones. Hand hygiene at this point will prevent cross-colonization of the patient and sometimes, exogenous infection [42]. The *second* moment occurs before an aseptic task develops within the patient zone and includes hand exposure to patient's clothes, skin, or any object, usually with the health-care worker engaging in an aseptic task such as giving an injection, performing wound care or handling a venous access. Hand hygiene at this point aims to prevent colonization and a subsequent health-care associated infection [42]. The *third* moment happens after body fluid exposure risk; this moment is associated with the risk of exposing hands to a fluid contaminated site, occurs within the patient's zone and requires immediate hand hygiene before any hand-to-surface exposure within the patient zone. These measures aim to reduce the risk of colonization or infection of a health-care worker with highly infectious organisms and decrease the transmission of bacteria from an infected or colonized body site to a potentially clean site on the same patient [42]. Immediate action is required at this moment since hands are not sufficiently protected by gloves and additional hand hygiene is required after glove removal [46]. The *fourth* moment occurs after patient contact; this moment happens when leaving the patient zone and before touching an object in the health-care zone. Hand hygiene at this point substantially reduces contamination of health-care worker's hands with the patient's flora and intends to prevent the risk of dissemination to the health-care environment (mostly in the health-care worker zone) [42]. Finally, the *fifth* moment occurs after contact with patient surroundings and is a variant of moment *four*, occurring after hand exposure to any surface in the patient zone but without touching the patient. The moment involves objects contaminated by the patient's flora which are removed from the patient's zone and are taken to the health-care zone in order to be decontaminated or discarded. Due to hand exposure to these objects, hand hygiene is absolutely required at this time.

This strategy and multistep approach to hand hygiene behavior had been noted to be the most efficient technique to increase patient safety and decrease the risk of nosocomial infections [40, 46–49]. Thus, the understanding of the critical moments of hand hygiene helps in designing infection control programs by reducing the dissemination of

multidrug resistant microorganisms in the hospital environment with the objective of preventing nosocomial infections. A comprehensive approach for this "five moments" includes the training of health-care personnel, the designing of medical units, and a thorough performance assessment.

Treatment Based Strategies

Antibiotic Cycling

This strategy is based on the rationale that withdrawing a class of antibiotics or a specific compound for a defined period and reintroducing it at a later time can prevent the emergence of resistant bacteria to the particular antimicrobial class or agent [50]. The theoretical advantage of this approach is that it may increase the number of antibiotics active against multidrug resistant bacteria and maintain antibiotic "heterogeneity," a practice whereby multiple antibiotic classes are used in a clinical setting (i.e., intensive care or cancer unit) with the aim of reducing the emergence of resistant bacteria that otherwise might occur as a result of using a single or limited number of antibiotic classes [50]. A biological justification for the using of antibiotic cycling rests on the assumption that cyclic exposure to a homogeneous antimicrobial class or compound creates an environment of reduced antibiotic resistance because resistant strains may have a growth disadvantage when selective pressure is withdrawn and because exposure to a new class of antibiotics (assuming no cross-resistance) is presumed to eliminate the resistant organisms selected during the previous cycle [51]. Three methods have been advocated to achieve this goal: (1) mixing of antibiotic classes, (2) scheduled changes of antibiotic classes and (3) rotation of antibiotics [50].

The first clinical evaluation of this strategy was performed by Gerding et al. [52], who cycled aminoglycosides over a 10-year period in a Minneapolis Veterans Affairs hospital. Using cycles of 12–51 months, the investigators found significantly reduced resistance to gentamicin when amikacin was used, but a return of resistance with the rapid reintroduction of gentamicin. Thus, the researchers decided to reintroduce gentamicin more gradually and were able to prevent the emergence of gentamicin resistant strains [52]. Kollef et al. [53] evaluated the influence of scheduled antibiotic changes on the incidence of nosocomial infections among patients undergoing cardiac surgery. The investigators cycled third generation cephalosporins with fluoroquinolones for a period of 6 months each. The overall incidence of ventilator-associated pneumonia was significantly reduced in the second 6-month period, compared with that in the first 6-month period. This effect was mainly due to a significant reduction in the incidence of ventilator-associated pneumonia attributed

to antibiotic-resistant Gram-negative bacteria [53]. In a similar investigation, different classes of antibiotics were cycled for the treatment of suspected or documented Gram-negative infections during three consecutive 6 months periods in intensive-care units and involving more than 3,600 patients [54]. The researchers found that the hospital mortality rate significantly decreased during the third antibiotic cycle for the most critically ill patients [54] supporting some benefit of cycling. Raymond et al., published the results of a 2-year study analyzing the effect of specific antibiotic rotation schedules for the treatment of pneumonia and intra-abdominal infections [55]. Outcome analysis revealed significant reductions in the incidence of infection due to resistant Gram-positive and Gram-negative bacteria and mortality in the study population [50, 55]. Another more recent study cycled linezolid and vancomycin every 3 months for a period of 2 years in a surgical intensive-care unit [56]. During 4 years prior to cycling, 543 infections with Gram-positive organisms were documented, including 105 by MRSA (8.8./1,000 patient days) and 21 by VRE (1.8/1,000 patient-days). In the 2 years after implementation of cycling, the rate of MRSA infections dropped to 1.8/1,000 patient days ($p < 0.00001$) whereas VRE infections remained the same, suggesting that quarterly cycling of linezolid and vancomycin may help reduce the rates of MRSA infection in particular units. The cycling strategy has also been evaluated in a bone marrow transplant unit. Cadena et al. studied the effect of cycling in a hematology-oncology unit over a period of 5 years from January 1999 to June 2004, alternating piperacillin-tazobactam and cefepime in 3 months periods [57]. During this study, the rates of susceptibility among Gram-negatives to cefepime and piperacillin-tazobactam remained stable, but the rates of isolation of vancomycin and ampicillin-resistant *Enterococcus* spp. increased.

Several caveats should be noted when interpreting these studies since important methodological limitations are present in the majority of them: (1) due to the complexity of the issue, the real effect of a single intervention can only be determined when all variables (including infection control practices) are controlled or accounted for in complex statistical analysis (which has not been always the case and it is difficult to ascertain in the studies), (2) the dynamics of antibiotic-resistance in critical care units depend on different factors including the natural fluctuations of colonized patients [58, 59]; the often rapid turnover of ICU patients could influence enormously the rates of colonization and subsequent infection, (3) several of these studies have used only historical controls. Another important issue to consider is the biology of antibiotic resistance; a susceptible bacterial species can become resistant either by undergoing mutational changes or by horizontal acquisition of resistance genes. Some of the genetic units carrying resistance genes also harbor genes that make the bacteria more "fit" to colonize human tissues and produce

disease and these genes are not necessarily selected by antibiotics. For example, *Enterococcus faecium* from clonal cluster 17 appear to recruit in the same plasmid determinants that enhance their ability to colonize the gastro-intestinal tract, produce disease, and become resistant to antibiotics. Releasing the antimicrobial pressure or changing it will do little to prevent the dissemination of these plasmids in the hospital environment since other factors are at play in the survival of the organism. Finally, mathematical models have repeatedly predicted that antibiotic cycling might paradoxically create the opposite effect: create more resistance [21, 60], a fact that has been supported by some clinical studies [61, 62]. Thus, it seems unlikely that cycling will ever prevent the resistance problems in nosocomial settings.

Shorter Antibiotic Courses, Narrow Spectrum and Combination Therapies

Although large prospective-randomized studies assessing the optimal duration of antimicrobials in clinical practice are still lacking in many infections, the sustained and prolonged use of antimicrobials beyond the recommended duration is a common practice among physicians, particularly those caring for critically ill patients. The unnecessary use of antimicrobials has been shown to be a major risk factor for the development of multidrug resistant bacteria [63, 64]. Shorter courses of antimicrobial therapy have been shown to prevent the emergence of resistance and thus have been advocated as a strategy to ameliorate antibiotic resistance. For example, a prospective randomized double-blinded clinical trial was conducted in 151 intensive care units in France to determine whether 8 days of antimicrobial therapy was as effective as 15 days for the treatment of ventilator-associated pneumonia (1999–2002). The overall conclusion was that in nonbacteremic patients receiving initial appropriate empirical therapy, the 8-day regimen was clinically comparable to the 15-day regimen with the possible exception of nonfermenting Gram-negative organisms [65]. Furthermore, among those who developed recurrent pulmonary infection, multidrug resistant pathogens emerged less frequently in those receiving 8 days of antibiotic therapy compared to patients receiving the longer course of antibiotic therapy. Similar studies have been performed in other diseases such as urinary tract infections, pyelonephritis [66] and community acquired pneumonia [67], but more studies are required to reach consensus.

An alternative strategy is to use narrow-spectrum antibiotics and several well-conducted studies suggest that certain infections such as nonlife threatening community-acquired pneumonia can be successfully treated with narrow-spectrum antibiotics such as doxycycline [68]. In a randomized prospective trial, the efficacy of intravenous doxycycline with other routinely used antibiotic regimens was assessed in 87 patients admitted with the diagnosis of community-acquired pneumonia. The mean interval between starting an antibiotic and the clinical response and the mean length of hospitalization were significantly decreased in the doxycycline group compared with the other group. Thus, it was concluded that doxycycline was an effective and inexpensive therapy for the empirical treatment of hospitalized patients with mild to moderately severe community-acquired pneumonia. Similarly, the use of narrow-spectrum agents such as penicillin, trimethoprim, and gentamicin (instead of cephalosporins) plus infection control measures have been shown to decrease the occurrence of *Clostridium difficile* infections [69]. Thus, the use of narrow-spectrum compounds for specific infections should be further explored in future studies and appropriate clinical settings.

Finally, the use of combination therapies is yet another approach that may be useful in the prevention of the emergence of antimicrobial resistance. The clinical efficacy of combination antimicrobial therapies for the treatment of severe bacterial infections has been a matter of debate. The rationale for the use of combination antibiotic therapies is that this approach may offer increased synergistic activity to the treatment strategy and thus, may prevent the emergence of antibiotic resistance; a hypothesis that has been supported by mathematical modeling studies (see above) [16]. The majority of studies have included the combination of a β-lactam and an aminoglycoside antibiotic; a recent Cochrane collaboration review performed to assess the efficacy of β-lactam monotherapy vs. β-lactam plus aminoglycoside combination therapy in sepsis (64 trials, randomizing 7,568 patients) concluded that the addition of the aminoglycoside did not offer any additional benefit and the all-cause fatality was unchanged; moreover, aminoglycoside use increased the risk of nephrotoxicity [70]. Similarly, several clinical studies in bacteremia also found no significant reduction in mortality when using the combination (β-lactam plus aminoglycoside) vs. monotherapy (β-lactam only) [71–73]. Nonetheless, reduced mortality has been documented using the aminoglycoside-/β-lactam combination for treatment of patients with bloodstream infections caused by *Pseudomonas aeruginosa* [73–75], *Klebsiella* species [76], and in the setting of bacteremia cause by Gram-negative bacilli in neutropenic patients [72, 77]. A meta-analysis showed similar mortality, more favorable clinical outcomes and less nephrotoxicity using the combination of ciprofloxacin plus β-lactams compared to β-lactams plus aminoglycosides to treat patients with febrile neutropenia [78]. The use of the combination of the β-lactam/fluoroquinolones is supported by in vitro and in vivo studies that confirm the synergistic effect of the combination [79, 80]. A recent retrospective cohort analysis that included 398 and 304 unique patients with bacteremia caused by Gram-negative bacillus who received single and combination antibiotic therapy, respectively, found that combination

therapy with β-lactams and fluoroquinolones was associated with a reduction in 28-day all-cause mortality among less severely ill patients, but there was no difference in critically ill patients [81]. Overall, combination therapy is most likely of clinical benefit when treating bacteremia caused by *P. aeruginosa*, Gram-negative bacilli bacteremia in neutropenic patients and when used to assure treatment with at least one agent that is active against the organism in vitro (provide adequate therapy). Importantly, *P. aeruginosa* bacteremia among patients on admission to the hospital is significantly more likely among immunocompromised patients with central venous catheters (the cancer patient receiving chemotherapy) than immunocompetent persons [82]. Of note, the above studies have evaluated clinical efficacy and not prevention of resistance, thus, it is not clear that combination therapy will be an effective strategy to prevent the emergence of antimicrobial resistant bacteria.

Future Perspectives

Containing the spread of antibiotic resistance organisms is a major public health priority, since advances in clinical medicine can only be achieved if we maintain an upper hand against these bacteria. The dearth of antibacterial compounds in development for the treatment of emerging resistant pathogens calls for new strategies to combat this problem. The "ideal" scenario would be to have a vaccine available (including active and passive immunization strategies) for each "superbug," a prospect that is not realistic at the present time. An interesting and potentially suitable approach is the use of bacteriophages (or their products) to eradicate colonizing and infecting multidrug resistant bacteria [83]. Phages are the most abundant biological entities on earth and most significantly, they destroy half of the world's bacterial population every 48 h [84]. Phages are very specific for their host, kill bacteria efficiently, and have been used in the clinic for decades [85]. Moreover, the Food and Drug Administration approved in 2006, a "cocktail" of six individual purified phages as treatment for *Listeria monocytogenes* contamination of ready-to-eat meat and poultry products [83].

Several approaches for the phage-based therapy have been evaluated including the use of lysis-deficient phages [86], which can kill bacterial cells without lysis thus avoiding release of endotoxin and precipitating shock [86], and the use of whole phages as transport vehicles for delivery of lethal genes [87] or chemically linked antibiotics for specific bacterial species [88]. However, important drawbacks to the use of phages for therapy include the rapid development of resistance to phage attachment, the release of bacterial cell wall products that can trigger a systemic inflammatory response in humans leading to shock [86] and the production of neutralizing antibodies upon extended or repeated treatment of the

same individual [89]. A variation of the phage-based therapy is the utilization of phage products (instead of the whole phage) to kill bacteria. Fischetti et al., have successfully used phage enzymes as therapeutic tools against some bacteria including *Streptococcus pyogenes* [90, 91], pneumococci [91], and *Bacillus anthracis* [92]. These peptidoglycan degrading enzymes (designated lysins) are highly evolved molecules that quickly destroy the bacterial cell wall. Nanograms quantities can kill up to 10^7 bacteria in a matter of seconds [93]. Animal models have corroborated the potential of these enzymes as agents to eradicate colonization. For example, animals were rapidly (48 hrs) cleared of the colonizing strains of streptococci or pneumococci after the administration of small amounts of lysins; however, the lysins were not able to eradicate infecting intracellular bacteria [90, 91]. Such a strategy could be useful in the eradication from patients of colonizing antibiotic-resistant bacteria and thus decrease the risk of developing a subsequent infection.

Summary

The discovery and development of antimicrobial agents is one of the most significant advances in the history of clinical medicine. The delivery of aggressive invasive and immunosuppressive medical care, as occurs with cutting edge therapies today, will not be possible in the absence of effective antimicrobial agents. This concept is particularly crucial in the care of cancer patients who receive complex chemotherapeutic regimens that damage their immune system. The emergence of increasingly multidrug resistance bacteria is a limiting challenge to successful cancer therapy and is accentuated by the absent development of new antimicrobials that are active against the most recalcitrant bacterial species. A concerted and integrated effort among clinicians, hospital epidemiologists, academic medical centers, pharmaceutical companies and government agencies is essential if the "tide" of antimicrobial resistant microorganisms that threaten the future of modern medical care is to be arrested.

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Part V
Infection Prevention: Antimicorbial Prophylaxis and Immunization

Chapter 46
Antibacterial, Antifungal, and Antiviral Prophylaxis in High-Risk Cancer and Stem Cell Transplant Population

Marcio Nucci and John R. Wingard

Abstract Infection represents a major cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients and cancer patients. Antimicrobial prophylaxis is justifiable in these immunosuppressed patients, but its benefits may be offset by potential problems such as the selection for resistant organisms, an increase in toxicity and cost. Therefore, any attempt to administer an antimicrobial agent should be accompanied by a reflection of the potential benefits and risks of prophylaxis. This chapter reviews the rationale and current recommendations for antimicrobial prophylaxis of infections in HSCT recipients and in high-risk cancer patients, the latter group represented mostly by patients with hematologic malignancies, including those with acute leukemia, multiple myeloma, and lymphoma.

Keywords Prophylaxis • Antibacterial • Antifungal • Antiviral • Resistance • Prevention

Introduction

Infection represents a major cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients and cancer patients. This chapter will focus on antimicrobial prophylaxis of infections in HSCT recipients and in high-risk cancer patients. The latter group is represented mostly by patients with hematologic malignancies, including those with acute leukemia, multiple myeloma, and lymphoma. These patients are usually severely immunosuppressed by the underlying disease and its treatment, and strategies to prevent the occurrence of infection include the use of antimicrobial agents.

Antimicrobial prophylaxis is justifiable in these immunosuppressed hosts due to various reasons. First, infections are frequent; second, clinical signs of infection are subtle, making their early diagnosis (critical for the success of therapy) a great challenge; third, response to treatment is usually suboptimal mostly because recovery of host defenses is a key factor for resolution of infection. On the other hand, the use of antimicrobial agents for prophylaxis of infection is not devoid of problems. Its wide use may increase the possibility of the development of resistance; it may select for resistant organisms; it may increase toxicity and may increase the cost. Therefore, any attempt to administer an antimicrobial agent should be accompanied by a reflection of the potential benefits and risks of prophylaxis. In general, the higher is the incidence of infection the more beneficial is likely to be antimicrobial prophylaxis. However, the prediction of an incidence of infection is not simple, and requires an analysis of various factors including patient's prior exposure to pathogens, underlying disease, previous and current treatment, geographic area, and others.

Antimicrobial prophylaxis may be primary, when prevention targets an individual who has not been infected in the past, and secondary, when prevention is used to avoid recurrence of infection in an individual who has been previously infected.

Antibacterial Prophylaxis

Prophylaxis in Neutropenic Patients

Infection is a common complication of myelosuppression caused by antineoplastic chemotherapy. Neutropenic fever requires antibiotics and frequently costly hospitalization and may result in impairment in quality of life, toxicity, life-threatening complications, or death. Even when well controlled, infection may necessitate interruptions in the antineoplastic treatment regimen. Bacteria are by far the most common infectious pathogens during neutropenia.

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Fever is often the only manifestation of bacterial infection during neutropenia, and thus considerable efforts have been directed toward management of neutropenic fever. Likewise, there has been considerable study of ways to prevent infection to reduce its complications.

Who Is at Risk?

Key to a prophylactic strategy is the identification of those patients at high risk for infection. The duration and depth of neutropenia are the most prominent risk factors both for any bacterial infection but also serious bacterial infection. In addition, the disease, treatment regimen, and host characteristics also influence the risk for neutropenic bacterial infection. Acute leukemia is associated with substantially higher risk for bacterial infection than solid tumors. Even for solid tumors, many chemotherapy regimens are associated with a very low (<10%) risk for neutropenic infection. Examples of chemotherapy regimens with low risks for neutropenic infection are listed in several reviews [1, 2]. Indeed, it is estimated that only 10–15% of patients treated for solid tumors have sufficient risk for infection to warrant consideration for prophylaxis [3]. There is considerable heterogeneity in the risk for infection within groups of patients with similar risk factors. Increasingly, it is recognized that polymorphisms in immune responses account for at least some of this heterogeneity.

Prevention Strategies

Two strategies to prevent infection during neutropenia have been evaluated: antibiotics and myeloid growth factors. The intent of the two strategies differs: antibiotics are intended to reduce tissue invasion and bloodstream dissemination of pathogens colonizing mucosal and integumentary surfaces while myeloid growth factors are intended to reduce the risk for infection by shortening the at-risk interval. Antibiotics have been mostly evaluated as prophylaxis in the patients at greatest risk: patients with hematologic malignancies with prolonged neutropenia. Myeloid growth factors have been best evaluated in patients with solid tumors, a group at lower risk for serious infections.

Antibiotic Prophylaxis

Numerous trials have evaluated antibiotic prophylaxis with a variety of antibiotics, but most studies have used a fluoroquinolone. A variety of benefits have been noted in single trials, and these benefits have been assessed in meta-analyses [4–8]. Benefits documented include a reduction in febrile episodes,

Table 46.1 Parameters affected by antibiotic prophylaxis

Parameter	Odds ratio	95% Confidence interval
Febrile episodes	0.67	0.56–0.81
Clinically documented infections	0.53	0.36–0.80
Microbiologically documented Infections	0.50	0.35–0.70
Infections due to gram negative organisms	0.26	0.20–0.35
Infections due to gram positive organisms	0.29	0.22–0.38
Bacteremia	0.64	0.52–0.77
Infection-related deaths	0.58	0.55–0.81
Mortality	0.67	0.55–0.81

From [6]

fewer clinically and microbiologically documented infections by both Gram-positive and Gram-negative organisms, lower likelihood of bacteremia, and fewer infection-related deaths (Table 46.1). A survival benefit has also been noted [6]. Two trials in patients receiving cyclic chemotherapy for solid tumors and lymphoma demonstrated reduced infections and infectious complications [9, 10], but the magnitude of benefit in these patients was less than in patients with hematologic malignancy. For example, the number of patients needed to treat to prevent one febrile episode was 5 for patients with hematologic malignancies, but 23 for solid tumor/lymphoma patients. Some trials also showed a reduction in the need for empiric antibiotics [11] and a shorter treatment course of empiric antibiotics [12, 13]. The fluoroquinolones have been associated with less toxicity than trimethoprim-sulfamethoxazole (TMP-SMX) [6] and have activity against *Pseudomonas aeruginosa* in contrast to the TMP-SMX and thus have become preferred agents for prophylaxis. Some studies indicate a benefit for combinations of antibiotics over single agent therapy as prophylaxis, but the benefits have not been consistent and no survival benefit has been shown.

One of the concerns with antibiotic prophylaxis is the potential for antibiotic resistance, which may compromise patient safety and thwart the effectiveness of the prophylactic regimen but also compromise the effectiveness of other antibiotic regimens not only for the individual patient but also the entire population of patients. Fluoroquinolone resistance has been increasing [14]. A nonsignificant increase in resistant colonizing Gram-negative organisms has been noted in patients given fluoroquinolone prophylaxis [6], although no increase in resistant infecting organisms has been noted as yet. One meta-analysis did not show any trends to increases in resistant organisms [7]. Another concern is the risk for an increase in *Clostridium difficile* infections. Again, this has not been seen to date [4]. Yet another concern is a higher rate of Gram-positive infections, but this too has not been a consistent finding [4]. Important to note is that although these concerns have not been realized at present, ongoing surveillance is necessary.

Myeloid Growth Factors

Infection results in accelerated destruction of neutrophils and the release of proinflammatory cytokines, which may slow neutrophil production and temporarily counter the endogenous stimulatory signals to increase neutrophils. Thus, the net effect of infection is typically prolongation of neutropenia longer than otherwise expected. Exogenously administered myeloid growth factors are uniquely suited to speed neutrophil recovery. Given prophylactically, multiple trials demonstrate convincingly that granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) can substantially shorten neutropenia resulting from multiple solid tumor chemotherapy regimens. As a consequence, there are fewer febrile episodes, fewer infection-related deaths, and improved overall survival benefits [15] (Table 46.2).

In solid tumor therapy, most regimens are given in timed cycles, and adherence to the scheduled treatment regimen without treatment delays or reduction in chemotherapy doses has been found to be associated with antineoplastic effectiveness. A number of studies have examined the ability of myeloid growth factors to maintain chemotherapy dose intensity and have found G-CSF to permit better maintenance (95 vs. 87%, $p < 0.001$) [15].

As noted earlier, there is considerable heterogeneity in the risk for neutropenic fever or infection according to the chemotherapy regimen. Most studies of myeloid growth factors have been conducted in solid tumor patient populations receiving chemotherapy regimens associated with a high risk of neutropenic fever (risk of 40% or higher). In recent years, examination of their use in regimens associated with lower risks of infection (20–40%) [16, 17] has documented similar benefits of myeloid growth factors. It is important to note that most patients (>80%) with solid tumors receive chemotherapy regimens associated with neutropenic infection risks substantially less than 20% [3]. Consensus panels recommend that in low-risk patients (risk less than 10%) myeloid growth factors are not justified since they are associated with high costs, toxicity, and some inconvenience of administration [1, 2, 18, 19]. For patients receiving chemotherapy regimens associated with a risk of neutropenic fever between 10 and 20%, the presence of comorbidities that increase risk provides justification of the use of myeloid growth factors.

For leukemia therapy, myeloid growth factors have some benefits during induction therapy, but there are no effects on remission and survival and thus their usefulness is marginal. However, their use has been associated with reduced febrile episodes and hospitalizations for infection during postremission consolidation therapy.

Combinations of Myeloid Growth Factors and Antibiotics

Several studies have noted that the combination of growth factors and antibiotics is more effective than either alone with reductions in neutropenic febrile episodes [15, 20, 21].

Which Is Appropriate for Individual Patients?

When the decision is made that the patient's treatment is associated with sufficient risk to warrant consideration for infection prophylaxis, one should weigh what the goal is. If the most important consideration is chemotherapy dose intensity, then G-CSF is preferable. This would be applicable when the therapeutic intent is curative. If the goal is primarily to protect the patient from neutropenic infection, antibiotics are a suitable alternative, or alternatively, a reduction in the chemotherapy doses. In a setting in which there is a high rate of fluoroquinolone resistance, antibiotic prophylaxis would be much less desirable.

Prophylaxis for Nonneutropenic Patients

Patients with Impaired Humoral Immunity

Hypogammaglobulinemia is a frequent accompaniment of chronic lymphocytic leukemia and multiple myeloma as well as other hematologic malignancies and contributes to the susceptibility for infection, particularly by encapsulated bacteria, and life-threatening infectious complications. Multiple studies have shown that the administration of intravenous immunoglobulin (IVIG) can be beneficial in reducing the risk of clinically and microbiologically documented infection rates, and meta-analyses have confirmed these single studies [22]. IVIG has been given at 2–4-week intervals in various studies, and the optimal dose schedule has not been adequately established. The role for IVIG prophylaxis in patients with lymphoproliferative disorders seems most suitable for those with recurrent infections associated with hypogammaglobulinemia. An alternative strategy would be antibiotic prophylaxis by agents active against the encapsulated organisms, but no comparative trials have been performed.

Table 46.2 Parameters affected by myeloid growth factors

Parameter	Risk reduction	95% Confidence interval
Febrile episodes	0.54	0.43–0.67 (11)
Documented infections	0.51	0.36–0.73 (10)
Infection-related deaths	0.55	0.33–0.90 (11)
Early mortality	0.60	0.43–0.83 (11)

From [15, 84]

Splenectomy

Patients who have undergone splenectomy or who have conditions that result in hyposplenism are susceptible for serious infections by polysaccharide encapsulated bacteria, especially *Streptococcus pneumoniae*. Immunization with vaccines for *S. pneumoniae, H. influenzae,* and *N. meningitidis* prior to elective splenectomy is advisable when possible since immune responses after splenectomy are impaired. Nevertheless, immunization after splenectomy should be performed although one should recognize that protection may not be complete. Antibiotic prophylaxis with antibiotics active against the encapsulated bacteria should be given, with choice determined by local susceptibility patterns. The optimal drug, duration, and dose schedule have not been established. Young age and the early period after splenectomy appear to be associated with greater risks for infection [23].

Chronic Graft Versus Host Disease (GVHD)

Patients with chronic GVHD are susceptible for serious pneumococcal disease. Pneumococcal vaccination should be given to all HSCT patients, but since responses often are impaired, antibiotic prophylaxis is also recommended during active therapy for chronic GVHD [24].

Antifungal Prophylaxis

Prophylaxis in Neutropenic Patients

Risk Assessment

Neutropenia is a risk factor for invasive fungal infections (IFI). In patients not receiving antifungal prophylaxis, invasive candidiasis (yeast) and aspergillosis (mold) account for more than 80% of IFI in neutropenic patients [25]. Other pathogens include yeast of the genus *Trichosporon* [26] and the molds *Fusarium* species [27, 28] and Zygomycetes [29]. While candidiasis may occur early in the course of neutropenia, invasive aspergillosis (IA) and other mold infections occur almost exclusively in patients with prolonged (>2 weeks) and profound (<100/mm^3) neutropenia [28]. This distinction is very important because most chemotherapy regimens are not associated with prolonged and profound neutropenia and do not require antimold prophylaxis. Table 46.3 lists the most frequent situations associated with prolonged and profound neutropenia. Other important risk factors for candidiasis are gastrointestinal mucositis and the presence of a central venous catheter. By contrast, neutropenic patients at high risk to develop mucosal candidiasis are those with severe oral and gastrointestinal mucositis.

Primary Prophylaxis, *Candida*

Prophylaxis against invasive candidiasis is not indicated in all neutropenic patients. In allogeneic HSCT recipients, two randomized clinical trials (RCTs) showed that fluconazole reduced the frequency of superficial and systemic candidiasis, as well as infection-related mortality [30, 31]. In both trials, fluconazole was given at a dose of 400 mg/day. Considering these two trials and the drug profile (good compliance, few side effects), fluconazole is considered the drug of choice for the prophylaxis of invasive candidiasis before engraftment in allogeneic HSCT recipients, and may be started from the beginning or just after the end of the conditioning regimen. A lower dose of fluconazole (200 mg/day) was also effective in preventing superficial and systemic candidiasis in one RCT [32].

Fluconazole is not effective in preventing infection caused by all *Candida* species. *Candida krusei* is intrinsically resistant

Table 46.3 Duration of neutropenia according to different chemotherapy regimens for high-risk cancer patients and hematopoietic stem cell transplantation

Disease/type of HSCT	Treatment/stem cell source	Duration of neutropenia (days)	Additional risk factors for IFI
AML	Induction "7 + 3" or HDARAC	20–30	Mucositis, catheter
AML	Postremission consolidation with HDARAC	10–15	Mucositis, catheter
ALL	Induction	15–30	Corticosteroids
Large cell NHL[a]	Salvage treatment regimens	7–15	Corticosteroids, mucositis
Pediatric lymphoma	Various regimens	7–10	Corticosteroids, mucositis, catheter
Allogeneic HSCT	Peripheral blood	10–15	Corticosteroids, cyclosporine, mucositis, catheter, acute GVHD
Allogeneic HSCT	Cord blood	20–60	Corticosteroids, cyclosporine, mucositis, catheter, acute GVHD
Autologous HSCT	Peripheral blood	7–10	Corticosteroids, mucositis

HSCT hematopoietic stem cell transplantation; *IFI* invasive fungal infection; *AML* acute myeloid leukemia; *HDARAC* high-dose cytarabine; *ALL* acute lymphoid leukemia; *NHL* non-Hodgkin's lymphoma; *GVHD* graft versus host disease

[a]Primary treatment for large cell NHL is usually associated with neutropenia of short duration (<7 days)

to fluconazole, and *Candida glabrata* exhibits minimal inhibitory concentrations (MIC) higher than other species. As a consequence, fluconazole has shown to select for these less-susceptible *Candida* species [33, 34], and is not recommended for the prevention of infection due to these two species.

In addition to preventing invasive candidiasis, fluconazole administered concurrently with cyclophosphamide may be associated with less hepatic and renal toxicities because of a possible protective effect of fluconazole in the hepatic metabolism of cyclophosphamide, caused by its inhibition of cytochrome P450 2C9 [35].

Other than fluconazole, itraconazole oral solution (but not capsules) [36–38], voriconazole [39], and micafungin [40] effectively prevent the occurrence of invasive candidiasis in HSCT recipients during the preengraftment period. Itraconazole is less well tolerated than the other azoles [36, 38].

The incidence of invasive candidiasis is not homogeneous across all types of allogeneic HSCT. Transplants with myeloablative conditioning regimens are associated with severe neutropenia and mucositis, and are likely to benefit from anti-*Candida* prophylaxis during neutropenia. By contrast, some conditioning regimens of nonmyeloablative HSCT do not induce mucositis and are associated with neutropenia lasting <7 days. Although usually prescribed, anti-*Candida* prophylaxis may not be necessary in these instances. The same is true for most autologous HSCT recipients in which routine anti-*Candida* prophylaxis may be not indicated. However, even without strong evidence from RCTs, most experts recommend anti-*Candida* prophylaxis for autologous HSCT recipients who have underlying hematologic malignancies who will receive intense conditioning regimens associated with severe mucositis, or with an expected prolonged neutropenia due to graft manipulation.

The evidences for prophylaxis for invasive candidiasis during neutropenia in other settings are not as solid as in allogeneic HSCT. One meta-analysis examined 16 trials including more than 3,700 patients receiving fluconazole or placebo, no treatment or oral polyenes as prophylaxis during neutropenia, and found that outside the setting of HSCT, fluconazole was effective in preventing superficial fungal infections but not systemic fungal infections or fungal-related death. However, in studies with >15% incidence of IFI, fluconazole was effective [41]. Therefore, the ineffectiveness of fluconazole in non-HSCT neutropenic patients is probably related to the heterogeneity of the populations of neutropenic patients studied (with different incidences of invasive candidiasis) rather than an absence of efficacy. In general, the higher is the risk for the patient to develop severe mucositis during neutropenia, the higher is the risk for invasive candidiasis.

Primary Prophylaxis, *Aspergillus*

Prophylaxis for IA is indicated for patients with expected duration of neutropenia >14 days. This typically occurs in induction remission of acute myeloid leukemia (AML) and in allogeneic HSCT transplants with bone marrow or cord blood as the source of stem cells. By contrast, recipients of autologous transplantation and allogeneic HSCT with non-myeloablative conditioning are expected to have neutropenia of shorter duration and are at very low risk to develop IA. An intermediate group of risk is represented by allogeneic HSCT recipients receiving peripheral blood stem cells, patients with acute lymphoid leukemia (ALL) in induction remission and AML patients receiving consolidation treatment. These patients may develop prolonged neutropenia but in the majority of instances neutropenia last <14 days. However, severe T-cell-mediated immunodeficiency may be present and add as an important risk factor for IA in such patients.

In allogeneic HSCT, micafungin given from conditioning until engraftment was associated with a trend suggesting ability to prevent aspergillosis. In this trial, the incidence of IA was 0.2% among 425 patients receiving micafungin and 1.5% among 457 patients receiving fluconazole ($p = 0.07$) [40].

The use of itraconazole oral solution in HSCT recipients resulted in a reduction in the frequency of IPA in two RCTs, but about 25% of patients discontinued itraconazole because of gastrointestinal side effects [36, 38]. In patients with AML, a reduction in the incidence of IA was not observed in trials comparing itraconazole with fluconazole, and itraconazole was associated with more adverse events [42, 43]. A recent meta-analysis of itraconazole trials suggest that there is a reduction in *Aspergillus* infections, but only if a certain threshold of bioavailable dosing is used [44]. Its ability to prevent IFI has been associated with trough itraconazole concentrations >500 ng/mL, best achieved with the IV formulation (followed by the oral solution if the gastrointestinal function is intact). The oral capsule formulation suffers from erratic bioavailability and is best avoided.

Posaconazole was tested in patients with AML or myelodysplasia receiving induction therapy, and shown to be as effective as fluconazole, with good tolerability [45]. This study also showed that posaconazole was effective in preventing aspergillosis, with a reduction in fungal-related mortality. A limitation of this study is the fact that in the majority of cases of IA in the fluconazole arm, the diagnosis was based on the results of serum galactomannan. The lower number of cases of IA in the posaconazole arm could be due to the fact that serum galactomannan has a low performance in patients receiving mold-active azoles.

Taken together, the results of these studies using mold-active azoles and their impact in reducing the incidence

of IPA are appealing [46]. These findings, however, should be balanced against our significantly improved ability for the early detection of fungal infections and the potential undesirable consequences including toxicities, drug–drug interactions, costs, and emergence of resistance [47]. Finally, it is important to keep in mind the limitations of global prophylaxis defined as prophylaxis to all patients with a certain diagnosis (e.g., all patients undergoing therapy for acute leukemia). Indeed, the risk among these patients is variable. It is highest among patients with relapsed/refractory disease who should probably receive primary yeast and mold prophylaxis; the risk is somewhat lower among patients undergoing remission induction chemotherapy and in whom yeast prophylaxis and a surveillance guided diagnostic-based preemptive strategy is best. The lowest risk for IFI is during consolidation therapy. These patients may not even require systemic prophylaxis.

A randomized trial in patients with prolonged neutropenia showed no benefit for nebulized amphotericin B [48]. More recently, in a double-blind placebo-controlled trial, the frequency of IPA was lower in patients receiving nebulized liposomal amphotericin B (4 vs. 14%, $p = 0.005$). However, discontinuation of prophylaxis due to poor compliance was frequent [49].

Secondary Prophylaxis

Because the risk of reactivation of IMIs is high following resumption of immunosuppression, secondary prophylaxis is indicated in such patients [50]. A recent review of secondary antifungal prophylaxis included 197 patients with previous proven or possible IA who received additional cytotoxic chemotherapy or HSCT while receiving secondary prophylaxis with amphotericin B, itraconazole, or flucytosine or combinations of these agents. Documented relapse of IA was only 16% (31 of 197) who received prophylaxis compared to 62% (26 of 42) who did not ($p < 0.0001$) [51]. In allogeneic HSCT patients with history of aspergillosis, the risk of reactivation is lower if treatment was given for >30 days and radiographic abnormalities resolved [52]. In another series of HSCT recipients, among 129 patients with prior history of IA, reactivation of infection was more likely to occur in patients with longer duration of neutropenia before transplant, advanced status of the underlying disease, and short period (<6 weeks) between IA and HSCT. The risk of IA early after HSCT (within 30 days) was higher in transplants with myeloablative conditioning regimens, while Cytomegalovirus (CMV) disease, bone marrow or cord blood transplant, and grades II–IV acute GVHD increased the risk of IA occurring 30 days posttransplant [53]. Options for secondary prophylaxis include amphotericin B and its lipid formulations, caspofungin, itraconazole, voriconazole, and lipid amphotericin B followed

by voriconazole [51, 54–56]. In addition to secondary chemoprophylaxis, strategies to abbreviate the duration of neutropenia, such as the use of reduced-intensity conditioning regimens and peripheral blood stem cells, and the use of granulocyte transfusions may be employed [57, 58].

Prophylaxis in Nonneutropenic Patients

IFI occur in allogeneic HSCT recipients who develop severe GVHD. Although the number of neutrophils is normal in these patients, there is a paucity of inflammatory cells in lung tissues, indicating that these patients are functionally neutropenic [59].

Whereas invasive candidiasis may occur in this period, HSCT recipients with severe GVHD are at very high risk for invasive mold infections (aspergillosis, fusariosis, zygomycosis, and others). Similar to the early posttransplant period (during neutropenia), fluconazole is the drug of choice for the prevention of invasive candidiasis. In one RCT, fluconazole was given from conditioning until day +75 posttransplant [31]. A post-hoc analysis of this trial has shown that fluconazole was associated with prolonged protection against invasive candidiasis, even beyond the period of prophylaxis [60]. Options form anti-*Candida* prophylaxis in the postengraftment period include itraconazole oral solution (with the limitations of poor gastrointestinal tolerance) [36, 38], posaconazole [61], and voriconazole [39].

For antimold prophylaxis, the two RCT of itraconazole oral solution showed a benefit in reducing the incidence of IA, but again, the ~25% discontinuation for gastrointestinal side effects offsets its benefit [36, 38]. In one RCT, posaconazole was compared with fluconazole in patients with GVHD. There was a trend toward a lower incidence of IFI in patients receiving posaconazole, and a significant reduction in the incidence of IA (2% in patients receiving posaconazole vs. 7% in fluconazole recipients, $p = 0.006$) [61]. In another study, voriconazole was compared to fluconazole in a double-blind RCT. Patients received prophylaxis from conditioning until day +100 (or +180 if patients developed GVHD). In addition, serum galactomannan monitoring was performed twice a week in the first 60 days, and once a week thereafter (unless patients developed GVHD). There were no differences in the incidence of IFI, but there was a trend for a lower incidence of IA (5.4% in the voriconazole arm and 7% in the fluconazole arm, $p = 0.05$) [39].

As mentioned before, the results of these studies using mold-active azoles indicate that they indeed reduce the incidence of IA. However, the trial comparing fluconazole and voriconazole suggests that active monitoring with biweekly serum galactomannan and chest CT scan is an alternative to the use of a mold-active azole. Therefore, several factors

should be taken into consideration in determining if prophylaxis is appropriate at a specific treatment center, for a given patient or patient population to target a specific infection, or if prophylaxis should be withheld and a diagnostic-based preemptive strategy used instead.

Antiviral Prophylaxis

Prophylaxis in Neutropenic Patients

Herpes Simplex Virus (HSV)

Active infection by HSV is common in patients with cancer undergoing antineoplastic therapy [62]. Most HSV infections are due to reactivation of latent virus from an infection much earlier in life; namely, seropositive patients are those chiefly at risk. Thus, HSV serology offers a good way to determine if the patient is at risk. The likelihood of reactivation is influenced by the intensity of cytotoxic treatment. Reactivation occurs in approximately 70% of patients undergoing induction chemotherapy for AML or those receiving intensive conditioning regimens for HSCT. Randomized trials have demonstrated the effectiveness of acyclovir to prevent recurrent infection in AML and HSCT patients [62]. Prophylaxis is generally given until neutrophil recovery. It is important to note that acyclovir does not totally prevent reactivation, but rather delays its occurrence during antiviral administration. Generally, reactivation after neutrophil recovery occurs but its occurrence once host defenses are more robust results in milder disease or is subclinical.

Prophylaxis in Other Settings

Cytomegalovirus (CMV) After HSCT

CMV seropositive patients undergoing allogeneic HSCT are at risk for reactivation, and serious disease typically occurs after engraftment during the second or third month after HSCT. Asymptomatic viremia generally occurs 1–2 weeks before onset of clinical disease, which is most commonly in the form of interstitial pneumonia, or less frequently, enterocolitis. Ganciclovir, acyclovir, and valacyclovir have been shown to be associated with a reduction in the risk for CMV disease in seropositive patients [63–65]. Because of its myelosuppressive effects, ganciclovir is generally begun at time of engraftment in patients at risk. The course of prophylaxis is given during the chief risk period, until day 100–120. An alternative strategy is monitoring patients by testing blood samples weekly with the pp65 antigen assay or CMV quantitative PCR to detect virus

activation, and then once viremia is detected, antiviral therapy is initiated with ganciclovir (or foscarnet) "preemptively," to prevent subsequent development of clinical disease.

Seropositive patients undergoing autologous HSCT can also experience reactivation of CMV but CMV disease is infrequent in contrast to allogeneic HSCT; thus, similar prophylaxis and preemptive strategies are not necessary. However, in patients who have T-cell depletion of the stem cell graft, or who have received immunosuppressive therapies such as purine analogs, alemtuzumab, rituximab, or chronic corticosteroids, CMV disease can occur and routine CMV monitoring and preemptive therapy if reactivation is detected are advisable [66, 67].

CMV seronegative patients are also at risk for CMV infection from virus transmitted from the donor stem cell graft or blood products from CMV seropositive donors. A stem cell graft from a seronegative donor (when feasible) and blood products from CMV seronegative donors should be given to negate the risk of CMV transmission.

Varicella-Zoster Virus (VZV)

VZV reactivation in seropositive patients is common after both autologous and allogeneic HSCT [62]. Onset of disease occurs several months after HSCT (median onset 5 months). Acyclovir prophylaxis is effective in prevention of reactivation and should be given for 1 year since shorter duration (6 months) has been associated with rebound overt zoster after discontinuation [68–70]. Valacyclovir can be substituted for acyclovir. Patients with chronic GVHD should continue acyclovir beyond 1 year for at least the duration of active immunosuppressive therapy but perhaps longer until lymphocyte recovery. Bortezomib given for therapy of multiple myeloma has also been associated with reactivation of VZV in approximately 13% of patients [71]. The reason for this is not known, but is perhaps related to its inhibition of production of NFκB, which is necessary for T-cell activation.

Epstein–Barr Virus (EBV)

EBV activation can occur after allogeneic HCT, and patients with profound T-cell immunodeficiency are especially vulnerable to EBV disease, which typically occurs during the first 9 months after HCT. The most common and serious manifestation of EBV is lymphoproliferative disease. The risk is mostly in patients with profound T-cell deficiency, such as seen after T-cell depletion of the stem cell graft, use of anti-T-cell antibodies, cord blood as stem cell source, and after mismatched or haploidentical transplantation. Monitoring EBV load by assaying blood samples for EBV DNA by quantitative PCR can identify patients at greatest risk for

lymphoproliferative disease. In patients with high titres of EBV, a reduction of immunosuppression (if possible) can be useful or rituximab can be given preemptively [72].

Other Pathogens

Antipneumocystis

Risk groups in which prophylaxis should be considered against *Pneumocystis jirovecii* include lymphoreticular cancers and myeloablative therapy with HSCT in which treatment regimens result in suppression of T-lymphocyte immunity (e.g., corticosteroids, purine analogs, monoclonal antibodies directed against T cells, and others) [73]. Infection can be prevented by TMP-SMX, which can be given as one double strength tablet (160 mg TMP plus 800 mg SMX) once or twice daily, but 2 or 3 times weekly also is effective [74]. Aerosolized pentamidine given once monthly at a 300-mg dose or dapsone (100 mg/day orally) are alternatives, but they are less effective. A retrospective study in 327 HSCT recipients, failure of prophylaxis was observed in 4 of 44 patients receiving pentamidine, 1 of 31 receiving dapsone, and in none of 105 patients receiving TMP-SMX [75]. In HSCT recipients, prophylaxis is usually started just after engraftment, and continued for 6 months posttransplant, or until discontinuation of immunosuppressive therapy.

Antiparasitic

Toxoplasmosis

Toxoplasmosis in cancer patients occurs as reactivation of primary infection, in the context of severe depression of T-cell-mediated immunity (GVHD, chronic use of corticosteroids, use of purine analogs, alemtuzumab, and others) [76, 77]. In allogeneic HSCT recipients who were seropositive for toxoplasmosis, PCR screening in the serum showed positive tests in 16% of patients [78]. PCR screening has been recommended in recipients of cord blood graft who develop GVHD and are not receiving TMP-SMX. Indeed, although reactivation has been rarely reported in patients receiving TMP-SMX, this is the drug of choice for prophylaxis against toxoplasmosis.

Strongyloidiasis

Strongyloides stercoralis is endemic in a large area in the globe (in general moist temperature areas such as the tropics, sub-tropics, and southeast of Europe and the USA). The great

concern about strongyloidiasis is the possibility for the occurrence of hyperinfection and the frequently fatal disseminated syndrome. The later occurs in patients with T-cell immunodeficiency, but it is difficult to select a group of immunosuppressed patients at higher risk since there are reports of its occurrence in patients receiving topical corticosteroids [79]. In addition, considering the high incidence of strongyloidiasis in endemic areas, the disseminated syndrome seems to be quite rare. A retrospective study in 253 patients with hematologic malignancies from a single center in Brazil reported an incidence of 21% of strongyloidiasis, but only one case of disseminated syndrome [80]. In a prospective study from the same institution, 13% of 164 hematologic patients who were screened with three stool examinations had at least one positive exam. No patient developed the disseminated syndrome [81]. Taking these data into consideration, it is difficult to make formal recommendations regarding prophylaxis, especially in endemic areas. In nonendemic areas, it has been suggested that patients with unexplained eosinophilia or who have resided in or traveled to an endemic area should be screened for strongyloidiasis with an enzyme-linked immunosorbent assay (ELISA). In immunocompromised patients living in an endemic region, the ELISA test showed sensitivity, specificity, positive, and negative predictive values of 68, 89, 48, and 95%, respectively [81]. The use of an antiparasitic drug for patients with positive screening test is tempting, but there is no support in the literature. In a randomized study in Brazil, 103 patients with hematologic malignancies and negative stool examinations received thiabendazole (50 mg/kg/day for 2 days) or placebo every month. Five patients had strongyloidiasis, four in the placebo and one in the thiabendazole arm ($p > 0.05$) [82]. The use of ivermectin (200 µg/kg/day for 2 days; repeated after 2 weeks) has been suggested in patients from nonendemic areas and positive screening tests [83].

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Chapter 47
Controversies in Antimicrobial Prophylaxis

Ben de Pauw and Marta Stanzani

Abstract The risk of life-threatening infection in association with chemotherapy-induced neutropenia coincided miraculously with the development of a second generation of antimicrobial agents. Even after having randomized more than 10,000 patients in clinical trials on prophylaxis during neutropenia, there is still no convincing scientific evidence to support the apparently attractive strategy. Even trials that at first glance appear to provide a positive answer do not survive a meticulous dissection. Two major factors are accountable for this unfortunate situation: a lack of trials with an adequate number of patients and a shortage of reliable diagnostic tools to establish infections in neutropenic patients. Meta-analysis has become a fashionable approach to meet the problem of low numbers to a certain extent, but the outcome has to be interpreted with caution. Trials that do not include statistically significant findings tend to be rejected by peer-reviewed journals, which may lead to an overestimation of the prophylactic effect. A comprehensive discussion of controversies related to antimicrobial prophylaxis is provided in this chapter.

Keywords Prophylaxis • Neutropenia • Fungal infection • Antifungals

Introduction

Gerald Bodey's description of the risk of life-threatening infection in association with chemotherapy-induced neutropenia coincided miraculously with the development of a second generation of antimicrobial agents [1]. The oldtimers, sulphonamides, penicillin, and gentamicin were replaced by more potent and less toxic compounds that, with due restrictions, even could be administered orally. Without delay, these new antibiotics were introduced into the standard management of patients treated for malignant disease who had acquired an infection. Unfortunately, the overall impact of the new drugs was rather disappointing because, before therapy was started, infections were often already in a stage beyond cure. Late recognition of serious infections was related to the absence of typical signs and symptoms of infection in neutropenic patients in conjunction with a lack of sensitive diagnostic tools. A typical standard diagnostic program consisted of chest X-ray and culturing of blood and material from any clinically suspicious lesion. Against this background, earlier initiation of antibiotic therapy seemed an attractive option to prevent rapidly fatal infections. When it became clear that approximately 80% of the bacterial pathogens responsible for infection during neutropenia originated from patients' own endogenous flora, half of them acquired during hospitalization, the idea of prophylaxis, i.e., warding off an overwhelming event, was born and numerous prophylactic regimens of increasing complexity were designed [2]. The ultimate schemes included a protected environment program with high-efficiency particulate air (HEPA) filtration, strict patient isolation, special water-purification systems, special handling of patients washes, and food restrictions to prevent acquisition of exogenous organisms in combination with so-called "intestinal decontamination." This strategy implied administration of nonadsorbable antibiotics aiming at complete suppression of the endogenous intestinal bacterial flora and at prevention of acquiring exogenous organisms. The most common antibiotics for that purpose were gentamicin, vancomycin, framycetin, colistin, neomycin/polymyxin. A limited patient's compliance was the major obstacle to success of such programs. Moreover, the protective effect remained at least questionable. Elimination of the complete microbial flora of the digestive system obviously created space for colonization of the gut by aggressive micro-organisms during the hospitalization, whenever the carefully constructed protective barrier was broken. As a result, the majority of infections that occurred in chemotherapy-induced neutropenic patients were caused by these difficult-to-treat nosocomial pathogens. Subsequently, "selective decontamination," eradication of Gram-negative aerobic organisms

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from the digestive tract while leaving the commensal nonpathogenic anaerobic flora untouched, became popular. This concept, based on several studies in immunocompromised mice, offered promise in a few small randomized trials in patients who were treated for cancer, but a statistically convincing trial was never conducted [3]. Shortly after its introduction in clinical practice, clinicians started to use trimethoprim/sulfamethoxazole, usually given together with oral polymyxin and nystatin or amphotericin B, for prophylactic purposes. In fact this approach combined selective decontamination of the gut with systemic antibiotic cover, since trimethoprim/sulfamethoxazole is well absorbed and does achieve therapeutic blood levels. In many centers trimethoprim/sulfamethoxazole containing regimens, which also protected the patients against pneumocystosis, became the regimens of choice until the arrival of the fluoroquinolones. The spectrum of activity of these antibiotics that were well tolerated generated a myriad of industry-sponsored large clinical trials on their use in a prophylactic setting. When the dust of these trials settled, fluoroquinolone-based schedules appeared as the new standard for antibacterial prophylaxis. Antifungal prophylaxis evolved more or less along the same route. Mouth rinsing with and/or swallowing of either amphotericin B or nystatin were poorly tolerated by patients who experienced a remarkable similarity between these drugs and sticky sand. The first azoles, miconazole and ketoconazole, were hardly better appreciated and their use was often accompanied by allergic reactions. The availability of fluconazole and itraconazole seemed to change the scene but, alike the situation with fluoroquinolones for antibacterial prophylaxis, the cumulative data from all clinical trials were not sufficiently convincing to gain antimicrobial prophylaxis an unequivocal positive recommendation in the current guidelines from the Infectious Diseases Society of America [4]. To see what went wrong in the assessment of the feasibility of antimicrobial prophylaxis that remains intuitively attractive to a large majority of clinicians we need to scrutinize the pivotal data.

Clinical Trials on Antibacterial Prophylaxis

Soon after their introduction in the 1980s, the fluoroquinolones became the most fashionable antibiotics in the prophylaxis of bacterial infections in neutropenic patients. There were many reasons for this popularity. Fluoroquinolones show clinical activity against most Gram-negative and many Gram-positive micro-organisms, as well as against atypical mycobacteria. After oral administration of the fluoroquinolones, high levels are achieved in the gastrointestinal tract, which results in an almost complete suppression of the Gram-negative enterobacteria without interfering with the endogenous anaerobic flora. This class of drugs has an excellent bioavailability, an excellent tolerance, a limited number of side effects and interactions, and does not cause myelosuppression. In 8 out of 9 placebo-controlled clinical trials that were conducted between 1983 and 1993 and included almost 1,000 patients, ciprofloxacin and norfloxacin were found safer and appeared to be more effective in reducing the incidence of Gram-negative bacteremia than their comparators, principally trimethoprim/sulfamethoxazole. Conversely, no differences in overall mortality and episodes of fever were found. Streptococci became the most frequently isolated pathogens, and extensive use of the quinolones did raise the concern of the development of resistances against enterobacteriaceae, especially *Escherichia coli*. The introduction of levofloxacin, a fluoroquinolone with improved Gram-positive coverage, fostered two new large clinical studies in more than 2,300 patients who were treated for a hematological malignancy. The results of these two large, multi-center, randomized, double-blind, placebo-controlled trials were published in prominent medical journals [5, 6]. Cullen et al. addressed the potential of orally administered levofloxacin, given once daily at a dose of 500 mg for 7 days, to cover low-risk patients against infection during neutropenia ($<0.5 \times 10^9$/L) induced by standard chemotherapy for solid tumors or malignant lymphoma. In this placebo-controlled study, which included 1,565 patients, levofloxacin reduced the incidence of clinically documented infections during the first cycle of chemotherapy from 8 to 3.5% ($p < 0.001$), while, considering the whole course of chemotherapy, the rate of febrile episodes was reduced from 15 to 11% ($p = 0.01$). No difference was found with regard to infection-related mortality and overall mortality or in the development of antibacterial resistance [5]. The second trial by Bucaneve and his group comprised 760 patients with hematological malignancies who underwent aggressive antineoplastic therapy with an anticipated profound and protracted neutropenia ($<1.0 \times 10^9$/L for more than 7 days). The occurrence of fever was 85% in the placebo group to 65% in the levofloxacin group ($p = 0.001$). In fact, the data generated by this trial was quite similar to those from previous trials on quinolone prophylaxis with a statistically significant decrease in the rate of microbiologically documented infections from 39 to 22% with a reduction in the number of bacteremias sustained by Gram-negative bacteria ($p < 0.001$). However, once more, no difference was observed in infection-related mortality and overall mortality [6]. In the same year, Gafter-Gvili et al. performed a meta-analysis on 14 randomized, controlled trials of antibiotic prophylaxis that included more than 1,200 neutropenic patients and that compared quinolones to either a placebo or no treatment. The study populations consisted mainly of patients who were treated for an acute leukemia or who received an autologous bone marrow transplantation. It was concluded that prophylactic administration of a quinolone would result in a reduction

of the rate of febrile neutropenia and documented bacterial infections, and lower mortality. Moreover, there seemed to be no increase in the number of fluoroquinolone-resistant bacteria. Unfortunately, the quality of some of the trials that were included in this analysis was not sufficient to allow a firm conclusion [7]. The biggest and most recent meta-analysis on 101 clinical trials, which comprised around 12,600 neutropenic patients, the majority suffering from hematological malignancies, performed by the same group demonstrated that prophylaxis significantly reduces the overall mortality when compared to placebo or no intervention [8].

Clinical Trials on Antifungal Prophylaxis

More than 25 years ago, the rationale for chemoprophylaxis of fungal infections appeared already persuasive enough to initiate clinical trials on this subject. The poor tolerance and limited efficacy of orally administered polyenes have abandoned this approach. The trend-setting paper by Goodman et al. on fluconazole given as prophylaxis in bone marrow transplant recipients showed a reduced rate of proven invasive candidal infections [9]. In a reaction to this publication fluconazole was widely introduced as a safe drug for prophylactical purposes, and the choice for this strategy appeared to be endorsed by the improved overall survival registered in a similar trial conducted by the Seattle bone marrow transplant team [10]. Van Burik et al. reviewed 355 autopsies performed in Seattle between 1990 and 1994. Among transplanted individuals who had been protected by fluconazole prophylaxis, *Candida* infections amounted to 8% as compared with 27% in those without [11]. However, a follow-up of the Slavin study learned that the superior survival registered in the fluconazole arm was maintained, but this advantage could not be attributed to a decreased fungal infection-related death rate only [12]. Disappointingly, even 38 comparative trials were not enough to establish a positive impact of fluconazole on candidiasis-related mortality in patient populations other than bone marrow transplant recipients unequivocally. The way out of this labyrinth of statistically underpowered trials was meta-analysis; it showed a convincing beneficial effect of prophylactic fluconazole among certain subgroups such as patients who are colonized by *Candida* species and received highly dosed remission-induction therapy for acute myelogenous leukemia [13, 14]. This observation makes sense as disseminated candidiasis is supposed to be preceded by colonization of the gastrointestinal tract in combination with immunosuppression and damage of the mucosal lining by cytotoxic therapy [15]. Orally administered fluconazole both reduces the *Candida* burden in the gut and eliminates the organisms if they gain access to the bloodstream. This explanation helped to grant the label of evidence-based medicine to what already had become common practice.

In the endeavor to prevent infections by *Aspergillus* species and other molds, the focus was directed at itraconazole as soon as it became available for clinical use. For many reasons, the results were not as good as was hoped for. First of all, the drug was poorly tolerated and had an erratic bioavailability, although this was improved by the introduction of an oral suspension. After a few negative clinical trials, a British and American group of investigators found itraconazole to protect neutropenic patients better against invasive aspergillosis than did fluconazole in the comparative arms [16–19]. Unfortunately, the difference in infections due to *Aspergillus* species in British trial was related to an outbreak at one institution. The population of the American study consisted of allogeneic bone marrow transplant recipients. Three of 71 patients given itraconazole (4%) and 8 of 67 patients given fluconazole (12%) acquired aspergillosis; this difference was not statistically significant, and prophylaxis with itraconazole did not result in an improved survival. A similar trial by the Seattle corroborated these findings and indicated that itraconazole might interfere with the metabolism of cytostatic drugs like cyclophosphamide [20]. Posaconazole has in vitro activity against a wide range of molds including *Aspergillus* species and it also appeared well tolerated and safe. This new azole featured as the main comparator in two randomized prophylactic trials. In the first study among patients undergoing chemotherapy for hematological malignancies, the incidence of invasive aspergillosis was 1% after posaconazole compared with 7% after alternative prophylaxis without there being a difference in survival. The second study was done among stem cell transplant recipients on immunosuppressive therapy for graft-versus-host disease. In the posaconazole arm, 2% of cases showed evidence of proven or probable invasive aspergillosis as compared to 7% in the fluconazole arm. In addition, there were fewer deaths among those receiving posaconazole that was well tolerated. It needs to emphasize that most of the probable aspergillosis cases were based on a positive galactomannan antigen test, whereas it is a fact that mold-active antifungal drugs lower concentrations of this antigen. Remarkably, these studies were performed without posaconazole having first won its spurs as primary therapy of invasive aspergillosis. A prophylactic trial in bone marrow transplant recipients that compared voriconazole with fluconazole learned that invasive aspergillosis occurred in 5% of the fluconazole-treated patients and in 2% of the voriconazole group, a result similar to that obtained with posaconazole in a different setting [21].

As the airways serve as main portal of entry for *Aspergillus* spores, there was a rationale to explore the role of inhalation of antifungals. Aerosolized particles of Amphotericin B of a size to similar *Aspergillus* conidia are supposed to travel the same route, which was supposed to prevent colonization of the airways by molds. The hypothesis is appealing, but the results obtained in the only prospective randomized study were

disappointing; the aerosol of amphotericin B offered no advantage with respect to the number of documented infections or overall survival. Moreover, intolerance forced about one third of patients to discontinue inhalations prematurely. Tolerance appeared better with aerosolized liposomal amphotericin B, which resulted in a lower rate of proven aspergillosis without a survival benefit in comparison with a placebo [22].

The use of intravenous amphotericin B for prophylactic purposes has been limited, presumably due to its inherent toxicity. This scene changed with the introduction of the lipid preparations, but so far none of these drugs have been evaluated in landmark trials on antifungal prophylaxis. As a rule, the trials were small and none the amphotericin B formulations did produce results, such as a reduction in the number of cases with invasive aspergillosis or a lower mortality rate that would urge a modification of standard treatment schedules. The use of low doses of polyenes may be a major reason for the disappointing outcome. Enthusiasm for this strategy was generated by the observation that low-dose amphotericin B prophylaxis, alone or in combination with nasal amphotericin B, seemed to decrease the incidence of aspergillosis in bone marrow transplant recipients as compared with historical controls. However, none of the prospective, randomized trials could confirm these hope giving findings [23, 24]. The interest in low doses of intravenous amphotericin B, such as 0.10 mg/kg daily or 0.5 mg/kg three times a week, or liposomal amphotericin B, 3 mg/kg 3 days a week, is astonishing. Where the lack of success of itraconazole is commonly attributed to poor tolerance and difficulty in achieving satisfactory serum and tissue levels, found investigators motivation to test a homoiopathic dose of amphotericin B. If lower toxicity constitutes a valuable argument to use a suboptimal dose of amphotericin B, completely refraining from this type of prophylaxis to avoid all toxicity would be the next logical step.

Caspofungin and micafungin, the latest arrivals to the antifungal armamentarium, were shown to be as effective as their azole comparators, itraconazole and fluconazole, respectively [25, 26]. The studies showed indeed that candins are effective in this setting, but the need for these compounds for prophylactic purposes is rather limited given the availability of equally efficacious, cheaper oral antifungal drugs. Moreover, the large micafungin study in bone transplant recipients did not cover the fungal-prone episode of graft-versus-host disease, which precludes a genuine assessment.

Considerations

Even after having randomized more than 10,000 patients in clinical trials on prophylaxis during neutropenia, there is still no convincing scientific evidence to support the apparently attractive strategy [27]. The discussion sections of the papers written on these trials accentuate the investigators' disappointment by way of detailed explanations for the failure to show a benefit of the intervention. Even trials that at first glance appear to provide a positive answer do not survive a meticulous dissection. One single study showing that a particular regimen was superior to another would end the controversy on the value of prophylaxis. As this is not the case, the question raises whether all regimens are equally good or equally bad. Two major factors are accountable for this unfortunate situation: a lack of trials with an adequate number of patients and a shortage of reliable diagnostic tools to establish infections in neutropenic patients. A small sample size, typically around a 100 patients per arm where more than 1,000 are required, will result in an insignificant finding due to a type II error. Besides, recruiting large numbers of unselected patients will hardly improve the situation, because it implies inclusion of many low-risk cases, which only will make the analysis more difficult. Meta-analysis has become a fashionable approach to meet the problem of low numbers to a certain extent, but the outcome has to be interpreted with caution. Trials that do not include statistically significant findings tend to be rejected by peer-reviewed journals, which may lead to an overestimation of the prophylactic effect. Moreover, meta-analysis do not account for flaws in the original trial designs, such as cover of the wrong risk episode and selective exclusion of a category of patients. Lack of reliable diagnostic tools is responsible for the fact that there is no generally accepted endpoint for clinical studies on prophylaxis. Success is usually defined as a survival of the neutropenic episode without infections that require broad-spectrum antimicrobial therapy and no need for interruption of the prophylactic drugs. Hence, parameters of outcome like fever, culture results, antigen levels, CT abnormalities, overall survival, infection-related death, infection, administration of broad-spectrum antimicrobials or antifungal agents, and side effects feature prominently in reports on clinical trials. However, each of these parameters has serious shortcomings. At first glance, overall mortality may appear a sensitive, unbiased measure of the effect of prophylaxis, but other independent factors such as the type of cytotoxic therapy, patient age, or status of the underlying disease do have their impact on the risk of death. Infection-related death is difficult to establish, particularly when no autopsies are performed. Indeed, in spite of systematic diagnostic workup with cultures, antigen testing and CT scans, more than half of the fatal invasive aspergillosis and candidiasis cases remain undetected [28]. Finally, broad-spectrum antibiotics and antifungals are usually instituted on suspicion of infection, a subjective parameter but cherished by clinicians who are minimally interested in colonization rates.

Drawing up the sheet on antimicrobial prophylaxis must include an assessment of the likely negative effects, i.e.,

toleration, toxicity, costs, and development of resistance to the involved antimicrobial drugs. Antibiotics appear to be more safe than antifungal drugs, which are, depending on the class, nephrotoxic or hepatotoxic and display numerous interactions with possible comedication due to their P-450-dependent metabolism in the liver. Development of resistance is an issue with the extensive use of fluoroquinolones and other bacterials but less so with antifungals. Widespread introduction of fluconazole as anti-*Candida* prophylaxis in neutropenic patients was associated with the appearance of *Candida* species other than *Candida albicans* and an increased *Aspergillus*-related mortality from 18 to 29% in the autopsy study by Van Burik et al. These changes are rather due to selection as a result of elimination of susceptible strains and, presumably, a prolonged survival that may dispose toward acquisition of other fungal infections [11, 29]. The same mechanism may play a role in the emergence of Zygomycetes during or after the use of voriconazole. Likewise, even a huge meta-analysis on the effect of quinolone prophylaxis does not allow definite conclusions on the rate of occurrence of bacterial resistance in neutropenic patients [30]. Several observational studies examined the impact of suspending the use of antibacterial prophylaxis when a high incidence of resistance to fluoroquinolones was documented, but the results of this strategy were not consistent and, therefore, the validity of this approach remains questionable [31–34].

It is clear that prophylaxis does not make the clinician's life easier because the strategy is not foolproof and has some serious pitfalls. On the other hand, using our knowledge of the pathophysiology of infections in neutropenic patients, supported by the results of subgroup analysis, it has become clear that it is possible to protect patients at high risk against rapidly fatal infections by bacterial and fungal pathogens (see Table 47.1).

Table 47.1 Situations to consider the use of prophylaxis

Prevention of bacterial infections
– Prolonged chemotherapy-induced neutropenia
– (Functional) asplenia

Prevention of fungal infections
• *Candida* species
 – Colonization gastrointestinal tract and/or skin
 – Radio/chemotherapy-related mucosal damage
 – Central venous line
 – Prolonged use of antibacterial agents
• *Aspergillus* species
 – Depressed cellular immunity, as in graft-versus-host disease
 – Prolonged chemotherapy-induced neutropenia
 – Prolonged use of corticosteroids or other immunosuppressive agents
 – Cytomegalovirus infection in a transplant recipient

Guidelines for Clinical Practice in Neutropenic Patients

McQuay and Moore proposed four questions that need to be considered before a reasonable decision on the use of prophylaxis can be made [35]. First, would the event we are trying to prevent, i.e. overwhelming infection, be difficult to treat if it occurred? Second, is an overwhelming infection a serious event in a neutropenic cancer patient? Third, is prophylaxis safe and well tolerated? Fourth, is the prophylaxis effective, i.e., is the number needed to treat to save one patient relatively low such as <20, i.e., is the incidence of the infectious complication high? A firm "yes" would be the answer to first three questions, albeit that the adverse events associated with the use of antifungals are not neglectable but without appropriate therapy the mortality would exceed 90%. On the other hand, given the availability of the modern powerful antibiotics and antifungal compounds, the answer to the first question depends on local diagnostic facilities since early detection would allow a timely treatment of a disseminated infection. The answer would be different for centers vigilantly pursuing a preemptive approach with structured diagnostic surveillance and for centers that do not have the facilities or the means to do so [36]. Answering the fourth question is extremely complicated and probably responsible for most of the controversies that surround the employment of antimicrobial prophylaxis in neutropenic patients.

An ideal prophylactic antimicrobial agent should be safe to be administered over long periods of time, effective against those pathogens that cause life-threatening infections, available in both oral and intravenous formulations, inexpensive, and associated with a very low propensity to emergence of resistance. As there are no drugs that meet all these criteria, individual clinicians have to make up the balance between advantages and disadvantages of prophylaxis.

Taking Gram-negative sepsis for a target, the number-of-needed-to-treat patients to prevent the event may be as low as 2. This looks impressive but in general it does not translate into an improved survival since nowadays all clinicians adhere to prompt empirical cover by very efficacious broad-spectrum antibiotics at the onset of fever. However, if the focus is directed at the use of antibacterial prophylaxis in high-risk patients, the situation is quite different. A recent meta-analysis of studies that included only patients who received high-dose chemotherapy for acute leukemia or stem cell transplantation indicated a reduced death rate among individuals on prophylaxis with fluoroquinolones [37]. So, high-risk patients should be considered as candidates for antibacterial prophylaxis with quinolones. Prophylaxis should commence at the start of chemotherapy and stop at the resolution of the neutropenia or when fever occurs. Similarly, there is a reasonable consensus on the value of

fluconazole prophylaxis in patients at high risk for invasive *Candida* infection. This high-risk population also consists of patients with expected protracted and profound neutropenia and severe mucositis. Indwelling central venous access devices pose an additional risk factor. Based on previous findings, it appears that body surveillance cultures may help to determine the subset of patients who are most likely to develop hematogenous candidiasis. Antibacterial and anti-candidal prophylaxis should be terminated after recovery from neutropenia.

The prevention of infections by *Aspergillus* species and other molds is a more complicated issue. Neutropenia is not the leading risk factor. A depressed cellular immunity is more important and this implies the time that the risk period stretches from the start of bone marrow suppression until the tapering of immunosuppressive drugs at the resolution of graft-versus-host disease. Keeping this in mind, it is perplexing that anti-*Aspergillus* prophylaxis under these extremely risky circumstances does not ensure a survival benefit among bone marrow transplant recipients treated for graft-versus-host disease [38]. Secondly, aspergillosis is an airborne disease. Since spores of *Aspergillus* are ubiquitous in nature, the patient may acquire infection both during his hospital stay and while at home. This explains why the protective influence of HEPA filtration is rather unsatisfactory. Furthermore, the incidence of invasive aspergillosis varies highly between centers and ranges from 0% to as high as 25% or more, which makes a universally applicable guideline on the use of prophylaxis difficult. When prophylaxis is deemed necessary, the flexibility afforded by the parenteral and oral formulations of anti-*Aspergillus* azoles is a most attractive feature, since it allows patients to leave the hospital while continuing therapy.

In summary, the decision in favor of prophylaxis hinges around incidence and risk factors. If we accept this conclusion, we have left the field of prophylaxis *strictu sensu*, i.e., giving an antibacterial or antifungal drug to an unselected cohort of patients with a defined underlying disease who undergo a specified cytoreductive therapy. Concentration on specific risk groups means that we have turned to targeted prophylaxis, in between a prophylactic and a preemptive strategy. A preemptive approach is a treatment of early, subclinical disease when therapy would be maximally effective [39]. The major advantage of this strategy is that patients who do not need therapy are not exposed to potentially toxic drugs. The cornerstones of its success are careful clinical and laboratory examination of the patient in conjunction with understanding of the temporal sequence of microbial events after transplantation or intensive chemotherapy. Applications of the new diagnostic tools that have a rapid turn-around time are vital to the feasibility of this strategy. If antigen testing, PCR techniques, high-resolution CT-scanning, and extensive clinical experience are not available, one should rather rely on prophylaxis and empirical therapy to avoid confrontation with an infection in a stage beyond cure. So, the choice of the most appropriate strategy does not only depend on the prevalence of a given infection but also on the local circumstances. It might be expected that improvement of disease markers will further decrease the need for prophylaxis [40, 41]. Toll-like receptors are essential components of the immune response to fungal pathogens. Seropositivity for cytomegalovirus in donors or recipients or in both, as compared with negative results, was associated with an increase in the 3-year probability of invasive aspergillosis (12 vs. 1%). Development of immunogenic vaccine would change the scene completely, but the prospects of having a safe and effective vaccine are not bright [42].

The role of antimicrobial drugs clarified leaves the question of dosing. The official registration of fluconazole refers to 400 mg daily, the dosage used in the hope to cover *Aspergillus* species during the initial trials, while subsequent studies suggested that lower doses suffice for *Candida* species [43]. Anyhow, a therapeutic dose of the prophylactic compound is mandatory since it is not likely that respective pathogens are more sensitive to the antimicrobial agents when they are about to enter the body.

Secondary prophylaxis is a completely different issue. Patients with a proven or probable invasive fungal infection run a high risk when they must undergo further cycles of chemotherapy or a bone marrow transplant. Without additional precautions, reactivation rates as high as 50% have been reported. Hence, this group of patients should receive a therapeutic dose of a systemically active antifungal when the next course of chemotherapy is started. This, in fact, preemptive strategy proved effective in the prevention of recrudescence in the majority of patients. An oral azole might be considered for bridging the period between two consecutive neutropenic episodes.

To conclude, Benjamin Franklin is supposed to have said that "an ounce of prevention is worth a pound of cure." It is not known in which context this brilliant man made his statement, but it is hardly imaginable that he was referring to the prophylactic use of antimicrobial agents in immunocompromised patients.

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Chapter 48
Infection Prevention – Protected Environment and Infection Control

J. Peter Donnelly

Abstract In our daily life, we all encounter a range of microorganisms by breathing, eating and drinking and by direct contact with each other and the objects around us. This routine occasionally leads to infection. By contrast, patients who are given chemotherapy to treat cancer can succumb dramatically when confronted with these common-place infections. Moreover when death ensued it was all the more tragic since in many cases it might have been avoided altogether had effective treatment been instituted early enough or, better still, if the infection had been prevented in the first place. In this chapter, an overview of infection control measures including protected environment for severely immunocompromised cancer patients is presented.

Keywords Infection control • Hand hygiene • Universal protection • Airborne protection • Prophylactic topical oral non-absorbable antimicrobials • Protected environment

In our daily life, we all encounter a range of microorganisms by breathing, eating and drinking and by direct contact with each other and the objects around us. This routine occasionally leads to infection. We acquire viral infections by inhalation and ingestion, bacterial infections through cuts and abrasions and occasionally through contaminated food and drink. Any infection that ensues is usually short-lived, often self-limiting and if medical care is needed it is usually straightforward and simple. By contrast, patients who are given chemotherapy to treat cancer can succumb dramatically when confronted with these commonplace infections. Moreover when death ensued it was all the more tragic since in many cases it might have been avoided altogether had effective treatment been instituted early enough or, better still, if the infection had been prevented in the first place.

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Infections Risks

Fifty years ago it was already apparent that patients with leukaemia were exquisitely vulnerable to infectious complications arising from a state of compromised immunity induced by their underlying disease and, more crucially, the therapy employed to treat them. Fever was the signal but could only be explained in about half of cases by microbiologically defined infections and clinically defined infections [1]. The causes of infection identified were found to be common or garden bacteria such as *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* and an unusually high proportion were due to *Pseudomonas aeruginosa*, a known resident of the hospital environment (Fig. 48.1). It was clear to the early pioneers that the source of these opportunistic pathogens was either the patient (endogenous origin) or his or her immediate environment (exogenous origin). *Candida* and *Aspergillus* (respectively endogenous and exogenous opportunistic pathogens) were also known even then to pose a threat [2]. What was termed "fever of undetermined origin" was thought likely to be related to tissue injury. This together with the absence of neutrophils rendered some, though not all patients, particularly susceptible to some of his or her own normal commensal flora as well as to some of the interlopers that had taken up residence on the skin and mucosal surfaces primarily of the oral cavity and gastrointestinal tract. This hypothesis lead naturally to a two-pronged approach namely, decontamination of the body surfaces and protection from the environment. Within a decade, the "Life Island" was born and experiments with antibiotics to sterilise the gastrointestinal tract had lead to the choice of a cocktail of antibiotics know as GVN (gentamicin, vancomycin and nystatin) to suppress Gram-negative bacilli, Gram-positive bacteria and yeasts [3, 4]. With uncanny prescience, it was also appreciated that the use of antibiotics was likely to be attended by a shift of infecting agents to those that were more resistant and of "low-order pathogenicity" and that the approach may suffer from diminishing returns [2]. This was because the normal commensal flora loses its ecological balance under the selective pressure of antibiotics allowing free

Sources of exogenous microorganisms
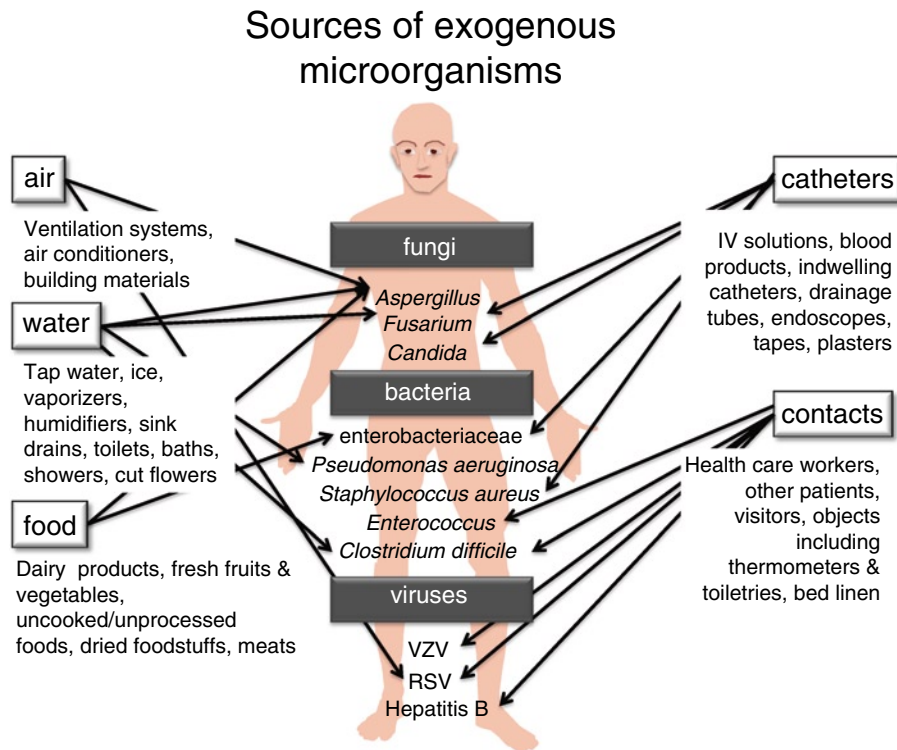
Fig. 48.1 Sources of exogenous microorganisms that can be cause infection

access to exogenous organisms that readily take up residence on the mucosa. The partnership was established between antimicrobial prophylaxis and the physical means of protecting patients from acquiring microorganism from the environment. Indeed, they became, and still are, inextricably bound up with each other to this day.

Basic Principles of Infection Control

Before considering measures that pertain to the patient with cancer it is useful to consider the basic principles of infection control (Table 48.1). Many of these are plain common sense such as good hygiene. Others such as limiting contact with potentially pathogenic microorganisms are considered essential. Others such as a double door entry to the ward to restrict traffic and help exclude outside air are considered desirable if not always possible. However, there are surprisingly few studies that have examined every aspect of physical infection prevention listed in the table and none that have investigated the relative importance of each one in a multifactorial way. The knowledge that exists was due to the energy and insight of a few pioneers who were driven by the desire to show deaths due to infection was avoidable and that prevention was indeed better than cure.

The Protected Environment

The early pioneers of cytostatic chemotherapy knew how devastating infection could be and took the intuitive step of instituting preventative measures drawn up to reduce exogenously acquired infections and minimise the endogenous variety. The notion of the protective environment combined with prophylactic antibiotics (PEPA) was born [3, 5–8]. This required building units in which physical contact was minimised, food was sterilised, the air was filtered and the patients oral cavity and gastrointestinal tract was coated with an antibiotic cocktails to suppress potential pathogens. Small early studies supported the efficacy of the measures insofar as they reduced at least bacteraemia though they failed to improve overall remission rates [9]. Other problems were tackled as and when they arose. Water needed to be filtered to remove harmful bacteria particularly *P. aeruginosa*, the then undisputed queen of the hospital pathogens. Moreover, keeping sinks free of this bacterium also required unusual measures such as heating the drain. Floors had to be sealed and patients were either housed in laminar flow rooms or sealed tents such as the "Life Island." All objects entering the tent were sterilised or disinfected and were passed through a lock system. There were dividends, but also costs among which were psychological feelings of being isolated. Moreover Life Islands were very expensive to purchase and maintain. Opinions were also divided about their true utility

Table 48.1 Prevention and control of infections

Accommodation	Single occupancy wherever possible
Ventilation	Adequate number of air exchanges
	No air from outside
	HEPA filtration
	Directed airflow
	Positive air pressure from room to corridor
	Continuous monitoring of pressure
	Anteroom
	Self closing doors
	Double door entry at the main entrance to the ward
Furnishing	No carpets
	Smooth, nonporous surfaces that are easily cleaned
Water supply	Fungal free, *Pseudomonas* free
Sanitation	Separate sinks in room and anteroom
	On-suite toilet and shower
	Separate toiletries and toothbrush
Equipment	Keep clean and dust-free
Cleaning	Remove dust safely
	Highest level of cleaning
	Disinfection of surface as necessary
Decorations	No fresh cut flowers
	No potted plants
Laundry	Fresh laundered clothing and bedding
Hygiene	Hand-washing
	Protective clothing if necessary
Food & drink	Low-microbial content e.g. cooked foods, pasteurised dairy products, no lettuce or other raw vegetables, only fruit and vegetables that can be washed and disinfected before being peeled, bottled water for drinking and rinsing of the mouth
	Ice cubes from filtered water

and the studies designed to show their efficacy often lacked power due to small numbers [10]. This is not a rebuke by any means since few centres had such facilities and studies of sufficient power as would be demanded nowadays proved impossible to mount and complete. More importantly the advances in antibiotic development were more effective and treatment and drugs for effective prophylaxis were beginning to appear (see previous chapter) offering an effective alternative.

However, isolation did not disappear entirely. The idea of cohorting patients in to separate wards was ingrained and enshrined in the discipline. Moreover dedicated nursing staff was a *sine qua non*. It was also considered plain common sense to nurse neutropenic patients in well ventilated rooms with a supply of filtered air to remove bacteria and fungi. Also using dedicated equipment as far as possible was already becoming a standard of care and minimising contact between patients was considered a necessary precaution. Patients at high risk of infection were essentially confined to their protected space until the risk diminished, which could be several weeks.

Hence although many studies of antimicrobial prophylaxis have been done, most take some degree of protective isolation so much for granted that they do not think it worth mentioning in the reports.

Protected Environment and Prophylactic Antibiotic Programmes

Protected environment (PE) and prophylactic antibiotic programmes (PEPA) were developed to reduce the incidence of infections due to exogenous and endogenous opportunistic pathogens during periods of high risk and incorporated a raft of measures. These included HEPA filter air supply, strict patient isolation, water purification, special handling of waste matter including that produced by the patient and food restrictions [11]. As early as 1971, a 5-year analysis of protective isolation showed that exogenous organisms could be virtually eliminated as a source of risk, thus increasing the chances of recovery or remission from disease [12]. However, it was also clear that endogenous pathogens presented the greatest risk [13]. This observation was confirmed by others as some aetiological agents of infection such as *P. aeruginosa* could be identified in surveillance samples before the onset of infection [14–16]. In some cases, the opportunistic pathogen was acquired from the environment and it colonised the patients before causing infection [17]. None the less, interest in preventing bacterial infections by relying partly on protective isolation waned especially once the clear effectiveness of empirical broad spectrum

antibacterial therapy became widely accepted [18–24]. However, it was appreciated that HEPA filtered air could still reduce exposure to unwelcome mould spores and, given the meagre choices of drugs available for prophylaxis and therapy it was considered prudent, if not essential, to maintain a PE for this purpose.

The availability of patient PEs in the form of isolation units plus the development of prophylactic topical and oral non-absorbable antimicrobial regimens (PA) led to studies of the efficacy of such PEPA programmes. These programmes were generally designed to make the patient and his environment as free of micro-organisms as possible.

The first PE was essentially a bed surrounded by a plastic canopy with gauntlets attached to the canopy to access the patient [8]. All items entering the unit were sterilised, food was prepared aseptically and the air was HEPA filtered. Subsequently, permanently installed and semi-portable laminar air flow (LAF) units were utilised [25]. These were rooms with one entire wall consisting of HEPA filters, providing high rates of minimally turbulent air exchange. Special water and toilet facilities were provided. Personnel dressed in sterile attire when they entered the units and all items placed in the rooms were sterilised.

Institutions utilising LAF units developed individualised programmes for microbiological monitoring of patients and their environment. Usually, environmental monitoring included air sampling, floor and surface sampling and settling plates. In a study comparing results obtained from LAF rooms with those from regular hospital rooms, none of the air samples from hospital rooms were sterile whereas 53% of samples from LAF rooms were sterile. Only 1% of air samples from LAF rooms contained potential pathogens compared to 59% from regular hospital rooms [26].

Patient culture specimens were collected 1–2 times weekly from ears, nose, throat, stool, urine and skin (and other body sites at some institutions). Special techniques were developed to obtain semi-quantitative throat and total body skin culture specimens. Some of these procedures were time-consuming and eventually had to be discontinued. A study of the effects of the oral antimicrobial regimen in 91 patients demonstrated that a majority of aerobic bacteria were no longer cultured during prophylaxis [27]. A substantial number of persistent organisms were non-pathogenic. Despite the administration of large doses of antifungal agents, most isolates of *Candida* spp. persisted or increased in concentration during prophylaxis and a substantial number of new isolates were cultured. Weekly cultures of stool specimens demonstrated that although some bacteria could not be isolated during antibiotic prophylaxis, they rapidly reappeared when prophylaxis was discontinued, indicating that they had only been suppressed. Only a few of these persistent organisms had developed resistance to the PA regimen. In a study conducted by Klastersky et al. of PEPA vs. PA

only, they concluded that isolation did not reduce the frequency of persistent bacteria from patient cultures which suggested that these persistent bacteria originated from the faecal flora rather than the environment [28]. Unlike the previous study they found that persistent bacteria were more resistant to PA.

Persistent organisms were likely to be the cause of the infections occurring in patients on the PEPA program [29]. In a study of 102 patients there were 68 single organism bacterial infections. Fifty were caused by organisms cultured before entry on the program, including 13 of 18 *Pseudomonas* infections. Klastersky et al. noted that Gram-negative bacilli that were cultured repeatedly from patients on PA were often responsible for subsequent infections [28]. Schimpff et al. reported that patients receiving PA who discontinued the regimen while still on ant leukaemic therapy were at substantial risk of morbidity and mortality from infection [30].

The first study comparing outcomes of patients receiving antileukaemic chemotherapy on the PEPA program with controls was a case-controlled, but not randomised study [9]. The complete remission rate was not significantly higher (61 vs. 48%) for the PEPA group, but the duration of remission and survival were significantly longer in the PEPA group, which was most likely because the PEPA patients received more intensive chemotherapy. Three prospective randomised comparative studies of PEPA programmes were conducted in patients with acute leukaemia in the USA. All of the studies included a third group who received only PA [30–32]. The remission rates between PEPA and control patients were not statistically significant in two of the studies. However, in the study of Schimpff et al. the complete remission rates were significantly higher in the PEPA and PA alone groups than in the controls (54, 63 and 24%, $p < 0.05$). The median survival was also nearly twice as long in the PEPA and PA groups.

All of the studies demonstrated some beneficial effect from the PEPA program on infection. Bodey et al. [9] found that the proportion of days on study with severe infection was higher among the controls and the difference was statistically significant for those infections when the number of neutrophils was $<1 \times 10^9$/L ($<1,000$/mm^3), but not when it was $<0.1 \times 10^9$/L (<100/mm^3). Levine [32] found that the numbers of episodes of severe infection per 100 days on study were 0.67 for PEPA patients, 1.73 for PA patients, and 1.88 for controls, differences that were statistically significant ($p < 0.025$). Deaths due to infection occurred in 0, 24 and 25% respectively ($p < 0.05$). In the study of Schimpff et al. [30], PEPA, PA only and control patient groups spent equivalent times with severe neutropenia. The patients assigned to PEPA and PA contracted half as many severe infections as control patients. Only 17% of PEPA patients died of infection compared to 32% of PA and 52% of controls ($p < 0.05$). The complete remission rates were 54, 63 and

24% ($p < 0.05$). The median duration of survival was half as long for control patients than the other two groups.

During the early 1970s, seven European hospitals conducted a prospective randomised trial of PEPA in 137 evaluable patients undergoing anti-leukaemic chemotherapy [68]. There was a great diversity in age, chemotherapy regimens, number of prior regimens, isolation units and prophylactic antimicrobial regimens. Groups A consisted of 42 patients assigned to PEPA, Group B consisted of 44 patients assigned to PE only and the 51 patients in Group C received routine hospital care. Patients in Groups B and C received oral amphotericin B or nystatin, but no antibacterial agents. The proportion of days spent with <100 PMN/mm^3 were 25, 29 and 19%, respectively.

The number of episodes of severe infection and frequency of fever were essentially the same in the three groups. Only 14% of patients in Group A were free of potential pathogens in their gastrointestinal flora during the entire induction period and none in the other two groups. Patients in Group A had a greater proportion of infections caused by Gram-positive cocci which responded better to therapy. Lower respiratory tract infections were significantly more frequent in Group C (6, 7, and 24%, respectively) suggesting some benefit from isolation. The complete remission rates of 69, 61 and 49% were not significantly different and the differences were more likely due to the chemotherapy than the prophylactic measures. Survival at 30 days after end of therapy was 79, 79 and 75%. The authors concluded that the program was not effective in preventing infection.

Subsequently, studies were initiated in other malignancies, such as small cell carcinoma of the lung and breast carcinoma. Randomised trials were designed for patients with lymphoma and soft tissue sarcoma (tumours which were susceptible to chemotherapy regimens) to determine if the reduction in risk of infections during periods of neutropenia accomplished by the PEPA program would permit dosage escalation of chemotherapeutic agents [33, 34]. Also, did dosage escalation improve remission rates and duration of remission and survival? Unfortunately, the results were not sufficiently encouraging to justify continuing such investigations. For example, in the lymphoma study, patients on the PEPA program had more prolonged severe neutropenia (255 vs. 147 days) and a lower proportion of days with major infection (2 vs. 10%) [33].

Full dosage escalation was achieved in 96% of PEPA patients compared to 77% of controls ($p < 0.09$). Unfortunately, despite these benefits, the complete remission rate among patients who received full dosage escalation was only modestly higher than for those with no dosage escalation.

The PEPA program was very labour intensive and expensive, hence, programmes at most institutions were discontinued or extensively modified. LAF rooms were replaced by HEPA filtered units, and cooked food for sterile food.

Trimethoprim-sulphamethoxazole and, later, fluoroquinolones were used for anti-bacterial prophylaxis with and without patient isolation [35]. Unfortunately, the benefits of such prophylaxis have been offset by emergence of resistant organisms at some institutions.

Letters and articles began to appear questioning whether it was all necessary especially after the almost universal acceptance of the principle of promptly starting therapy with broad spectrum antibiotics as soon as a patient became febrile [18, 19]. Proponents of PEPA also divided into different camps with the Europeans, in particular the Netherlands, advancing the cause of selective gut decontamination as being the most effective measure for reducing infection. The introduction of cotrimoxazole and later the broad-spectrum quinolones such as ciprofloxacin seemed to spell the demise of PEPA. However, as stated above, even the most comprehensive study of antimicrobial prophylaxis is predicated on their being an advanced degree of protective isolation – single rooms, HEPA filtered air, good ventilation, contact restrictions, low microbial content food and drink, etc.

HEPA filtration relies on the use of fibres arranged at random that remove at least 99.97% of airborne particles of bigger than 0.3 μm diameter (Aspergillus spores are 2.5–3.5 μm in diameter). Strictly speaking particles are not filtered, but rather are trapped by sticking to the fibres. The air flow is set to achieve at least 12 exchanges of air every hour. Originally developed for the Manhattan project to prevent dissemination of radioactive particles they have found uses across industry from aerospace to the pharmaceutical industry, computer manufacturing to nuclear power plants as well as in health care and even the humble vacuum cleaner. The main purpose now of HEPA filtration is to rescue the number of extraneous mould spore in the patient's immediate environment. That the system works in principle was shown many years ago. Indeed it has been shown that spores can be reduced dramatically such that the acquisition by the patient is minimal.

A recent systematic review of the value of HEPA in preventing fungal infection concluded that "The placement in protected areas of patients with haematological malignancies with severe neutropenia or patients with bone marrow transplants appears to be beneficial, but no definitive conclusion could be drawn from the data available" [36]. In a rebuttal, Bodey pointed out that *Aspergillus* was airborne and a reasonable endpoint to consider whereas *Candida* is transmitted by contact and was, in fact, more predominant than the mould. Hence, PEPA would be expected to have an impact on the incidence of aspergillosis, but not candidiasis. The flaw in the meta-analysis was the result of lumping two different disease entities into the same category simply because the microorganisms in question belong to the fungal domain [11]. Intriguingly, Eckmanns et al. complained that none of the studies on HEPA filtration they analysed had been blinded. Quite how this idealised state could be achieved was not mentioned, but it suffices to say that the

logistics of such a study alone would defeat even the avid adherent of the approach. The meta-analysis was not all bad as it did suggest that HEPA filtration was beneficial in preventing fungi despite the lack of definitive evidence, the paucity of studies, the discordant end-points and other deficiencies [36]. A recent meta-analysis identified 20 studies that reported randomised or nonrandomised controlled studies of protective isolation and showed that PEPA led to reduced clinically and microbiologically defined infections and also to a lower mortality [37]. However, the authors emphasised that prophylactic antibiotics within a PE provided the greatest effect. This essentially confirms that PEPA works when coupled with prophylactic antibiotic therapy. The authors also concluded that these measures had little effect on mould infections. This supports the results of an earlier systematic review of the influence of HEPA filtration on the mortality and fungal infections [36]. The review failed to discover any significant advantages of HEPA filtration in reducing mortality among patients with haematological malignancies with severe neutropenia. However, the study was not with its critics [11]. The studies reviewed by Eckmanns et al. used data of studies designed to examine the whole PEPA programmes and not just those focussed on air control. They also made the conceptual error of including *Candida* infections among the fungal infections when HEPA is not expected to have any impact whatsoever on yeast infections that are not transmitted through air. Indeed single centre studies have reported an impressive reduction in the incidence of invasive aspergillosis after patients were relocated from LAF rooms to a facility that implemented positive pressure isolation [38]. Clearly the subject remains as contentious as ever as there is no study involving multiple centres of sufficient size and power to prove the case conclusively. None the less it does not seem unreasonable to mange high risk patients in an environment of clean air devoid of as many spores as possible.

Whether or not HEPA filtration impacts on the incidence of invasive aspergillosis under normal circumstances, it has been shown effective in reducing the incidence of invasive aspergillosis in the setting of an outbreak [39]. HEPA filtration has also be shown to reduce spore counts arising from building activities and other measures such as enhanced cleaning, sealing of windows and antifungal prophylaxis also have a role [40, 41] especially when building works are going on, a common fact of life. One way to ensure a relatively safe environment is to conduct air sampling to establish that the ventilation system is working, but not to use it to predict infection [41, 42]. Others have also shown that HEPA filtration alone is insufficient to prevent invasive aspergillosis during building renovation, which requires other measures such as sealing off the building site, wetting the rubble and work area, and limiting traffic in wards housing patients are also necessary [43]. Hence, on balance, it seems reasonable to recommend maintaining PEs for those at high risk of developing invasive mould diseases. Who is at high risk will depend upon the mix of patients and the treatment they receive, but recipients of an allogeneic HSCT following myeloablative therapy certainly fall into this category for as long as they remain neutropenic. Other high-risk patients may include those receiving intensive remission induction therapy for acute myeloid leukaemia or myelodysplastic syndrome in those centres that use PEs.

Water and Moulds

Air is not the only potential source of moulds as *Aspergillus* has been found in hospital water in centres in the USA as well as in Europe [44–46]. Other moulds such as *Fusarium* have been identified in water in certain centres [47]. This emphasises the fact that even though water from the community supply meets standards for potable water it may not meet the requirements of the patient at high risk of developing mould infections. However, given that the problem may be a local concern, it can be identified by examining the water from taps and showers and dealing with it using appropriate measures as and when needed rather than adopting a blanket measures. Moreover DNA may be more likely found in kitchen sinks in the community than in hospital water supplies [48].

There is also evidence that patients may be entering the hospital already colonised with *Aspergillus* conidia. which can be distinguished from those found in the air in and around the hospital [49]. Also, finding *Aspergillus* conidia in the air of transplant units may be completely unrelated to infection [50]. Indeed the latter authors abandoned microbiological surveillance opting for the emphasis to be placed on maintaining the ventilation system, ensuring the integrity of the unit and good environmental cleanliness.

Ideally what is needed is a large randomised controlled trial of protected isolation alone vs. prophylactic antimicrobial agents vs. both vs. neither. However, such a trial is unlikely to take place practically as much as any other reasons.

Infection Control

Control of infection should be achieved by adhering to the guidelines propagated by the CDC, SHEA and WIP that apply to any hospital supplemented by any measures.

Hand Hygiene

In these days of unabated hospital acquired infections, this simple measure cannot be emphasised enough. From Pontius Pilate to Lady Macbeth, hand washing has been seen as a rite of purification. It took an almost obsessive pursuit by Ignatius

Semmelweis to discover the reason behind this. In his hospital in Vienna, in the 1840s, maternal deaths due to puerperal infections were 2–4 fold higher in one of the maternity clinics, where he worked, than in the other. He eliminated meticulously all other conceivable explanations for this difference and concluded sombrely that he and his colleagues as well as medical students were unwittingly carrying the contagion from autopsies back to their patients. Serendipity also played her role insofar as his friend died after being accidentally stabbed by a scalpel while performing a post-mortem. The pathological findings were enough to convince Semmelweis of the connection between the cause of his friend's demise and that of many of the women in labour. Hands were the obvious culprit so he introduced hand washing in bleach, which lead to a dramatic fall in the death rate to almost zero in a matter of months. Evidence enough one would think that hand disinfection could reduce infectious mortality dramatically. However, the medical world remained sceptical as the conventional wisdom favoured the notion that diseases spread in the form of miasmas or rather pollution of the air and water. Vested interests could simply not countenance the idea that germs that had not yet been proven to exist could possibly be necessary and sufficient to explain sepsis, contagions and major outbreaks of diseases like cholera. In Glasgow, a fellow surgeon, Joseph Lister, introduced an alternative method disinfection using carbolic acid and achieved similar impressive results even with compound fractures and other injuries. Unlike Semmelweis, Lister had the advantage that time was at his side as the Germ Theory was beginning to win converts. Still it took the efforts of Florence Nightingale to effect the radical change necessary for hygiene to become a mainstream. During the Crimean war, she arrived at the British barracks in Scutari to find wounded soldiers being badly cared for by overworked medical staff trying to cope with insurmountable problems in the face of official indifference. Medicines were in short supply, hygiene virtually absent and 10 times more soldiers were dying of disease than from battle wounds. Cleaning the sewers and improving ventilation brought down death rates sharply. She insisted on adequate lighting, a proper diet and, importantly, on cleanliness, now known as hygiene, as it alone was a major barrier to infection. Her activities and mobilisation of the establishment proved a tipping point leading ultimately to the clean and sterile techniques of modern medicine. She was also instrumental in helping Linda Richards to become the first professionally trained American nurse who established nursing training programmes in the USA as well as in Japan. She is also credited with creating the first system of keeping individual medical records for patients in hospitals.

Curiously, despite being fully aware of the fact that microorganisms are the cause of such diseases we seem no better now at washing our hands than our forbears were. Why should this be so is beyond the scope of this chapter, but it is worth reflecting on the fact that we subject ill patients to complex and expensive therapies and yet still risk the entire enterprise by failing to wash our hands enough thereby allowing infection to loom.

Food and Drink

It was recognised early that food and drink could allow patients to become colonised with potential pathogens [51, 52]. Indeed the risk of uncooked foods such as salads was already known [53]. Attempts at serving sterile foods were made, but these were not exactly appetising and gave way to the notion of serving foods with low-microbial content. These were essentially freshly cooked meals served while hot, fresh fruits whose skins were disinfected before peeling and serving only pasteurised dairy products. A survey of transplant centres conducted in 1999 showed that the majority served sterile foods, although 1 in 5 used a microwave to disinfect foods and half restricted normal foods [54]. This sort of diet has been dubbed the "Neutropenic diet." A survey done among 156 institutions belonging to the Association of Community Cancer Centres showed 120 (78%) placed patients with neutropenia on restricted diets with 9 in 10 starting once neutropenia had occurred, while only 9% of institutions restricted diets when cancer treatment was initiated [55]. The most commonly restricted foods were fresh fruits and juices, fresh vegetables, and raw eggs although few restricted tap water. A more recent study of given remission induction therapy for AML or high-risk MDS explored the issue in a trial of cooked diet vs. one that allowed fresh fruit and vegetables washed in tap water and found no difference in the incidence of major infections involving bacteraemia and pneumonia [56]. All patients were nursed in a protected environment, received prophylaxis with levofloxacin and an antifungal agent with activity against moulds, and were given empiric therapy at the onset of fever. Hence it seems fair to conclude that any impact on the potential infection through consuming the raw foods was likely to minimal given the activity of levofloxacin against the sort of enteric gram-negative bacilli known to contaminate fruit vegetables.

Similarly the availability of the microwave oven makes it possible to serve hot, wholesome meals that are palatable as well as safe. The quality and abundance of bottled water also makes obviates the need for relying on the sometimes variable quality of water, which may be potable under normal circumstances but unsuitable for patients who are severely immunocompromised and may also be suffering from oral mucositis. Restrictions on the consumption of uncooked vegetables is a necessary precaution given that

these can be imported from all over the world including from countries that allow raw sewage sludge to be used as fertiliser. Indeed the complexities of the modern food supply chain and the recurrent outbreaks associated with salad vegetables make it impossible to be sure of product safety [57–60]. Hence complete avoidance of lettuces and ready made fresh salads is prudent given the concern that plants might be more important as a carrier for human enteric pathogens like *E. coli* O157:H7 and *Salmonella enterica* serovars [61]. The same *E. coli* has also been implicated in several outbreaks traced back to the ground beef used for commercial hamburgers [62–65]. Other foodstuffs are a potential source of fungal contamination including dried pepper, tea and the like.

Future Perspectives

The treatment of cancers has never been better with new therapies that are more specific and therefore less likely to lead to collateral damage to the immune defences [66]. Modalities to prepare for haematopoietic stem cell transplants are also less myeloablative so should lead to less injury to the bone marrow and mucosal barrier. There are many national and international guidelines for the prevention of infection e.g. the National Comprehensive Cancer Network *Prevention and Treatment of Cancer-related Infections* (http://www.nccn.org/professionals/physician_gls/PDF/infections.pdf), and international collaborations such as the European Conference on Infection in Leukaemia organised under the auspices of the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC), the Infectious Diseases Working Party of the European Group for Blood and Bone Marrow Transplantation (EBMT), the Supportive Care Group of the European LeukaemiaNet (ELN) and the International Immunocompromised Host Society (ICHS) [67] are also widely available and are moving towards presenting a common approach. However offering comprehensive guidelines in a weighty document is one thing. Spreading the message to all health care workers is another. The basis of infection prevention can perhaps be summarised as shown in Fig. 48.2 – finger tips – minimise contact, know the patient, remain alert, clean the hands and maintain the highest standards of care. Each of these is the tip of the iceberg and presuppose a knowledge base, adequate resources, trained personnel, regular evaluation, and continuous education. Risks for infection and perhaps the causes of infection may change with the disease and its treatment. But the basic principles remain the same.
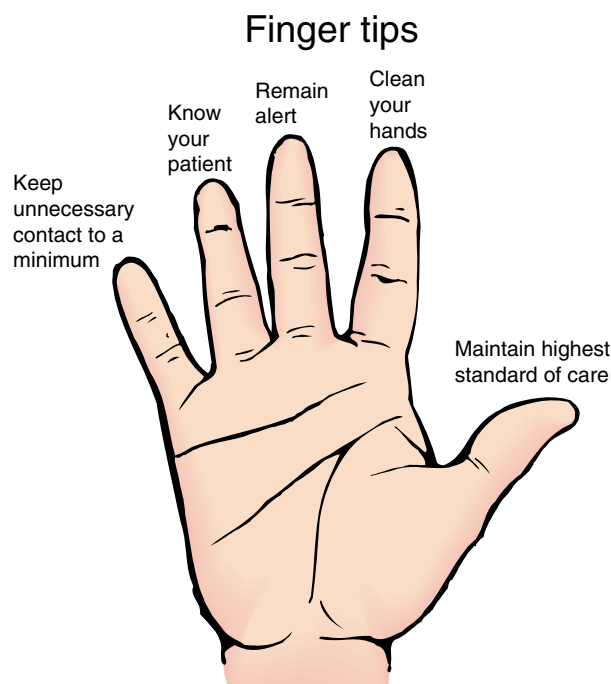
Fig. 48.2 Finger tips as an aid to reducing infections

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Chapter 49
Prevention of Tropical and Parasitic Infections: The Immunocompromised Traveler

Francesca F. Norman and Rogelio López-Vélez

Abstract The number of immunocompromised travelers is increasing and persons with significant preexisting medical conditions may be exposed to infectious diseases at their destination of choice. The risks of developing severe disease are increased and advising these complex patients may be challenging for health care professionals. Recommendations for prevention of specific travel-related infections and vaccination in immunocompromised patients as well as general advice for the cancer patient wishing to travel are outlined.

Keywords Travel medicine • Immunocompromise • Cancer • Transplant • Vaccination

Introduction

The dramatic increase in international travel which has occurred over the last few decades with the massive increase in tourism and international migration has also had an impact on the quality of travel, as more people visit remote and exotic destinations and activities become more adventurous [1]. As limits to travel disappear and new therapeutic approaches for many illnesses develop, persons with significant preexisting medical conditions are now more able to travel and may be exposed to a variety of infections at their destination [2–5]. The risk of developing certain geographically restricted infectious diseases tends to diminish after abandoning endemic areas, but some infections may persist for decades and reactivation of dormant infection may occur particularly in the immunocompromised [1].

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Immunocompromised patients who wish to travel constitute a special risk group who often do not seek or do not receive adequate travel advice [6]. These travelers are therefore a particular challenge for health care professionals advising on the varied aspects of travel medicine as "safe" travel becomes a priority [7]. Health promotion and education are essential and advice for this group of travelers should be tailored according to individual needs and should be planned well in advance, preferably at least 2 months prior to departure and at specialized clinics.

Immunosuppressed individuals have a potentially increased susceptibility for many infections and for each patient the benefits of possible interventions, such as vaccination or prophylaxis for specific infections, should be balanced against the risks involved.

Special Considerations for Immunocompromised Travelers

For practical purposes, immunocompromised travelers may be divided into categories according to the degree or cause of the immune suppression [8]. This chapter deals with severely immunocompromised patients (non-HIV) and more specifically with oncological patients including those with associated conditions resulting from the disease or its treatment. Patients with active leukemia or lymphoma, generalized malignancy, aplastic anemia, persons who have received recent radiotherapy or chemotherapy, solid organ transplant (particularly in the first post-transplant year) or bone marrow transplant (especially first 2 years post-transplantation or longer but with graft versus host disease) are all considered to have severe immunocompromise. Solid organ transplantation may be a therapeutic option in the management of certain solid tumors such as hepatocellular carcinoma and transplant patients have also been shown to have an increased risk for developing malignant tumors secondary to the immune suppression; so recommendations for transplant patients will also be reviewed [9, 10]. For solid organ recipients the degree of immune suppression may vary depending

on the organ involved (less severe immune suppression for renal than for cardiac or liver transplants, with pulmonary and small intestine transplants requiring the most profound suppression). Immunosuppression is maximal during the first 3–6 months after transplantation and usually diminishes after 1 year, but a degree of suppression persists long-term and this should be taken into account when considering recommendations in this subset of patients.

Medication which may cause significant immunosuppression includes high dose of corticosteroids (dose of ≥2 mg/kg or 20 mg/day of prednisone or equivalent when administered for ≥2 weeks, so that live vaccines should be administered at least 1 month after discontinuing this therapy) and most chemotherapy agents: alkylating agents (e.g., cyclophosphamide, cisplatin, carboplatin), antimetabolites (e.g., azathioprine, mercaptopurine), plant alkaloids and terpenoids (e.g., vinblastine, paclitaxel), anthracyclines (e.g., doxorubicin, daunorubicin), topoisomerase inhibitors (e.g., irinotecan, etoposide), transplant-related immunosuppressive drugs (e.g., cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil), monoclonal antibodies (e.g., rituximab) and methotrexate [8, 11–13].

Situations not associated with significant immunologic compromise include the use of low dose, topical or inhaled steroid treatment or local steroid injections, patients in remission after leukemia, lymphoma or cancer and at least 3 months after last chemotherapy treatment, patients who are longer than 2 years post-bone marrow transplant, without graft versus host disease and who are not on immunosuppressor drugs, and patients on chronic hormonal therapies (e.g., tamoxifen, gonadotrophin release inhibitors) [8].

Certain conditions which may arise during the management of cancer patients may be associated with only limited immune deficits, but may predispose to specific complications of infections acquired during travel. Asplenia increases the risk of meningococcal disease, *Streptococcus pneumoniae* and *Hemophilus influenza B* infection, severe malaria or babesiosis [14, 15]. Patients with underlying thrombocytopenia may be at increased risk of hemorrhagic complications due to dengue infection [16]. Patients with chronic liver disease would be at increased risk of severe disease and complications if travel-related hepatitis A infection is contracted [17].

For most cancer patients the main period of immunocompromise is during or immediately after therapy (chemotherapy or radiation) and most are unlikely to travel at this time [18]. However, patients should be advised against traveling immediately post chemotherapy or radiotherapy, at least until treatment is complete, blood counts have stabilized and the patient is not requiring transfusions. In the case of solid organ transplant or bone marrow transplant recipients, travel should be postponed if possible beyond 6–12 months especially if proposed travel is to developing areas of the world [19].

General Recommendations for Immunocompromised Travelers

For travelers with preexisting medical conditions, gathering additional information regarding travel health insurance, insurance for repatriation if significant illness while abroad and the addresses of health clinics at the destination of choice would be useful prior to departure. Sufficient medication should be carried to last the entire duration of the trip, and if possible, this should be distributed between hand and checked luggage. Patients should be advised not to purchase medication while abroad, especially in developing countries, due to the possibility of unknowingly acquiring counterfeit drugs. In specific cases, a physician's letter, translated if applicable, specifying the patient's medical history and treatment, should be given to the patient. High risk patients may wish to carry a supply of antibiotics for standby self-treatment in circumstances such as prolonged traveler's diarrhea or respiratory infections with specific instructions on appropriate use.

Recommendations for Prevention of Specific Infections

The risk of acquisition of certain infections varies depending on the geographical area visited. Knowledge of world distribution of infectious diseases and agents facilitates risk assessment. Relevant infectious risks for travelers according to world area are shown in Map 49.1 and Table 49.1.

Enteric pathogens: Immunocompromised individuals are at increased risk for food and waterborne infections and advice should be given regarding the necessary precautions to minimize this risk. Raw or undercooked food (including fruit, vegetables, dairy products, seafood and meat) should not be consumed. Special emphasis should be made on the importance of consuming safe water (generally bottled), avoiding drinks prepared with tap water, and avoiding the consumption of ice (made with tap water). During specific activities, such as teeth brushing or swimming, water should not be swallowed. Hands should be washed often and especially after any contact with animals. Children may be particularly at risk if they have been playing with dirt or sand. Infections caused by *Salmonella* spp., *Campylobacter* spp., *Listeria* spp., *Vibrio* spp., *Cryptosporidium* spp., *Yersinia enterocolitica, and Toxoplasma* spp. may be transmitted in this way and may cause severe, acute, and in some cases, chronic infections in these patients.

Diarrhea is the most common illness in travelers and constitutes an important health problem affecting up to 40% of individuals traveling from low-risk countries to high-risk developing areas. High-risk regions of the world for acquiring
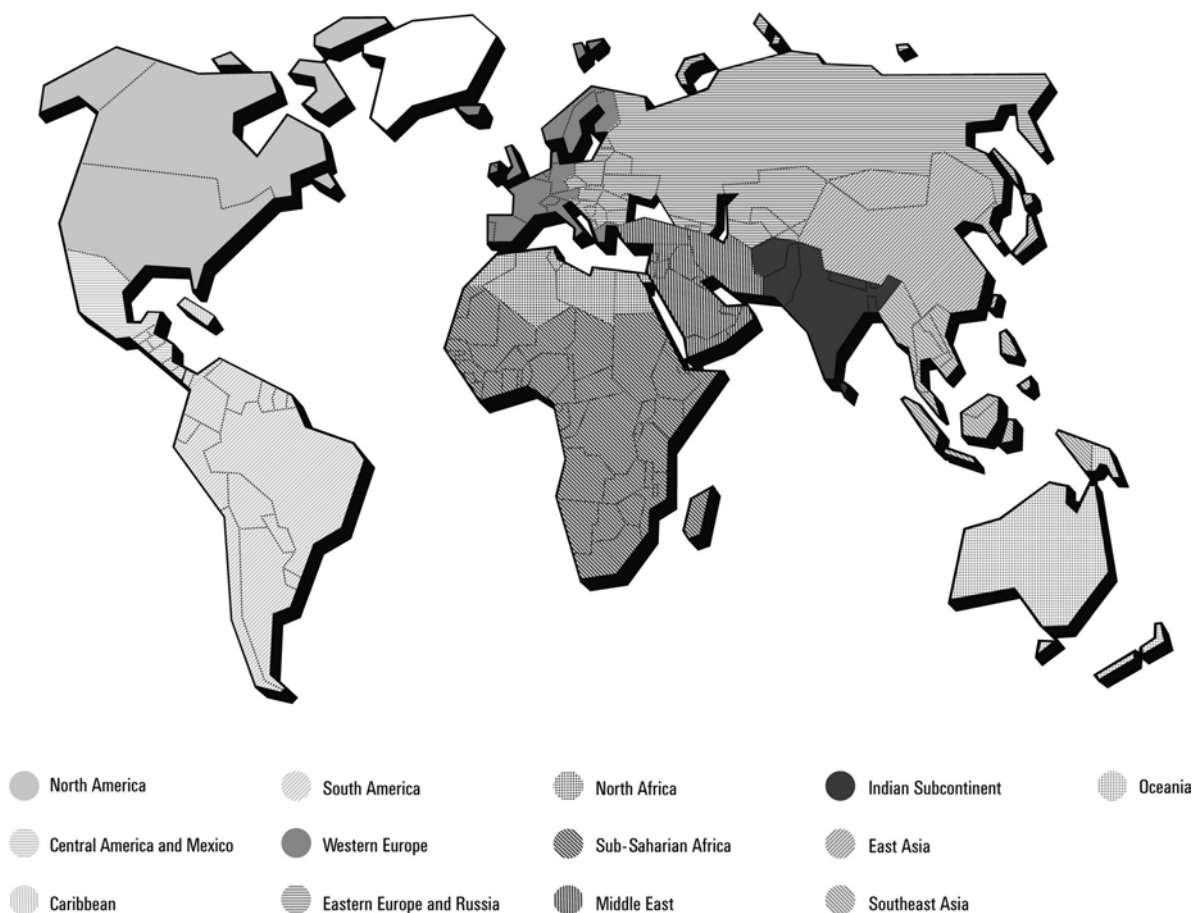
Map 49.1

Table 49.1 Geographical distribution of infectious diseases and agents

Geographical area	Countries	Infectious disease
North Africa	Algeria, Egypt, Libya, Morocco, and Tunisia	Dengue, West Nile virus, rabies, hepatitis A/E, tuberculous (TB), leptospirosis, typhoid fever, malaria (very low risk), leishmaniasis, schistosomiasis (Nile delta), and lymphatic filariasis (Nile delta)
Sub-Saharan Africa	Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde Islands, Central African Republic, Chad, Congo, Democratic Republic of Congo (Zaire), Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Reunion Islands (France), Rwanda, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Swaziland, Togo, Sao Tome and Principe, Tanzania, Uganda, Western Sahara, Zambia, and Zimbabwe	Dengue, HTLV-I (in certain countries), West Nile virus, rabies, yellow fever, polio (outbreaks in certain countries), hepatitis A/B/E, typhoid fever, rickettsiosis, cholera (outbreaks in some countries), TB, meningococcal meningitis (African meningitis belt), histoplasmosis, malaria, human African trypanosomiasis, filariasis, leishmaniasis, schistosomiasis, and strongyloidiasis
North America	Canada, and USA (including Hawaii)	West Nile virus, rabies, rickettsiosis, Lyme disease, TB (sporadic cases), leptospirosis (Hawaii), coccidioidomycosis, histoplasmosis, blastomycosis, strongyloidiasis, and babesiosis
Central America and Mexico	Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, and Panamá	Dengue, West Nile virus, rabies, hepatitis A/B/E, leptospirosis, TB, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, malaria (mainly *Plasmodium vivax*, risk of *Plasmodium falciparum* in Panama), leishmaniasis, Chagas disease, and strongyloidiasis

(continued)

Table 49.1 (continued)

Geographical area	Countries	Infectious disease
Caribbean	Antigua and Barbuda, Aruba, Bahamas, Barbados, Bermuda (UK), Cayman Islands (UK), Cuba, Dominica, Dominican Republic, Grenada, Guadeloupe (including St. Barthelemy and St. Martin), Haiti, Jamaica, Martinique (France), Montserrat (UK), Netherlands Antilles (Bonaire, Curaçao, Saba, St. Eustatius, St. Maarten), Puerto Rico (US), St. Vincent and the Grenadines, St. Kitts and Nevis, St. Lucia, Trinidad and Tobago, Virgin Islands (British), and Virgin Islands (USA)	Dengue, HTLV-I, hepatitis A/B/E, leptospirosis, TB, histoplasmosis, malaria (*P. falciparum* in Haiti, isolated cases in Dominican Republic, Jamaica and Bahamas/ Great Exuma), lymphatic filariasis (Haiti and Dominican Republic), leishmaniasis, and schistosomiasis
South America	Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela	Dengue, HTLV-I, rabies, yellow fever (specific areas), hepatitis A/B, typhoid fever, TB, cholera, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, malaria (except Chile and Paraguay), leishmaniasis, Chagas disease, lymphatic filariasis (in certain countries), strongyloidiasis, and schistosomiasis
Western Europe	Andorra, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, and United Kingdom	Rabies, tick-borne encephalitis, TB, brucellosis, leishmaniasis (Mediterranean basin), and babesiosis
Eastern Europe and Russia	Albania, Armenia, Azerbaijan, Belarus, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Montenegro, Poland, Slovakia, Slovenia, Romania, Russia, Serbia, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan	West Nile virus, rabies, hepatitis A/B, tick-borne encephalitis, diphtheria (outbreaks in some countries of the former Soviet Union), typhoid fever, TB, malaria (in certain countries), and leishmaniasis
Middle East	Bahrain, Cyprus, Iraq, Iran, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, and Yemen	Dengue, HTLV (in certain areas of Iran), West Nile virus, rabies, hepatitis A/B/E, cholera, typhoid fever, meningococcal meningitis (pilgrims to Mecca), brucellosis, TB, malaria (in certain countries), leishmaniasis, filariasis (Yemen), and schistosomiasis (in certain countries)
East Asia	China (including Hong Kong and Macau), Japan, Mongolia, North Korea, South Korea, and Taiwan	Dengue, Japanese encephalitis, HTLV-I, West Nile virus, rabies, hepatitis A/B/E, TB, leptospirosis, rickettsiosis, typhoid fever, penicilliosis, malaria (in certain countries), leishmaniasis, schistosomiasis, strongyloidiasis, filariasis, and food borne trematodiasis
Indian Subcontinent	Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka	Dengue, rabies, Japanese encephalitis, hepatitis A/B/E, typhoid fever, TB, leptospirosis, meningococcal meningitis (Afghanistan and Nepal), malaria (except Maldives), leishmaniasis, lymphatic filariasis, and schistosomiasis
Southeast Asia	Brunei, Burma (Myanmar), Cambodia, East Timor, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand, and Vietnam	Dengue, rabies, Japanese encephalitis, hepatitis A/B/E, typhoid fever, TB, penicilliosis, malaria, lymphatic filariasis, schistosomiasis, strongyloidiasis, and food borne trematodiasis
Oceania (Pacific area)	Australia, Fiji, French Polynesia, Kiribati, Marshall Islands, Micronesia, Nauru, Niue (NZ), New Caledonia (France), New Zealand, Palau, Papua New Guinea, Samoa, Solomon Islands, Tokelau (NZ), Tonga, Tuvalu, Vanuatu, Wallis and Futuna	Dengue, Japanese encephalitis, HTLV-1, hepatitis A, TB, leptospirosis, malaria (in certain countries), lymphatic filariasis, and strongyloidiasis

traveler's diarrhea include developing countries of Africa, Asia, Latin America, and parts of the Middle East [20]. Bacterial pathogens are the most important etiologic agents of traveler's diarrhea, with enterotoxigenic *Escherichia coli*, *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Aeromonas* spp., *Plesiomonas shigelloides*, and noncholera vibrios accounting for the majority of infections. Viruses (mainly norovirus, rotavirus, and enteric adenoviruses) have

also been isolated in cases of traveler's diarrhea. Diarrhea caused by parasites (*Giardia intestinalis*, *Entamoeba histolytica*, *Cryptosporidium parvum*, and *Cyclospora cayetanensis*) is less frequent in travelers and tends to be chronic, affecting long-term travelers visiting developing countries [21].

Traveler's diarrhea usually resolves without treatment within a few days, but in a proportion of cases the infection causes significant morbidity, immunocompromised

individuals being at specific risk. The use of appropriate antimicrobials for self-treatment in the event of diarrhea lasting more than 1–2 days especially if there is associated vomiting, fever and/or bloody stools would be recommended in these patients [19]. Suitable agents would be fluoroquinolones (e.g., ciprofloxacin 500 mg orally every 12 h for 3–5 days) or short courses of azithromycin mg (500 mg) every 24 h for 1–3 days. The nonabsorbable drug rifaximin may also be an option, although the role of this drug in the management of traveler's diarrhea is still being reviewed. In specific cases, short-term prophylaxis for traveler's diarrhea may also be considered, usually with one of the fluoroquinolones, although side effects such as the development of *Clostridium difficile*-associated diarrhea preclude long-term or widespread use in all immunocompromised travelers [22, 23].

Respiratory pathogens: Respiratory infections are the second most common infections which may affect travelers [24]. Seasonal influenza is currently the second most frequent vaccine-preventable infection in travelers [25]. In tropical and subtropical countries, the risk of influenza is year-round whereas in the Southern hemisphere the risk peaks from May to October, opposite to that of the Northern hemisphere. Yearly influenza immunization should be considered for all adults in at risk groups, including persons who have immunosuppression or chronic pulmonary, cardiovascular, renal, hepatic or hematologic disorders, especially if traveling to at risk areas [26]. Outbreaks of influenza with high transmission have also been documented in cruise ships [25]. Endemic mycoses (histoplasmosis, penicilliosis, and coccidioidomycosis) may also be acquired by this route and immunocompromised patients are at particular risk of severe disseminated disease. Certain activities, such as visiting caves, having contact with bats or birds and excavating, have been associated with a higher risk of transmission and these should be avoided, especially as protective gear has been demonstrated to have only a limited effect [27]. Due to the risk of tuberculous, including multi-drug resistant and extremely drug resistant tuberculous particularly in developing countries [28], documenting a baseline tuberculin test should be considered in these patients prior to travel, especially in the case of long-stay travelers and if certain risk activities are planned. Repeating the test 4–6 weeks post-travel would enable early detection of conversion so that any necessary therapeutic measures may be established.

Infections transmitted by arthropod bites: Mosquitoes, ticks and flies are the main vectors for transmission of tropical or geographically-restricted infections such as malaria, leishmaniasis, yellow fever, dengue, trypanosomiasis, filariasis, specific rickettsial diseases, borreliosis, and viral encephalitis. Effective vaccinations exist for some of these infections and specific prophylaxis may be used to minimize the risk of malaria, but for the majority no specific prevention measures exist, or these, such as the yellow fever vaccine cannot be used in immunocompromised patients. Some vaccines may offer limited protection in the immunocompromised as demonstrated by a study, which found decreased seroconversion rates in heart transplant patients compared with healthy subjects following tick-borne encephalitis virus vaccine [29]. All travelers to risk areas should be advised to avoid bites through the use of insect repellents, protective clothing (impregnated with insecticide if possible) and insecticide-treated bed nets.

Malaria and dengue are the most frequent infections transmitted by arthropods in travelers. In the healthy host, most clinical cases of dengue are self-limiting and there is currently insufficient data regarding complications in immunosuppressed individuals. Malaria is a significant risk for all types of travelers. There are no specific data regarding increased malaria risk in immunocompromised hosts [19, 30]. However, splenectomized patients do have an increased risk of severe malaria [14, 15]. Choice of malaria prophylaxis will depend, amongst other factors, on destination and specific itinerary. Chloroquine would be the first choice in areas of the world with chloroquine-sensitive malaria (mainly in Central America and Caribbean). Chloroquine may increase cyclosporine levels in transplant patients and drug levels should be carefully monitored. For areas with chloroquine-resistant malaria the options are atovaquone-proguanil, mefloquine and doxycycline. The latter two drugs may also interact with some of the common immunosuppressant drugs and drug levels should be monitored accordingly. Co-medication commonly used by travelers such as antidiarrheals, cardiovascular drugs, and analgesics do not appear to have a significant clinical impact on safety and effectiveness of mefloquine and chloroquine prophylaxis [31]. Caution is advised in diabetic travelers using mefloquine due to the possibility of hypoglycemia in certain situations [32]. Folic acid supplements should be given to patients taking proguanil who are on other antifolate medication such as trimethoprim-sulphamethoxazole. Before initiating malaria prophylaxis, important side effects such as the possibility of cardiac toxicity associated with chloroquine and mefloquine use in patients with chronic cardiac disease should also be considered, bearing in mind that these may be particularly harmful in patients with underlying disease. Indications, recommendations, and side effects of the main drugs used for malaria prophylaxis are shown in Table 49.2.

Infections transmitted through skin and mucous membranes: Patients should avoid swimming in fresh water and walking barefoot due to the risk of infections like schistosomiasis, leptospirosis, and geohelminthiasis (ancylostomiasis and strongyloidiasis). Schistosomiasis is endemic in Sub-Saharan

Table 49.2 Main drugs used for malaria prophylaxis

Drug	Dose	Indication	Side effects	Precautions
Chloroquine Tablets with 150 mg base (250 mg salt)	Adult patient 40–80 kg: 2 tablets (300 mg base), orally, once a week Children: 5 mg/kg base, orally, once a week, up to max. adult dose of 300 mg base Start 1 week prior to travel and continue for 1 month after return	Areas with chloroquine sensitive *Plasmodium* May be used in children and during pregnancy	Mild reactions (5–10%): abdominal pain, nausea, vomiting, diarrhea May worsen symptoms of psoriasis Agranulocytosis, neutropenia, thrombocytopenia, aplastic anemia Rare: psychosis, convulsions, retinopathy when used at prophylactic doses	Contraindicated if chloroquine hypersensitivity or retinopathy Use with caution if: G6PD deficiency CNS disease Myasthenia gravis Epilepsy Psychosis Impaired hearing Hematologic disease Liver disease
Atovaquone + Proguanil (Malarone®) Adult tablets: 250 mg atovaquone + 100 mg proguanil Pediatric tablets: 62.5 mg atovaquone + 25 mg proguanil	1 adult tablet every day if >40 kg Children 5–10 kg: ½ pediatric tablet every day; 11–20 kg: 1 pediatric tablet a day; 21–30 kg: 2 pediatric tablets a day; 31–40 kg: 3 pediatric tablets a day Start 1–2 days before departure, take daily and continue for 1 week after return	Areas with chloroquine-resistant *Plasmodium* and areas with multi-drug resistant *P. falciparum*	Abdominal pain, vomiting Headache, occasionally difficulty in sleeping Fever Rash	Contraindicated in children <5 kg, should not be used in pregnancy (insufficient data), and if severe renal failure (creatinine clearance<30 mL/min)
Mefloquine 250 mg (salt) tablets	5 mg/kg salt in children >5 kg and older than 3 months (once a week) In adults: 1 tablet per week Start 1 week prior to departure and continue for 1 month after return	Areas with chloroquine resistance (areas in Southeast Asia with reported mefloquine-resistant *P. falciparum*) Recommended in children 3 months or older and >5 kg, appears to be safe in pregnancy	Neurologic: may affect the central and peripheral nervous system (headache, dizziness, vertigo, and convulsions) Psychiatric: changes in sleep patterns, anxiety, mood changes Severe neuropsychiatric symptoms are rare Gastrointestinal symptoms	Contraindicated in psychiatric patients, epilepsy, and ventricular arrhythmias Caution if used with other potentially cardiotoxic drugs Caution when used by professionals who require great dexterity (e.g., pilots)
Doxycycline 100 mg tablets	100 mg daily Start 1 day before entering at-risk area and continue for 1 month on return	Areas with chloroquine resistance and with multi-drug resistant *P. falciparum* (no reported resistance to doxycycline)	Photosensitivity (4–16%) Gastrointestinal symptoms: nausea, abdominal pain and esophagitis Vaginal candidiasis	Contraindicated in children <8 years and in pregnancy Caution if liver failure

Africa, in Asia, and in restricted areas of America. Areas associated with greatest risk for tourists/short-term travelers are the Dogon country in Mali and Lake Malawi. *Strongyloides stercoralis*, which may cause severe complications such as the hyperinfestation syndrome in immunocompromised hosts, may also be transmitted by direct contact with bare skin.

Infections transmitted by animal bites: Depending on the type of travel and the activities undertaken whilst traveling, patients may have greater exposure and contact with animals than in their home environment. Immunocompromised hosts are at risk for severe life-threatening infection with

Capnocytophaga canimorsus (DF2 bacillus) following a dog bite. *Bartonella henselae*, *Pasteurella multocida* and *Mycobacterium marinum* may also be transmitted through animal contact [28]. Canine rabies is prevalent among stray dogs in India, several countries of Southeast Asia and Latin America. Indications for rabies vaccine are outlined below. Patients should take pertinent precautions and avoid contact with animals if necessary while traveling abroad.

Sexually and parenterally transmitted infections: Sexual activity may increase during travel [8] and so the possibility of sexually transmitted infections also increases if adequate

protective measures are not used. Infections which may be transmitted through sexual contact include HIV, hepatitis B and C, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum* (syphilis), *Haemophilus ducreyi*, *Calymmatobacterium* (*Klebsiella*) *granulomatis*, *Herpes simplex* type II, human papillomavirus, and *Trichomonas vaginalis*, and these all constitute a risk for immunocompromised patients. Hepatitis B or C, HIV, and other sexually transmitted infections have a high prevalence in developing countries. As well as advising on the practice of safe sex, travelers should also be aware of the risks of particular infections (mainly HIV, hepatitis B and C) associated with other practices such as piercing, tattooing, acupuncture, or dental procedures and these should be avoided while abroad. The importance for cancer patients of traveling only once blood counts are stable and transfusions are not required should be stressed. The safety of blood transfusions whilst abroad, particularly in developing counties, may not be guaranteed (higher prevalence of some transmissible agents such as HIV in the general population and substandard screening of the blood supply), exposing these patients to an increased risk of blood-borne infectious agents [33–35].

Vaccination in the Immunocompromised Traveler

Immunocompromised individuals may benefit from pretravel vaccination for certain conditions. Infections normally prevented by vaccination may be life-threatening in the immunocompromised host and may even contribute to graft rejection in transplant patients [19, 36]. Although there have been reports of graft rejection temporally associated with vaccination, data from other studies do not support this association [37–39]. With respect to healthy travelers, vaccine responses may be suboptimal and immune responses may wane more rapidly in the immunocompromised, so that protection may be decreased and additional vaccine doses may be necessary [8, 18, 19]. Travelers with severe immunocompromise cannot be given live virus or bacterial vaccines [8, 36, 40, 41]. The majority of vaccines with killed and attenuated microorganisms may be safely used in immunocompromised individuals with minimal reported side effects. Vaccine response appears to be best if given prior to immune suppression with chemotherapy, radiotherapy, or high dose corticosteroids (administer preferably more than 2 weeks before these therapies) or at least 3 months after completion of chemotherapy and/or radiotherapy. Live vaccines should be avoided within 3 months of last chemotherapy and should only be used if in remission or no significant immunocompromise [18, 42, 43]. Patients with hypogammaglobulinemia

and certain hematologic malignancies such as chronic lymphatic leukemia may respond particularly poorly to vaccines, but response has been shown to improve for certain vaccines if administered at an early stage of the disease [44]. In the case of solid organ transplant recipients, where immunosuppressive medication is maintained long-term, vaccination should be undertaken when immunosuppression is at baseline levels, but live vaccines should not be used. Patients with post-transplant hypogammaglobulinemia have an increased frequency of recurrent infections and may have a poor response to vaccination [45–47]. Although there are no specific guidelines on when to restart immunizations in transplant patients, a minimum period of 6–12 months post-transplant would seem reasonable [48].

For immunocompromised patients who wish to travel before these specified time periods, concerns may be raised about vaccine coverage and passive immunization for certain infections by utilizing specific immunoglobulins may be a possibility. The administration of immunoglobulins in patients with IgA deficiency would be contraindicated due to the possible risk of anaphylaxis [49].

Specific Recommendations for Vaccination in Immunocompromised Travelers

Before undertaking any vaccination in immunocompromised patients the recommendations outlined above should be taken into account.

Routine vaccines: During the pretravel consultation enquiries can be made regarding immunization status of routine vaccines, schedules may be completed and any necessary booster doses may be administered. Specifically, the risk of exposure to vaccine-preventable infections such as diphtheria and polio may be increased for travelers to certain geographical areas due to recent outbreaks in some countries. Measles is prevalent in many areas of the developing world: as live vaccines are contraindicated in immunocompromised patients, the administration of specific measles immunoglobulin should be considered in susceptible travelers. Vaccines for special risk groups such as the influenza and pneumococcal vaccine should also be recommended as per official guidelines [18, 26, 50].

Specific vaccines for travelers: For immunocompromised travelers the use of hepatitis A, hepatitis B, meningococcal, rabies, tick-borne encephalitis, and parenteral typhoid fever vaccine should be evaluated according to specific travel destination, itinerary, planned activities, and other risk factors. Recommended vaccines for travelers and indications for use are outlined in Table 49.3 [19, 51, 52].

Table 49.3 Vaccination recommendations in immunocompromised travelers

Vaccine	Indication	Recommendation[a]
Routine killed (inactivated) vaccines		
Tetanus-diphtheria-pertussis (Td or Tdap)	Non immune traveler. Diphtheria may be a specific risk in areas with epidemic outbreaks (areas of eastern Europe and countries of the former Soviet Union)	Booster indicated every 10 years Same schedule may be used in immunocompetent and immunocompromised children
Inactivated poliovirus (parenteral IPV)	Non immune traveler Consider booster dose in high risk travelers	Use recommended schedule based on age and time before departure Oral polio vaccine (OPV) is *contraindicated* in immunocompromised hosts and in household contacts of these patients
Killed (inactivated) vaccines with special indications		
Pneumococcal (23-v polysaccharide or 7-v conjugate vaccines)	In high risk groups	May be given and is recommended in immunocompromised patients and in other patients with specific chronic medical conditions also associated with an increased risk of pneumococcal disease (e.g., chronic pulmonary, hepatic, renal or cardiovascular disease, diabetes mellitus, functional or anatomic asplenia: if elective splenectomy vaccinate ≥2 weeks before surgery) Pneumococcal conjugate vaccine recommended for children <5 years, consider use of polysaccharide vaccine in children >2 years with certain medical conditions[a]
Influenza (inactivated)	In high risk groups	Indicated yearly in immunocompromised patients >6 months of age. Live intranasal influenza vaccine is *contraindicated* in immunosuppressed patients
Inactivated vaccines for travelers		
Hepatitis A	Non immune traveler, especially if long-term travel in high-risk endemic areas	A single dose offers protection 1 month after vaccination and at least during 6 months, a second dose at 6–12 months may offer protection of longer duration. In immunocompromised patients the same schedule may be used as for healthy hosts but additional booster doses may be necessary, due to decreased response. If no time for vaccination prior to departure or poor response to vaccination immunoglobulin may be administered (protects for 3–6 months)
Hepatitis B (viral recombinant particles)	Long-stay travelers, health professionals/cooperation work, travelers with behavioral indications (sexually active not in a monogamous relationship, intravenous drug users, etc.)	May be administered to immunosuppressed patients. Test for anti-HB-Abs response after vaccination and revaccinate accordingly. High dose hepatitis B vaccination may increase seroconversion rates in patients with higher rates of vaccine failure such as certain immunocompromised hosts (CCDR)
Meningococcal (polysaccharide or conjugate)	Travelers to Mecca during the annual Hajj and to areas within the "meningitis belt" in Sub-Saharan Africa, especially from December to June	Either one of the vaccines may be used (Quadrivalent ACYW135 conjugate vaccine preferably) Proof of vaccination required by the government in Saudi Arabia for travelers to Mecca during the Hajj
Rabies	Pre-exposure immunization in long-term travelers and those with risk of occupational exposure	May be used in immunocompromised patients although response may be diminished in certain patients (e.g., patients with lymphoma) (Hay et al. [51]) Vaccine may be administered intradermally although a better response is achieved in immunosuppressed patients if the im route is used. When used as postexposure prophylaxis concomitant use of immunosuppressant medication should be avoided
Japanese encephalitis	Travelers to certain rural areas of Asia, especially if staying >1 month during the Monsoon season	May be administered to immunocompromised patients. New inactivated vaccine currently licensed
Tick-borne encephalitis	Travelers to central and eastern Europe, especially during the Summer months and in forest areas	May be administered to immunocompromised patients but response may be decreased
Typhoid (Vi)	At risk travelers especially if long-term or areas with potential outbreaks	May be used in immunocompromised patients The oral live vaccine (Ty21a) is *contraindicated* in immunocompromised patients

(continued)

Table 49.3 (continued)

Vaccine	Indication	Recommendation[a]
Cholera (inactivated bacteria + recombinant B subunit)	Not routinely indicated in travelers. May be indicated if traveling to area with major ongoing outbreak, but only confers brief/incomplete immunity	May be used in immunocompromised hosts
Live vaccines CONTRAINDICATED in immunocompromised host		
BCG	Not routinely indicated in travelers	Contraindicated in immunocompromised patients
MMR (Measles Mumps Rubella)	Nonimmune travelers	Consider MMR vaccine prior to immunosuppression if favorable immunologic situation. May use specific Ig (measles) in susceptible immunocompromised travelers traveling to endemic countries
Varicella	High-risk nonimmune travelers	Consider vaccination prior to immunosuppression if favorable immunologic situation
Yellow fever	Traveler to endemic areas. Subject to international legislation	Very few studies evaluating risk of yellow fever vaccination among severely immunocompromised but vaccine contraindicated in these patients. Some governments allow entry with an official vaccination waiver letter but other countries will not accept entry without vaccination. Official sites for the proposed country of destination should be consulted prior to departure

[a] See official Advisory Committee on Immunization Practices (ACIP) recommendations for specific doses and timing [26, 50]

Summary

– Pretravel advice for special risk groups such as immunocompromised travelers should be individually tailored and should be planned in advance (at least 2 months prior to departure).
– During the immediate post radiotherapy or chemotherapy period, travel to developing countries should be avoided if possible.
– Patients given any pretravel vaccine doses ≥2 weeks before start of immune suppression need not be revaccinated, unless additional doses are required as per schedule.
– Live vaccines are contraindicated in patients considered to have severe immunosuppression.
– For cancer patients with persistent immunologic compromise such as in the case of disseminated malignancy, active hematologic malignancy, or if undergoing active treatment, killed vaccines may be used, but response may be suboptimal and additional booster doses may be necessary.
– For cancer patients in remission, administration of vaccines (both live and killed) should be deferred for at least 3 months after completion of chemotherapy or radiotherapy to ensure safe administration (in the case of live vaccines) and to optimize response.
– For solid organ transplant patients live vaccines should not be used and appropriate killed vaccines should be deferred until at least 6 months post-transplantation or when immunosuppression has been reduced.
– Stem cell transplant recipients, longer than 2 years posttransplant, not on immunosuppression regimes and without graft versus host disease are considered to have no significant immunologic compromise, so both live and killed vaccines may be used as indicated in normal host.
– Monitoring antibody levels to determine if adequate protective levels have been achieved following vaccination may be useful in specific circumstances.
– The use of nonpharmacological protective measures to avoid infections while traveling abroad should be emphasized: immunocompromised patients may be less than adequately protected by vaccinations and the risk of potential drug interactions may be minimized.
– If a patient becomes ill, even years after returning, the possibility of infections acquired during travel should be considered, bearing in mind that infections may run an atypical course with severe complications in immunocompromised individuals.

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Chapter 50
Prophylactic Vaccination of Cancer Patients and Hematopoietic Stem Cell Transplant Recipients

William Decker and Amar Safdar

Abstract Prophylactic immunization in cancer patients is safe and cost-effective in reducing the disease burden and complications arising from vaccine preventable infections. For maximal effectiveness, patients should be vaccinated with inactivated vaccines at least 2 weeks prior or 3 months subsequent to myeloablative chemotherapy. Hematopoietic stem cell transplant recipients should similarly be vaccinated 6–12 months posttransplant, immune reconstitution permitting. Vaccination of patients with B-cell malignancies is more problematic, but difficulties can be somewhat ameliorated by applying higher doses of vaccine in greater frequencies than would be typical for immunocompetent individuals. Live vaccines are typically considered to be unsafe for oncology patients, but may be safely administered to HSCT recipients who are >2 years posttransplant. While many common infections can be managed through a strategy of conscientious vaccination, there are many other serious infections that specifically afflict immunocompromised patient populations and for which effective vaccines do not yet exist. While vaccines that will address some of these infectious conditions are currently in development, it is unlikely that all important oncological infections will ultimately be addressed by a vaccine approach as market-based development strategies are unlikely to target infections with a negligible impact upon immunocompetent populations. In this chapter, we present a comprehensive review of vaccination in oncology patients.

Keywords Vaccines • Cancer • Transplant • Influenza • Pneumococcus • Varicella • Bioimmune adjuvant • Immune suppression • Chemotherapy • Graft versus host disease • Stem cell transplantation

Cancer patients and recipients of hematopoietic stem cell transplant (HSCT) are unusually susceptible to infectious disease due to the potent one-two punch of immunosuppressive disease and immunoablative treatment regimens. Given this increased susceptibility, patient morbidity and mortality can be favorably impacted by prophylactic vaccination against a myriad of infectious diseases, even diseases for which most individuals possess preexisting immunity from childhood vaccination. Clinical experience with a variety of vaccines including influenza, pneumococcal, meningococcal, HiB, hepatitis B, herpes zoster, and polio has indicated that prophylactic vaccination of cancer patients should be a routine part of standard of care treatment [1–3]. It is further suggested that HSCT patients be revaccinated with MMR and DPT childhood vaccines at 12 months posttransplant, immune reconstitution permitting [4]. Results from existing cancer patient vaccination programs suggest that morbidity and mortality will continue to be impacted favorably as new vaccination strategies are developed for pathogens that are particularly detrimental to immunocompromised patient populations and for which vaccines do not currently exist. This list of pathogens could include CMV, EBV, community-acquired respiratory viruses (RSV, parainfluenza virus, rhinovirus), adenovirus, and polyomavirus as well as a variety of eukaryotic molds, yeasts, and fungi that do not typically infect immunocompetent individuals [5].

Effects of Neoplastic Disease upon Immunity

Many different tumor types are known to actively subvert immune surveillance via an extremely broad and diverse array of mechanisms (Table 50.1). While some such mechanisms subvert immune detection in an antigen-specific fashion via the generation of tumor-specific regulatory T-cells or myeloid-derived suppressor cells [6–11], others more broadly and nonspecifically suppress global immunity by inducing dendritic cell dysfunction or by a general skewing of adaptive immunity away from Th-1, thereby dampening the cell-mediated responses that typically govern tumor immunity. Tumors may acquire the ability to secrete a wide variety of pleiotropic

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Table 50.1 Tumor-derived factors implicated in functional modulation of dendritic cells

Factor	Effect on DC
Cytokines	
IL-10	Impairment of differentiation, maturation, and function in vitro and in vivo
	Increased apoptosis in vitro
IL-6	Impairment of differentiation and maturation in vitro and in vivo
M-CSF	Inhibition of differentiation from CD34$^+$ progenitors in vitro
GM-CSF	Generation of immature APC with inhibitory role in vitro and in vivo
VEGF	Alteration of differentiation of multiple lineages including DC in vitro and in vivo
	Accumulation of immature cells with inhibitory function in vitro and in vivo
Other mediators	
Gangliosides	Impairment of phenotypic and functional differentiation in vitro
	Phenotypic alteration and apoptosis in vitro
Prostanoids	Impairment of maturation and activity in vitro
NO	Induction of apoptosis in vitro
Hyaluronan	Induction of apoptosis through induction of NO in vitro
Polyamines	Induction of altered maturation in vitro
Tumor antigens	
MUCl	Impairment of maturation and function in vitro
PSA	Alteration of differentiation and maturation in vitro
HER-2/neu	Alteration of antigen processing function in vitro

Table derived from Pinzon-Charry et al. [19]

HER-2/neu HER-2/neu oncogene product; *MUC1* tumor-derived mucin; *NO* nitric oxide; *PSA* prostate-specific antigen; *VEGF* vascular endothelial growth factor

factors that impact dendritic cell differentiation, maturation, function, and longevity. Cytokines such as IL-10, IL-6, IL-4, or TGF-β inhibit the generation of Th-1 responses by skewing T-cell responses toward a Th-2 or toward a regulatory phenotype [6, 8, 9, 12–21]. Other cytokines such as M-CSF, GM-CSF, or VEGF prevent development and differentiation of dendritic cells or produce DC with impaired functional capacities [17, 19, 22–30]. Other tumor-derived molecules such as gangliosides, prostanoids, nitric oxide, hyaluronan, and polyamines can inhibit function or accelerate the induction of programmed cell death [19, 31–38]. Even certain tumor-specific antigens such as PSA, MUC-1, and HER-2/neu are known to inhibit DC function by a variety of mechanisms [19, 39–41]. Indoleamine 2,3-dioxygenase (IDO), the expression of which is frequently elevated in cancers, is also known to play an important and potent role in immune suppression [42, 43]. Tumors may even avoid immune detection in the absence of T-cell suppressive factors via the downregulation of MHC class I (i.e., HLA-A, B, and C) on the cell surface with the concomitant upregulation of NK cell suppressive factor HLA-G [44, 45]. Tumor-related B-cell immunodeficiencies exist as well, chiefly evidenced by the hypogammaglobulinemia observed among many patients afflicted with chronic lymphocytic leukemia (CLL). Th-1 responses are also negatively impacted in CLL patients [46].

The net results of altered DC differentiation, maturation, function, and longevity become manifest, not only by the failure of the immune system to recognize and eradicate tumors but also through the inability of memory T-cells to respond to recall antigens [26]. This inability to respond to recall antigens can be further exacerbated by myeloablative

chemotherapy, which may result in apoptosis of dividing lymphocyte subsets and suppression of de novo hematopoiesis by marrow stem cell populations. The degree of myelosuppression between different chemotherapeutic agents is not uniform, varying significantly by class and mechanism of action; however, acute myelosuppression, neutropenia, and/or pancytopenia typically reach nadirs 7–14 days post therapy with significant recoveries observed 3–4 weeks post therapy. Accordingly, nearly all vaccination protocols stipulate administration of the vaccine no later than 2 weeks prior to initiation of myeloablative chemotherapy and no sooner than 3 months after cessation [1].

Clinical Experience with Vaccination in Oncology Populations

There are a variety of important reasons to vaccinate oncology patients against community-acquired infectious diseases or to revaccinate them against common childhood diseases. The incidence of disease among cancer patients is not necessarily higher than that of the general population for all infections; however, once a cancer patient develops clinically relevant disease, incidence of morbidity and mortality are almost always more severe than in the population at large. Additionally, long-term survivors of HSCT will find themselves in need of revaccination against the common childhood diseases as their emerging, naïve immune systems become fully reconstituted. Clinical experience with the vaccination of oncology patients has indicated that, though these

patients tend to respond is a less robust fashion than healthy controls, significant clinical benefit may frequently be achieved.

Influenza

There is an exceptional amount of clinical experience with influenza vaccination in patients with solid malignancies, those undergoing myeloablative chemotherapy, and those who have received HSCT for hematologic malignancy. Clinical studies have demonstrated that case fatality rates among these high-risk patient groups can be quite high, exceeding 30% in one study [3, 47–57]. Table 50.2 outlines ten clinical studies that report significantly elevated mortality rates among various different oncology populations. Given the high case fatality rate, influenza vaccination of cancer patients should be considered standard of care treatment, and a number of studies have demonstrated that cancer patients, when vaccinated appropriately, can achieve rates of seroconversion nearly as high as those of healthy controls [1, 58–62] (i.e., selected studies in Table 50.3). In general, seroconversion is poor when vaccination occurs less than 2 weeks prior to myeloablative chemotherapy or less than 3 months after myeloablative chemotherapy [1, 63–66], when vaccination of HSCT patients is attempted sooner than 6 months posttransplant [1, 67, 68], or when patients are suffering from malignancies like CLL or multiple myeloma that

severely impact B-cell function [1, 69–71]. Recent work by Safdar et al. indicated that rates of enhanced seroconversion among non-Hodgkin's lymphoma patients given a ninefold higher dose of a subunit vaccine could be up to 50% higher than patients receiving standard dose levels (135 vs. 15 μg); nevertheless, seroconversion was still relatively poor, indicating that prophylactic approaches other than traditional vaccination will likely be needed in order to adequately protect this patient population [72].

Herpes Zoster

Transplant recipients or those with hematologic malignancies exhibit reactivation rates of herpes zoster that are several times higher than the population at large, and persons with certain types of leukemia exhibit reactivation rates up to 100 times higher than those of the general population. While the live varicella vaccine is contraindicated in stem cell transplant or leukemic patients, it is the presence of varicella-specific antibody titers that most directly correlates with reactivation, hence the heat-inactivated varicella vaccine may be administered in the oncology setting [2, 4, 73–75]. A number of studies have demonstrated that the timing of vaccine administration is crucial to its success. Two studies in which HSCT patients received vaccine within 6 months of transplant demonstrated no differences in the incidence of herpes zoster reactivation than among control subjects [2, 76];

Table 50.2 Influenza frequency and case fatality in HSCT and cancer patients

	Population and setting	Influenza years	Number of patients under observation	Frequency of influenza[a]	Case fatality
Couch	HSCT, hospitalized, single center	1992–1995	[b]	[b]	5/20 (25%)
	Leukemia, hospitalized, single center	1992–1995	[b]	[b]	9/27 (33%)
Ljungman	HSCT, single center[c]	1989–1996	545	15 (2.8%)	2/15 (13%)
	Allogeneic HSCT, 37 European centers[c]	1997–1998	819	14 (1.7%)	4/14 (29%);
	Autologous HSCT, 37 European centers[c]		1154	2 (0.2%)	0/2 (0%);
	Allogeneic HSCT, 37 European centers[c]	1997–2000	More than 819	[a]	7/30 (23%);
	Autologous HSCT, 37 European centers[c]		More than 1,154	[a]	2/9 (22%)
Hassan	Allogeneic HSCT, single center[c]	1996–2001	230	5 (2.2%)	1/5 (20%)
	Autologous HSCT, single center[c]		396	0 (0%)	
Nichols	HSCT, 120 days within transplantation date only, single center	1989–2002	4,797	62 (1.3%)	6/62 (10%)
Machado	HSCT, respiratory symptoms present, single center[c]	2001–2002	179	41/179 (23%)	0/41 (0%)[d]
Whimbey	HSCT, hospitalized, local influenza epidemic present, respiratory symptoms present, single center	1991–1992	28	8/28 (29%)	1/8 (13%)
Yousuf	Leukemia, hospitalized, local influenza epidemic present, respiratory symptoms present, single center	1993–1994	45	15/45 (33%)	4/15 (27%)
Schepetiuk	Nosocomial outbreak in oncology ward, single center	1997	19		2/19 (11%)
Elting	Leukemia, local influenza epidemic present, respiratory symptoms present, single center	1991–1992	37	4/37 (11%)	1/4 (25%)

Table derived from Kunisaki and Janoff [3]
[a]Frequencies are those reported during the total observation period (influenza years)
[b]Not reported
[c]Outpatient or inpatient status not specified
[d]Only reported mortality from pneumonia, not all-cause mortality

Table 50.3 Overview of clinical studies evaluating influenza vaccine in oncology patients

References	Population	No.	Seroconversion
Ortbals et al. [62]	Malignant diseases	42 cancer; 96 controls	Fourfold increase in antibody titer 71% cancer patients; 94% controls
Ganz et al. [60]	Various cancers	17 cancer patients; 15 controls	No significant difference in antibody response
Gross et al. [65]	Children with various malignancies	120 cancer	HI antibody titer >40; 30% on chemotherapy within 1 month; 89% off chemotherapy by 1 month
Hodges et al. [69]	Hematology patients	31 cancer; 41 controls	Fourfold increase in titer to H1N1 16/31 (52%); (78% in healthy volunteers)
Lange et al. [66]	Children with ALL	22 on chemotherapy; 16 no chemotherapy	Children off chemotherapy had three times the antibody titers after first vaccine administration compared to those on chemotherapy
Schafer et al. [71]	Hematologic malignancies	52 cancer; 28 control	Fourfold increase in antibody titer 26/52 (50%) cancer patients; 23/28 (82%) controls
Anderson et al. [58]	Lung cancer patients	59 cancer; 0 controls	Fourfold increase in antibody titer 49/59 (83%) cancer patients
Robertson et al. [70]	Multiple myeloma	48 cancer	HI antibody titer >40; 9 (19%) cancer
Brydak et al. [59]	Women with breast cancer	9 cancer; 19 controls	HI antibody titer >40; 88.8% cancer; 100% controls
Chisholm et al. [64]	Children with various malignancies	42 cancer patients	
Nordoy et al. [61]	Various cancers	35 cancer; 38 controls	Antibody titer >40; 72% cancer; 87% controls

Table derived from Sommer et al. [1]

Table 50.4 Overview of clinical studies evaluating pneumovax-23 in oncology patients

References	Population	No.	Valent	Seroconversion
Levine et al. [79]	Hodgkin disease	24 cancer; 24 controls	14	12% response rate after prior chemotherapy
				14% response rate after prior radiation treatment
				9% response rate after both chemotherapy and radiation
Siber et al. [81]	Hodgkin disease	53 cancer; 10 controls	11	49% 6-month response rate
Siber et al. [82]	Hodgkin disease	51 cancer; 4 controls	14	25% response rate
Molrine et al. [78]	Hodgkin disease	70 cancer; 20 controls	23	75% of control response rate
				95% of control response rate
Robertson et al. [70]	Multiple myeloma	43 cancer	23	24/43 (56%) response rate
Hartkamp et al. [80]	Chronic lymphocytic leukemia	24 cancer	23	5 (22%) patients responded to vaccine
Nordoy et al. [61]	Various malignancies	35 cancer; 38 controls	23	73.7% response rate

Table derived from Sommer et al. [1]

however, a subsequent study demonstrated that vaccine given 30 days prior to transplant was extremely effective in preventing viral reactivation. In this study, the incidence of reactivation among vaccinated transplant recipients was 13% whereas the incidence among subjects receiving a placebo vaccine was 33% [2, 77].

Pneumococcal Pneumonia

The pneumococcal vaccine is a multivalent conjugate vaccine that protects recipients against infection from the most clinically relevant strains of *Streptococcus pneumoniae*, a common source of infection and sepsis in oncology populations. In two studies, administration of the vaccine to cancer patients resulted in antibody titers that were nearly comparable to those of healthy adults [1, 61, 78]; however, vaccination during radiation therapy and myeloablative chemotherapeutic treatment regimens [1, 79] or vaccination of patients with

B-cell malignancies [1, 70, 80–82] tended to result in suboptimal response rates in a majority of patients (Table 50.4). As with other vaccination strategies, it appears to be important that patients are vaccinated more than 2 weeks prior to the start of myeloablative chemotherapy or more than 3 months after cessation. In the transplant setting, where incidence of pneumococcal infection has been estimated to be as high as 36%, it is recommended that patients receive the vaccine between 6 and 12 months post transplant [4, 83–85].

Haemophilus influenzae B

Haemophilus influenzae type B (HiB) is another opportunistic pathogen that commonly afflicts oncology populations, and broad-based themes and vaccination strategies for HiB infection follow the same general guidelines as preceding infections. Vaccination for HiB should occur more than 2 weeks prior to or more than 3 months subsequent to myeloablative

chemotherapy and/or radiation therapy. When these guidelines are followed, cancer patients have been shown to achieve protective antibody titers at levels similar to those of healthy adults [1, 70, 86]. The US transplant guidelines stipulate the administration of the HiB vaccine at 12 months post transplant [4]. Further, repeated or booster doses of vaccine have been shown to significantly increase the percentage of post-transplant individuals who are able to achieve protective antibody titers, generally considered to be 1 μg/mL [4, 87, 88].

Hepatitis B Virus

A large number of studies have demonstrated that responses to the hepatitis B virus (HBV) vaccine are very poor, on the order of only 20%, when the vaccine is administered concomitantly with myeloablative chemotherapy (Table 50.5) [1, 89–95]; however, Hovi et al. [1, 96] demonstrated that, similar to other vaccines, seroconversion to the HBV vaccine among cancer patients can occur with equal frequency as healthy controls when the vaccine is not administered during an active chemotherapeutic regimen. Subsequently, Zignol et al. [1, 97] demonstrated that a booster dose given 1 year following myeloablative chemotherapy was successful in recovering protective HBV titers in 91% of individuals whose titers diminished during active chemotherapy. For patients who must be vaccinated during myeloablative chemotherapy, a high-dose formulation exists, and booster doses should be given until antibody titers reach the protective threshold of 10 mIU/mL [1]. In transplant populations, Jaffe et al. evaluated immunity to the standard three dose HBV vaccine regimen among patients who met minimum eligibility requirements including a CD4+ T-cell count of >200 cells/μL, a circulating IgG concentration of >5 mg/mL, and who were no longer taking immunosuppressive medications. In this study, mean time to vaccination was 23.4 months, and seroconversion occurred among 64% (187/292) of participants [4, 98].

Poliovirus

While the risk of contracting polio infection is low in the US and Western Europe, revaccination is still recommended for transplant and other oncology populations, especially those individuals who might be at elevated risk for exposure. There are few studies demonstrating the efficacy of inactivated poliovirus vaccine among oncology populations; however, in a long-term follow-up study, Ljungman et al. determined that the probability of transplant patients retaining immunity to poliovirus at 10 years post vaccination was 94%, provided that the vaccine had been administered at the conclusion of active treatment [1, 99]. Predictably, Bosu et al. also determined that vaccination of ALL patients with inactivated poliovirus vaccine during myeloablative chemotherapy typically produced antibody titers that were suboptimal and inadequate to mediate immunity [1, 100].

In addition to standard inactivated vaccines that may be administered to oncology populations, there is also a need to rebuild immunity to childhood diseases among transplant recipients who have acquired new immune systems. Two vaccines that may be considered in the transplant setting are the diphtheria-pertussis-tetanus (DPT) vaccine and the measles-mumps-rubella (MMR) vaccine, given the severity of pertussis and measles infections among adult populations. There is very little information regarding the incidence or severity of pertussis among transplant recipients, with information in the literature limited to anecdotal case reports [4, 101–103]. Nevertheless, given the safety profile of the vaccine, there appears to be little argument for withholding the DPT vaccine from transplant recipients, at least until such time that contraindicating data might arise. The MMR vaccine is a live, heavily attenuated virus vaccine, and as such is not appropriate for administration within 2 years of transplant unless a specific outbreak has developed. In the absence of an outbreak, the vaccine has been used successfully and safely >2 years posttransplant, and administration at this time point has become the standard recommendation [4, 104–106].

Table 50.5 Overview of clinical studies evaluating HBV vaccine in oncology patients

References	Population	No.	Seroconversion
Locasciulli et al. [90]	Children with leukemia	38 ALL; 11 ANLL	12.2% (6/49) response rate
Weitberg et al. [94]	Various malignancies	26 cancer	42% (5/11) responded to vaccine
Rosen et al. [91]	Breast cancer	32 cancer; 7 controls	6/32 (19%) cancer; 6/7 (86%) controls
Hovi et al. [96]	Children with various malignancies	51 on chemotherapy; 114 no chemotherapy	67% on chemotherapy; 97% off chemotherapy
Goyal et al. [89]	ALL	152 cancer	16/152 (10.5%) cancer
Somjee et al. [92]	ALL	111 cancer	21/111 (19%)
Yetgin et al. [95]	ALL	94 cancer	33/94 (35%) response rate
Somjee et al. [93]	ALL	29 cancer	5/29 (21%) response rate
Zignol et al. [97]	Children with various malignancies	67 cancer	35/67 (52%) lost protective antibody titers after chemotherapy; 29/32 (91%) recovered protective antibody titers after booster dose >1 year after chemotherapy

Table derived from Sommer et al. [1]

Unmet Needs: Oncology-Associated Infections for Which Vaccines Do Not Exist

While vaccination of oncology patients can ameliorate morbidity and mortality of diseases that are common among all patient populations, there are a number of serious infections that are observed almost exclusively among immunocompromised individuals. Accordingly, vaccines that might offer protection from these uncommon infections do not currently exist, yet their ultimate production, in some form or fashion, might be able to greatly alleviate a significant amount of morbidity among oncology populations. The kinds of infectious agents that can be deadly to cancer patients but relatively harmless to the general population tend to be either viral or eukaryotic (i.e., yeasts, molds, fungi) in nature.

Viral Infections

Cytomegalovirus (CMV) reactivation is thought to occur in 80% of seropositive patients following HSCT, though a wide variety of prophylactic treatments including acyclovir, valacyclovir, ganciclovir, and foscarnet can be used to prevent the onset and/or ameliorate symptoms [5]. Some investigators have suggested that universal CMV vaccination would be a cost-effective prophylactic enterprise for society as a whole by virtue of the cost savings that would be accrued from the treatment of symptomatic infants and, later in life, from adult HSCT recipients [107]. Accordingly, a significant amount of effort and resources have been placed upon vaccine development, and it is anticipated that CMV vaccination could be relatively commonplace in the future [108, 109]. In 2009, Pass et al. reported that administration of an adjuvanted recombinant CMV envelope glycoprotein B vaccine achieved about 50% efficacy in seronegative adults and also seemed to have some efficacy in preventing viral transmission from seropositive mothers to newborn infants [110].

Epstein–Barr virus (EBV), the causative agent of mononucleosis, is acquired by over 90% of individuals in industrialized Western nations by the age of 40. Like CMV, it is never wholly cleared by the immune system and can be reactivated following HSCT or myeloablative chemotherapy, resulting in a spectrum of uncontrolled lymphoproliferative diseases. Though the condition is known as posttransplant lymphoproliferative disease (PTLD) in the transplant setting, it can occur under any circumstance in which immune suppression exists. Treatment of EBV-associated PTLD consists primarily of reducing immunosuppressive treatment regimens; there are however, a number of other active therapies including adoptive immunotherapy, chemoprophylaxis (i.e., with acyclovir or ganciclovir), α-interferon, anti-B-cell antibodies, and anti-IL-6 antibodies [5]. The presence of EBV-associated disease among healthy individuals (i.e., mononucleosis) and the association of EBV infection with a variety of malignancies suggest that the population at large could benefit from an efficacious vaccine, and efforts at vaccine development are apparent in the literature [111–113].

Community acquired respiratory viruses such as respiratory syncytial virus (RSV), influenza, parainfluenza, and rhinovirus play a very significant role in morbidity and mortality of the immunocompromised host. Clinical experience at the Fred Hutchinson Cancer Research Center, the University of Texas MD Anderson Cancer Center, and The European Group for Blood and Marrow Transplantation indicates that mortality can approach 63% following RSV infection, 43% following influenza infection, 16% following parainfluenza infection, and 31% following rhinovirus infection among oncology populations [5, 50, 114–121]. While the development of vaccination strategies for large subgroups of multivalent vectors is an inherently challenging proposition, some progress is being made toward the development and implementation of universal RSV vaccination [122] and parainfluenza virus vaccination [123] among pediatric populations. Even if such efforts are slow to result in a vaccine that might be appropriate for immunocompromised oncology populations, enhancements to herd immunity should dramatically reduce the incidence of infection among all populations. Nonetheless, given the ubiquity and infectiousness of these broad groups of viruses, infection control strategies will necessarily play a crucial role in the prevention of acquisition and transmission for the foreseeable future.

Other important viruses that may affect immunocompromised oncology populations include adenovirus and polyomavirus. Adenovirus infection has been reported in up to 21% of HSCT recipients and is a major contributor to mortality in about 10% of these patients. Common serotypes isolated from oncology patients include 1, 2, and 5; however, the existence of nearly 50 clinically relevant serotypes confounds reasonable efforts at vaccine production [5, 124–129]; moreover, adenoviral infections are of limited pathological relevance in immunocompetent populations. The two clinically relevant polyomaviruses, JC virus and BK virus, ubiquitously infect most individuals by adolescence, establishing latent infections in kidney, blood, and brain. Polyomavirus reactivation following HSCT most commonly presents as progressive multifocal leukoencephalopathy (PML), interstitial nephritis, or hemorrhagic cystitis (HC) [5]. As with adenovirus, there do not appear to be any serious candidate polyomavirus vaccines currently in the clinical development pipeline.

Eukaryotic Infections

The profound neutropenia and mucosal toxicity induced by myeloablative chemotherapy and/or cytotoxic conditioning

regimens allow a number of yeasts to establish opportunistic infections in oncology patients. *Candida*, *Trichosporon*, and *Malassezia* species may be observed among individuals with immune suppression. Individuals with prolonged immune suppression including recipients of HSCT and chronic corticosteroid use are also susceptible to infection by *Cryptococcus neoformans* and endemic dimorphic fungi like *Histoplasma*, *Blastomyces,* and *Coccidioides* species. Systemic disseminated candidiasis may have an associated mortality as high as 60%, despite aggressive intervention and chemoprophylaxis with a variety of antifungal drugs [5, 130–133]. Closely related to yeast species, molds are another eukaryotic pathogen that are very important in the oncology setting. Most invasive mold infections are caused by *Aspergillus*, particularly *A. fumigatus*, but *Scedosporium*, *Fusarium*, and zygomycotic fungi of the *Rhizopus*, *Mucor*, and *Rhizomucor* genera are also important clinical pathogens. As with yeast species, chemoprophylaxis is the mainstay of prevention and treatment in immunosuppressed patient populations. Aspergillosis is a common complication following HSCT with mortality exceeding 80% in leukemic patients with refractory cancer and prolonged neutropenia [5, 134]. Mortality following infection with *Scedosporium* and *Fusarium* species is also exceedingly high with few, if any, neutropenic or myelosuppressed patients recovering in the absence of immune reconstitution and recovery of immune function [5, 135–138]. Yet in spite of the clear need for alternative treatment regimens to eukaryotic pathogens, eukaryotic vaccine development appears limited primarily to preclinical efforts [139].

Summary

Prophylactic vaccination of oncology patients is a safe an extremely cost-effective way to manage common infections that play a significant role in morbidity and mortality. For maximal effectiveness, patients should be vaccinated with inactivated vaccines at least 2 weeks prior or 3 months subsequent to myeloablative chemotherapy. Hematopoietic stem cell transplant recipients should similarly be vaccinated at least 2 weeks prior to transplant or 6–12 months posttransplant, immune reconstitution permitting. When these guidelines are followed, seroconversion among oncology patients rivals that of healthy controls, and immunity to disease can be fairly robust. Vaccination of patients with B-cell malignancies is more problematic, but difficulties can be somewhat ameliorated by applying higher doses of vaccine in greater frequencies than would be typical for immunocompetent individuals. Live vaccines are typically considered to be inappropriate for oncology patients, but may be safely administered to HSCT recipients who are >2 years posttransplant. While many common infections can be managed through a strategy of conscientious vaccination, there are many other serious infections that specifically afflict immunocompromised patient populations and for which effective vaccines do not yet exist. While vaccines that will address some of these infectious conditions are currently in development, it is unlikely that all important oncological infections will ultimately be addressed by a vaccine approach as market-based development strategies are unlikely to target infections with a negligible impact upon immunocompetent populations. For these niche infections, it will be a continuing challenge for physicians and scientists to apply innovative and cost-effective approaches to disease management.

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