Joyce M.C. Teng
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Therapy in Pediatric Dermatology

Management of Pediatric Skin Disease

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Preface

We are very excited about the publication of the first edition of Therapy in Pediatric Dermatology: Management of Pediatric Skin Disease. Given limited number of high quality clinical trials available in pediatric dermatology, we aim to address the need for comprehensive review of therapeutic options that are known to be efficacious in management of cutaneous diseases in children. This book summarizes evidence-based literature on clinical responses among pediatric patients, including age-appropriate management strategies. It is our wish to create a succinct, user-friendly, and up-to-date therapeutic dermatologic textbook for physicians who care for children with skin disorders.

A significant percentage of the treatments used in pediatric dermatology are currently off-label. Large scale, well-designed clinical trials are lacking for many of the dermatologic treatments that we recommend on a regular basis. For each skin condition discussed in this book, the investigative and treatment recommendations provided are based on extensive review of the literature. The treatment algorithms are provided using evidence scale A to E as recommended by the Center for Evidence-Based Medicine.

There have been extraordinary developments in understanding of the genetics and pathogenesis of many cutaneous disorders during the past decade. Novel therapeutic options and repurpose of old drugs have been investigated for the management of some of the most challenging skin disorders. The quantum of medical information that physicians receive has grown exponentially and is becoming overwhelming. It is our goal that this book will provide unbiased yet concise information that is valuable to practitioners who manage pediatric patients in their practices.

It has been a tremendous opportunity for Joyce, Ann, and Latanya to work with so many experts and trainees in the field. We thank all our contributors who have helped us create this book. We are indebted to our families, colleagues, and administrative staff. We offer special thanks to Kris Arao, our administrative assistant at Stanford, and Cheryl Winters-Tetreau, developmental editor at Springer, who worked tirelessly with many authors and saw the completion of this project. Our deepest thank you goes out to all the challenging patients we see on a daily basis in our busy clinical practices and who serve as the inspiration for the creation of this book. We hope this textbook proves to be an important body of work and resourceful to all who desire a greater understanding of dermatologic therapies and their uses in the pediatric population.

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Abbreviations

AA	Alopecia areata
AAP	American Academy of Pediatrics
ACD	Allergic contact dermatitis
ACE	Angiotensin converting enzyme
ACIP	Advisory Committee on Immunization Practices
ACR	American College of Rheumatology
AD	Atopic dermatitis
AE	Acrodermatitis enteropathica
ALA	Aminolevulinic acid
ALCL	Anaplastic large-cell lymphoma
AMT	Anxiety management training
AN	Anorexia nervosa
ANA	Antinuclear antibodies
AP	Actinic prurigo
APEC	Asymmetric periflexural exanthem of childhood
APKH	Acquired progressive kinking of the hair
aPL	Antiphospholipid antibodies
APS	Antiphospholipid antibody syndrome
ARCI	Autosomal recessive congenital ichthyosis
ARCL	Autosomal recessive cutis laxa
AT	Alopecia totalis
AU	Alopecia universalis
AVM	Arteriovenous malformations
BCCs	Basal cell carcinomas
BCH	Benign cephalic histiocytosis
BCNS	Basal cell nevus syndrome
BD	Behçet's disease
BDD	Blistering distal dactylitis
BDD	Body dysmorphic disorder
BMI	Body mass index
BN	Bulimia nervosa
BP	Bullous pemphigoid
BSA	Body surface area
BSLE	Bullous systemic lupus erythematosus
CAPS	Cryopyrin associated periodic syndrome
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CBC	Complete blood count
CBDC	Chronic bullous disease of childhood
CBT	Cognitive behavioral therapy
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention

CEP	Congenital erythropoietic porphyria
CGCT	Congenital granular cell tumor
CGD	Chronic granulomatous disease
CHS	Chediak-Higashi syndrome
CIE	Congenital ichthyosiform erythroderma
CINCA/NOMID	Chronic infantile cutaneous articular syndrome/neonatal-onset multi-systemic inflammatory disease
CL	Cutaneous leishmaniasis
CL	Cutis laxa
CM	Capillary malformations
CMCC	Chronic mucocutaneous candidiasis
CMN	Congenital melanocytic nevi
CMP	Complete metabolic panel
CMV	Cytomegalovirus
CNS	Central nervous system
CoA	Coenzyme A
CSD	Cat scratch disease
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
CTCL	Cutaneous T-cell lymphomas
CXR	Chest X-ray
DEB	Dystrophic epidermolysis bullosa
DEJ	Dermo-epidermal junction
DEXA	Dual-energy X-ray absorptiometry
DFA	Direct fluorescent antibody
DFSP	Dermatofibrosarcoma protuberans
DGI	Disseminated gonococcal infections
DH	Dermatitis herpetiformis
DI	Delusional infestation
DIC	Disseminated intravascular coagulation
DIF	Direct immunofluorescence
DIHS	Drug-induced hypersensitivity syndrome
DISH	Diffuse idiopathic skeletal hyperostosis
DMARD(s)	Disease-modifying antirheumatic drug(s)
DOC	Disorders of cornification
DOT	Direct observed therapy
DPWH	Diffuse partial woolly hair
dsDNA	Double-stranded DNA
EAC	Erythema annulare centrifugum
EB	Epidermolysis bullosa
EBA	Epidermolysis bullosa acquisita
EBS	Epidermolysis bullosa simplex
EBV	Epstein-Barr virus
ECP	Extracorporeal photopheresis
EDS	Ehlers-Danlos syndrome
EDSF	Ectodermal dysplasia with skin fragility
EDV	Epidermodysplasia verruciformis
EF	Eosinophilic fasciitis
EFA	Essential fatty acids
EI	Epidermolytic ichthyosis
EIAs	Enzyme immunoassays
EKV	Erythrokeratodermia variabilis

ELISA	Enzyme-linked immunosorbent assay
ELVIS	Enzyme-linked virus inducible system
EM	Electron microscopy
EM	Erythema migrans
EN	Erythema nodosum
ENS	Epidermal nevus syndrome
EOS	Early-onset sarcoidosis
EPP	Erythropoietic protoporphyria
EPS	Elastosis perforans serpiginosa
ERA	Enthesitis-related arthritis
ERP	Exposure and response prevention
ERT	Enzyme replacement therapy
ESR	Erythrocyte sedimentation rate
EVHC	Eruptive vellus hair cysts
FDE	Fixed drug eruption
FDH	Focal dermal hypoplasia
FH	Familial hypercholesterolemia
FMF	Familial Mediterranean fever
FSH	Follicle-stimulating hormone
FTI(s)	Farnesyl transferase inhibitor(s)
FWH	Familial woolly hair
GA	Glycolic acid
GA	Granuloma annulare
GAG	Glycosaminoglycan
GCS	Gianotti-Crosti syndrome
GEH	Generalized eruptive histiocytoma
GGA	Generalized GA
GI	Gastrointestinal
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCT	Hematopoietic cell transplant
HEP	Hepatoerythropoietic porphyria
HFMD	Hand-foot-and-mouth disease
HGA	Human granulocytic anaplasmosis
HGPS	Hutchinson-Gilford Progeria Syndrome
HHT	Hereditary hemorrhagic telangiectasia
HIV	Human immunodeficiency virus
HME	Human monocytic ehrlichiosis
HoFH	Homozygous familial hypercholesterolemia
HPLC	High-pressure liquid chromatography
HPV	Human papillomavirus
HRT	Habit reversal therapy
HSCT	Hematopoietic stem cell transplantation
HSP	Henoch-Schonlein purpura
HSV	Herpes simplex virus
HV	Hydroa vacciniforme
HWH	Hereditary woolly hair
IBD	Irritable bowel disease
ICD	Irritant contact dermatitis
IFA	Indirect fluorescence assay
IFAG	Idiopathic facial aseptic granuloma
IFM	Immunofluorescence mapping
IgE	Immunoglobulin E

ILAR	International League of Associations for Rheumatology
ILD	Interstitial lung disease
ILVEN	Inflammatory linear verrucous epidermal nevus
IM	Infantile myofibromatosis
IM	Infectious mononucleosis
IPL	Intense pulsed light
ISD	Infantile seborrheic dermatitis
IVIG	Intravenous immunoglobulins
JDM	Juvenile dermatomyositis
JEB	Junctional epidermolysis bullosa
JIA	Juvenile idiopathic arthritis
JPD	Juvenile plantar dermatosis
JSE	Juvenile spring eruption
jSSc	Juvenile systemic sclerosis
JXG	Juvenile xanthogranuloma
KHE	Kaposiform hemangioendotheliomas
KID	Keratitis-ichthyosis-deafness [syndrome]
KLC	Keratosis lichenoides chronic
KMP	Kasabach Merritt Phenomenon
KMS	Kasabach-Merritt syndrome
LA	Lactic acid
LAD	Leukocyte adhesion deficiencies
LAHS	Loose anagen hair syndrome
LCH	Langerhans cell histiocytosis
LED	Light-emitting diode
LDL	Low-density lipoprotein
LEN	Linear (verrucous) epidermal nevi
LFT(s)	Liver function test(s)
LH	Lutenizing hormone
LI	Lamellar ichthyosis
LM	Lymphatic malformations
LN	Lichen nitidus
LP	Lichen planus
LS	Lichen sclerosus
LSC	Lichen simplex chronicus
LUMBAR	Lipoma, urogenital anomalies/ulceration, myelopathy, bony deformities, anorectal malformations/arterial anomalies, and renal anomalies syndrome
LYP	Lymphomatoid papulosis
MAP	Mitogen-activated protein
MATP	Membrane-associated transporter protein
MCL	Mucocutaneous leishmaniasis
MCRH	Multicentric reticulohistiocytosis
MCTD	Mixed connective tissue disease
MEN 1	Multiple endocrine neoplasia syndrome 1
MF	Mycosis fungoides
MMA	Methylmalonic acidemia
MMRV	Measles, mumps, rubella, and varicella [vaccine]
MMS	Mohs micrographic surgery
MPSs	Mucopolysaccharidoses
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRS	Melkersson-Rosenthal syndrome

MRSA	Methicillin-resistant S. aureus
MSSA	Methicillin-sensitive S. aureus
MSUD	Maple syrup urine disease
MUD	Minimal urticaria dose
NAAT	Nucleic acid amplification testing
NCM	Neurocutaneous melanosis
NF	Neurofibromatosis
NS	Netherton syndrome
NS	Nevus sebaceous
NSAIDs	Nonsteroidal anti-inflammatory drugs
NTM	Non-tuberculous mycobacteria
NXG	Necrobiotic xanthogranuloma
OCA	Oculocutaneous albinism
OI	Osteogenesis imperfecta
PA	Pityriasis alba
PAH	Phenylalanine hydroxylase
PALCL	Primary cutaneous anaplastic large cell lymphoma
PAN	Polyarteritis nodosa
PAPA	***P***yogenic ***a***rthritis, ***p***yoderma gangrenosum, and ***a***cne conglobata syndrome
PAPASH	Sterile ***p***yogenic ***a***rthritis, ***p***yoderma gangrenosum, ***a***cne and ***s***uppurative ***h***idradenitis syndrome
PBMC	Peripheral blood mononuclear cells
PC	Pachyonychia congenita
PCOS	Polycystic ovarian syndrome
PCR	Polymerase chain reaction
PCT	Porphyria cutanea tarda
PDGF	Platelet derived growth factor
PDL	Pulsed dye laser
PDT	Photodynamic therapy
PF	Pemphigus foliaceus
PG	Pyoderma gangrenosum
PHACE syndrome	Posterior fossa anomalies, Hemangioma, Arterial lesions, Cardiac abnormalities/coarctation of the aorta, Eye anomalies
Phe	Phenylalanine
PIPA	Post-inflammatory pigment alteration
PKU	Phenylketonuria
PL	Pityriasis lichenoides
PLC	Pityriasis lichenoides chronica
PLE	Polymorphous light eruption
PLEVA	Pityriasis lichenoids et varioliformis acuta
PMLE	Polymorphous light eruption
PNH	Progressive nodular histiocytoma
POTS	Postural orthostatic tachycardia syndrome
PP	Pseudoporphyria
PPD	Purified protein derivative [test]
PPGSS	Papular-purpuric gloves and socks syndrome
Ppi	Inorganic pyrophosphate
PPK	Palmoplantar keratoderma
PR	Pityriasis rosea
PRP	Pityriasis rubra pilaris
PSD	Perineal streptococcal dermatitis
PUVA	Psoralen plus UVA

PV	Pemphigus vulgaris
PXE	Pseudoxanthoma elasticum
RAMBA	Retinoic acid metabolism blocking agent
RCT(s)	Randomized, controlled clinical trial(s)
RDFC	Recurring digital fibroma of childhood
ReA	Reactive arthritis
RF	Rheumatoid factor
RMSF	Rocky mountain spotted fever
RP	Relapsing polychondritis
RT-PCR	Reverse transcription-PCR
SA	Salicylic acid
SAPHO	***S***ynovitis, ***a***cne, ***p***ustulosis, ***h***yperostosis, and ***o***steitis syndrome
SCC(s)	Squamous cell carcinoma(s)
SCID	Severe combined immunodeficiency
SGA	Subcutaneous nodules granuloma annulare
SHML	Sinus histiocytosis with massive lymphadenopathy
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SLS	Sjogren-Larsson syndrome
SPF	Sun protection factor
SPTCL	Subcutaneous panniculitis-like T-cell lymphoma
SSc	Systemic sclerosis
SSRIs	Selective serotonin reuptake inhibitors
SSSS	Staphylococcal scalded skin syndrome
SSTI	Skin and soft tissue infections
TA	Tufted angiomas
TB	Tuberculosis
TBCO	Tuberculosis cutis orificialis
TEN	Toxic epidermal necrolysis
TND	Twenty-nail dystrophy
TNF	Tumor necrosis factor
TSC	Tuberous sclerosis complex
TSS	Toxic shock syndrome
TTM	Trichotillomania
TVC	Tuberculosis verrucosa cutis
TWEL	Transepidermal water loss
Tyr	Tyrosine
UBOs	Unidentified bright objects
ULE	Unilateral laterothoracic exanthem
UV	Ultraviolet
VM	Venous malformations
VZV	Varicella zoster virus
WHN	Woolly hair nevus
WS	Werner syndrome
YAG (laser)	Yttrium aluminum garnet
XD	Xanthoma disseminatum
XLCL	X-linked cutis laxa
XLDPP	X-linked dominant protoporphyria

Contents

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Overview of Dermatologic Care in Children

1

Leslie Potter Lawley

Skin Care of Normal Newborn Skin

Clinical Features

- Full-term infants are born with skin at near normal pH and a natural barrier in the form of the vernix caseosa. A combination of shed epithelial cells, sebum, and lanugo hairs, the vernix caseosa appears as a chalky-white cheesy film on the skin surface of full-term infants. It is not present in post-term neonates, whose skin is drier, and may not have fully formed in a pre-term infant, depending on the age of gestation. The formation of the vernix starts around week 28 and peaks at 33–37 weeks' gestation. The vernix caseosa should not be removed, but allowed to naturally resolve, as it aids in temperature regulation, skin hydration, protection from bacteria, and wound healing. Fine desquamation of the skin develops around 2 days of life for term infants. In preterm infants, desquamation may not be apparent until 2–3 weeks of life, while post-term infants may be born with dry, peeling skin [3, 6].
- Over a period of weeks to months the acid level of stratum corneum increases to transform into the acid mantle. The acidic pH of the acid mantle provides a normal permeability barrier, enhancing cohesion and integrity of the stratum corneum. When cleansing newborns there is balance of removing bacteria, saliva, urine, feces, secretions, and soil while not over-drying the skin or harming the barrier created by the stratum corneum. As the infant ages and the acid mantle develops, skin care should not alter that natural barrier [3].
- Considerations for timing of the first bath for the newborn include stability of the neonate's vital signs. Bathing can lead to hypothermia, increased oxygen demands, and respiratory distress if performed too soon [3].
- At birth, the umbilical cord is clamped, leaving a stump of umbilical tissue. Over a period of weeks (up to 8) it naturally undergoes necrosis and detaches from the body. Typically the process takes an average of 2 weeks. As the umbilical cord stump undergoes this process, the infant is at risk of local secondary infections. Keeping the umbilical stump dry helps reduce this risk.

Management Strategies

- Protect the skin barrier while maintaining cleanliness.

Investigations Recommended [3]

Evaluation
Prior to first bath after birth, measure temperature, oxygen status, respiratory rate and heart rate and ensure these signs are stable for 2–4 h

Therapies [3, 6, 9, 11]

Bathe neonates every 2–3 days
Do not scrub to remove the vernix caseosa, but allow it to resolve naturally
Sponge bath until the umbilical cord naturally falls off
Immersion bathing is less harmful to temperature stability in newborns
Utilize baby washes with neutral pH, free of fragrance and dyes
In situations of home birth where hygiene sterile practices may be suboptimal, a one-time cleansing with chlorhexidine wipes as soon after birth as possible may reduce the mortality rate in low birth-weight babies (no significant change in mortality for normal weight neonates)
Apply petrolatum-based emollients (fragrance-free, preservative-free, dye-free) every 6–12 h as needed for dryness of the skin
Remove emollient from container with a clean tongue blade or other tool to prevent contaminating the moisturizer with bacteria

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Therapies: Daily Umbilical Cord Care [6]

Cleanse area with chlorhexidine. Then remove any excess soap to minimize local necrosis and absorption
Consider the powder form of chlorhexidine which allow for more drying
Avoid isopropyl alcohol or hexachlorophene
Fold diaper away from stump to keep dry

Principles of Pediatric Skin Care

Clinical Features

- When considering cleansing skin, there are no significant differences between infant and adult skin. Infants produce skin surface lipids similar to adults, with a varied ratio of sebum to keratinocyte lipids compared to adults. During childhood these lipids are decreased. Starting in pre-adolescence, increases in circulating hormones (adrenal androgens followed by gonadal androgens) stimulate production of sebum. In many adolescents the increased sebum leads to more oily complexion and hair, contributing to acne and seborrhea [7].
- Most studies on tolerance of skin care products have been in children with certain disease states such as atopic dermatitis. We lack evidence as to how often to bathe children with a normal skin barrier, what cleansers to use, how often to shampoo hair, and how often to use emollients. At this point we can only extrapolate information from studies on infants and children with skin barrier defects and atopic dermatitis to determine skin care for those children with normal skin. It must be considered that children with skin barrier defects have drier, more sensitive skin. Most soaps are made of animal or vegetable fats to remove dirt and oils and are alkaline in nature. Because the skin surface is acidic (acid mantle), synthetic detergents have been developed to protect the pH of the skin. The use of these neutral and even acidic pH cleansers are likely more important for children with skin barrier defects. Most normal children can tolerate the soap and shampoo their parents prefer to use [3, 7].
- Sun protection throughout childhood and adolescence is important. Studies indicate that at least 25–50 % of lifetime sun exposure occurs before age 18 years. In the first 2 years of life melanin production is limited, and skin may be more susceptible to UV damage. After 2 years, the skin of a child is similar to an adults' skin, however, the dermal papillae may be closer to the skin surface, leading to increased UV exposure to the basal layer. As children enter pre-adolescent ages they often become more independent in their skin care, so education of proper sun protection at that time is paramount to preventing damage from UV that can lead to skin cancers later in life [5].
- To date there is not evidence that any of the sun filters used in sunscreen harm children, however, controversy exists over the safety of organic protectors such as oxybenzone (benzophenone-3). Studies have shown absorption of oxybenzone with excretion in the urine, however, no known adverse effects have been seen. Allergic contact dermatitis can develop to organic blockers, leading to advice to avoid them, especially in children with skin barrier defects. Risk is minimized by using inorganic sunscreens (zinc oxide and titanium dioxide), where even the micronized nanoparticle forms do not absorb systemically through the skin, and no cytotoxic or genotoxic effects have been found. The combination of N,N-dimethyl-meta-toluamide (DEET) insect repellent and sunscreen leads to increased absorption of the DEET. For this reason, the combination sunscreen-insect repellent products should be avoided, as well as concomitant application of both products. In addition, sunscreen needs to be applied more frequently than insect repellent [5, 7].

Management Strategies

- No evidence-based guidelines are available for pediatric skin care. Goals are to maintain clean skin and protect against drying and sun damage.

Investigations Recommended

For diagnosis
None

Table 1.1 First line therapies [1, 2, 4, 5, 10]

Bathe every day to every other day in childhood using a mild cleanser. Bathe after heavy perspiration from sports or playing outdoors on hot days
Adolescents should bathe every day and wash their faces once to twice daily using a mild cleanser
Oily hair can be washed daily, whereas dry hair should be washed less frequently, up to once every 1–2 weeks
Apply moisturizers to dry skin and hair
Heavier emollients can be used in the winter (ointments and creams)
Lighter emollients should be used in hot and humid weather to prevent miliaria (lotions)

Table 1.1 (continued)

Follow good sun protection:
Cover up with clothing (lightweight long sleeves and pants, tightly woven fabric), hats (3-in. brim or greater), and sunglasses
Direct sun exposure should be avoided prior to 6 months age
For areas not covered by clothing, apply adequate amount of broad-spectrum sunscreen of SPF 30 or greater (1 oz/application for an adult)
Sunscreen should be reapplied every 2 h or sooner if needed
Use inorganic broad spectrum sun filters to minimize any risk of allergic reaction (zinc oxide and titanium dioxide)
Avoid sun exposure during the peak sun hours (11 am–4 pm), seek shade
Avoid combination sunscreen–insect repellent products

Premature Skin

Clinical Features

- The epidermis in premature infant skin is 55% thinner than term infant skin. The stratum corneum alone is only one cell thick compared to 15 cells in a term infant stratum corneum. The structures that anchor the epidermis cell together (desmosomes, anchoring filaments, anchoring fibrils, and hemidesmosomes) are smaller and fewer in number. This difference translates to increased fragility of the skin and increased permeability (increased transepidermal fluid loss, electrolyte imbalance, increased heat evaporation, and increased absorption of topically applied products). The skin matures quickly after birth, over a period of 2–3 weeks, to reach stages seen in term newborns, unless the skin is in a high-humidity environment or covered with occlusive materials, which can slow maturation [3, 8].

Management Strategies

- Replace fluids, prevent fluid loss, maintain electrolyte balance, maintain environmental temperature.

Investigations Recommended [3, 6]

For diagnosis
Measure sensible fluid losses (urine, feces) and insensible fluid losses
Correct caloric intake to support growth and energy losses
Monitor electrolytes

Table 1.2 First line therapies [3, 6]

Humidified incubator with radiant warmer
Semipermeable skin dressings
Bathe every 2–3 days with a pH neutral, fragrance-free, preservative-free, dye-free cleanser if weight over 1,000 g; if weight under 1,000 g, bathe in water alone

Therapies: Daily Umbilical Cord Care [6]

Cleanse area with chlorhexidine; then remove any excess soap to avoid local necrosis and absorption
Consider the powder form of chlorhexidine which allows for more drying
Do not use isopropyl alcohol or hexachlorophene
Fold diaper away from stump to keep dry

Therapies [3, 6, 8, 9]

Apply petrolatum-based moisturizers (fragrance-free, preservative-free, dye-free) every 12 h for the first 2–4 weeks, then as needed for dryness
Remove emollient from container with a clean tongue blade or other tool to prevent contaminating the moisturizer
Gently remove any unnecessary adhesives
Caregivers should use good hand hygiene
Avoid potentially hazardous compounds (see Appendix)

Special Considerations for Newborn Skin

Clinical Features

Certain transient skin phenomena occur in newborns and infants, but not later in life.

- Harlequin color change represents a transient alteration in blood flow on one side of the body with a sharp cutoff in the midline. One side of the body becomes impressively more erythematous for seconds to minutes and resolves with position change. It occurs more often in premature infants and when the infant is lying on one side. There is no disease state or underlying systemic disorder related to the phenomena and it spontaneously resolves.
- Cutis marmorata and acrocyanosis: The cutaneous vasculature of infants is immature and may not respond normally to environmental changes. Vasomotor instability leads to vasoconstriction of skin vessels, producing a reticulated pattern on the skin called cutis marmorata. In some infants acral vasoconstriction in the setting of colder

temperatures results in acrocyanosis, a bluish discoloration of the lips, hands, and feet. Both cutis marmorata and acrocyanosis occur more frequently in premature infants. No diagnostic studies are needed. These vascular changes improve with re-warming of the skin.

- Sebaceous gland hyperplasia: Hormonal stimulation in utero leads to hypertrophy of sebaceous glands on the face of newborns. Yellow-white, smooth papules result, most often symmetrically spaced on the nose and upper lip. Up to 50 % of newborns present with sebaceous gland hyperplasia. No diagnostic studies are indicated, and treatment is not needed as the hyperplasia spontaneously resolves.
- Sucking blisters: Vigorous sucking in utero may lead to a sucking blister present at birth. Most often located on the hand or forearm, a solitary, non-inflamed vesicle or bullae is present at birth and spontaneously resolves within 2 weeks. Diagnostic studies are not needed unless the morphology is not typical, or additional vesicles develop after birth to indicate other etiologies (i.e. herpes virus, impetigo, epidermolysis bullosa, etc.).
- Diaper dermatitis is a common manifestation, increasing in frequency after 1 month of age with a prevalence of 4–5 %. It is an irritant dermatitis resulting from a combination of an occlusive moist environment, resulting in macerated skin with increased skin permeability, reduced acid mantle protection (due to alkaline urine, thus activating fecal enzymes), and growth of microorganisms. Typically the dermatitis spares the inguinal folds.
- Seborrheic dermatitis (aka cradle cap) affects up to 10 % of infants. In most cases the scalp is involved with development of greasy, yellow scales, hence the colloquial term "cradle cap." Intertriginous areas may also be involved and, rarely, the dermatitis can be generalized in more severe cases.

Investigations Recommended

Evaluation
The presence of pustules, crusts, hemorrhagic crusts, or ulcerations should prompt cultures and biopsy to investigate for secondary infection or Langerhans cell histiocytosis

Management Strategies

- Diaper dermatitis: Supra-absorbant diapers help reduce the moisture and prevent irritant diaper dermatitis. Once the dermatitis develops, use of non-medicated, fragrance-free wipes is advised, along with frequent diaper changes. A zinc oxide-based diaper paste should be applied as a barrier with every diaper change [3].
- Seborrheic dermatitis: The treatment of cradle cap depends on severity. Most cases respond to a mild anti-dandruff shampoo containing zinc or selenium, or an anti-yeast shampoo such as ketoconazole. Oils may be used to gently lift scales from the scalp.

Table 1.3 First line therapies [2, 3]

Seborrheic Dermatitis Treatment
Salicylic acid should be avoided, due to risks of percutaneous absorption in the newborn. For more inflammatory cases, a low-potency topical corticosteroid may be implemented

Skin Care Products to Avoid

Clinical Features

- Infants and children have increased skin surface-to-body weight ratio which can increase relative absorption of topical medications, and potentially lead to adverse events and toxicity. In addition, the skin has increased absorptive capacity in premature and newborn infants that should be considered when choosing topical therapies. Certain compounds are known to be more hazardous to preterm infants compared to term neonates. For example, providone-iodine may cause local cutaneous necrosis and also hypothyroidism due to absorption of the iodine in premature infants. Salicylic acid used as a keratolytic can be absorbed, leading to salicylism in infants and children [2, 3, 8].

Management Strategies

Avoid the use of agents known to have increased absorption and that lead to toxicity in newborns, infants, and children, or those with a defective skin barrier. Be cautious in using topical agents in newborns, infants, and children.

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Management of Skin Disorders of the Newborn

2

Nika Finelt and Brandi M. Kenner-Bell

Evidence Level

A: Double blind study
B: Clinical Trial ≥20 subjects
C: Clinical trial <20 subjects
D: Series ≥5 subjects
E: Anecdotal case reports

Neonatal Cephalic Pustulosis

For diagnosis
Clinical–facial eruption of pustules that begins at age 5–30 days. It resembles neonatal acne but lacks comedones and is associated with colonization with Malassezia
Giemsa stain–yeast form, neutrophils
For treatment
None, self-limiting

Table 2.1 First line [1, 2]

Ketoconazole 2 % cream applied topically twice a day	D

Neonatal/Infantile Acne (Fig. 2.1)

For diagnosis
Clinical–comedones and inflammatory papules and/or comedones. It usually begins in the first year of life and is secondary to a physiologic increase in adrenal and gonadal androgens.
If severe consider work-up for hyperandrogenism
For treatment
Treat to avoid formation of pitted scarring from acne

Table 2.2 First line [3–6]

Gentle cleansing	E
Mild retinoid (adapalene 1 % gel or tretinoin 0.025 % cream)	C
Benzoyl peroxide 2.5 % cream	D

Fig. 2.1 Neonatal acne

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For Severe Acne Consider

Oral erythromycin, azithromycin, or trimethoprim-sulfamethoxazole	D
Oral isotretinoin	D

Seborrheic Dermatitis

For diagnosis	
Clinical–greasy yellow scale and erythematous patches on the face, scalp, ears, and intertriginous areas. Appears between 2 and 10 weeks of age and may be associated with colonization of *Malassezia furfur*	
Consider culture for bacteria and candida for any weeping intertriginous area	
KOH preparation and fungal culture to exclude superficial dermatophyte infection	
For treatment	
None, self-limiting within a few weeks to months	

Table 2.3 First line [6–15]

Emollients. For thick scale, application of mineral or baby oil followed by gentle scalp massage with a soft toothbrush	A
Frequent shampooing with gentle shampoo or anti-seborrheic shampoo	E
Bifonazole 1 % shampoo	B
Ketoconazole 2 % shampoo	A
Ketoconazole 2 % cream	B
Hydrocortisone 1 % cream	B

Acrodermatitis Enteropathica

For diagnosis	
Clinical–well demarcated scaly perioral and acral plaques, which may be accompanied by alopecia and diarrhea. It is secondary to an autosomal recessive mutation in intestinal zinc-specific transporter gene SLC39A4. Acquired forms of zinc deficiency will have the same clinical presentation and may be secondary to inadequate intake, excessive losses, malabsorption, and increased demands. Mothers may have low zinc secretion into milk caused by a mutation in the SLC30A2 gene, which encodes the transporter responsible for secreting zinc into breast milk	
Blood plasma or serum zinc levels, fasting; serum zinc levels <50 µg/dl	
Low alkaline phosphatase levels	
Urine zinc excretion	
Physical exam and routine laboratory evaluation, lipid profile, copper levels	
Genetic testing	
For treatment	
Blood plasma or serum zinc levels q 3–6 months	

Table 2.4 First line therapy [16–21]

Oral zinc supplementation	A
Inherited deficiency – 3 mg/kg/day for life (50 g elemental zinc per 220 mg zinc sulfate)	
Acquired deficiency – 0.5 to 1.0 mg/kg/day until corrected	

Table 2.5 First line for acropustulosis of infancy [22, 23]

Potent topical corticosteroids	D
Oral antihistamines	E

Acropustulosis of Infancy

For diagnosis	
Clinical–pruritic recurrent pustules on palms and soles	
Rule out scabies	
Skin biopsy–intraepidermal pustules with neutrophils, occasional eosinophils	
For treatment	
None	

Table 2.6 Second line [24]

Oral dapsone	E

Aplasia Cutis Congenita [14] (Figs. 2.2 and 2.3)

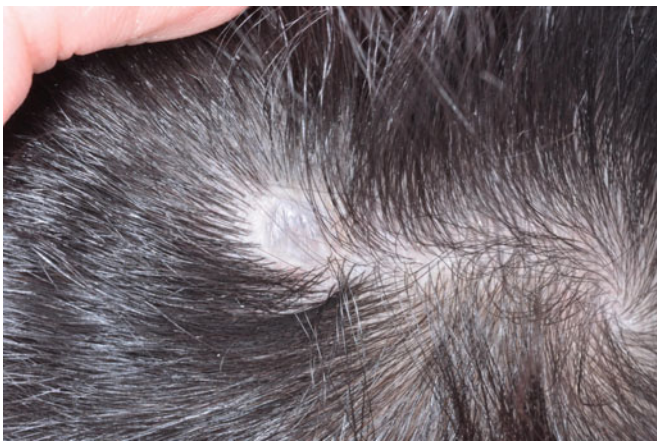
For diagnosis	
Clinical–discrete ovoid defect covered with a membrane that may be bullous or flat at birth that eventually heals with a scar. Aplasia cutis congenita may present sporadically or may be inherited as part of a syndrome	
Thorough history and physical for other developmental anomalies	
If hair collar sign (ring of longer, darker hair around the defect) and midline, need evaluation for underlying neural tube defect; ultrasound or MRI if concerned	
For treatment	
Follow-up proper formation of scar	

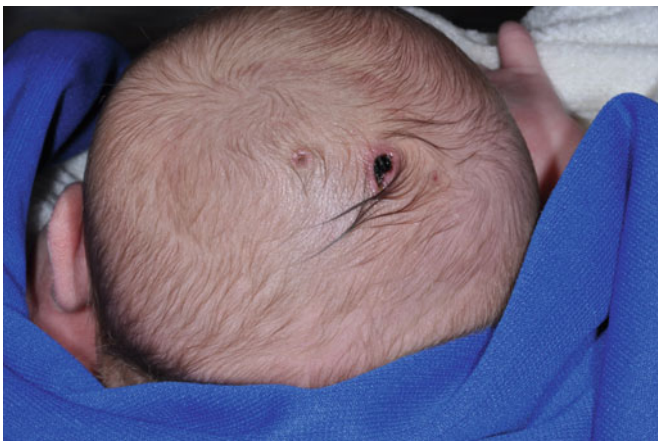
Bronze Baby Syndrome

For diagnosis	
Clinical–hyperpigmentation of the skin, serum, and urine during treatment for neonatal jaundice with phototherapy. It occurs in infants with cholestasis and elevated levels of unconjugated and conjugated bilirubin	
Evaluate for underlying cause of jaundice	
Evaluate for underlying hepatocellular disease	
For treatment	
Monitor for jaundice, cholestasis, hepatocellular disease	

Congenital/Neonatal Herpes Simplex Virus (HSV)

For diagnosis	
Clinical–vesicles on an erythematous base; three recognized syndromes: skin, eyes, and mouth infection (SEM); disseminated infection; central nervous system infection	
Viral Culture (swab from mouth, nasopharynx, conjunctiva, anus, and any vesicles), Viral DFA or immune peroxidase slide test, PCR (skin vesicle, CSF, blood), Tzanck Preparation, ALT elevation, skin biopsy	





Figs. 2.2 and 2.3 Aplasia cutis congenita

Must rule out CNS disease
CT brain, MRI brain, EEG
For treatment with acyclovir
Serial absolute neutrophil count (ANC) twice weekly
Adjust dose of Acyclovir for renal failure or sustained ANC <500 mm^3
For infants with CNS disease- consider daily suppressive therapy with oral acyclovir for 6 months after parenteral regimen

Table 2.7 First line for Bronze Baby Syndrome [6, 14, 25]

Improves with discontinuation of phototherapy	E

Table 2.8 First line [6, 26, 27]

Oral Acyclovir–20 mg/kg IV q8 × 14 (SEM)-21 days (disseminated or CNS)	B

Congenital/Neonatal Candidiasis

For diagnosis
Clinical; congenital–pustules on palms and soles birth to first few days of life, may have respiratory distress; neonatal–diaper (beefy erythema and satellite pustules or vesicles), oral thrush (white plaques on oral mucosa), and also commonly associated with intertrigo (erythema and maceration in skin folds). This warrants a high index of suspicion in premature and immunocompromised infants
Smear of pustule with KOH, Giemsa, Gram, or calcofluor stain (budding yeast or pseudohyphae), fungal culture
PCR, restriction fragment endonuclease digestion of chromosomal DNA, electrophoretic karyotyping, Southern blot hybridization analysis with DNA probes, B-glucan assay, gas chromatography mass spectrometry for D-arabinitol, buffy coat smear microscopy
CBC (leukocytosis), Glucose (elevated)
Congenital–evaluate placenta and umbilical cord for lesions; if suspect disseminated systemic disease (premature and low birth-weight), must culture blood, urine, cerebrospinal fluid
For treatment
Monitor for sepsis
Follow monitoring guidelines for any PO or parenteral antifungals

Table 2.9 First line [28–37]

Thrush–nystatin solution (100,000 u/ml) applied to oral mucosa 4×/day; fluconazole (2–3 mg/kg/day)	A
For localized disease–topical anti-yeast preparations, Imidazoles, nystatin, allylamines	A
Invasive–oral fluconazole, itraconazole, amphotericin	A, B (amphotericin)
Prophylaxis in infants <1 kg-Fluconazole IV	A

Table 2.10 Second line [28–37]

Thrush–Itraconazole (2 mg/kg/day)	D
Localized–1 % gentian violet, or 2 % eosin	E

Staphylococcus Aureus Pustulosis (Fig. 2.4)

For diagnosis
Clinical–discrete vesicles and pustules, or superficial erosions and crust
Bacterial culture and gram stain of fluid from vesicle, pustule, or beneath crust. Nasal swabs to evaluate for S. Aureus carriage
Consider work-up for deeper or systemic infection if any constitutional signs of illness (fever, temperature instability, irritability, lethargy, etc.)
For treatment
Monitor for signs of deeper or systemic infection
Monitor sensitivities of culture
Consult with colleagues and local resources regarding resistance patterns in your hospital and community

Table 2.11 First line [6, 38–44]

Oral antibiotics–choose agent based on sensitivity and local resistance patterns	A
Topical antibiotic ointment (mupirocin, fusidic acid, or retapamulin ointments)	A
Decolonization of neonates and close contacts	A (adults– trial results pending in neonates)

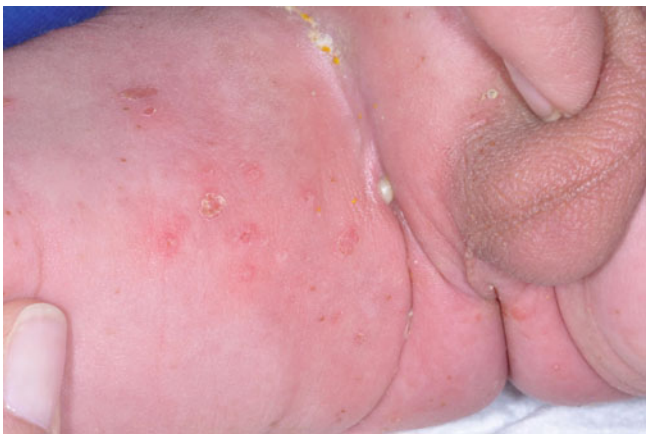


Fig. 2.4 Staphylococcal pustulosis

Neonatal Scabies (Fig. 2.5)

For diagnosis
Clinical–pruritic contagious infestation of the Sarcoptes scabiei mite that commonly involves the palms, soles, and axillae but also may involve the scalp of infants. Burrows, vesicles, erythematous papules, and nodules may be present
Mineral oil examination–apply a drop of mineral oil and scrape with No. 15 blade then smear contents onto glass slide, cover with mineral oil and evaluate for mite, eggs, or feces
Dermoscopy
For treatment
May have pruritus for 1 month following treatment

Table 2.12 First line [14, 45]

Permethrin 5 % cream–approved for over 2 months of age but commonly used under 2 months of age, traditionally applied to all skin from neck down and rinsed after 8 h, but scalp must also be treated in infants; should be repeated after 1 week	A
Sulfur 6 % ointment–safe in infants and pregnant women; apply as above for 3 consecutive nights and rinse 24 h after last application	D
Treat all close contacts	E
Launder all linens following treatment	E

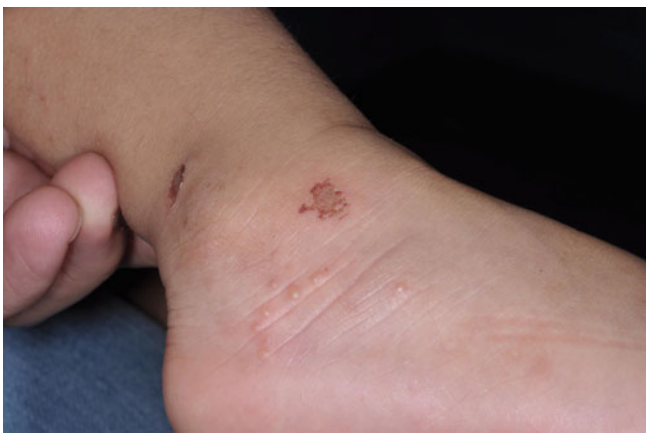


Fig. 2.5 Neonatal scabies

Cutis Marmorata Telangiectatica Congenita (Figs. 2.6 and 2.7)

For diagnosis
Clinical–localized or generalized fixed reticulate erythema, may see limb hypo or hyperplasia over affected extremity
Evaluate for other vascular anomalies, macrocephaly (rule out macrocephaly-capillary malformation syndrome)
Consider ophthalmology referral for facial involvement
Consider neurology referral for neurological symptoms
For treatment
Monitor as above

Table 2.13 First line [46, 47]

Monitor for signs of hypoplasia or hyperplasia	D

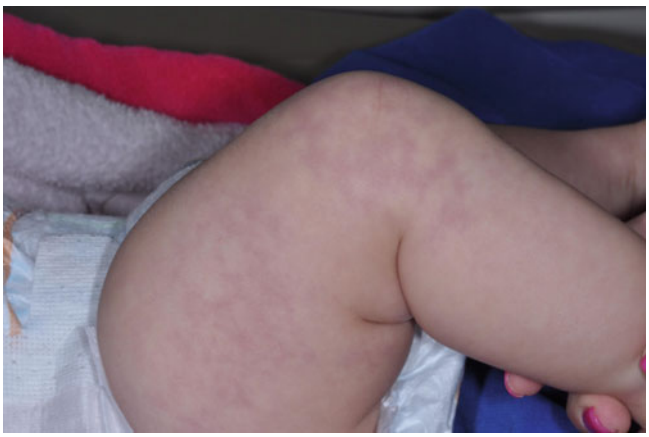


Fig. 2.6 Cutis marmorata telangiectatica congenita

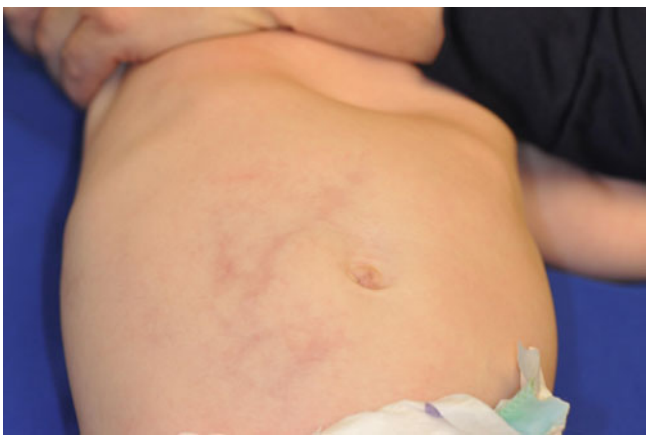


Fig. 2.7 Cutis marmorata telangiectatica congenita

Eosinophilic Pustular Folliculitis (Fig. 2.8)

For diagnosis
Clinical–Pruritic follicular based pustules, commonly on the scalp, that recur in crops
Culture with sensitivity from pustule
Gram stain and mycology from touch prep, Tzanck or scraping

Biopsy- dense perifollicular mixed infiltrate with eosinophils
CBC, immunologic work-up for immunodeficiency
For treatment
Consider monitoring peripheral eosinophilia
Self-limiting

Table 2.14 First line [48–51]

Topical corticosteroids	D
Topical tacrolimus	E
Oral anti-histamines	E

Table 2.15 Second line

Erythromycin PO	E

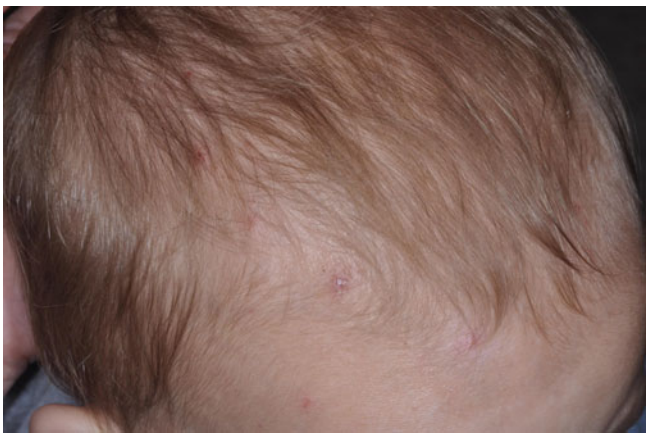


Fig. 2.8 Eosinophilic pustular folliculitis

Granuloma Gluteale Infantum (Fig. 2.9)

For diagnosis
Clinical– purple-red nodules on the skin of the groin in response to local inflammation, maceration, and possibly Candida superinfection, often preceded by topical corticosteroids
For treatment
Self-limiting

Table 2.16 First line therapy [14, 52]

Treat cause of chronic irritation	E
Frequent use of barrier product	E

Sclerema Neonatorum

For diagnosis
Clinical–rare diffuse hardening of the skin that spares the genitalia, palms, and soles; seen in severely ill premature neonates
Biopsy
For treatment
Close monitoring for sepsis and thermodynamic instability
Poor prognosis

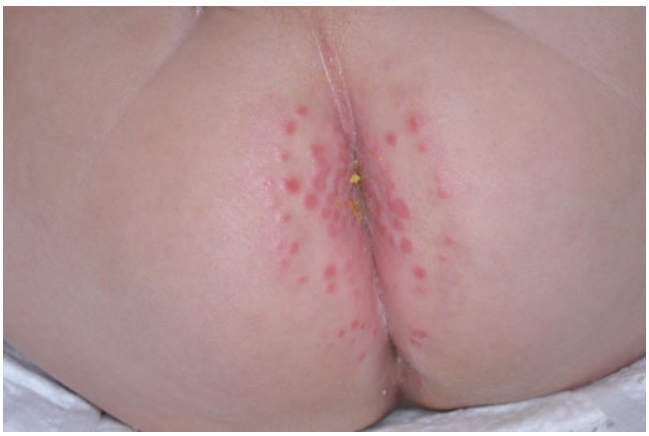


Fig. 2.9 Granuloma gluteale infantum

Table 2.17 First line therapy [53–55]

Treatment of underlying disorder, treat sepsis, ventilator support, thermodynamic support	D

Table 2.18 Second line therapy [54, 55]

Exchange transfusions	B

Table 2.19 Third line therapy

Systemic Corticosteroids– questionable value	D

Subcutaneous Fat Necrosis [56, 57]

For diagnosis
Clinical–circumscribed indurated nodules seen in full term neonates
Monitor serum and urine calcium level weekly for up to 6 months
MRI or ultrasound to evaluate for renal or other organ calcifications
Biopsy
For treatment
Self-limiting
If hypercalcemia detected monitor calcium biweekly
Calcium/creatinine ratio in urine

Table 2.20 First line therapy [58]

No treatment	C
Low calcium diet and low vitamin D (breast milk or formula)	C

Table 2.21 Second line therapy [59]

IV saline	E
Calcium wasting diuretics: Furosemide 1 mg/kg two to three times daily	E

Table 2.22 Third line therapy [56, 60–64]

Oral prednisone 1–3 mg/kg daily in divided doses for 2–21 days	E
Subcutaneous calcitonin 4–8 IU/kg every 6–12 h	E
Bisphosphonates: Pamidronate 0.5 mg/kg infused IV over 4 h; Etidronate 5 mg/kg/dose twice daily	E

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Atopic Dermatitis and Eczematous Eruptions

3

Eric L. Simpson and Kevin B. Yarbrough

Atopic Dermatitis

Clinical Features of the Disorder

Atopic dermatitis (AD) is a common, chronic, relapsing, pruritic inflammatory skin condition affecting approximately 10–20 % of children in several industrialized countries, and is increasing in prevalence in many parts of the world. The majority of cases begin before age 5, but onset may occur at any age [1–3]. Due to the unrelenting pruritus associated with the inflammatory skin lesions, sleep is often disturbed. Studies reveal the quality of life of children with AD is similar or worse than many chronic diseases of childhood such as asthma. Chronic itching and lack of proper sleep lead to measurable psychological, behavioral, and emotional consequences [4]. Having a child with AD often impacts the entire family, with one study finding that having a child with AD in the family to be comparable to having a child with type I diabetes [5]. The development of AD often heralds the onset of allergic comorbidities, specifically asthma, allergic rhinitis, and food allergy. Children with AD are also at higher risk of developing skin infections and neurodevelopmental disorders such as attention-deficit-hyperactivity disorder [6].

Clinical criteria aid in the diagnosis of AD and were proposed by Hanifin and Rajka in 1980 [7]. Key features that should be present to make a diagnosis of AD are shown in Table 3.1. The distribution of skin lesions varies with age. In infants, AD affects the cheeks and extensor surfaces of the limbs most commonly, while in older children and adults, lesions typically involve flexor surfaces (Figs. 3.1, 3.2, and 3.3). The groin and axillae are typically spared at all ages. A diagnosis should only be made when other conditions have been considered, such as scabies or contact dermatitis [8]. The presence of atypical morphology or distribution, or a history of repeated severe sino-pulmonary infections, should prompt the consideration of an immunodeficiency syndrome [8].

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Management Strategies

Management begins with disease education, followed by the creation of an individualized treatment plan using a sequential approach, primarily based on disease severity. Key educational points to deliver during the initial encounter with a patient and family include information on pathogenesis, the role of food allergy, topical steroid risks and benefits, prognosis, proper skin care, and avoidance of triggers (Table 3.2). Families should be asked about the presence of immediate hypersensitivity symptoms to foods such as lip swelling, urticaria, abdominal pain, or vomiting within 2 h after food consumption. If these are not present, there are few data to support the idea that foods contribute to the eczematous lesions, and food avoidance should not be routinely recommended [9].

Treatment Overview

Management can be roughly thought of in two parts—a *Clearance Phase* where inflammation becomes controlled rapidly and a *Maintenance Phase*, where therapy choices should consider long-term safety. If flares occur during maintenance therapy, an abbreviated *Clearance Phase* protocol may be needed.

Clearance Phase

Very mild disease may be managed with emollients alone. For mild to moderate disease, topical steroids should be prescribed in adequate quantities and potency to achieve near

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Table 3.1 American Academy of Dermatology Criteria for AD

Essential features:
Pruritus
Eczema (acute, subacute, chronic)
Typical morphology and age-specific patterns[a]
Chronic or relapsing history
Important features—seen in most cases, adding support to the diagnosis:
Early age of onset
Atopy
Personal and/or family history
Immunoglobulin E reactivity
Xerosis
Associated features—these clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for diagnosing AD in isolation:
Atypical vascular responses (e.g., facial pallor, white dermatographism, delayed blanch response)
Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis, ocular/periorbital changes
Other regional findings (e.g., perioral changes/periauricular lesions), perifollicular accentuation/lichenification/prurigo lesions
Exclusionary conditions—it should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:
Scabies
Seborrheic dermatitis
Contact dermatitis (irritant or allergic)
Iichthyoses
Cutaneous T-cell lymphoma
Psoriasis
Photosensitivity dermatoses
Immune deficiency diseases
Erythroderma of other causes

Adapted from AAD Consensus Conference on AD, 2003

[a]Patterns include: (1) Facial, neck, and extensor involvement in infants and children (2) Current or previous flexural lesions in any age group (3) Sparing of the groin and axillary regions

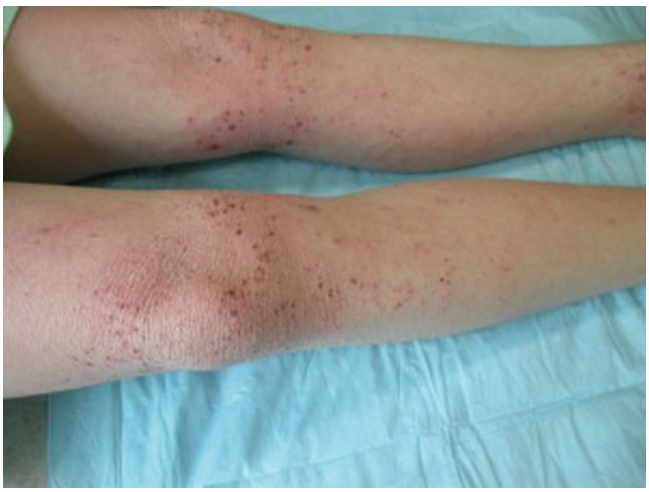

Fig. 3.1 Typical erythematous crusted and excoriated plaques with lichenification in two children with atopic dermatitis

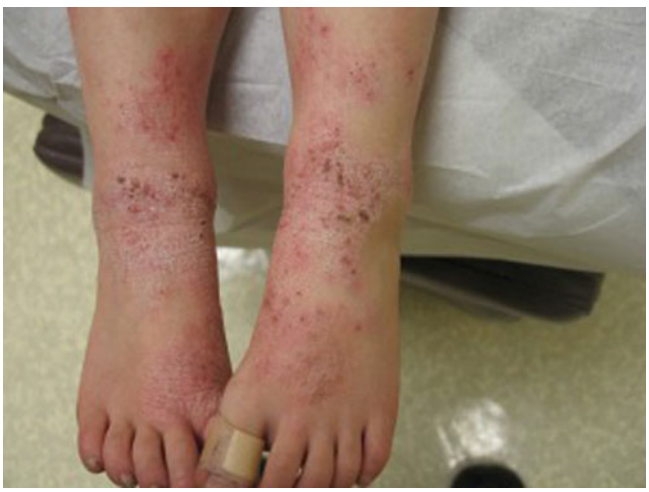

Fig. 3.2 Typical erythematous crusted and excoriated plaques with lichenification in two children with atopic dermatitis

clearance of the disease within 1–3 weeks. Topical steroids may be applied once or twice daily, with data showing little clinical difference between the two frequencies [10]. Ointment preparations are generally preferred over creams and lotions because of their enhanced efficacy and reduced possibility of causing stinging or contact dermatitis. One small study found that daily bathing followed immediately by topical steroid ointments ("soak and seal") led to 95 % of patients with moderate to severe disease achieving mild disease or better after 1–2 weeks of treatment [11]. Another study found 3 days of a medium-potency topical steroid was just as effective as 2 weeks of low-strength steroid [12].

Clinically relevant hypothalamic-pituitary-adrenal axis suppression typically occurs only in the setting of inappropriate use (i.e., prolonged duration with daily application). The short-term use of daily topical steroids has proven to be safe, but topical steroid therapy should not be used daily for long-term control [13, 14]. Topical calcineurin inhibitors may be used as first-line treatment in areas of the body prone to steroid side effects such as the face, but are not often tolerated when skin is flaring due to burning and stinging (Table 3.3).

Maintenance Phase

After achieving disease control in the Clearance Phase with topical steroids, the Maintenance Phase begins. The Maintenance Phase involves reducing topical steroid use to twice-weekly application to newly active or residual lesions. This reduction in steroid frequency prevents potential side effects such as skin atrophy, telangiectasias, and striae. Topical calcineurin inhibitors may be added at this stage if twice-weekly application of topical steroids is not adequate to maintain disease control [13]. Daily use of topical steroids to the same areas of skin for longer than 4–6 weeks should be avoided. For patients with severe disease that frequently relapses, intermittent topical steroid (two times per week) or calcineurin inhibitors (three times per week) may be used on *normal-appearing skin* at sites that frequently flare, so-called "proactive therapy," to reduce the probability of relapse [15, 16].

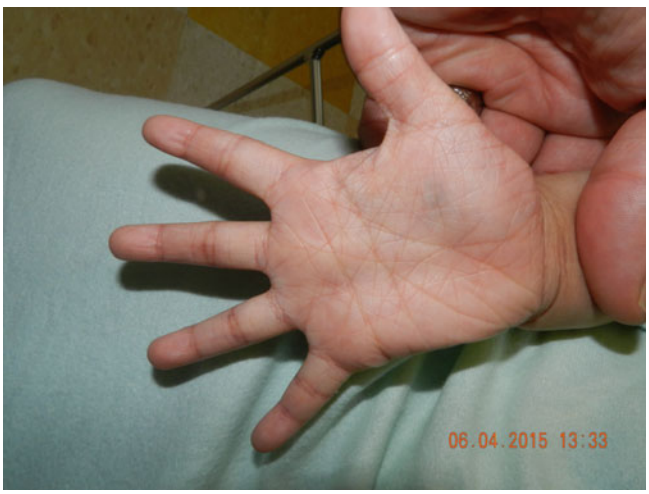

Fig. 3.3 Hyperlinear palms are a common finding in patients with AD (Photo courtesy of Alfons Krol, MD)

Rescue of Flares

If a patient experiences a disease flare, the cause of the flare, such as a bacterial infection of the skin, should be identified and treated. Other common causes of flares include upper respiratory viral infections, change in season, and non-adherence to the prescribed skin care or maintenance regimen. A shortened version of the Clearance Phase may then be instituted, such as 3–7 days of daily topical steroid.

Adjunctive Interventions

Twice-weekly dilute sodium hypochlorite baths (1/4 to ½ cup of household bleach to a full standard tub) may improve the severity of AD when added to routine therapy; their use may be especially helpful in patients with moderate-to-severe disease who experience frequent bacterial infections [17]. Some controlled studies also support oral vitamin D3 supplementation [18]. While oral antihistamines may be useful for treating allergic comorbidities, or may be needed as a short-term sleep aid, there are little data supporting their effectiveness in treating the itch or inflammation of atopic dermatitis [19]. Some data support the use of acupressure as an adjunctive treatment for itch [20]. Narrowband ultraviolet B phototherapy may be added if topical therapy does not achieve satisfactory results [21]. Topical calcineurin inhibitors should be discontinued during phototherapy, given the theoretical photocarcinogenesis potential of these two interventions used concomitantly.

Table 3.2 Key educational points to be delivered in first visit

The cause of the disease	The cause of AD may be thought of as a disease driven by genetic and environmentally derived alterations in both the skin barrier and immune regulation
The prognosis and disease course	Parents should be informed that AD is a chronic disease that needs continued management. Early aggressive control of the inflammation will improve a patient's itch and quality of life
Role of food allergy	Patients with atopic dermatitis are more likely to have immediate reactions to foods like egg, milk, and peanut. However, in the absence of immediate hypersensitivity symptoms, there are no convincing data that altering a child's diet will improve the eczema
Avoiding triggers and exacerbating factors	Avoid common triggers to reduce itch such as contact with wool, a warm environment, harsh soaps, or lotions with fragrance
Steroid phobia and steroid side effects	A thorough explanation of the risks and benefits of topical steroids should take place with a discussion on how those risks may be mitigated
Patient support and education	Written instructions and information regarding patient support organizations such as the National Eczema Association (nationaleczema.org) are important resources for patients
Skin care	Gentle skin care should be encouraged with the use of mild cleansers and the daily use of emollients (moisturizers)

Refractory Disease

Patients with moderate or severe disease that fail to respond adequately to intensive topical therapy are candidates for systemic therapy. The diagnosis in patients failing intensive topical therapy should be reconsidered, with consideration given to scabies infection, skin infection, contact dermatitis, cutaneous T-cell lymphoma, or other dermatosis. Oral immunosuppressive/immunomodulatory medications are the current mainstay of treatment for this subset of patients, with cyclosporine being the treatment of choice for acute disease control given its rapid onset of action and well-documented efficacy. Cyclosporine is normally started at a dose of 3–6 mg/kg/day, with higher initial doses likely leading to more rapid clinical response [21]. Once disease control is obtained with cyclosporine, patients may be transitioned to safer longer-term options such as phototherapy, methotrexate, azathioprine, or mycophenolate mofetil (Tables 3.4, 3.5).

Table 3.3 First line therapies [8, 13, 22, 23]

Topical corticosteroids	A
Emollients	A
Topical calcineurin inhibitors	A

Table 3.4 Second line therapies [17, 18, 21]

Sodium hypochlorite baths	A
Vitamin D3 supplementation	A
Phototherapy (NBUVB, UVA1, PUVA)	A

Table 3.5 Third line therapies [21, 24–29]

Cyclosporine	A
Methotrexate	A
Azathioprine	B/A*
Mycophenolate mofetil	C/A*
Interferon-gamma	A*
Apremilast	C*
Ustekinumab	E
Rituximab	D

Specific Investigations Recommended

No routine investigations are required. The diagnosis is primarily clinical and based on the presence of the criteria listed in Table 3.1. If symptoms of immediate hypersensitivity are present, referral to an allergist for allergy testing may be needed to confirm the history. Referral to an allergist may also be useful for supervised oral food challenges if children are on overly restrictive diets based on the results of allergy testing. Biopsy, immunologic evaluation, KOH preparation, or genetic testing may rarely be needed if an alternative diagnosis is suspected, or in cases of severe refractory disease.

Topical corticosteroids remain the mainstay of acute therapy in AD in evidence-based guidelines supported by extensive literature review. Evidence-based guidelines also strongly support topical calcineurin inhibitors as a proven option for long-term control. A systematic review of "proactive" therapy (i.e., intermittently treating normal-appearing skin that frequently flares to prevent flares) reported that both topical steroids and topical tacrolimus trials showed efficacy, with twice-weekly topical steroids possibly being slightly superior to tacrolimus.

Huang et al. published the first controlled trial showing the effectiveness of twice-weekly sodium hypochlorite, or dilute bleach baths, in reducing AD severity in 2009; prior to this, only anecdotal evidence was available. A randomized trial of oral calciferol (1,000 IU/day) showed improved disease severity at 1 month over placebo in children aged 2–17 years. Strong evidence is also available supporting various light modalities in AD, with narrowband UVB representing the treatment of choice.

Multiple studies document the efficacy and safety of cyclosporine in pediatric and adult patients with atopic dermatitis, with a systematic review of controlled trials revealing cyclosporine consistently improves AD severity by greater than 30–50 %. Methotrexate in controlled trials also has been found to be safe and effective in both the pediatric and adult population; one study in adults reported comparable efficacy of both methotrexate and azathioprine, but with fewer side effects, especially hematological abnormalities, in the methotrexate group. Mycophenolate mofetil has also been shown effective and safe in adult and pediatric patients; however, response can often be delayed. A randomized, controlled study in which adult patients were cleared with 6 weeks of 5 mg/kg cyclosporine, then randomized to maintenance therapy with either 3 mg/kg cyclosporine or mycophenolate sodium, showed equivalent responses; however several patients in the MMF group received oral steroid rescue, while none in the CsA group needed rescue during the treatment phase. In an adult randomized controlled trial, almost half of patients treated with interferon gamma achieved more than 50 % clearance.

Pityriasis Alba

Clinical Features of the Disorder

Pityriasis alba (PA) is characterized by ill-defined, oval, hypopigmented to pink macules, small patches or very thin plaques with fine overlying scale (Fig. 3.4). The hypopigmented lesions are typically not preceded by obvious signs of inflammation. Multiple lesions are normally present and distributed most often over the cheeks, forehead, perioral

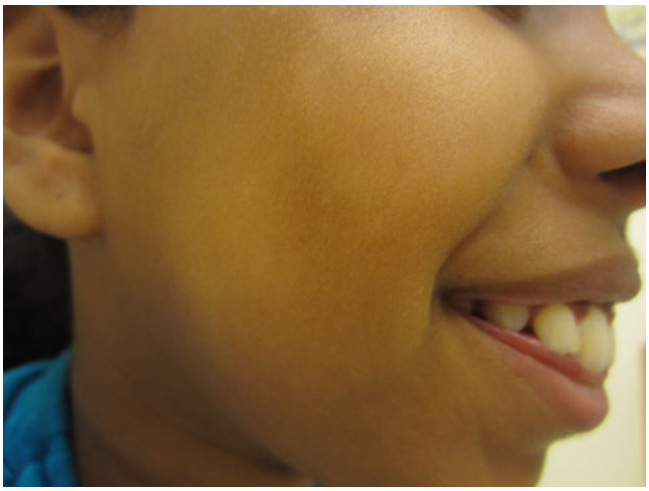

Fig. 3.4 Pityriasis alba characterized by round hypopigmented macules of the cheeks (Photo courtesy of Sabra Leitenberger, MD)

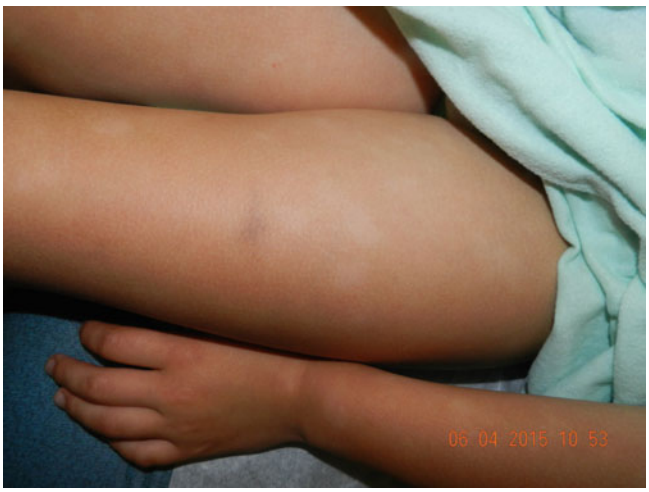

Fig. 3.5 Pityriasis alba involving the arms and legs of a young girl with atopic dermatitis (Photo courtesy of Alfons Krol, MD)

skin, and proximal arms. Less commonly, involvement of the trunk and legs can be seen (Fig. 3.5) [30–32].

PA is frequently associated with atopic dermatitis, and in these patients likely represents a form of post-inflammatory hypopigmentation. PA has been described in an endemic form associated with poor hygiene, parental income, and more siblings [33, 34]. The role of exposure to sunlight is controversial, as it has been reported to both improve PA as well as exacerbate it. A portion of the change seen with sunlight could be due to increasing pigment of skin surrounding the PA lesions. This condition is more readily apparent in children of darker skin types. The lesions are most often asymptomatic, although mild itching may be present. Histologically, PA shows spongiotic dermatitis and, less often, hyperkeratosis and acanthosis [35].

Management Strategies

Treatment can be frustrating, and in some cases may not be necessary, as lesions often resolve spontaneously over months to years. Very few controlled studies have been performed evaluating the treatment of PA. The most often recommended treatments include gentle skin care with mild cleansers, emollients, and sunscreen (Table 3.6). The efficacy of these recommendations has not been thoroughly evaluated, but they likely counteract possible causative factors. The gentle skin care combats any role xerosis and inflammation may be playing, and the sunscreen is helpful in that it lessens the contrast between involved and uninvolved skin and may help prevent new lesions. In cases with suspected dermatitis, low-potency topical corticosteroids (such as hydrocortisone 1 % or 2.5 %) and calcineurin inhibitors may be of benefit. Calcineurin inhibitors have been the most studied treatments, suggesting the role of subclinical inflammation in the etiology of PA.

Specific Investigations Recommended

PA in most cases is diagnosed clinically. Biopsy may be necessary to rule out hypopigmented mycosis fungoides if the lesions are extensive with significant involvement off of the face [36]. Testing for a loss of sensitivity to light touch, pinprick, or temperature can be useful in patients in which leprosy is suspected [37].

Biopsy if hypopigmented MF is suspected
Skin scraping for KOH to exclude dermatophyte infection or tinea versicolor
Testing for loss of sensitivity if patient is at risk for leprosy

In a review of 67 cases seen at the Mayo Clinic, bland lubricants such as white petrolatum were equivalent in effectiveness when compared to 5 % ammoniated mercury in petrolatum, 2 % crude coal tar in petrolatum, Whitfield's ointment, and Myconef ointment. A randomized, controlled study of tacrolimus 0.1 % ointment versus placebo showed improvement over the 9-week study period in hypopigmentation, pruritus, and scaling, with significantly greater improvement in pruritus and hypopigmentation in the tacrolimus group at all three time points. A similar study randomizing to three groups—tacrolimus 0.1 % ointment, calcipotriol 0.0003 % ointment, and petrolatum ointment for 8 weeks—showed improvement in all groups, but the improvement in the tacrolimus and calcipotriol groups was superior to petrolatum. A study using pimecrolimus 1 % cream also showed efficacy in pediatric and adult subjects, with clearance of scaling for most patients by week 3 and evening of pigmentation by week 12.

A study of 12 patients (skin types III–V) reported complete clearance of PA lesions with twice-weekly for 12 weeks with Excimer. Another study reported clearance or marked improvement in five of six patients treated with 4 weeks of oral methoxsalen, followed by exposure to midday summer sun or exposure to UVA cabinet.

Contact Dermatitis

Clinical Features of the Disorder

Contact with various exogenous compounds can induce an eczematous dermatitis either by delayed type IV hypersensitivity (allergic contact dermatitis), or through direct injury to skin cells (irritant contact dermatitis).

Allergic contact dermatitis (ACD) is becoming increasingly recognized as a cause of dermatitis in children and may be under-recognized, as children are not often patch tested [2, 3, 44]. ACD is classically characterized in its acute form by well-demarcated erythematous edematous and often vesicular plaques that are quite pruritic (Fig. 3.6) Chronic ACD appears as lichenified scaling plaques and can be more difficult to distinguish from irritant contact dermatitis (ICD) and atopic dermatitis (AD) (Fig. 3.7). The distribution of ACD depends on the contactant, and can be major clue to the diagnosis and likely causative agent. Geometric angular streaks raise the possibility of exposure to plants, usually of the toxicodendron family. Involvement of the eyelids, face, and anterior neck is typical for airborne allergens such as fragrances or sesquiterpene lactones. Pruritic eczematous dermatitis of the plantar and dorsal feet should raise suspicion of an ACD to a component of shoes. ACD should also be considered in patients with AD that have a sudden worsening of their disease or that is difficult to treat, especially when the flare involves areas of the body not typically involved in AD. Any asymmetric dermatitis or eruption limited to one area of the body (i.e., feet, eyelids, buttocks) should also raise suspicion for contact dermatitis. Patch testing is the standard for establishing the diagnosis of ACD and should be done when the history and clinical exam supports a diagnosis of ACD. Positive reactions must be interpreted in the clinical context to identify those that are truly relevant to the patient. The most common allergens causing ACD in children are shown in Table 3.8, below.

Table 3.6 First line therapies [38–41]

Low potency topical corticosteroids	C
Topical calcineurin inhibitors	A
Emollients	B
Sunscreen	B

Table 3.7 Second line therapies [40, 42, 43]

Excimer laser	D
Calcitriol 0.0003 %	C
PUVA	D

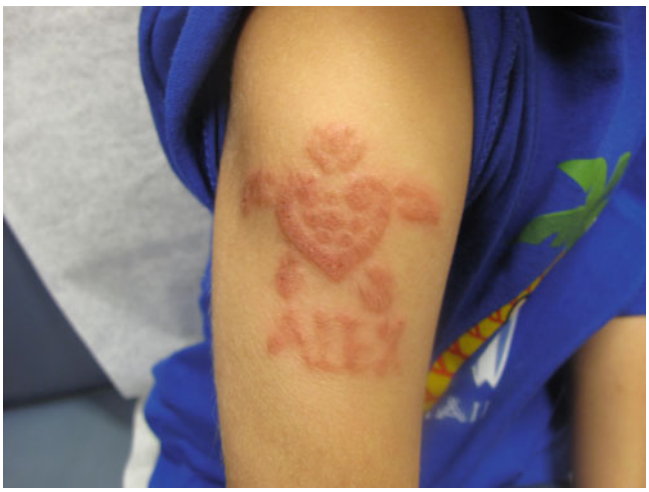

Fig. 3.6 Young boy with ACD to p-Phenylenediamine in a temporary tattoo (Photo courtesy of Patricia Norris, MD)

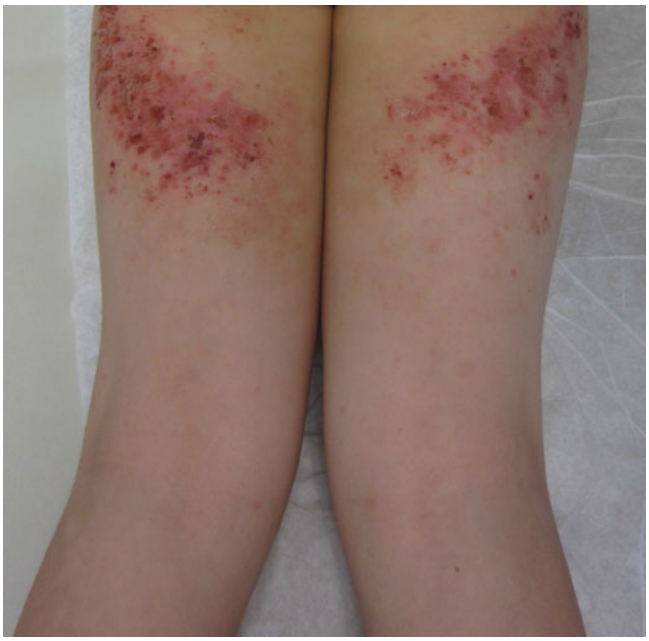

Fig. 3.7 ICD or ACD from household cleaners used on toilet seats between uses. So-called "toilet seat" dermatitis (Photo courtesy of Julianne Mann, MD)

Management Strategies

The principal goal in treating contact dermatitis is removal and avoidance of the causative agent. For irritant contact dermatitis, the offending agent is often obvious such as soap and

Table 3.8 Most common allergens causing allergic contact dermatitis in children

Allergen	Most common source
Nickel	Jewelry
Cobalt	Jewelry
Neomycin sulfate	Topical antibiotics
Balsam of Peru	Fragrance in perfumes and toiletries; flavoring in food and drink
Lanolin	Pharmaceutical preparations, cosmetics, and toiletries
Fragrance mix	Cosmetics, toiletries
Bacitracin	Topical antibiotics
Formaldehyde	Cosmetics, toiletries, and skin- and health-care products
Quaternium-15	Cosmetics, toiletries, and skin- and health-care products
p-Phenylenediamine	Hair dyes, temporary tattoos

Adapted from Zug et al. [48]

water for hand dermatitis. See Chap. 2 for a discussion of diaper dermatitis, another form of irritant contact dermatitis. Identification of the causative agent in allergic contact dermatitis is not always straightforward and depends on correct identification of the contactant, with a careful comprehensive history and patch testing. Parents and patients must be thoroughly educated about the compounds responsible for their ACD. Handouts describing common products containing the suspected contactant as well as suggesting alternative products that do not contain them can be helpful in educating parents and patients. For acute ACD, or in cases when avoidance alone does not lead to improvement, topical steroids can be helpful. Topical calcineurin inhibitors are often useful for treating the face or intertriginous areas [45]. In severe acute ACD, systemic therapy with oral corticosteroids or other immunosuppressants may be necessary (Table 3.9). Many authors recommend systemic treatment for acute severe ACD (such as seen with rhus dermatitis) covering greater than 10 % of the skin surface. A common regimen involves prednisone, 1 or 2 mg/kg/d, as a single morning dose for 7–10 days, with the dose tapered over an additional 7–10 days. Premature cessation may result in rebound dermatitis. Barrier creams and specialized soaps also exist for occasions when exposure cannot always be avoided, such as when outdoors in areas with poison oak/ivy. If the causative allergen can be successfully identified and avoided, long-term treatment is usually not necessary. As is the case with many pediatric conditions, research specifically evaluating the treatment of contact dermatitis in children is lacking.

Table 3.9 First line therapies [45]

Patch testing and removal of contactant	Expert opinion
Topical corticosteroids	A*
Avoidance of irritants	C*
Emollients (lipid rich moisturizers)	A*
Barrier creams (dimethicone or perfluoropolyethers)	B*

Specific Investigations Recommended [46–49]

For diagnosis

Patch testing

Multiple studies have been performed using patch testing in symptomatic children and adolescents. Most showed one or more positive patch test reaction in 62–83 % of patients (one study was only 25.1 % of those tested), of which 55–77 % were considered to be relevant. The most common sensitizers were metals, fragrances, and hair dyes.

A thorough systematic review of 49 studies (pulled from 413 initial articles) of adult patients was performed with multiple evidence-based findings. Barrier creams containing dimethicone or perfluoropolyethers, cotton liners, and softened fabrics were able to prevent irritant CD. Lipid-rich moisturizers both prevent and treat irritant CD. Topical skin protectant and quaternium 18 bentonite (organoclay) can prevent rhus dermatitis. Diethylenetriamine pentaacetic acid (chelator) cream prevents nickel, chrome, and copper dermatitis. Potent or moderately potent steroids (fluticasone propionate 0.05 %, clobetasone butyrate 0.05 %, and clobetasol propionate 0.05 %) effectively treat allergic CD.

Multiple studies report statistically significant improvement in adult patients with ACD with tacrolimus 0.1 % ointment when compared with petrolatum or vehicle alone. In studies comparing tacrolimus 0.1 % ointment and mometasone ointment, both showed efficacy. Tacrolimus 0.1 % ointment in the treatment of eyelid ACD led to improvement in erythema, edema, scaling, and lichenification at 30 days of treatment, though fissuring did not improve. In a study of adult patients with nickel-induced ACD, pimecrolimus 0.6 % cream was comparable to betamethasone-17-valerate 0.1 % cream and was more effective than the vehicle.

Several authors recommend oral prednisone in cases of widespread and/or severe reactions. Dosing recommendations include 1 mg/kg/day for 10–14 days (>10 % body

Table 3.10 Second line therapies [50–54]

Topical calcineurin inhibitors	A*

Table 3.11 Third line therapies [44, 55–58]

UVB/PUVA for CD of hands	B
Systemic corticosteroids	Expert opinion

surface area) up to >3 weeks (severe reactions, such as from poison ivy exposure).

Studies show treatment with UVB or PUVA can lead to improvement in ACD, though amount and duration of improvement varied. One study of ten patients treated with UVB led to complete resolution of hand ACD; however, treatment duration was lengthy at 5 months) and maintenance therapy was required. Two studies compared UVB and PUVA. One using left–right comparison of the two modalities showed no significant different between the two, though side effects were seen more often in the PUVA group. The other study showed significant improvement but not clearance in UVB-treated patients, whereas all patients treated with PUVA has clearance of their dermatitis, but over half experienced relapse within 3 months.

Juvenile Plantar Dermatosis

Clinical Features of the Disorder

Juvenile plantar dermatosis (JPD) is characterized by shiny erythema and superficial scaling primarily involving the weight-bearing surfaces of the forefoot, toes (especially great toes), and the heel (Fig. 3.8). In more extensive cases, painful fissures may develop. JPD presents in school-age children and early adolescents and typically resolves by age 12–16. Pruritus is variably present. The etiology is unclear but it is often associated with a personal or family history of atopy. There may also be a relationship with excessive sweating and occlusive footwear [2, 3].

Management Strategies

Interventions are aimed at preventing maceration and irritation from repeated moistening and drying of the plantar skin. This is accomplished by wearing breathable footwear, cotton socks, and application of barrier emollients such as white petrolatum. Changing out damp socks with a fresh dry pair after applying white petrolatum to the affected skin can be a useful strategy. In more severe cases with significant pruritus and fissures, mid- to high-potency topical steroids may be helpful (Table 3.12). Topical tacrolimus 0.1 % used in combination with emollients has also been reported to be helpful (Table 3.13). In patients with significant hyperhidrosis, aluminum chloride can be helpful.

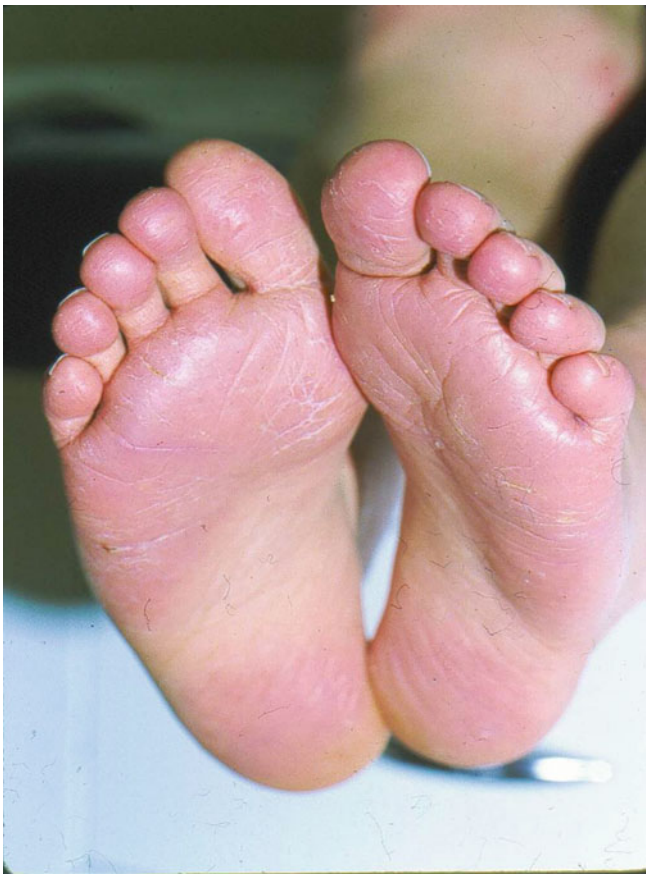

Fig. 3.8 Shiny erythema and superficial scaling on the weight-bearing surfaces of the forefoot (Photo courtesy of Alfons Krol, MD)

Specific Investigations Recommended [59]

For diagnosis
Skin scraping for KOH to exclude dermatophyte infection
Biopsy rarely necessary but can be useful if psoriasis is suspected
Patch testing if ACD is suspected

The diagnosis is primarily clinical. Potassium hydroxide preparation can be useful to evaluate for tinea pedis, although the absence of interdigital involvement supports a diagnosis of juvenile plantar dermatosis. Patch testing is helpful in cases where allergic contact dermatitis (ACD) is suspected. ACD involving the feet typically is more pruritic than JPD and often involves the dorsal aspects of the feet. Palmoplantar psoriasis can involve the soles but tends to be more sharply demarcated, have thicker scale, and typically extends beyond the weight-bearing surfaces.

Table 3.12 First line therapies [60–62]

Corticosteroids	D
Emollients	D
Cotton socks	D
Breathable footwear	
Reducing friction	

Table 3.13 Second line therapies [63]

Topical calcineurin inhibitors	E

Retrospective reviews of patients with JPD have reported disease duration averaging 4.5–8.4 years. Patient report of associated factors varied, including friction, wearing cotton socks, and switching from sporting footwear or "trainers" to leather shoes. Response to any treatment also varied, with one study showing only 54 % of patients felt that treatment had any effect on their condition. Improvement was reported with the use of emollients alone in 22–57 %, and with topical steroids in 20–34 % of patients.

A single case report of an 8-year-old boy with JPD, treated with BID application of 0.1 % tacrolimus ointment as well as regular emollients, reported improvement within 4 weeks.

Lichen Simplex Chronicus

Clinical Features of the Disorder

Lichen simplex chronicus (LSC), also called neurodermatitis, is characterized by pruritic ill-defined hyperpigmented thickened lichenified plaques. It is rarely seen in infants or young children but can be seen in older children and adolescents. Locations that tend to be involved are the nape of the neck, ankles, wrists, genitalia, and pretibial skin. LSC results from repetitive rubbing and scratching of the skin, most often in response to localized pruritus. The lesion may be found in isolation with no apparent inciting event, or may be seen in the setting of atopic dermatitis, or other pruritic skin disease. Insect bites or poison ivy exposure have also been reported to initiate pruritus leading to LSC. Scratching can increase c-fiber responsiveness, which in turn leads to increased pruritus and further scratching. This cycle can cause intensifying pruritus, repetitive rubbing and, ultimately, LSC [2, 3].

Management Strategies

No evidence-based guidelines for the treatment of LSC in children exist. Most treatment recommendations are based on studies in adults. Key to management of LSC is breaking the itch–scratch cycle. This is most often accomplished with high-potency topical steroids, with or without occlusion, and patient behavior modification. Improvement is not seen if the rubbing continues. Occlusion can play a dual purpose in that it increases penetration of the topical steroid while also acting as a protective barrier. Flurandrenolide-impregnated tape can be used to provide occlusion as well as deliver corticosteroid. Intralesional triamcinolone is often used and effective in adults, but is frequently not tolerated by children. Any xerosis should be managed with emollients and optimizing bathing habits. Oral antihistamines may be of some benefit and are potentially helpful with nighttime sedation when pruritus is often at its peak. Menthol preparations can provide a cooling sensation that can help alleviate itch. Topical pimecrolimus and tacrolimus can be used as alternatives to topical steroids. Topical doxepin cream has also been shown to be effective, including use in a 3-year-old child. Its use however, has been limited by transcutaneous absorption leading to sedation, as well as development of allergic contact dermatitis. Topical aspirin has also been used with success in treatment of recalcitrant LSC.

Specific Investigations Recommended

In the absence of generalized pruritus, no specific investigations needed. Patients with new-onset generalized pruritus should undergo evaluation for systemic illnesses associated with pruritus.

A randomized, controlled trial of two topical corticosteroids, 0.05 % halobetasol propionate ointment and 0.05 % clobetasol 17-propionate ointment, showed significant improvement in adults with chronic, localized AD or LSC. One pediatric case report documents successful treatment of LSC on the forehead with tacrolimus 0.1 % ointment. A case series of adult female patients with vulvar LSC treated with pimecrolimus 1 % cream showed improved signs and symptoms in all patients.

In a small study of 18 patients with LSC, 10 treated with flurandrenolone tape and 8 with topical steroid without occlusion, lasting remission was seen in a greater number (70 %) of patients using flurandrenolone tape versus topical steroid alone (25 %). Topical doxepin cream showed significantly greater pruritus relief than those treated with vehicle in all efficacy parameters measured in a large multicenter double-blind trial of mostly adult patients (aged 12–65, mean age 38 years) with different eczematous conditions, of which 136 had LSC. Doxepin 5 % cream also was successful in treating persistent lichenification in a 3-year-old patient. A small double-blind study of 29 patients with LSC treated with either topical aspirin/dichloromethane or placebo showed significant therapeutic response in 46 % of treatment group compared to 12 % in the placebo group.

Table 3.14 First line therapies [64–66]

Corticosteroids	A*
Topical calcineurin inhibitors	C*

Table 3.15 Second line therapies [67–70]

Flurandrenolone tape	C
Topical 5 % doxepin cream	E/A*
Topical aspirin	A*

Table 3.16 Third line therapies [71–77]

Biofeedback, cognitive behavioral therapy, hypnosis	D
Gabapentin	E*
Botulinum toxin type A injection	E*
Acupuncture	C*
Ketotifen	C

There is some evidence to support modalities such as biofeedback, cognitive-behavioral methods, and hypnosis in the treatment of LSC and other aspects of dermatology. A case series of four patients, including one 16-year-old, reported significant improvement in neurodermatitis with a single treatment session using the "habit-reversal" technique. Another case report showed temporary, partial response of LSC to gabapentin. A case series of three patients receiving Botulinum toxin type A injections directly into chronic LSC lesions showed pruritus subsided within 3–7 days in all patients. Small clinical studies also show improvement in neurodermatitis with electro-acupuncture (with needles inserted around diseased areas) in adults and with ketotifen in children.

Lichen Striatus

Clinical Features of the Disorder

Lichen striatus presents as a transient linear eruption consisting of erythematous and lichenoid papules following the lines of Blaschko (Fig. 3.9) It most commonly presents on the extremities, but can be seen on the trunk and face. Lesions can be a few centimeters or extend over an entire limb. Involvement of a digit can lead to nail dystrophy, which may precede skin findings (Fig. 3.10) This is a self-limited condition that can persist for several weeks to 2–3 years, with occasional relapses [78, 79]. Post-inflammatory pigmentary changes can follow inflammatory lesions (Fig. 3.11) [2, 3]. Biopsy of lesions typically shows a mixed lichenoid and spongiotic pattern. This can vary depending on the age of the lesion biopsied. The etiology is unclear, but the Blaschko-linear distribution suggests genetic mosaicism with inflammation caused by loss of tolerance to a keratinocytic clone [78]. Several possible

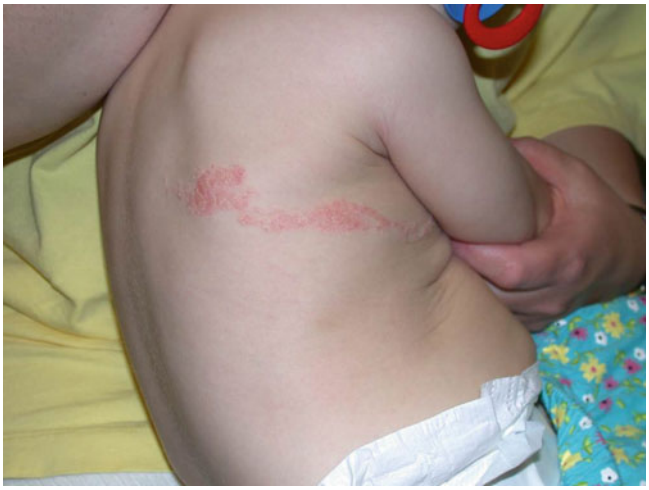

Fig. 3.9 Erythematous and psoriasiform papules following the lines of Blaschko on the back (Photo courtesy of Alfons Krol, MD)

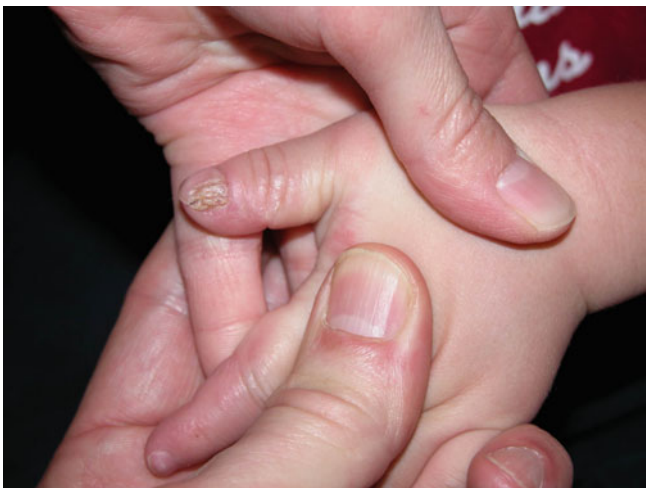

Fig. 3.10 Lichen striatus causing nail dystrophy (Photo courtesy of Alfons Krol, MD)

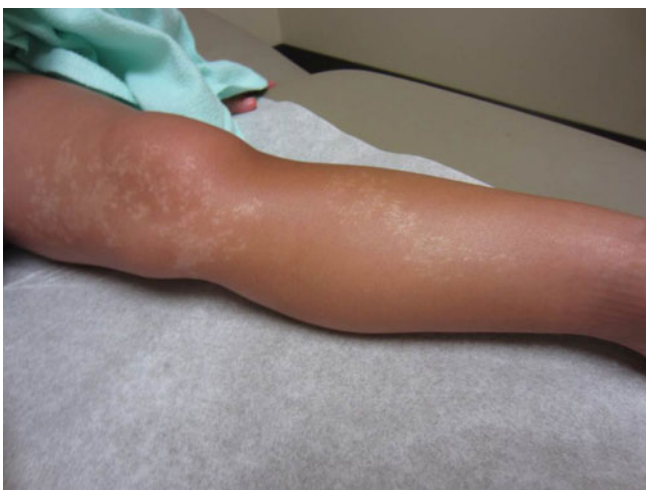

Fig. 3.11 Hypopigmented stage of lichen striatus on the leg (Photo courtesy of Sabra Lietenberger, MD)

Table 3.17 First line therapies [78–81]

Observation	Expert opinion
Topical corticosteroids	D
Emollients	D
Topical calcineurin inhibitors	E

Table 3.18 Second line therapies [82]

Hydroxychloroquine	E

triggers for a loss of tolerance have been proposed, including viral infection, atopic dermatitis, contact dermatitis, and ultraviolet light.

Management Strategies

Intervention is rarely necessary for this self-limited process. For the minority of patients with associated pruritus, mid potency topical steroids can be helpful. Topical tacrolimus may hasten resolution and possibly reduce hypopigmentation.

Specific Investigations Recommended

In cases where the diagnosis is unclear, biopsy may be needed to differentiate from other linear inflammatory skin conditions such as linear lichen planus, linear lichen nitidus, linear psoriasis, and inflammatory linear verrucous epidermal nevus.

In a series of 18 patients, mean duration of eruption was 9.5 months without treatment. A review of 61 patients with LS also reported eventual resolution without treatment, though they did note that several patients treated with medium-strength topical corticosteroids seemed to have faster resolution of inflammatory lesions, with lesions becoming non-erythematous within 2–4 weeks of commencing treatment. Case reports also have found improvement in erythema and hyperpigmentation with topical tacrolimus.

Case series of four patients initially thought to have a lupus erythematosus LS overlap. Three were treated with hydroxychloroquine, with resolution of lesions in 3–15 months. The fourth patient was treated with prednisolone valerate cream, with improvement after 9 months.

Nummular Dermatitis (Discoid Eczema)

Clinical Features of the Disorder

The term nummular is used to describe the round "coin-shaped" eczematous lesions characteristic of this condition. The round eczematous plaques often begin with the coalescence of pruritic exudative papules or papulovesicles. The distribution is less predictable than nummular dermatitis seen in adults, but tends to first involve extensor surfaces of the extremities then spread to trunk and dorsal hands. Nummular dermatitis is often associated with atopic dermatitis, and in these children may represent a nummular form of atopic dermatitis, but it can be seen independently. Xerosis seems to be a major predisposing factor. The eruption tends to last for several months with flares in the winter. It can be worsened by use of harsh soaps and other irritants [2, 3]. Medications including isotretinoin, interferon, ribavirin, gold, and anti-tumor necrosis factor inhibitors, are reported to induce nummular dermatitis [83]. Occult infections (dental infections, H. pylori) have rarely been reported in association with nummular dermatitis in adults [84].

Management Strategies

Nummular dermatitis can be challenging to treat, and response to treatment is often slow. Treating xerosis with regular emollients and gentle bathing is important. Crusted or exudative lesions should be cultured and the patient treated with topical or oral antibiotics if superinfection is present. Mid- to high-potency topical steroids are often needed. Antihistamines such as hydroxyzine have also been recommended. No evidence-based guidelines exist for the treatment of this condition in children.

Specific Investigations Recommended [83–86]

Consider patch testing
Skin scraping for KOH examination
Bacterial culture of skin lesions
Consider other infections (dental, H.pylori) in persistent cases
Consider causative medications

In a retrospective review of 48 adult patients who underwent patch testing, 33 % had positive patch tests thought to be clinically relevant. The most common allergens were rubber chemicals, formaldehyde, neomycin, chrome, and nickel. In a larger review of 1,022 patients (including some children), 35 % had at least one positive patch test, of which 69 % of these were thought to be relevant. The most common allergens were nickel sulfate, potassium dichromate, cobalt chloride, paraphenylenediamine, and ethylenediamine.

Most studies group nummular eczema with other forms of eczema, making it difficult to judge specific responses and form evidence-based treatment recommendations. For patients with a discoid/nummular variant of AD, evidence-based treatment recommendations for AD can be used (see previous AD section).

Table 3.19 First line therapies [87]

Topical corticosteroids	C*
Topical calcineurin inhibitors	C
Topical antibiotics	C
Emollients	C
Oral antibiotics if infection present	C
Oral antihistamines	E

Table 3.20 Second line therapies [88, 89]

Phototherapy	C*
Methotrexate	C

Mid- to high-potency topical corticosteroids are the normal first line treatment for this condition. These can be used with or without occlusion. Caution should be used when using potent corticosteroids under occlusion in children, given the risk of atrophy. Emollients and gentle skin care practices should be employed in conjunction. Any superinfection should be treated with topical or oral antibiotics. In one adult study, patients with "nummular eczema" cleared after 8 days of once-weekly clobetasol propionate lotion left under Duoderm occlusive patches.

In a case series of 25 children with refractory nummular eczema treated with methotrexate (dose range 5–15 mg), 16 patients (64 %) completely cleared after an average of 10.5 months of treatment. No serious adverse events were reported.

Seborrheic Dermatitis

Clinical Features of the Disorder

Seborrheic dermatitis is characterized by erythematous plaques with thick adherent yellow scale. The distribution depends on the age of presentation. This condition has two major forms, an infantile form and an adolescent form. Unlike many forms of eczema, pruritus is usually not a prominent feature of seborrheic dermatitis. These forms may represent two separate clinical entities, but share the same name and often respond to similar treatments [2, 3, 90]. Despite how commonly this condition is encountered, the exact etiology remains unclear. Many propose that commensal Malassezia yeasts (formerly called *Pityrosporum ovale*) are involved in the pathogenesis given the presence of this organism on affected skin as well as the response to treatment with antifungal agents. However, the total levels of Malassezia on affected skin do not seem to correlate with disease severity. This finding suggests an important role of host susceptibility in the etiology. The pathogenesis of infantile seborrheic dermatitis may have a similar etiology. In one study Malassezia was isolated more frequently from the skin of patients with infantile seborrheic dermatitis (ISD) than patients with atopic dermatitis (AD) and unaffected controls [91]. ISD also responds to antifungal treatments.

Infantile seborrheic dermatitis (ISD) presents most commonly in the first 4–6 weeks of life, and is characterized by erythema and thick scale over the frontal and vertex scalp, as well as intertriginous areas. The scalp is typically the first area of involvement, and has been colloquially referred to as "cradle-cap."

Adolescent seborrheic dermatitis presents with erythematous scaly plaques, with a greasy yellow scale over the seborrheic areas are the head, neck, and upper trunk. On the face it tends to be most prominent over the forehead, eyebrows, and alar creases. The retro-auricular folds and auditory canal are also often involved [2, 3].

Management Strategies

ISD tends to be self-resolving and does not always require treatment, but when necessary, conservative treatment will usually suffice. For the scalp, gentle removal of scale can be accomplished after softening with oil preparations or white petrolatum. After softening, the scale can be gently removed while washing with a gentle shampoo. A soft washcloth or baby toothbrush can be used to aid in removal of scalp scale, but over-vigorous scrubbing or brushing should be avoided. If the above is not helpful, addition of a mild topical corticosteroid or shampoo containing 2 % ketoconazole, selenium sulfide, or zinc pyrithione, may be necessary.

ISD involving the trunk and intertriginous areas tends to respond well to topical treatment with mild corticosteroids, as well as antifungal agents such as ketoconazole cream. Treatments containing tar and salicylic acid should be avoided in infants. TCIs have been shown effective as well, but they are not approved for use in children younger than 2 years of age.

Adolescent SD can be treated similarly to adult SD. Conventional treatment of the scalp in adolescent SD is comprised of intermittent use (two to three times weekly) of a medicated shampoo containing zinc pyrithione, selenium sulfide, coal tar, ketoconazole, or ciclopirox olamine. A shampoo with 5 % solution of maleluca oil may be effective, but many cases of allergic contact dermatitis have been reported to this botanical extract. Addition of a corticosteroid lotion or foam is occasionally needed in patients with significant erythema or pruritus. Adolescent SD involving the face is usually treated with hydrocortisone, ketoconazole, or a combination of the two. Pimecrolimus and tacrolimus creams may serve as an alternative to mild topical steroids. Other options with some evidence of effectiveness include other formulations of ketoconazole including gel and foam, metronidazole 0.75 % gel, ciclopiroxolamine 1 % cream, and

lithium gluconate 8 % ointment. Oral antifungals have been shown to be effective, but likely should be reserved for cases of severe refractory SD.

Specific Investigations Recommended

Biopsy to r/o LCH if the patient has refractory disease or an atypical presentation
HIV serology in adolescents with risk factors and severe refractory SD
Consider biopsy to distinguish from psoriasis or AD
Serum zinc levels

The differential for ISD includes AD, psoriasis, acrodermatitis enteropathica, and Langerhans histiocytosis (LCH). In early infancy, differentiating these conditions clinically can be challenging, as there can be significant overlap. Over time, however, the clinical features become more characteristic. The presence of xerosis and pruritus can be helpful in making the diagnosis of AD. AD also tends to involve the forearms and shins, in contrast to ISD, which is found more in the axillae and diaper area. Psoriasis can begin with erythematous well-demarcated scaly plaques in the diaper area. The presence or absence of greasy scale in the scalp can be helpful in making the distinction between psoriasis and ISD, as well as more characteristic lesions that tend to appear on the trunk. A family history of psoriasis can also be informative. The presence of crusting, atrophy, or hemorrhage should prompt the clinician to rule out LCH. Skin biopsy can easily differentiate LCH and ISD, and should be performed if LCH is suspected. The primary differential for adolescent SD is psoriasis. This can be a difficult differential, especially if only the scalp and face are affected. The presence of more typical psoriatic plaques elsewhere on the body, or nail changes, can be helpful in making this distinction [2, 3].

Multiple randomized studies of ketoconazole 2 % in various formulations (cream, foam, shampoo) show superior results, with less scale and less pruritus, when compared to placebo. One of these, a large multicenter double-blind study, compared cream and foam formulations and did not show a significant difference between them. Another large multicenter double-blind study showed the need for periodic prophylactic treatment and efficacy of ketoconazole shampoo as prophylactic treatment. In this study, 47 % of the patients using placebo relapsed, compared to 19 % of patients treating once weekly and 31 % of patients treating once every other week with ketoconazole 2 % shampoo. Studies of zinc pyrithione shampoo and selenium sulfide shampoo have also shown significant improvement compared to placebo. Studies in adult and pediatric populations of ketoconazole cream (2 % adult study, 1 % pediatric study) versus hydrocortisone 1 % cream showed significant improvement, with no significant difference between the two groups in global assessment at 4 weeks in the adult study. In the pediatric study of children age 2 months to 2 years old, all patients showed significant improvement at 1 week and complete clearance by 2 weeks. An adult study comparing ketoconazole 2 % foaming gel with betamethasone dipropionate 0.05 % lotion showed the response rate for ketoconazole was higher than for betamethasone, according to the global evaluation by the physician and the patient.

In a double-blind study of 96 adults with seborrheic dermatitis, pimecrolimus 1 % cream showed only slightly greater improvement when compared to placebo, and this improvement was significant only in the per protocol analysis and not significant in the intent-to-treat analysis. A randomized study of pimecrolimus 1 % cream versus betamethasone valerate 0.1 % cream showed significant improvement; betamethasone was slightly quicker in action, but patients in that group had more relapses and more pruritus upon treatment discontinuation. A study of 18 consecutive adult patients using tacrolimus 0.1 % ointment showed either clearance or 75–99 % improvement in all treated. Tacrolimus 0.1 % ointment also compared favorably to hydrocortisone 1 % ointment, with statistically significant improvement in both groups. A large, randomized double-blind study comparing ciclopirox shampoo to vehicle showed rates of "effective treatment"(global score of 0 or 1) with ciclopirox 1 % shampoo twice and once weekly were 57.9 % and 45.4 %, respectively, compared with 31.6 % for vehicle. As a prophylactic treatment, relapses occurred in 14.7 % of patients shampooing once weekly, in 22.1 % of

Table 3.21 First line therapies [92–100]

Corticosteroids-low potency	A
Topical ketoconazole foam/shampoo/cream	A
Topical calcineurin inhibitors	A
Zinc pyrithione shampoo	B
Selenium sulfide shampoo	A

Table 3.22 Second line therapies [101–106]

Topical calcineurin inhibitors	A*
Ciclopirox shampoo/cream	A*

Table 3.23 Third line therapies [107–117]

5 % Tee tree oil shampoo	B
Metronidazole gel	B
Lithium succinate/gluconate	A*
Bifonazole shampoo/cream	B*
Oral terbinafine	B*
Oral itraconazole	B*
Moisturizer containing 0.025 % licochalcone	A

those shampooing once every 2 weeks, and in 35.5 % of the vehicle group. In another large, randomized double-blind study, this time comparing ciclopirox 1 % cream to vehicle, responders at 1 and 2 months were 44 % and 63 % in the treatment group versus 15 % and 34 % in the vehicle group.

A randomized study of adolescents and adults reported greater improvement in the severity of seborrheic dermatitis with 5 % tea tree oil shampoo (41 %) versus placebo (11 %). Metronidazole 1 % gel showed statistically significant improvement versus placebo in adult patients over an 8-week treatment period, and a randomized, double-blind study comparing metronidazole 0.75 % gel versus ketoconazole 2 % cream in adolescent and adult patients showed improvement with decrease in clinical severity scores from baseline in both groups. Lithium succinate ointment also showed significant improvement compared to placebo in a double-blind trial of 227 adult patients. In adult patients, randomized studies of bifonazole shampoo (three times a week) and bifonazole 1 % cream (once daily) versus placebo showed significantly greater improvement in patients in the treatment groups. Both oral terbinafine and itraconazole have also shown efficacy in smaller studies, with oral terbinafine leading to statistically significant improvement in erythema, scaling and pruritus at 4 and 12 weeks.

Two studies have been performed in infants and young children. A study of bifonazole 1 % shampoo for scalp seborrhea in 34 infants and younger children also showed improvement or cure without any serious side effects noted. A randomized, prospective, split-side, double-blind study of 75 infants found that moisturizer containing 0.025 % licochalcone had a higher cure rate compared to 1 % hydrocortisone for the treatment of infantile SD at days 3–4; however, by the end of the first week, this difference was no longer significant, and both treatments led to significant improvement.

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Psoriasis and Other Papulosquamous Skin Disorders

4

Colleen H. Cotton and Wynnis L. Tom

Psoriasis

Clinical Features

Psoriasis is a chronic, immune-mediated inflammatory disease that primarily affects the skin, though broader systemic inflammation is noted. It affects 0.5–2 % of children and adolescents with no confirmed gender bias [1]. There is a known genetic component, as a first-degree family member with psoriasis increases risk of disease significantly, and at least 25 susceptibility loci have been identified [2]. The HLA-Cw6 genotype is associated with early-onset disease. Environmental factors play a role as well, as pharyngeal or perianal streptococcal infections can trigger lesion development. Up to 40 % of children will have nail involvement, including pitting, subungual hyperkeratosis, onycholysis, and oil spots [2]. Geographic tongue may also be seen. Psoriatic arthritis can occur in children, predominantly as an oligoarticular process involving smaller joints, although any joint may be involved. Co-morbid conditions include higher rates of anxiety, depression, rheumatoid arthritis, Crohn's disease, hyperlipidemia, metabolic syndrome, and fatty liver (even when controlling for obesity).

The diagnosis of psoriasis is generally made clinically, with the majority of children having mild disease. Plaque psoriasis is most common, consisting of erythematous, well-demarcated, scaly papules and plaques (Fig. 4.1). Removal of the sometimes micaceous, silvery scale results in pinpoint bleeding (Auspitz sign). Lesions may develop at sites of trauma (Koebner phenomenon, see Fig. 4.1). Classic sites of involvement are the extensor surfaces, nails, umbilicus, and scalp, with pinking of the gluteal cleft. Children also tend to have more involvement of the face and flexural areas (also known as inverse psoriasis), with thinner, more pruritic plaques (flexural sites have maceration and little scale). The scalp is often the first site of involvement and can be especially pruritic. A variant known as pityriasis/tinea amiantacea results in very thick, adherent scale and may cause non-scarring alopecia. Guttate psoriasis is the second most common type of psoriasis, sometimes arising after a streptococcal infection, and consisting of drop-like scaly papules with abrupt onset (Fig. 4.2). This type might improve following antibiotic treatment, but may recur. Most patients with persistent disease will go on to develop plaque psoriasis. Pustular psoriasis is rare in children, consisting of sterile pustules on an erythematous base. Erythrodermic psoriasis is also rare in children, seen less often than pustular psoriasis, though not unreported. One particular type of psoriasis unique to infants is diaper or napkin psoriasis (Fig. 4.3). It often presents as a recalcitrant diaper rash, involving the inguinal folds and extending outside the diaper area with more typical psoriatic lesions. Finally, palmoplantar psoriasis may exist in isolation, with thick scaling on palms and soles. This may be difficult to differentiate from eczema, contact dermatitis, and some palmoplantar keratodermas.

Management Strategies

Topical medications are the mainstay of treatment, with phototherapy and systemic agents utilized for more recalcitrant, diffuse disease. There is a significant risk of rebound of psoriasis with systemic corticosteroids and these should generally be avoided, particularly with pustular and erythrodermic types. Anthralin, coal tar, and keratolytics are best used for thicker plaques, in conjunction with topical corticosteroids. Salicylic acid is indicated only for children older than age 6 years. Topical treatments are recommended in conjunction with second- and third-line therapies, including narrowband-ultraviolet

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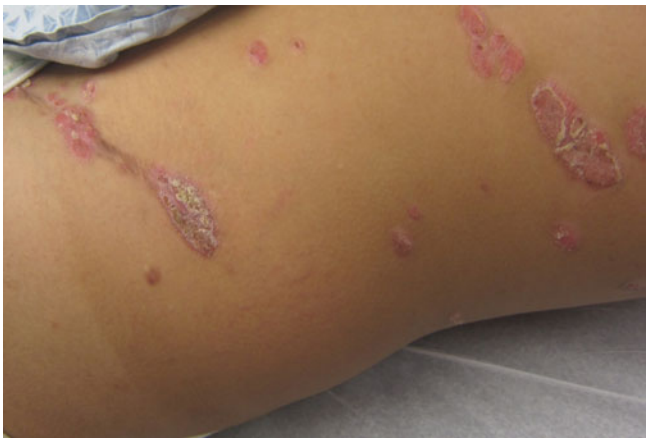

Fig. 4.1 Plaque psoriasis on the torso. Note the Koebnerization along the patient's surgical scar

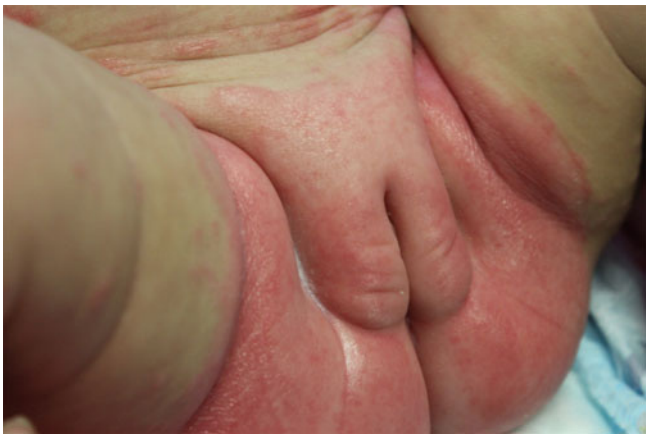

Fig. 4.3 Diaper psoriasis. Note the psoriatic lesions outside the diaper area (Courtesy of Magdalene Dohil)

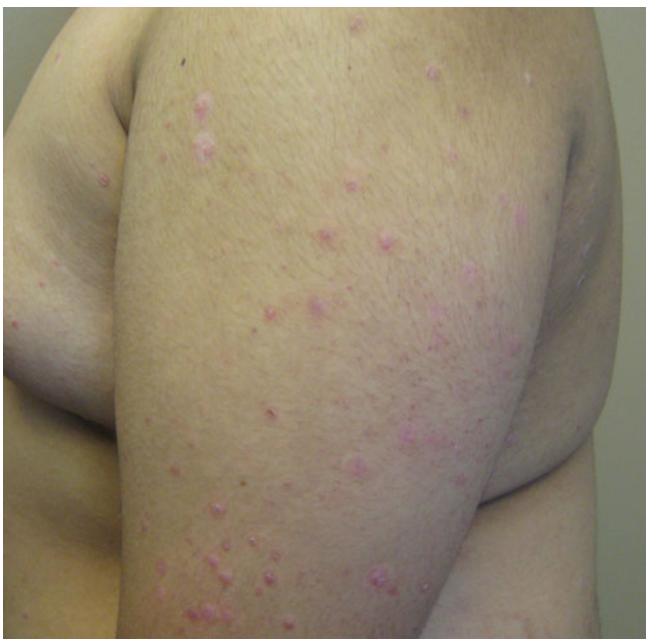

Fig. 4.2 Guttate psoriasis

B (nbUVB) and other forms of phototherapy, methotrexate, and other systemic medications. No treatment is without side effects, and the severity of disease and co-morbidities should be weighed against the risks with each form of treatment.

Investigations Recommended

For diagnosis
Most often a clinical diagnosis, but may consider biopsy if unable to distinguish from other papulosquamous disorders, especially pityriasis rubra pilaris
Streptococcal cultures and anti-streptolysin O (ASO) titer for guttate psoriasis
Complete blood count (CBC), complete metabolic panel (CMP) for severe generalized pustular disease
For treatment
For co-morbidities: consider measuring body mass index, blood pressure periodically. If overweight or obese, consider fasting glucose, fasting lipids, and alanine transaminase (ALT)
Methotrexate: pregnancy test (for women of child-bearing potential), CBC, CMP, tuberculosis testing at baseline, monitor CBC and hepatic panel during treatment with periodic repeat tuberculosis testing
Retinoids: pregnancy test (for women of child-bearing potential), CBC, AST, ALT, fasting lipids at baseline and during treatment
Cyclosporine: CBC, CMP, magnesium (Mg), uric acid, blood pressure at baseline and during treatment, tuberculosis testing at baseline with periodic repeat testing
TNF inhibitors: CBC, CMP, tuberculosis testing, consider hepatitis profile and HIV testing in at-risk groups before initiation, periodic re-assessment during therapy

Biopsy may be useful to differentiate psoriasis from other papulosquamous disorders. Histologically, psoriasis shows parakeratosis and orthokeratosis, epidermal hyperplasia with uniform elongation of the rete ridges, loss of the granular cell layer, and formation of spongiform pustules and parakeratotic microabscesses. The capillary vessels within the superficial dermis are slightly dilated and may have associated neutrophils and lymphocytes. If a positive streptococcal culture is obtained, antibiotics should be initiated to adequately treat streptococcus infection, although the benefits for psoriasis lesions are inconsistent. In overweight or obese patients, clinicians should consider screening for known co-morbidities such as fatty liver disease, diabetes, and hyperlipidemia, but no consensus regarding screening exists at present.

The potency of the topical corticosteroid chosen should be based upon disease severity and location. High-potency steroids are helpful for more severe disease on the palms and soles, with low-potency steroids and caution regarding quantity appropriate for less severe disease on the face or flexures.

Table 4.1 First line therapies

Low-, mid-, or high-potency topical corticosteroids BID	B
Calcipotriene (Dovonex) ointment BID	A
Calcitriol (Vectical) ointment BID	B
Tacrolimus (Protopic) 0.03 %/0.1 %[a] ointment BID	C
Pimecrolimus (Elidel) 1 % cream daily	E
Calcipotriene plus betamethasone propionate daily	B

[a]Strength used in the published literature

Table. 4.2 Second line therapies

Goeckerman regimen (daily application of crude coal tar ointment with UVB phototherapy)	D
Dithralin cream (0.01–4 %) cream via short contact, gradually increasing dosage	B
Tazarotene (Tazorac) 0.05 %/0.1 % cream or gel[a] daily	E
nbUVB for an average of 3 months	C
Methotrexate (typical dose 0.2–0.4 mg/kg/week; reported doses from 0.14 to 0.7 mg/kg/week)	D

[a]Formulation used in the published literature

Table 4.3 Third line therapies

Psoralen plus UVA (PUVA)	D
Excimer laser	D
Oral retinoids	
Acitretin (Soriatane) 0.5–1 mg/kg/day	D
Isotretinoin (Accutane) 0.75 mg/kg/day	E
Etretinate (where available) 0.5–1.25 mg/kg/day	D
Cyclosporine 1.5–5 mg/kg/day	D
TNF inhibitors	
Etanercept (Enbrel) 0.8 mg/kg/week, max 50 mg	A
Infliximab (Remicade) 3.3–5 mg/kg at weeks 0, 2, 6, then every 8 weeks	E
Adalimumab (Humira) 24 mg/m^2, max 40 mg, every 2 weeks	E
Ustekinumab (Stelara) 45 mg at weeks 0 and 4, then every 12 weeks	A
Colchicine (Colcrys) 0.25 mg TID or 0.5 mg BID	E
Fumaric acids (Fumaderm, Europe only)	E
Dapsone 1 mg/kg/day	E

Vitamin D analogs and topical calcineurin inhibitors are common adjunct therapies, and may even be monotherapy at sites at risk for corticosteroid side effects, such as the face or flexural areas. Combination calcipotriene and betamethasone propionate (Taclonex) was proven safe and effective in an open-label phase II trial, and is the first medication approved by the Food and Drug Administration (FDA) specifically for the treatment of pediatric psoriasis [3].

Goeckerman treatment is time intensive and is not as commonly used today, limited by odor, risk of folliculitis, staining of skin/clothing, and possible mutagenicity. Anthralin creams can be used as monotherapy or with keratolytics via short contact therapy, though skin irritation is frequently reported. Topical retinoids have been shown to be effective in adults, but there is limited evidence in children [4]. Several retrospective studies have shown nbUVB to be effective in children with widespread or recalcitrant disease, especially when used together with topical medications. It is the preferred type of phototherapy due to lower risk of burning and malignancy, although broadband UVB and UVA are other options [1]. Methotrexate is the most commonly used systemic medication for psoriasis worldwide due to cost and availability [4]. Despite a lack of prospective trials in children, several case studies show significant benefit [5].

PUVA can be effective in children who have failed other forms of phototherapy, but it should be used with caution given a higher risk of burning and malignancy. Excimer laser may be even more effective for localized thick lesions in children than in adults [6]. Acitretin can augment therapy with topical or nbUVB treatments. Oral retinoids are particularly beneficial in pustular and erythrodermic psoriasis [7, 8]. Cyclosporine may be beneficial, but due to nephrotoxicity risks, should not be used for more than 1–2 years. It additionally should not be used with nbUVB due to elevated risk of malignancy. TNF inhibitors are effective for moderate to severe disease not responding to topicals or phototherapy, but may have the potential for severe infections. Results from randomized controlled trials in adolescents have shown positive effects compared to placebo for both etanercept and ustekinumab [9, 10]. There are also isolated case reports of successful treatment with colchicine, fumaric acid, and dapsone.

Reactive Arthritis

Clinical Features

Reactive arthritis (ReA, formerly known as Reiter's syndrome) is a seronegative spondyloarthropathy characterized by the classic triad of urethritis, conjunctivitis, and arthritis. Although more commonly seen in adult males, many cases have been reported in children. ReA usually arises several weeks after a sexually transmitted infection (endemic) or diarrheal illness (epidemic). Epidemic cases are far more common in the pediatric population. HLA antigen haplotype-B27 (HLA-B27)-positive individuals make up 60–80 % of patients, and they have more frequent skin findings. Involvement of the heart, kidneys, and CNS is rare in ReA. Chronic disease occurs less often in children.

Diagnosis is based on the clinical picture, which may be difficult as only one-third of patients present with the classic triad. Symptoms may be separated by years, although fever and vague constitutional symptoms may provide clues to the diagnosis. Several specific mucocutaneous manifestations, when present, may be diagnostically helpful. Keratoderma blenorrhagicum is the most "classic" (albeit rare) cutaneous

finding, appearing as psoriasiform and hyperkeratotic papules, pustules, and plaques most commonly on the palms and soles. Circinate balanitis/vulvitis is more common and is rarely seen outside of ReA, with well-demarcated erosions (females and circumcised males) or hyperkeratotic plaques (circumcised males) on the genitalia. Ocular and urogenital symptoms are common, while painless oral and psoriatic nail changes may occur.

Management Strategies

Most studies of ReA have focused on treating the arthritis, not mucocutaneous findings. Management is multidisciplinary, centered on treating the triggering infection and managing symptoms. No consensus exists regarding the benefit of antibiotics, but positive serologies should be treated. For patients in whom a urogenital infection is found, sexual partners also require treatment. NSAIDs are the mainstay of initial arthritis treatment, with immune-modifying therapies used for recalcitrant disease. Further discussion regarding treatment of arthritis and other non-cutaneous symptoms is beyond the scope of this chapter. Treatment of mucocutaneous lesions can largely be achieved with topical therapy, although systemic treatments may be helpful in recalcitrant or severe disease.

Investigations Recommended

For diagnosis
Consider biopsy
Blood, urine, and stool cultures
Synovial fluid culture, white blood cell count
Serologic tests: CBC, ESR, CRP, rheumatoid factor, ANA
Urinalysis
Ophthalmologic exam
Consider HIV RNA PCR
Consider tuberculin skin prick test or Quantiferon gold
For treatment
HLA-B27 testing
Sulfasalazine: CMP, CBC at baseline and during treatment
Methotrexate: pregnancy test (for women of child-bearing potential), CBC, CMP, tuberculosis testing at baseline, monitor CBC and hepatic panel during treatment with periodic repeat tuberculosis testing
Cyclosporine: CBC, CMP, Mg, uric acid, blood pressure at baseline and during treatment, tuberculosis testing at baseline with periodic repeat testing

Septic arthritis is always in the differential for mono- or oligoarthritis, and should be ruled out with joint aspiration and blood cultures. Serologies for common ReA pathogens, such as *Chlamydia trachomatis. Neisseria gonorrhea, Mycoplasma genitalium, Yersinia, Salmonella, Shigella,* and *Campylobacter jejuni,* should be assessed. HIV testing is warranted when disease onset is severe and sudden. ESR and CRP may be elevated, while rheumatoid factor and ANA must be negative. HLA-B27 typing assists in prognosis, as positive patients have a greater risk of chronic disease. If risk factors for tuberculosis (TB) are present, diagnostic testing should be performed, as there are a few case reports of TB-associated ReA.

Table 4.4 First line therapies

Low-, mid-, or high-potency topical corticosteroids plus salicylic acid	D
Topical salicylic acid and hydrocortisone plus aspirin	E
Tacrolimus (Protopic) 0.03 %/0.1 %[a] ointment	E[b]
Tazarotene (Tazorac) 0.05 %/0.1 %[a] cream or ointment[a] daily	E[b]
Calcipotriene (Dovonex) cream daily	E[b]

[a]Strength and formulation used in the published literature
[b]Based on adult data (used due to lack of pediatric data)

Table 4.5 Second line therapies

Sulfasalazine (Azulfidine) 500 mg daily, increased to 2,000 mg daily	A[a]
Methotrexate between 10 and 50 mg/week	E
Dapsone 50 mg daily plus tacrolimus (Protopic) 0.1 % ointment	E[a]

[a]Based on adult data

Table 4.6 Third line therapies

Oral retinoids	
Acitretin (Soriatane) 0.3–0.75 mg/kd/day	E[a]
Etretinate (where available) 0.5–1 mg/kg/day	E[a]
Cyclosporine 0.5 mg/kg/day slowly tapered	E[a]
TNF inhibitors	
Infliximab (Remicade)	E[a]
Etanercept (Enbrel)	E (C[a])
Adalimumab (Humira)	E[a]

[a]Based on adult data

There has been success with topical steroids ranging from class VII to class I. Salicylic acid aids in the penetration of corticosteroids. One combination of topical salicylic acid and hydrocortisone plus oral aspirin (concentrations/dosages not given) resulted in complete remission in a 6-year-old girl, with clearing of skin lesions within 3 weeks [11]. Topical tacrolimus, calcipotriene, and tazarotene have been effective in treating skin disease for several adults already on systemic therapy [12, 13]

Sulfasalazine can induce remission if started within 3 months of onset [14]. Methotrexate is particularly effective for persistent skin symptoms [15]. One adult patient with circinate balanitis recalcitrant to class I topical corticosteroids responded within weeks to dapsone plus tacrolimus ointment, but was unable to wean off either therapy [16].

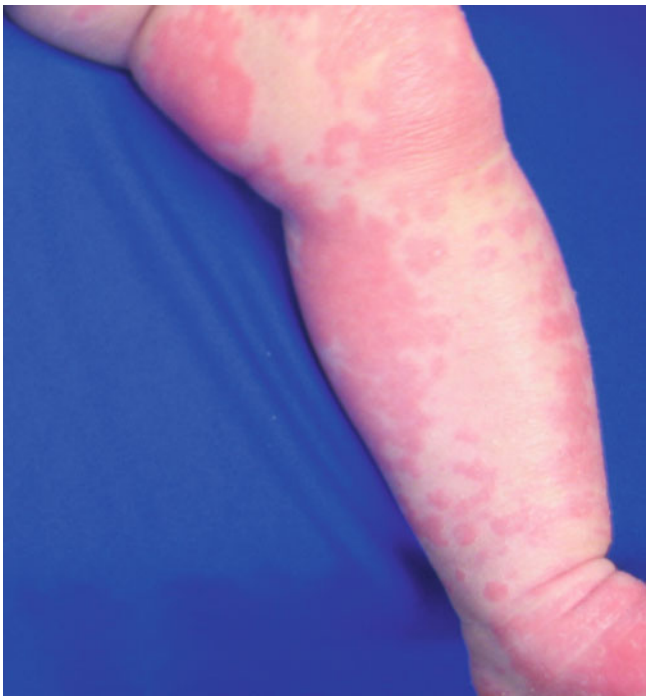

Fig. 4.4 "Islands of sparing" seen in classic (type III) pityriasis rubra pilaris

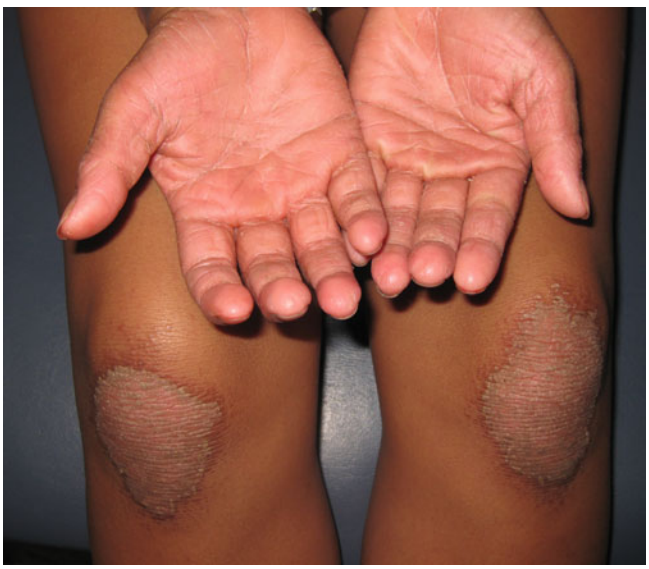

Fig. 4.5 Type IV, or circumscribed, pityriasis rubra pilaris (Courtesy of Dr. Sheila Fallon Friedlander)

Acitretin and etretinate are especially effective and safe in HIV-positive patients based on adult studies [15]. Cyclosporine treatment was successful in one patient who failed etretinate [17]. Anti-TNF therapies have also shown benefit, particularly when used in combination with other systemic treatments like methotrexate [18].

Pityriasis Rubra Pilaris

Clinical Features

Pityriasis rubra pilaris (PRP) is a papulosquamous disorder characterized by well-demarcated orange-red plaques, follicular keratosis, and palmoplantar involvement, often with "islands of sparing" within lesions (Fig. 4.4). Other findings include furfuraceous scaling of the scalp, yellow-brown discoloration and thickening of the nails, subungual hyperkeratosis, and splinter hemorrhages [19]. Ectropion and erythroderma can be serious complications. Unlike the adult form, pediatric PRP may show a predilection for males over females (3:2). Acute illness or trauma may precipitate the disease. PRP is a clinical diagnosis that may be supported by histopathology that shows acantholysis, an acanthotic epidermis with alternating orthokeratosis and parakeratosis in both vertical and horizontal directions, and follicular plugging.

Griffiths' classification is most commonly used to describe the different forms of PRP. Types I and II encompass adult disease. A description of the different types affecting children can be found in Table 4.7. Type III is the most common type in children, and is identical to type I in adults. Types IV (Fig. 4.5) and V are less common forms of the disease, and do not always fit the classic description of PRP. Type VI was not part of Griffiths' original classification, but has been proposed to encompass cases associated with HIV infection.

Management Strategies

No randomized, controlled trials exist in either the pediatric or adult literature evaluating treatment options for PRP and thus, recommendations are based on retrospective reviews

Table 4.7 Types of pityriasis rubra pilaris found in children

Type	Description	Characteristics
III	Classic juvenile type	Keratotic papules progress in a cephalocaudal pattern and may coalesce into plaques
IV	Circumscribed juvenile type	Keratotic papules and plaques confined to the elbows and knees (Fig. 4.4)
V	Atypical (familial) juvenile type	Ichthyosiform characteristics and more prominent erythema
VI	HIV-associated type	Often characterized by filiform keratosis with comorbid acne conglobata

and case reports. Initial treatment includes topical corticosteroids, keratolytics, and retinoids. If control cannot be achieved with topical therapies, oral retinoids are the preferred treatment. Immunomodulating drugs are an option if retinoids fail or have intolerable side effects. Timing of phototherapy initiation is unclear due to mixed results. Pruritus can be lessened with oral antihistamines or, in refractory cases, topical capsaicin has been used. Spontaneous resolution is possible, even likely, in type III patients within 1–3 years. For HIV-associated disease, highly active retroviral medications are required [20].

Investigations Recommended

For diagnosis
Usually a clinical diagnosis, but may biopsy to confirm or distinguish from psoriasis and other disorders (may need more than one sample to note definitive characteristics)
HIV testing
For treatment
Retinoids: pregnancy test (for women of child-bearing potential), CBC, AST, ALT, fasting lipids at baseline and during treatment
TNF inhibitors: CBC, CMP, tuberculosis testing, consider hepatitis profile and HIV testing in at-risk groups before initiation, periodic re-assessment during therapy
Methotrexate: pregnancy test (for women of child-bearing potential), CBC, CMP, tuberculosis testing at baseline, monitor CBC and hepatic panel during treatment with periodic repeat tuberculosis testing
Cyclosporine: CBC, CMP, Mg, uric acid, blood pressure at baseline and during treatment, tuberculosis testing at baseline with periodic repeat testing

Table 4.8 First line therapies

Low-, mid-, or high-potency topical corticosteroids	D
Tretinoin (Retin-A) 0.01 %/0.025 %/0.04 %/0.05 %[a]/0.1 % cream[a] or gel daily	E
Tazarotene (Tazorac) 0.05 %/0.1 %[a] cream or gel[a] daily	E
Pimecrolimus (Elidel) 1 % cream BID	E[b]

[a]Strength and formulation reported in literature
[b]Based on adult data

Table 4.9 Second line therapies

Oral retinoids	
Isotretinoin (Accutane) 1–2 mg/kg/day for 6 months (average)	D
Etretinate (where available) 0.5–1 mg/kg/day for 3–6 months	E
Acitretin (Soriatane) 0.3–0.75 mg/kg/day	E
Alitretinoin 30 mg daily for 22 weeks	D[a]
Vitamin A, at least 20,000 units daily	E
Calcipotriene (Dovonex) ointment	E
nbUVB with oral retinoids	E
PUVA	E
Goeckerman treatment	E

[a]Based on adult data

Table 4.10 Third line therapies

TNF inhibitors	
Etanercept (Enbrel) 50 mg twice weekly with slow taper	E
Infliximab (Remicade) 5 mg/kg/dose at weeks 0, 2, 6, and every 8 weeks after	E
Methotrexate	E
Cyclosporine 3 mg/kg/day with slow taper	E
Fumaric acids (Fumaderm, Europe only), start at 30 mg daily, maximum of 720 mg daily	E

As PRP can be associated with HIV, all patients with risk factors or other symptoms should undergo HIV testing. Classic histology showed alternating ortho- and parakeratosis, hypergranulosis, and a predominantly lymphocytic sparse superficial perivascular infiltrate. Laboratory evaluation is only required for systemic therapies and varies by drug (oral retinoids and TNF inhibitors shown here).

Initial treatment for PRP should focus on topical therapies. Several case reports have shown complete response to topical corticosteroids, ranging from low to high potency [21]. Single case reports of different topical retinoids have also shown efficacy [22, 23]. One adult case report demonstrated clearance with pimecrolimus cream [24].

Systemic therapies should be considered after failure of topical treatment or for more severe or diffuse disease, with topical therapies often continued as adjuncts. Retinoids are the mainstay of systemic treatment, with isotretinoin being the most commonly used in children [25]. Treatment with vitamin A or topical calcipotriene has shown benefit in single case reports [26, 27], but other reports contradict these findings. Phototherapy may be beneficial but may also aggravate PRP [28]. It should be reserved for cases refractory to retinoids and topical therapy. Goeckerman treatment, while effective in a few case reports, is not as commonly used.

Immunomodulating drugs show great promise for recalcitrant disease. There are a few case reports and one retrospective review of children receiving TNF inhibitors without significant side effects [29]. Numerous reports show no benefit with methotrexate, although one case report at an unspecified "low dose" was successful. Cyclosporine was effective in a single pediatric patient [30]. Fumaric acid treatment is currently only available in Europe [28].

Pityriasis Lichenoides

Clinical Features

Pityriasis lichenoides (PL) is an uncommon, acquired dermatosis encompassing a spectrum of disease states, with pityriasis lichenoids et varioliformis acuta (PLEVA) at one

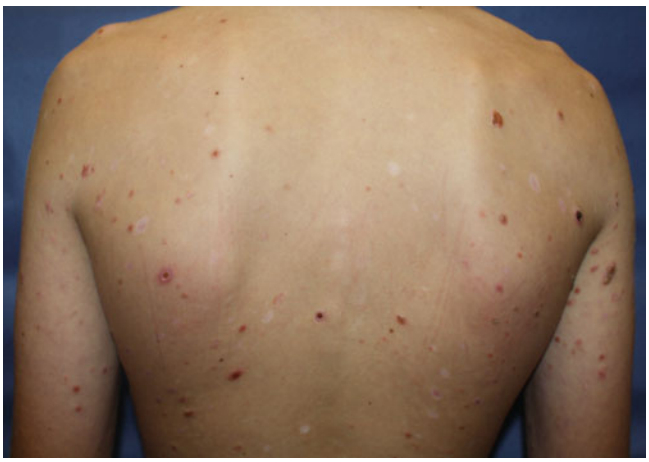

Fig. 4.6 Characteristic lesions of PLEVA with some varioliform scarring (Courtesy of Dr. Lawrence Eichenfield)

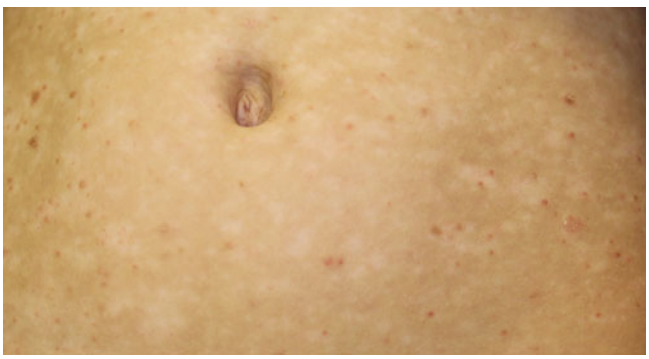

Fig. 4.7 Pityriasis lichenoides chronica

end and pityriasis lichenoides chronica (PLC) at the other. PL has a slight male predominance. Acute versus chronic describes the development of lesions, and not necessarily the disease course [31]. Overlap between PLC and PLEVA is common within the same patient. Etiology is unknown, although numerous viral triggers have been proposed and several viruses cultured from affected patients. Currently, PL is felt to lie at the benign end of a spectrum of clonal T-cell disorders. There are a few reports of PL progressing to cutaneous T-cell lymphoma, although some cases may have initially been misdiagnosed as being more benign. Differentiation of PLEVA from lymphomatoid papulosis is important (see section "Lymphomatoid Papulosis").

Diagnosis can be made clinically, but histology may be helpful for confirmation. Pruritus occurs in half of patients, while skin tenderness is rare. PLEVA begins as an acute, generalized eruption of papules that develop necrosis and form hemorrhagic crusts, with the potential for varioliform scars (Fig. 4.6). Mild constitutional symptoms may exist. A rare and severe subtype, febrile ulceronectrotic Mucha-Habermann disease (FUMHD), shows rapid and coalescent necrosis of skin lesions, severe systemic symptoms, and potential mucous membrane involvement. Fatalities have only been reported in adults. PLC consists of small, scaly, red to brown, polymorphic papules and plaques (Fig. 4.7). The lesions may occur in crops or continuously over time, leaving post-inflammatory dyspigmentation.

Management Strategies

No randomized, controlled trials have evaluated PL treatment options, with recommendations based on retrospective reviews and case reports. PLEVA usually runs a self-limited course, whereas PLC often relapses and remits over years. However, chronic disease and spontaneous remission are seen across the spectrum of disease, making treatment efficacy difficult to assess. Patients younger than 4 years of age may have a higher rate of relapse. Pediatric patients tend to have a longer disease course compared to adults, and residual dyspigmentation is more common [32].

Although mid- to high-potency topical corticosteroids and antihistamines may help pruritus, they do not alter the disease course. Phototherapy and oral antibiotics are the two mainstays for initial treatment. Refractory disease may be treated with methotrexate or the addition of acitretin. Slow tapering to prevent relapse is critical for all treatment plans.

Investigations Recommended

For diagnosis
Consider biopsy
FUMHD: blood cultures, imaging to rule out other etiologies, CBC, CRP, ESR, CMP, LDH
For treatment
Consider streptococcal swab and serologies for *Toxoplasma gondii*, EBV, HIV, CMV, VZV
Methotrexate: pregnancy test (for women of child-bearing potential), CBC, CMP, tuberculosis testing at baseline, monitor CBC and hepatic panel during treatment with periodic repeat tuberculosis testing

No consensus exists regarding the use of laboratory testing for diagnosis or follow-up of PL. The exception is FUMHD, as these patients are critically ill with multi-organ damage and secondary infections requiring close management. In other types, an infectious workup is obtained only if warranted by the history. If workup is positive, treatment should be directed accordingly.

Phototherapy, usually nbUVB, is first-line treatment for PL [33, 34]. Number of treatments and total dose varies

Table 4.11 First line therapies

Phototherapy (narrowband or broadband UVB)	D
Oral antibiotics	
Erythromycin 30–60 mg/kg/day (max 2 g/day) divided in 3–4 doses, at least 3 months	D
Azithromycin (Zithromaz) Z-pack dosing or 500 mg × 3 days, every other week	D
Tetracycline 2 g/day	D
FUMHD: Methotrexate 15–20 mg/week plus high dose IV corticosteroids 40–60 mg/kg/day minimum (dosing in young children not established)	E

Table 4.12 Second line therapies

Methotrexate 5–7.5 mg/week	D
PUVA ± acitretin (Soriatane)	D
Tacrolimus (Protopic) 0.03 % ointment BID, or 0.1 % ointment BID plus azithromycin	E

Table 4.13 Third line therapies

Bromelain	E[a]
FUMHD:	
Cyclophosphamide (Cytoxan), 1,000 mg/m^2 monthly	E
Infliximab (Remicade)	E[a]
Cyclosporine	E[a]
PUVA	E[a]
Prednisone plus nbUVB	E[a]
IVIG	E[a]

[a]Based on adult data

widely, with disagreement regarding maintenance. One retrospective study showed no benefit to concomitant systemic medications [34]. Oral antibiotics are first-line therapies as well, especially when phototherapy is not feasible. Traditionally, oral erythromycin is prescribed, but azithromycin is a newer option [35, 36]. Tetracyclines are reserved for patients older than 8 years of age. First-line treatment for FUMHD should include early initiation of high-dose corticosteroids and methotrexate, along with inpatient monitoring, aggressive wound management and debridement, and supportive care [37].

Methotrexate is second-line treatment for patients with unresponsive, severe disease. According to one study, 20 % of patients responded to PUVA alone, and addition of acitretin may provide additional benefit [38]. Topical tacrolimus, both as monotherapy and with azithromycin, showed promise in a few individual case reports [36].

Bromelain is a supplement that should only be considered in patients who refuse traditional medical therapy [39]. One case report of a child with FUMHD and CNS vasculitis responded to the addition of IV cyclophosphamide [40]. Individual adult case reports of several other treatments for FUMHD show varying success.

Lymphomatoid Papulosis

Clinical Features

Lymphomatoid papulosis (LyP) is a lymphoproliferative disease of CD30-positive T-cells, and is rarely seen in the pediatric population. It exists on a spectrum of clonal T-cell disorders, with malignant histologic characteristics but usually a benign clinical course. It may co-occur with lesions of PL or anaplastic large-cell lymphoma (ALCL). The disease displays three classic histologic subtypes, with two more recently proposed (see Table 4.14) [41]. Type A is the most common, with type B being uncommon and types C-E very rare. These subtypes all appear the same clinically, and have not been shown to affect disease course in pediatric patients. There are conflicting reports of CD4 versus CD8 predominance in children [42, 43]. While LyP lesions themselves are benign, they can be associated with lymphoma and hematologic malignancies. Although the risk is far lower than in adults with the disease, a few cases of lymphoma have been reported in affected children decades after onset, necessitating lifelong follow-up. There is a lower incidence of T-cell clonality in pediatric patients, which may account for the better prognosis.

Classic LyP lesions consist of erythematous papules and nodules, sometimes with central ulceration. Patients suffer from cyclic eruptions that last anywhere from 2 to 8 weeks if untreated, and multiple locations are often involved. They may report a preceding viral illness. The disease can be confused with PLEVA, but LyP lesions are usually fewer and larger, with the average age of onset between 7 and 9 years. Lesions may be pruritic or tender, and often leave behind scars. The tongue may rarely be involved. LyP can be difficult to differentiate from insect bites, especially when eosinophilia is present on histology. Singular lesions can also be mistaken for primary cutaneous ALCL.

Management Strategies

If lesions are limited in number, it is reasonable not to treat while maintaining close follow-up. More numerous lesions or those in cosmetically sensitive areas should be treated due to risk of scarring. In these cases, first line treatments in children include topical corticosteroids and judiciously increasing sun exposure. For more severe, symptomatic, or widespread cases, methotrexate and phototherapy are the best options. Recurrences are common no matter the treatment employed, although rare cases of complete resolution have been reported. Oral corticosteroids are not beneficial.

Table 4.14 Histologic subtypes of lymphomatoid papulosis

Type	Histology	Histologic mimic
A	Large, pleomorphic, atypical CD30-positive (Reed-Sternberg) cells with a wedge-shaped mixed inflammatory infiltrate. Eosinophilia in up to 40 %	Hodgkin's disease
B	Small, CD30-negative lymphocytes with cerebriform nuclei in an epidermotropic infiltrate	Plaque-stage mycosis fungoides
C	Monomorphous, atypical large CD30-positive cells in sheets, with fewer other inflammatory cells making up the infiltrate. No epidermotropism	CD30-positive large cell lymphoma
D	Epidermotropic infiltrate of both atypical CD8-positive and atypical CD30-positive lymphocytes	Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma
E	Angioinvasive CD30-positive infiltrates, often with medium-sized, atypical CD8-positive lymphocytes	Extranodal natural killer/T-cell lymphomas

Investigations Recommended

For diagnosis
Biopsy with immunohistochemistry
Consider T-cell receptor gene rearrangement (TCRGR) studies
CBC with differential, BMP, LDH
Chest x-ray or CT, lymph node ultrasound (if indicated)
For treatment
Methotrexate: pregnancy test (for women of child-bearing potential), CBC, CMP, tuberculosis testing at baseline, monitor CBC and hepatic panel during treatment with periodic repeat tuberculosis testing

Table 4.15 First line therapies

No treatment	D
Surgical excision	D
High potency topical corticosteroids BID × 2–3 weeks, then weekly	E
Sunlight	D
Tacrolimus (Protopic) 0.1 % ointment	E

Table 4.16 Second line therapies

UVB phototherapy	D
PUVA	E
Methotrexate 10–25 mg PO or SC weekly	D

Table 4.17 Third line therapies

Mycophenolate mofetil (CellCept) 1 g BID	E[a]
Topical carmustine 10 mg in alcohol daily	D[a]
Topical mechlorethamine (nitrogen mustard) 10–20 mg daily	B[a]
Topical or oral bexarotene	C[a]
Interferon-alpha (Multiferon) 3–15 million units for 2–6 weeks, then as maintenance	C[a]
Mistletoe by infusion	E
Chemotherapy	Variable

[a]Based on adult data

Biopsy may be helpful in making the diagnosis, although clinicopathologic correlation is imperative given the overlap of findings in clonal T-cell disorders. TCRGR studies may be performed, although their prognostic value in children is unclear. Baseline labs should be done to rule out occult malignancy. If laboratory abnormalities, lymphadenopathy, or hepatomegaly exist, patients should undergo imaging to assess for internal disease.

While lesions regress spontaneously, treatment can cause lesions to resolve faster and minimize scarring. Lesions may be excised, although disease recurrence is common [44]. Initial twice daily treatment with halobetasol or clobetasol propionate followed by weekly pulsed therapy successfully treated initial and recurrent lesions in three children [45]. Betamethasone dipropionate is also effective in pediatric patients. Exposure to sunlight or improvement of disease in the summer months has been noted in many children. One German case series noted improvement with topical tacrolimus in a 10-year-old child [46].

UVB was shown to be safe and effective in several pediatric patients [42]. While PUVA has more evidence in adults, UVB is generally safer in children. Methotrexate is the first-line treatment for severe disease, but recurrence is common after medication cessation [44].

Mycophenolate mofetil produced clearance within 2 months in a woman who failed methotrexate [47]. Nitrogen mustard was used in cases of concomitant LyP and mycosis fungoides in adults [48]. Topical carmustine helped lesions resolve faster in six of seven adults, but did not decrease rates of recurrence [49]. Bexarotene has been used both topically and orally in adults with good results [50]. Short-term benefit was also seen with interferon in a small adult open-label trial, although recurrence necessitated long-term therapy [51]. A possible complete response to mistletoe was seen in a young German girl with skin lesions and lymphadenopathy [52]. Various combinations of chemotherapy have also been used [44].

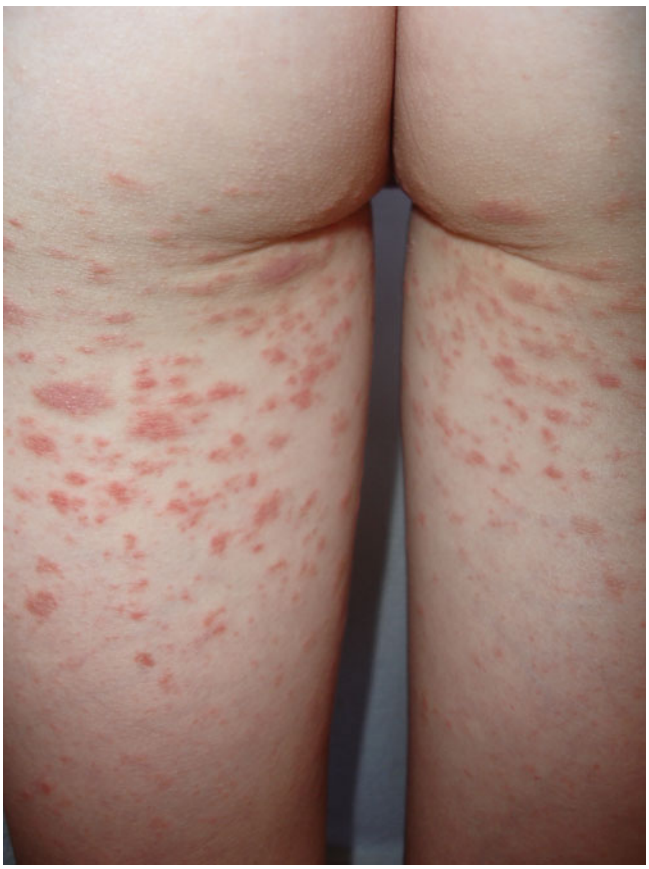

Fig. 4.8 Classic lesions of pityriasis rosea concentrated on the extremities. This patient developed lesions in the "inverse" distribution, most concentrated in the groin (Courtesy of Dr. Sheila Fallon Friedlander)

Pityriasis Rosea

Clinical Features

Pityriasis rosea (PR) is a common, self-limited dermatosis that often occurs in children. While its etiology is unknown, an infectious trigger is hypothesized, with human herpes virus (HHV)-6 and HHV-7 as the leading (though unconfirmed) contenders. This hypothesis is supported by reports of clustered outbreaks and a predilection for occurrence in the spring and fall. Rare cases of recurrence have been reported, with either a similar or less severe course than the initial outbreak [53]. Although a viral prodrome may be reported, PR is a benign disease with no systemic sequelae. The exceptions to this rule are pregnant women with PR, as the disease may herald premature delivery or fetal demise [54].

PR is a clinical diagnosis. Classically, it begins with a solitary, scaly, erythematous patch or plaque called a "herald patch" that is usually several centimeters in length. This lesion can be asymptomatic or pruritic, and may not always be present. After several days to weeks, a generalized eruption of approximately 1 cm, scaly, erythematous to salmon-colored patches develops on the trunk in a "Christmas-tree" pattern and may spread to the extremities. So-called "inverse PR" is a variant involving classic lesions distributed primarily over the extremities, as well as the peri-axillary and inguinal regions (Fig. 4.8). Darker skinned patients may have predominantly papular lesions, as well as an increased frequency of scalp and face involvement [55]. Vesicular PR has also been rarely reported. The disease lasts 6–8 weeks on average. Residual post-inflammatory dyspigmentation is common and more prominent in darker skinned individuals [55].

Management Strategies

Several randomized, double-blind, placebo-controlled trials have been conducted for the treatment of PR, but there is no consensus as to a single, most effective therapy. Current recommendations are to manage symptoms with topical corticosteroids and antihistamines, although these do not alter the disease course. As the disease is usually benign and self-limiting, additional treatment is reserved for persistent or severe cases. Pregnant women with PR may benefit from closer monitoring and referral to high-risk maternal fetal medicine specialists for management and counseling [54].

Conflicting evidence exists for efficacy of oral erythromycin, with one trial showing benefit and others showing it to be no better than placebo [56]. Azithromycin and clarithromycin have also failed to show benefit in randomized trials [57, 58]. Recently, acyclovir has been proposed as an effective treatment agent, possibly targeting HHV-6 [59].

Investigations Recommended

For diagnosis
Biopsy if atypical presentation
RPR and VDRL testing in sexually active patients to rule out syphilis
For treatment
None

Biopsy may be helpful in recurrent or atypical-appearing cases for definitive diagnosis. Histologic findings are generally nonspecific and more pronounced in severe disease, including parakeratosis, spongiosis, and a mild lymphohistiocytic infiltrate. Sexually active teenagers should also undergo rapid plasma reagent (RPR) and venereal disease research laboratory (VDRL) testing to rule out syphilis. No other laboratory testing is recommended for diagnosis or treatment.

Table 4.18 First line therapies

No treatment	A
Low-strength topical corticosteroids and antihistamines	D

Table 4.19 Second line therapies

Acyclovir, 80 mg/kg/day divided into four doses for 7 days (adults 800 mg five times per day for 7 days)	A

Table 4.20 Third line therapies

UVB phototherapy	C[a]
Dapsone, 100 mg BID	E[a]

[a]Based on adult data

Several studies have shown that most cases of PR fully resolve by 3 months without treatment, and often by 3–4 weeks. To avoid scarring and secondary infection from scratching, low-strength topical corticosteroids and antihistamines may be used to control pruritus.

Several small, randomized, double-blinded, placebo-controlled trials have recently shown high-dose acyclovir to be effective in rapid clearing of PR, with 76–87 % of cases showing complete resolution after 2 weeks [59, 60]. The drug has been compared to both placebo and erythromycin with positive results [61].

While one comparison study of UVB phototherapy showed an objective improvement in disease severity, this did not alter the disease course or patients' reported symptoms [62]. However, there have been several reports of improvement of PR with sun exposure. One report in the adult literature showed dapsone to be helpful in treating a case of vesiculobullous PR [63].

Lichen Planus

Clinical Features

Lichen planus (LP) is the classic "lichenoid eruption", named for the appearance of the lichen genus on a rock. It is caused by a cell-mediated immune reaction with an unknown trigger, possibly viral. While LP occurs frequently in older adults, it is rare in children, with conflicting data regarding sex predilection. There may be a genetic predisposition, as the disease is more common in patients from India [64, 65]. Familial cases are rare but may account for a higher proportion of pediatric cases than in adults. The inherited form is more often generalized and potentially erosive, with oral involvement, relapses, and a prolonged course [64].

Classic LP is often described using the 4P's: purple, polygonal, pruritic papules. Fine white linear scales (Wickham's striae) may be seen on violaceous, flat-topped papules and plaques (Fig. 4.9). Lesions may be diffuse, grouped, or localized, and may show Koebnerization. LP is usually bilateral and symmetric, predominantly affecting the legs, flexor wrists, neck, trunk, and genitalia. The lesions are extremely pruritic, with less than 20 % of patients without itch. There are several alternate forms of LP, outlined in Table 4.21 [64, 66]. Intense post-inflammatory hyperpigmentation typically remains after lesions resolve and is difficult to treat. Most children have complete resolution within 1 year with rare recurrence, similar to the course seen in adults. Oral and genital LP is not usually associated with an increased risk of squamous cell carcinoma in children, but these patients should still be followed over time.

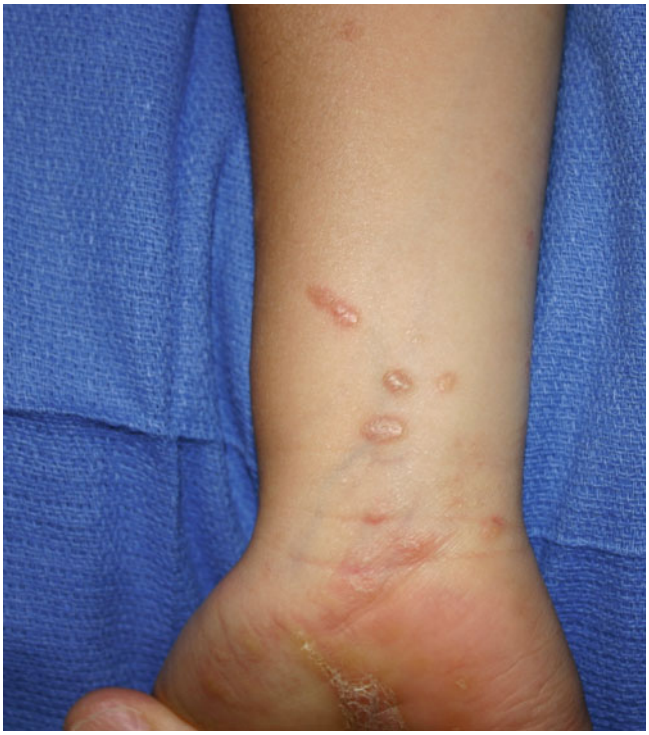

Fig. 4.9 Biopsy-proven lichen planus on the forearm of a young child (Courtesy of Dr. Lawrence Eichenfield)

Management Strategies

Since LP typically self-resolves, evaluation of treatment efficacy is difficult. Topical corticosteroids are first-line treatment, while oral corticosteroids are second-line and should be tapered on improvement. A number of systemic medications as well as phototherapy have been used for more severe or resistant disease. Any potentially aggravating or causative medications should be discontinued if possible (e.g. beta-blockers, penicillamine, NSAIDs, quinidine, methyldopa).

Several trials show conflicting results for griseofulvin [67]. Tetracycline is not effective. A number of potential treatment modalities have shown efficacy in individual adult

Table 4.21 The numerous clinical variants of lichen planus

Type	Description
Actinic	Also known as LP tropicus, LP subtropicus, LP atrophicus annularis, lichenoid melanodermatoses, or summertime actinic lichenoid reaction
	Thready, rolled edge and round borders on hyperpigmented to violaceous lesions
	Minimal to absent pruritus
	Usually affects exposed skin with sparing of nails and scalp, but can rarely involve oral mucosa and sun-protected skin
	More common in Middle Eastern and Indian individuals
	Avoidance of sun is generally curative
Annular	Very itchy, ring-like cluster of violaceous flat-topped papules with a clear or atrophic center, resembling granuloma annulare
	May also be single plaque that enlarges with central clearing
	Most common on penis and scrotum or lower back/abdomen
	Occurs at chronic site of LP plaque
	More prevalent in darker skin types, less common in children
	Single report of bullous annular lesion in a 4 year old
Atrophic	May represent resolving LP or the result of steroid use
	Common on the lower extremities
	Has been reported in children
Follicular (Lichen planopilaris)	Folliculocentric and topped by a horny spine
	Mostly found on the scalp, can result in alopecia
	Biopsy especially helpful in making diagnosis
Hypertrophic	Classic LP lesions that become verrucous and scaly
	Usually found on pretibial surfaces and ankles
	Very common in pediatrics
	Lasts longer than classic LP, leaves behind atrophy, scarring and/or post-inflammatory dyspigmentation
Inverse	Made up of macules and papules on exam
	Found in groin, axillae, and inframammary folds
	May have classic LP elsewhere
Linear	Linear LP in zosteriform, unilateral distribution
	More common in children though rare in adults
	Could be because of greater tendency towards scratches and Koebnerization in children
LP pemphigoides	Occurs 2–8 weeks after classic LP eruption
	Small blisters arising from normal skin
	May be on the extremities but especially on palms and soles
	Particularly rare
Nail	Extremely rare in children
	Can see thinning, ridging, subungual hyperkeratosis, fragility, pterygium, lifting of distal nail plate
	Ultimately may result in loss of the nail
Oral	Fine white reticulate pattern on buccal or lingual mucosa
	Violaceous papules along vermilion border of lip, may erode
	Lesions may be asymptomatic, pruritic, or cause burning
	Frequency much lower in children than adults
	Few case reports of isolated oral involvement in children
Vesiculobullous	Formation of bullae or vesicles within LP lesions from degree of inflammation in the lesions

Table 4.22 List of medications used successfully in the treatment of lichen planus, as outlined in limited adult case reports

Name of therapy
Phenytoin (Dilantin)
Thalidomide
Methotrexate
Trimethoprim-sulfamethoxazole (Bactrim)
Ciclopirox olamine cream
Terbinafine (Lamisil)
Mycophenolate mofetil (CellCept)
Azathioprine (Imuran)
Cyclosporine
Adalimumab (Humira)
Interferon
PUVA
Alitretinoin
Neodymium:yttrium-aluminum-garnet (Nd: YAG) laser plus topical tacrolimus (Protopic)
Cyclophosphamide (Cytoxan)

Note: These medications are not often used in children due to potential risks

case reports, but are not generally used in children due to risk (see Table 4.22) [64, 67]. While the treatment options outlined may help oral and/or nail LP, treatments for such isolated involvement are not reviewed here.

Investigations Recommended

For diagnosis
Consider biopsy to confirm diagnosis, if unclear
Consider hepatitis B and C serologies
For treatment
Dapsone: CBC, LFTs
Retinoids: pregnancy test (for women of child-bearing potential), CBC, AST, ALT, fasting lipids
Sulfasalazine: CMP, CBC at baseline and during treatment

While lichen planus is a clinical diagnosis, biopsy can be helpful given the different variations on the classic disease. Histopathology shows orthohyperkeratosis, apoptosis, hypergranulosis, a dense bandlike infiltrate just beneath the epidermis, and "saw-toothing" of rete ridges. Hepatitis B and C have a known association with LP, and serologic testing should be considered.

Topical corticosteroids are the mainstay of treatment, and may be used in conjunction with other systemic therapies [65, 67, 68]. In children who will tolerate them, intralesional injection of corticosteroids may help thick plaques [65]. Topical tacrolimus cleared lesions recalcitrant to topical corticosteroids in a young boy without side effects [69]. Topical calcipotriene showed more than 50 % improvement in one adult trial [70].

Table 4.23 First line therapies

Mid- to high-potency topical corticosteroids	D
Intralesional corticosteroids	D
Tacrolimus ointment (Protopic) 0.03 % BID × 3 weeks, then daily × 3 months	E
Calcipotriene ointment (Dovonex) BID × 3 months	C[a]

[a]Based on adult data

Table 4.24 Second line therapies

UVB phototherapy	D
Dapsone 1.5 mg/kg daily, at least 3 months	D
Prednisolone 1 mg/kg/day for about 8 weeks (30 mg daily × 10 days)	D (A[a])
Acitretin (Soriatane) 0.5 mg/kg/day × 12 weeks	E (A[a])

[a]Based on adult data

Table 4.25 Third line therapies

Metronidazole (Flagyl) 250 mg TID or 500 mg BID for 3 months	B[a]
Itraconazole (Sporanox) 200 mg BID × 1 week each month for 3 months	C
Enoxaparin sodium (Lovenox) 5 mg/week	B[a]
Hydroxychloroquine (Plaquenil) 200 mg daily × 3 months plus topical corticosteroids	E

[a]Based on adult data

UVB phototherapy is safe and effective for local and generalized disease, although there have been a few reports of exacerbation with phototherapy [68, 71]. Dapsone showed excellent response in a large pediatric cohort with low recurrence rates [65]. Oral prednisolone was used in this same cohort with some success, but recurrence and long tapers were noted for some patients [65]. A 10-day course of prednisolone

decreased disease duration in one placebo-controlled trial, and different steroid regimens have been proposed in the adult literature [71]. Care regarding adverse effects and prophylactic agents (calcium, vitamin D, acid blockers) should be considered with prolonged use of systemic steroids. Acitretin is beneficial for both oral and cutaneous LP [67].

One study demonstrated safety and efficacy of oral metronidazole in adults [72]. An open-label study including children showed benefit with itraconazole [73]. Enoxaparin was shown to improve lesions without significant side effects in adults, but with less improvement than oral prednisone [74]. One young girl with actinic LP responded to photoprotection, topical corticosteroids, and hydroxychloroquine with no recurrence for at least 1 year [75].

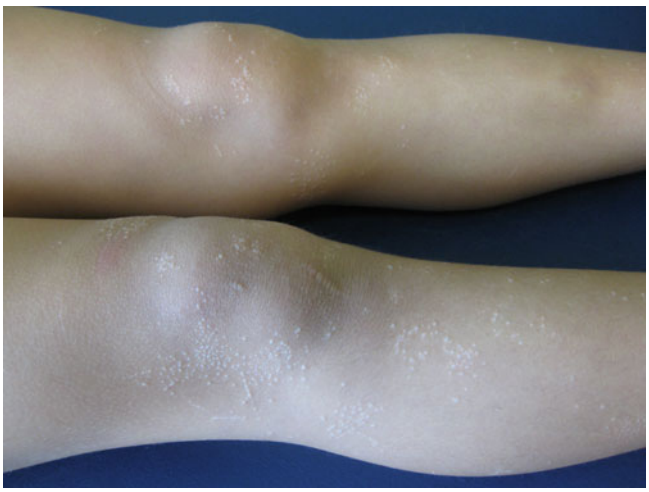

Fig. 4.10 Grouped lesions of lichen nitidus. Note the linear formation of some lesions secondary to Koebnerization (Courtesy of Dr. Sheila Fallon Friedlander)

Lichen Nitidus

Clinical Features

Lichen nitidus (LN) is a skin disorder with no sex predilection that primarily affects children. Typical lesions are localized, but there are a number of different types of the disease, including palmoplantar, perforating, confluent, vesicular, and generalized. The disease is usually asymptomatic, though mild pruritus has been reported. Patients from Africa, the Middle East, and India may develop lesions in a localized, photodistributed pattern known as actinic LN [76]. Generalized LN has been noted to be associated with some systemic diseases, including Down's syndrome, Crohn's disease, and juvenile chronic arthritis [64, 77]. Any type of LN may co-occur with LP or atopic dermatitis [64]. Rare familial cases have been reported.

LN is usually localized to the torso, upper extremities, and glans penis. Lesions are flesh-colored, flat-topped, pinpoint to pin-head sized papules that usually occur in groups (Fig. 4.10). They may have a yellowish or brown to purple hue, depending on underlying skin tone. The papules may be round or polygonal, but are usually monomorphic on any one patient. Scale and hyperkeratosis of lesions are sometimes seen, and the lesions may leave post-inflammatory dyspigmentation. The Koebner phenomenon is almost always observed. Nail involvement with ridging and pits is possible, usually when there is also palmar involvement [64]. Small, grayish flat papules can be found on the buccal mucosa.

Management Strategies

No controlled trials for treatment of LN have been conducted, with treatment recommendations based on expert opinion and case reports. LN usually resolves spontaneously after several years. Topical therapies are reasonable options in patients bothered by mild pruritus or who wish to try to clear the lesions faster. Systemic therapies should be reserved for diffuse or persistent involvement or cases with cosmetically sensitive or extremely pruritic lesions. Moisturizers are also an important adjunct to any treatment regimen.

Investigations Recommended

For diagnosis
Consider biopsy
Consider HIV RNA PCR if an acute, photodistributed eruption, particularly in those with risk factors
For treatment
Isotretinoin: pregnancy test (for women of child-bearing potential), CBC, AST, ALT, fasting lipids
Hydroxychloroquine: assess for glucose-6-phosphate dehydrogenase (G6PD) deficiency at baseline; CBC, CMP, and ophthalmologic exam at baseline and during treatment
Cyclosporine: CBC, CMP, Mg, uric acid, blood pressure at baseline and during treatment, tuberculosis testing at baseline with periodic repeat testing
Enoxaparin: CBC, BMP at baseline and during treatment

Histopathology of LN is lichenoid, but shows very distinctive characteristics that can aid in diagnosis (focal infiltrate close to the epidermis with granulomas, epitheliod and multinucleated giant cells circumscribed by elongated rete ridges, called the "ball-in-claw" sign). If LN presents as an

Table 4.26 First line therapies

No treatment	D
Mid- to high-potency corticosteroids plus moisturizers	D

Table 4.27 Second line therapies

Tretinoin (Retin-A) 0.1 % cream plus pimecrolimus (Elidel) 1 % cream daily	E
Pimecrolimus (Elidel) 1 % cream BID	E[a]
nbUVB	E

[a]Based on adult data

Table 4.28 Third line therapies

Isotretinoin (Accutane) 0.75–1 mg/kg/day × 4 months	E
Dinitrochlorobenzene (DNCB)	E[a]
Hydroxychloroquine (Plaquenil) 200 mg BID × 4 weeks, then 200 mg daily × 6 months plus clobetasol propionate 0.05 % daily	E[a]
PUVA	E[a]
Cyclosporine 4 mg/kg daily with gradual taper after 4 months	E[a]
Enoxaparin sodium (Lovenox) 3 mg SQ once weekly for 3 months	E[a]

[a]Based on adult data

acute, photodistributed eruption, HIV testing should be considered. Several third-line treatments require regular laboratory monitoring.

As lichen nitidus is a self-limited disorder and generally asymptomatic, treatment is not usually necessary [64]. Mid- to high-potency corticosteroids may possibly hasten resolution of lesions and help to control pruritus, if present [64].

Actinic LN has been treated successfully in several pediatric patients with a combination of tretinoin and pimecrolimus creams [76]. Pimecrolimus cream alone resulted in resolution of localized penile LN in a young adult [78]. A few pediatric case reports have shown response to nbUVB treatment [79].

Isotretinoin resulted in complete clearance of generalized LN in a teenager [80]. When coupled with photoprotection, hydroxychloroquine plus corticosteroids was beneficial in one adult case of actinic LN, although we do not recommend the use of clobetasol on the face as in this report [81]. PUVA has also been used in the adult literature. Topical DNCB induced resolution of localized LN at sites of application, but has not been used in children for this condition [82]. A case of purpuric LN resistant to oral retinoids and corticosteroids responded well to 4 months of cyclosporine [83]. One adult case report showed success with enoxaparin injections, resulting in complete resolution of generalized LN after 3 months and clearance for over 2 years [84].

Keratosis Lichenoides Chronica

Clinical Features

Keratosis lichenoides chronic (KLC) is an extremely rare skin disease, with fewer than 20 pediatric cases reported in the literature. The general consensus is that pediatric KLC may be a different disease than adult KLC, although adult-type KLC has been reported in teenagers [85]. A few familial cases have been described with childhood disease [85]. The course of KLC is chronic and progressive. It is rarely, if ever, associated with other systemic symptoms in children. The diagnosis may be made based on a patient's clinical presentation.

Lesions are usually asymptomatic, but can be pruritic. Classic KLC in adults presents with a linear, symmetric eruption of erythematous, hyperkeratotic, lichenoid papules on the extremities and buttocks that progress to become more reticulated and confluent. Seborrhea- or rosacea-like facial lesions are later findings. Conjunctival injection and other ocular abnormalities, oral lesions, palmoplantar keratoderma, and nail changes are commonly seen [86]. In contrast, pediatric KLC is often present from birth or early infancy. It initially presents with purpuric, erythematous macules and patches that become hyperpigmented. Body lesions later develop on the extensor aspects of the extremities and may be classically lichenoid in a parallel linear arrangement, individual keratotic papules, or coalescent keratotic papules forming retiform plaques [85]. Partial alopecia of the forehead, eyebrows, and eyelashes has also been noted.

Management Strategies

KLC is extremely difficult to treat. Only individual case reports of KLC exist in the literature, and recommendations are based off the reported successes and failures. No benefit has been shown with a number of attempted treatments, including topical or systemic corticosteroids, salicylic acid, anthralin, antimalarial drugs, gold, methotrexate, dapsone, erythromycin, radiotherapy and cyclosporine [86]. The most successful treatments appear to be oral retinoids, photochemotherapy, and topical vitamin D3 analogs, either alone or in combination. Improvement has also been noted with sun exposure in several cases. Spontaneous clearing has also

been reported. Patients may report itching, for which topical corticosteroids and antihistamines may be helpful.

Investigations Recommended

For diagnosis
Biopsy
For treatment
Retinoids: pregnancy test (for women of child-bearing potential), CBC, AST, ALT, fasting lipids

Biopsy of KLC lesions can help to make the diagnosis, showing specifically lichenoid changes. If oral retinoids are to be pursued, appropriate screening and monitoring labs should be performed, with care taken to counsel women of child-bearing potential against becoming pregnant (duration post-therapy varies by agent).

Since KLC is a benign disease, treatment is not strictly necessary if lesions are asymptomatic and not disfiguring. At least one case report showed spontaneous remission of disease after 13 years [87]. Safe exposure to sunlight should be encouraged in KLC patients, as there are multiple reports of improvement or clearing in the summer months with increased sun exposure [85, 87, 88]. Calcipotriene ointment has shown some efficacy in the adult literature, both as monotherapy and in combination with PUVA and oral retinoids [86, 89]. At least one pediatric case report showed no benefit from calcipotriene, but the treatment was of unknown duration and response in adults required at least 4 months of use [88]. One recent pediatric case report showed success with topical tacrolimus combined with a keratolytic moisturizer under occlusion (whereas topical tacrolimus was ineffective in an adult patient) [90, 91].

While oral retinoids have been prescribed for pediatric-onset KLC, no reports of success with them as monotherapy in pediatric patients have been published, and isotretinoin 0.5 mg/kg/day caused a flare of disease in one pediatric patient after 5 weeks [92]. Phototherapy and photochemotherapy have both been shown to be effective as monotherapy [91, 93]. Oral retinoids and photo-based treatments have also been used together in the adult literature, which may increase efficacy [86].

Table 4.29 First line therapies

No treatment	E
Sunlight	E
Calcipotriene (Dovonex) ointment daily	E[a]
Tacrolimus (Protopic) 0.1 % ointment BID (under occlusion at night) with 20 % urea cream	E

[a]Based on adult data

Table 4.30 Second line therapies

Oral retinoids: acitretin (Soriatane), etretinate (where available), or isotretinoin (Accutane) 0.5–1 mg/kg daily × 3–4 months	E[a]
PUVA	E
nbUVB	E

[a]Based on adult data

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Hereditary Disorders of Cornification

5

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Introduction

The disorders of cornification (DOC) can be divided into the ichthyosis and other genetic disorders that involve abnormal keratinocyte differentiation. The ichthyoses are a heterogeneous group of DOC that differ in pathomechanism, inheritance pattern, clinical features, course, and management. Their common features is dry, scaling, thickened skin, and variable degrees of associated inflammation. It is thought that the scaling and thickening, at least in part, are a mechanism to compensate for an impaired epidermal barrier. The most prevalent forms of ichthyosis are ichthyosis vulgaris (up to one in ten individuals, characterized by a poor barrier because of filaggrin deficiency, and frequently associated with atopic dermatitis) and recessive X-linked ichthyosis (RXLI; up to 1 in 2500 boys and resulting from deficiency of arylsulfatase C/steroid sulfatase). These more common forms of ichthyosis tend to respond to good emollients and sometimes require keratolytics (especially RXLI), as described below. They are not otherwise reviewed in this chapter.

Integrity of the epidermis is critical for the functional barrier of skin. The epidermis consists of stratified layers of progressively more differentiated keratinocytes from the basal layer (basal keratinocytes) towards the skin surface (corneocytes). Transglutaminase 1 plays a critical role in the cross-linking of upper epidermal proteins to form the dense, flattened layers of corneocytes. The corneocytes are surrounded by a lipid enriched extracellular matrix, that includes a variety of ceramides, cholesterol, and free fatty acids. To create hydrophobic lipid layers these lipids are delivered by specialized cutaneous organelles called lamellar bodies [1]. Keratin attachment to desmosomes and tight junctions are subcorneal epidermal components that contribute to barrier function. Epidermal cells become apoptotic and are shed (desquamated) through a process that requires the action of epidermal proteases. The various forms of ichthyosis are caused by mutation in genes encoding skin barrier components, leading to barrier dysfunction, abnormal keratinocyte differentiation, and disrupted desquamation [1].

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Classification of the Ichthyoses and Other DOC

In 2009, an international group of experts gathered to create a consensus for classification and terminology of the ichthyoses [2]. As a result, the ichthyoses were divided into non-syndromic and syndromic forms (Table 5.1). New umbrella groups were established for keratin mutations and autosomal recessive congenital ichthyoses. In addition, syndromic ichthyoses are classified by mode of inheritance (X-linked or autosomal), and then further classified by organ involvement (hair, neurological, etc.). Several other DOC are outside of the classification of the ichthyoses. Among these are Darier disease, Hailey-Hailey disease, and diffuse and focal palmoplantar keratodermas.

Management Strategies for DOC

Investigations for Diagnosis

Formal diagnostic guidelines for the DOC have not yet been established. Questions about history should ascertain prematurity and perinatal complications, presentation during the neonatal period (e.g., as a collodion baby, with erythroderma

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Table 5.1 Classification of Inherited Ichthyoses[a] (JAAD 2010)

Inherited ichthyoses		
Non-syndromic	Mode of inheritance	Genes
Common ichthyoses		
Ichthyosis vulgaris	Autosomal semi dominant	FLG
Autosomal recessive congenital ichthyosis		
Harlequin ichthyosis	Autosomal recessive	ABCA12
Lamellar ichthyosis	Autosomal recessive	TGM1/NIPAL4/ALOX12B/ABCA12
Congenital ichthyosiform erythroderma	Autosomal recessive	ALOXE3/ALOX12B/ABCA12/CYP4F22/NIPAL4/TGM1/CerS3/*PNPLA1*/*LIPN*
Keratinopathic ichthyoses		
Epidermolytic ichthyosis	Autosomal dominant	KRT1/KRT10
Superficial epidermolytic ichthyosis	Autosomal dominant	KRT2
Other forms		
Loricrin keratoderma	Autosomal dominant	LOR
Erythrokeratodermia variabilis; Progessive symmetric Erythrokeratodermia	Autosomal dominant	GJB3/GJB4/GJA1
Peeling skin syndrome	Autosomal dominant	CHST8 (Type A); CDN (Type B); TGM5 or CSTA (acral type)
Keratosis linearis- ichthyosis Congenita-keratoderma (KLICK) syndrome	Autosomal recessive	POMP
Syndromic		
X-linked ichthyosis syndromes		
Recessive X-linked ichthyosis	X-linked recessive	STS
Ichthyosis follicularis atrichia photophobia (IFAP) syndrome	X-linked recessive	MBTPS2
Conradi-hunermann-happle Syndrome	X-linked dominant	EBP
Autosomal ichthyosis syndromes with		
Prominent hair abnormalities:		
Netherton syndrome	Autosomal recessive	SPINK5
Ichthyosis hypotrichosis syndrome	Autosomal recessive	ST14
Ichthyosis hypotrichosis sclerosing Cholangitis syndrome	Autosomal recessive	CLDN1
Trichothiodystrophy	Autosomal recessive	ERCC2/XPD ERCC3/XPB GTF2H5/TTDA
Prominent neurologic signs:		
Sjogren-larsson syndrome	Autosomal recessive	ALDH3A2
Refsum syndrome	Autosomal recessive	PHYH/ PEX7
Mental retardation- enteropathy-deafness- neuropathy-ichthyosis-keratoderma (MEDNIK) syndrome	Autosomal recessive	AP1S1
Often fatal disease course:		
Gaucher syndrome type 2	Autosomal recessive	GBA
Multiple sulfatase deficiency	Autosomal recessive	SUMF1

Inherited ichthyoses		
Non-syndromic	Mode of inheritance	Genes
Cerebral digenesis- neuropathy-ichthyosis-palmoplantar keratoderma (CEDNIK) syndrome	Autosomal recessive	SNAP29
Arthrogryphosis-renal dysfunction-cholestasis (ARC) syndrome	Autosomal recessive	VPS33B
Other syndromic forms:		
Keratitis-ichthyosis-deafness (KID) syndrome	Autosomal dominant	GJB2
Neutral lipid storage disease with ichthyosis	Autosomal recessive	ABHD5
lchthyosis prematurity syndrome	Autosomal recessive	SLC27A4

[a]Modified from Tables II and III in: Oji et al. [2]. With permission from Elsevier

but not collodion membrane, blistering), course of the disorder, and experience with interventions. A pedigree should be obtained to suggest pattern of inheritance. Review of systems may reveal involvement of other organs (eyes, neurologic, etc.). Physical examination is crucial to define the cutaneous manifestations (character, severity and distribution of scaling, thickening and inflammation; presence of blisters or erosions; ectropion, eclabium, alopecia, and other hair changes) and observe any extracutaneous manifestations (see Table 5.1).

In some cases, diagnosis can be made prenatally. For example, pregnant mothers who carry a fetus with X-linked ichthyosis often have low serum unconjugated estriol levels during the second trimester, and FISH analyses can show the deletion in the fetal X-chromosome. Ultrasonographic findings may also suggest a diagnosis of ichthyosis, such as in Conradi syndrome (limb anomalies) or harlequin ichthyosis [3, 4]. If families have a risk of an affected fetus and the DNA mutation has been detected, prenatal diagnosis can be performed by amniocentesis or chorionic villus sampling to determine if the fetus is affected. Amniotic fluid itself may have a turbid appearance because of the large amount of desquamated skin floating in the amniotic cavity (the "snowflake sign") [5]. Preimplantation diagnosis is a technique using in vitro fertilization that enables only unaffected blastomeres to be implanted; preimplantation has been performed for an at-risk family for Netherton syndrome [6].

In addition to DNA analysis for a specific genotype, laboratory testing can aid in the clinical diagnosis of several forms of DOC. Routine assessment of skin sections is often nonspecific, but may show specific histological features, such as the orthokeratosis and epidermolysis of epidermolytic ichthyosis and the suprabasal acantholysis, corps rond, and grains of Darier disease. Biochemical testing may also be helpful, such as in detecting high serum cholesterol sulfate levels in recessive X-linked ichthyosis and increased levels of phytanic acid in the cerebrospinal fluid of individuals with Refsum disease [7]. Simply observing blood smears will demonstrate the lipid-containing vacuoles in circulating white blood cells of neutral lipid storage disease [8]. Another relatively simple diagnostic tool is a hair mount; observation of broken hairs may demonstrate the characteristic trichorrhexis invaginata ("bamboo hair") of Netherton syndrome, trichorrhexis nodosa (nodes along the hair shaft) or, under polarized light, the "tiger tail" patterning of trichothiodystrophy.

Genetic testing for mutation analysis is becoming more accessible as technology progresses, and can be a useful diagnostic tool for patients and families [9]. The more recent availability of amplicon-based tools for genotyping major forms of ichthyoses and of whole exome sequencing to find rare mutations in known genes and discover new genes that underlie DOC (for example, GJA1 mutations in a form of erythrokeratodermia variabilis) [10] have increased our understanding of these disorders and will drive pathogenesis-based personalized therapy.

General Approach to Therapy in Children

There is no cure presently for any of the DOC discussed in this chapter. The goals of therapy for DOC in infants and children are to: (i) preserve function; (ii) maximize the quality of life by improving itch, sleep, and appearance; and (iii) prevent complications such as infection, dehydration, and poor growth. For all children with DOC the mainstay of therapy is emollient application and bathing. Families spend hours a day on skin-directed therapy. In general, we take care not to subject young children to uncomfortable treatments for cosmesis alone. For children with widespread disease, specialists in the management of eye and ear complications should be engaged. Range-of-motion of fingers and toes should also be monitored carefully. Topical and systemic therapies, in addition to occupational and physical therapy, can be implemented to prevent or treat contractures. Because of their impaired barrier, infants and children with DOC lose water and heat through their skin, have greatly increased caloric needs, and can suffer from constipation. Their thicker stratum corneum and tendency keep their skin covered can lead to vitamin D deficiency and rickets [11]. Patients with DOC may also have micronutrient and vitamin deficiencies via other mechanisms as well [12]. In infancy and early childhood, weight and height should be measured frequently, and referrals to specialists in nutrition and gastroenterology should be considered for poor growth. Lastly, families and children can benefit from supportive networks of other families with similar conditions. The Foundation for Ichthyosis and Related Skin Types is an example of a wonderful patient and family support group (www.firstskinfoundation.org).

Specific Therapies

Emollients

Emollients (also called moisturizers) are considered a critical component of care for individuals with DOC. Emollients fill the empty spaces between the cells of the stratum corneum, resulting in a smoother and shinier skin surface [13]. There are two types of emollients: occlusives and humectants. Occlusives prevent transepidermal water loss (TEWL) and trap moisture derived from the deeper dermis and epidermis in the stratum corneum. Examples of occlusives include mineral oil, lanolin, and silicones. Petroleum jelly is by far the most effective occlusive, decreasing TEWL by 98 % when applied properly [13]. Humectants attract moisture from the environment when humidity is greater than 70 %. In

less humid environments, humectants attract water molecules from the deeper layers of the skin. Examples of humectants include glycerin, propylene glycol, and alpha-hydroxy acids [14]. When humectants are used in isolation, they can actually increase TEWL, emphasizing the importance of use of humectants in conjunction with an occlusive moisturizer to retain skin hydration [15]. Hydration of the skin affects its barrier function, thus playing a role in both the integrity of the stratum corneum and influencing penetration through the upper layers of the epidermis [14]. Emollients are thought to decrease TEWL, creating an optimal environment for repair of the stratum corneum and its associated lipids. Emollients also play a role in lipid regeneration and maintenance, can decrease inflammation, and help to rebuild a defective barrier. However, a recent study showed that emollients (with both occlusive and humectants) improved skin dryness in individuals with RXLI, but had no impact on TEWL, pH, or gene expression [16], suggesting that more study is needed to understand the role of emollients in the ichthyoses.

Keratolytics

DOC are often associated with hyperkeratosis, which is an increase in the thickness of the stratum corneum. Substances used to treat hyperkeratosis are termed keratolytics. Several types of keratolytics are used to decrease the scaling of these disorders:

- Lactic acid (LA) and glycolic acid (GA) are alpha-hydroxy acids. They decrease the hyperkeratosis associated with DOC by degrading corneodesmosomes, which promotes detachment of keratinocytes and accelerates stratum corneum turnover. Lactic and glycolic acids are commonly used for the treatment of DOC in combination with a petrolatum, cream, or lotion base and can be compounded or purchased over-the-counter in concentrations up to 12 %. Side effects include stinging, irritant contact dermatitis, and photosensitivity [13–15].
- Salicylic acid (SA), a beta-hydroxy acid, is used in concentrations of 1–6 %. The proposed mechanism of action for SA is to reduce corneocyte adhesion. Systemic absorption, leading to salicylism, is a risk and metabolic acidosis, especially in children. SA is toxic to the CNS at concentrations >35 mg/dL. Tinnitus is an early warning sign, as it is correlates with plasma salicylate concentration [17]. Despite this, SA is safe in children as long as it is used on a limited area of involved skin.
- Urea is both a keratolytic and a humectant. It causes physical alteration in the stratum corneum, leading to desquamation of corneocytes. Urea at a concentration of 10–25 % acts as a humectant and a mild keratolytic; concentrations of 40–50 % are required for hygroscopic keratolytic effects. Mild stinging and irritation are usually minimal, especially at lower concentrations [18].
- Ten percent N-acetylcysteine can be added to low concentrations of urea (5 %) and used to treat widespread areas of lamellar ichthyosis. Mild stinging and irritation are reported side effects. Rosemary oil can be added to mask the smell of sulfur [19]. N-acetylcysteine may work via inhibition of keratinocyte proliferation [20].
- Tar is both anti-inflammatory and anti-proliferative, causing progressive thinning of the stratum corneum. Although efficacious, tar can be difficult for patients to use due to its odor and color. Other side effects include phototoxicity, allergy, and possible carcinogenicity.
- Propylene glycol can act as a keratolytic at concentrations of 10–20 %. It is a strong contact allergen sensitizer, and must be used carefully in patients who already have disturbed barrier function.

Antimicrobials

Bacterial colonization and infection, especially with *S. aureus*, and dermatophyte infection is not uncommon in the retained scale and fissured skin of individuals with DOC. In particular, overgrowth of bacterial organisms contribute to the skin odor and discomfort of children, such as with EI, the lamellar phenotype of ARCI, Netherton syndrome and keratitis-ichthyosis-deafness (KID) syndrome. Prophylactic use of antibiotics should be avoided, especially in neonates, in order to prevent the development of resistance and creation of a growth environment favoring *Pseudomonas aeruginosa*. Although chronic or repeated administration of antibiotics should be avoided, systemic intervention is necessary for infection. Cephalexin (10–15 mg/kg/dose given three times daily for 10 days) is most commonly administered for staphylococcal infection, although intervention should be based on resistance patterns if MRSA infection. Very localized bacterial infection can be managed by topical antibiotics. Bacterial infection tends to be characterized by pustules, abscesses, crusting, or increased erythema and swelling, and can be associated with discomfort. Maintenance intervention with antiseptics in the bath and antibacterial soaps (see section on "Baths", below) are beneficial for colonization that leads to odor in the absence of infection [21].

Individuals with ichthyosis are also predisposed to the development of secondary fungal infections. Diagnosis of dermatophyte infection can be particularly tricky, given the generalized scaling (including of the scalp) and often associated inflammation of the ichthyosis. An annular patterning of the scaling and recalcitrance to therapy may be clues, but fungal infection may present only as worsening of itch and desquamation. The threshold for performing potassium hydroxide mount evaluation and fungal culture should be low in patients. Standard doses of griseofulvin (20 mg/kg/day divided into two doses; requires 2–4 weeks longer than terbinafine and other interventions), terbinafine (62.5 mg/day for

10–20 kg, 125 mg/day for 20–40 kg and 250 mg/day for more than 40 kg; given daily for 2–4 weeks for tinea corporis and 4–6 weeks for tinea capitis), itraconazole (5 mg/kg/day), or fluconazole (6 mg/kg/day). The dermatophyte infection in ichthyosis may be more persistent than in normal skin and require prolonged systemic antifungals courses [22].

Baths

Bathing should be encouraged to be a part of every ichthyosis patient's daily regimen. Many patients with ichthyosis find that soaking for long periods (even an hour) hydrates the skin and facilitates scale removal. Bath additives can be soothing, antiseptics, and may promote desquamation. Use of oils or lanolin in the bathtub [23] should be avoided with young children, because of the risk of increased slipperiness. Addition of two cups of baking soda to a full standard tub [24] has been suggested. Baking soda increases the pH of tap water to an alkaline range, which may increase protease activity and promote scale desquamation. Adding salt to bath water may also be soothing and lead to decreased pruritus [25]. Adding bleach (sodium hypochlorite) at a concentration of 0.005 % (one half-cup to a full standard bath; 1 cc per L) to the bath water can be a convenient and affordable measure to minimize bacterial overgrowth. Although no studies of its effect in ichthyosis have been performed, in individuals with atopic dermatitis, at least twice-weekly dilute bleach baths have been shown to decrease disease activity, including inflammation and scaling [26]. Recently, sodium hypochlorite has been shown to inhibit NF-kB signaling and reduce radiation dermatitis in a murine model [27], suggesting a direct anti-inflammatory effect. Hydrotherapy treatments showed to have short- and medium-term efficacy, but are only available in specific centers [28]. Application of emollient immediately after bathing and while the skin is well hydrated is essential (see section on "Emollients").

Patients with ichthyosis are more susceptible to overheating from hypohidrosis. Although occlusion of eccrine ducts by scaling has been blamed, many affected individuals continue to have issues with heat intolerance and inadequate sweating after therapeutic response to intervention, suggesting a developmental abnormality. Keeping a temperature-controlled environment throughout the year, wetting the skin with spray bottles of water or wet towels, and wetting clothing during outdoor activities in warm weather, or even using cooling suits, are highly recommended.

Physical Treatment

Soaking in water for prolonged periods softens the stratum corneum and allows for removal of the thickened skin with rough-textured sponges or abrasives [7]. The repetitive mechanical procedure may be physically and emotionally exhausting, but rewarding both cosmetically and symptomatically. Earwax from excessive desquamation in the ear canal can lead to conductive hearing loss. Earwax softeners (e.g., carbamide peroxide drops) can facilitate scale removal, which should be performed up to quarterly, as needed, by a trained professional. Although in general home earwax removal is discouraged, a flexible plastic loop with a safety stop (Ear-Wiz®) allows removal of excess wax without touching the eardrum. For patients with palmoplantar keratoderma, focal soaks and paring excess skin with a sharp hand tool is the most effective way to decrease thickening that interferes with performance of daily activities [29]. Surgical approaches, including CO_2 laser treatments and full thickness excision and grafting, have anecdotally been described for adult patients [30, 31]. Constrictive skin bands in neonates with harlequin ichthyosis may lead to contractures, compartment syndrome, circulatory compromise, and autoamputation; releasing the skin bands with a 2 mm curette [9], an 11 blade [32], or with a linear band incision technique [33] should be done by a skilled dermatologist, plastic surgeon, or orthopedist. Patients with localized problematic ichthyotic areas of CHILD syndrome may benefit from excision and grafting from the contralateral, unaffected donor region [34].

Retinoids

Both topical and oral retinoids are used to treat various DOC [35]. Their primary effect is to normalize epidermal differentiation, which improves epidermal thickness and hyperkeratosis. In general, topical retinoids are used for milder localized disease and oral retinoids are used for more severe, widespread disease.

Topical Retinoids

Adapalene, tretinoin, and tazarotene have all been used for DOC, although tazarotene is more widely used because of its greater efficacy [35, 36]. Both normalize epidermal thickness via effects on epidermal transglutaminase and other mediators. Topical retinoids have a better safety profile than oral retinoids and do not require monitoring, but can be onerous to apply to large areas. Tazarotene can be absorbed systemically at low levels, but is rapidly degraded and excreted [37]. Adverse effects include erythema, dermatitis, pruritus, and burning. Tazarotene is pregnancy category X.

Topical tazarotene 0.1 % gel and cream have been reported to be effective in treating localized disease associated with lamellar ichthyosis including ectropion [38] and digital contractures of a collodion baby [39]. Topical retinoids are also effective in treating palmoplantar keratodermas [40]. Frequency of application can be decreased to once every few days if there is excessive irritation, or started twice a week and increased as tolerated.

Oral Retinoids

Oral retinoids have been used for many years in the treatment of children with inherited DOC [41], primarily to decrease scale and hyperkeratosis. Oral acitretin and isotretinoin are the most widely used forms. Oral retinoids are used for lamellar ichthyosis, Darier disease, Sjogren-Larsson Syndrome, and palmoplantar keratodermas. When used in congenital ichthyosiform erythroderma (CIE) and epidermolytic ichthyosis (EI), retinoids can lead to increased fragility and erythema. Therefore, starting at a low dose and escalating as tolerated is recommended. The risk of irritation is greater with either topical or oral retinoids when the skin is close to normalizing. Doses of acitretin used in children are often close to 0.5 mg/kg/day [42]. Doses of isotretinoin under 1 mg/kg/day, and sometimes substantially lower, tend to be effective. Prolonged courses of treatment are the norm when used for DOC, but some patients take "drug holidays" periodically, especially to minimize potential irritation. Patients should be counseled that hyperkeratosis and scaling return within months of discontinuing treatment. Other topical treatments such as emollients and keratolytics should be continued while on retinoid therapy, if tolerated, because they often have synergistic effects [41].

Acitretin and isotretinoin have similar toxicities, including mucocutaneous, metabolic, and bone toxicities. Mucocutaneous toxicities include xerosis, cheilitis, and dry nose and eyes. Laboratory abnormalities such as lipid derangements, transaminitis, and abnormalities in the complete blood count (CBC) can be seen. Baseline tests should include CBC, chemistry panel, liver function tests, fasting triglyceride and cholesterol panel, and pregnancy testing for women of childbearing age. These should then be followed periodically. Enrollment in the FDA-mandated I-pledge program is required for prescribers and patients using isotretinoin. All oral retinoids are teratogenic, and women must not become pregnant while initiating or taking a retinoid and for a period of time after using systemic retinoids. For isotretinoin, women should wait one month after cessation of therapy before becoming pregnant. Because acitretin can be re-esterified to etretinate when taken with alcohol and persist in the fat for prolonged periods of time, the current FDA recommendation is that women wait 3 years after cessation of therapy before conceiving [41]. The risk with pregnancy makes acitretin an impractical treatment option for older girls and teenagers, but the onerous requirements for use of isotretinoin make acetretin the drug of choice otherwise.

Because retinoids are often used for prolonged periods of time by people with DOC, the skeletal side effects bear consideration. After long-term treatment hyperostosis formation, analogous to diffuse idiopathic skeletal hyperostosis (DISH), is seen in most patients. Hyperostoses are duration-dependent and are much more common in adults. Premature epiphyseal closure has been reported in children taking either isotretinoin or etretinate for prolonged courses (i.e., 4.5–6 years). In general, higher doses and longer courses of treatment seem to increase risk for these toxicities, but they can be seen with short courses and low doses [43]. There are no clear recommendations for monitoring bony toxicities, but many clinicians will obtain baseline bone surveys and then repeat at intervals of 1–3 years [41].

Retinoic Acid Metabolism Blocking Agent (RAMBA)

Liarozole, an imidazole derivative, is a RAMBA that has orphan drug status for topical and oral use for congenital ichthyosis in Europe, but is not available in the United States. Liarozole inhibits the oxidative metabolism of retinoic acid, leading to higher levels of retinoic acid in the plasma and skin, which then normalizes keratinocyte differentiation and proliferation. Via CYP inhibition, liarozole can affect synthesis of estrogen, androgens, and cortisone, but these effects do not appear to be clinically significant. Liarozole appears to have similar clinical efficacy to retinoids, with fewer retinoid side effects. Topical use did lead to systemic absorption of varying degrees, which led to a decrease in estradiol concentrations, but not to any significant systemic side effects [44, 45].

Targeted Therapy

The progress of understanding the genetic basis and the pathogenesis of many of the ichthyoses has enabled more targeted therapy. Approaches may be gene-based or pathway-based pharmacologic. Gene-based therapy requires knowing the specific gene and/or mutation of the patient to replace, correct, or modulate the expression of the mutant gene. At this time, gene-based therapy has yet to be performed for the ichthyoses, but transduction of the normal *SPINK5* gene using a viral vector normalized LEKTI expression in Netherton syndrome keratinocytes and restored normal skin architecture after transplantation; [46] phase I clinical trials are beginning using transplantation. Gene insertion also corrected the *TGM1* mutation in a mouse model of lamellar ichthyosis [47, 48] and the restored lipid secretion in lamellar granules of *ABCA12*-mutated harlequin ichthyosis keratinocytes [49].

An example of pathway-based pharmacologic therapy is correction of a deficient end product (cholesterol) and blockade of accumulation of toxic metabolites (by a statin) in CHILD syndrome. The clinical and histological cutaneous abnormalities are reversed after application of 2% cholesterol and 2% lovastatin [50]. Systemic administration of orlistat, an intestinal lipase inhibitor, has led to significant reduction of phytanic acid levels and improved the neurological and dermatological symptoms of two siblings with Refsum's disease [51].

Distinctive Features and Therapeutic Ladders for Selected DOC

Non-Syndromic Disorders: Autosomal Recessive Congenital Ichthyosis (ARCI), Epidermolytic Ichthyosis (EI), and Erythrokeratodermia Variabilis (EKV)

Epidermolytic Ichthyosis (EI)

Epidermolytic ichthyosis (Fig. 5.1) is a keratinopathic ichthyosis that results from mutations in one of three keratins: *KRT1*, *2*, and *10*. The vast majority of affected individuals have a dominant negative mutation on one allele (autosomal dominant), but rare recessive and mosaic forms (epidermolytic epidermal nevi) have been described. More than half of the cases are due to a de novo mutation and occur sporadically. Clinically, EI is a spectrum of diseases differing in distribution and severity. Patients present with erythroderma, generalized blisters, and denuded skin at birth. Later, blisters become focal and the epidermis becomes hyperkeratotic with dark thick scales, often with a corrugated or ridged pattern. Some patients experience palmoplantar keratoderma, which predicts a *KRT1* mutation.

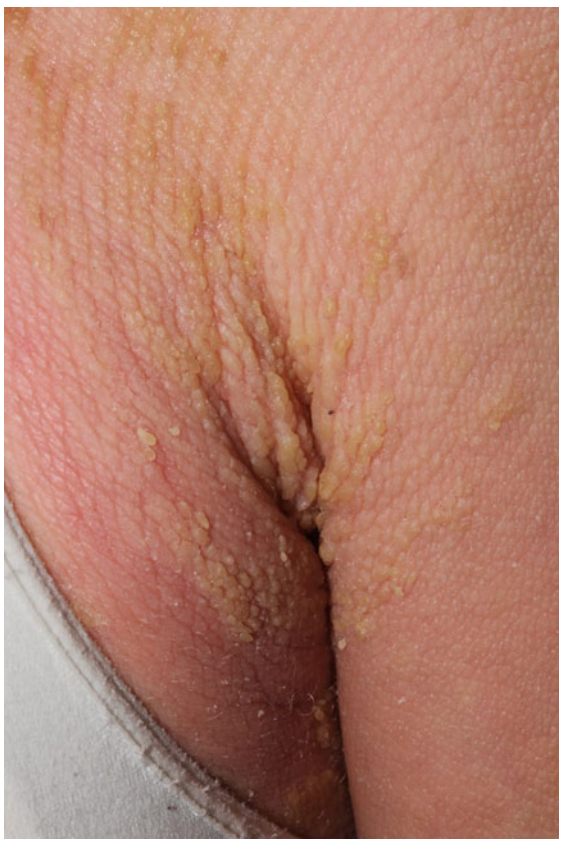

Fig. 5.1 Epidermolytic ichthyosis

Management Strategies

The approach to EI treatment is complicated by the skin fragility. All patients should use topical emollients and be monitored for skin infections, particularly *Staphylococcus aureus*. Topical and oral retinoids can decrease the hyperkeratosis, but risk increasing discomfort and skin fragility.

Investigations Recommended

- Skin biopsy
- Genetic testing, if available
- Bacterial and fungal cultures as needed to consider secondary infection

A 14-year-old boy, treated with topical adapalene gel 0.1 % for his facial lesions, sustained good results during 2 years of usage [36].

1. Four children, ages 4–13, treated with acitretin 0.77–1.07 mg/kg/day, showed improvement in >90 % of skin lesions with sustained effect for 14–24 months. No severe side effects were noted, and there was no adverse effect on growth and development [52].
2. A 7-year-old boy was treated with etretinate 0.75 mg/kg/day. The hyperkeratosis resolved in 2 months. The dosage was reduced to 0.5 mg/kg/day and continued intermittently for about 2 years. The hyperkeratosis was controlled well. No significant adverse effect of etretinate was observed [53].
3. A 9-year-old boy was treated with four different topical preparations—one on each limb: (1) calcipotriol ointment (50 mg/g) on the left leg; (2) tretinoin ointment 30 mg/100 g the right leg; (3) ointment containing urea (10 %), lactic acid (5 %) and glycerol (5 %) on the right arm; (4) ointment containing urea (10 %) and sodium chloride (10 %) on the left arm. Topical calcipotriol twice

Table 5.2 First line therapy

Emollients
Topical or systemic antimicrobials as needed

Table 5.3 Second line therapy

Topical retinoids

Table 5.4 Third line therapy

Systemic retinoids
Topical vitamin D analogs ± topical corticosteroids

daily was most effective, reducing scaling, itching, and skin tenderness in 3 weeks. Treatment was continued for 3 years with sustained results. Serum and urine calcium were within normal limits throughout this treatment [54].
4. A 2-year-old boy with linear EI (epidermal nevus type) used maxacalcitol ointment (25 μg/g) twice daily. After 2 months he showed improvement, and after 2 years the affected skin became depigmented with normal texture. Serum calcium remained within normal limits throughout the treatment [55].
5. A 5-year-old boy was treated with calcipotriol/ betamethasone propionate combination ointment once daily. After 2 months, the lesions became thinner and less erythematous [56].
6. Thirteen patients (75 % younger than 20 years old) with generalized epidermolytic hyperkeratosis were treated with either topical or oral retinoids. Retinoids were particularly effective in patients with *KRT10* mutations [40].

Autosomal Recessive Congenital Ichthyosis (ARCI)

ARCI is a group of disorders that most commonly presents at birth as a collodion baby. It encompasses a spectrum of ichthyosis phenotypes, ranging from mild to severe and from congenital ichthyosiform erythroderma (CIE) to lamellar ichthyosis (LI) (Fig. 5.2). All forms are autosomal recessive, although rare autosomal dominant cases of ARCI have been described. Mutations in at least nine genes have been found to underlie ARCI (Table 5.1).

The collodion baby shared phenotype (Fig. 5.3) presents at birth as encasement in shiny thickened skin, often with associated ectropion (eversion of the upper and lower eyelids) and eclabium (lip eversion), exposing the ocular and oral mucosae, respectively. Despite the thickening, the skin barrier of collodion babies is impaired. Transepidermal loss of water and electrolytes is increased, the skin is more permeable to topically applied agents, and there is a heightened risk of temperature instability and bacterial and fungal infection. The collodion membrane tends to be shed during the first month of life and the phenotype is revealed in the subsequent months.

As discussed under interventions above, individuals with ARCI often have severe pruritus and, especially with the thick scaling of lamellar ichthyosis, an odor in association with overgrowth of skin bacteria (see increased risk of bacterial and fungal infections, above). Ectropion and extensive scaling of the ear canals lead to issues that may require special expertise. The defect in sweating can manifest in overheating.

Investigations Recommended

- Biopsy is generally not useful
- Genetic testing, if available
- Bacterial and fungal cultures as needed to consider secondary infection

1. **Ichthyosis in the newborn** [8]. This article reviews the potential complications and management of ichthyosis, particularly collodion babies.

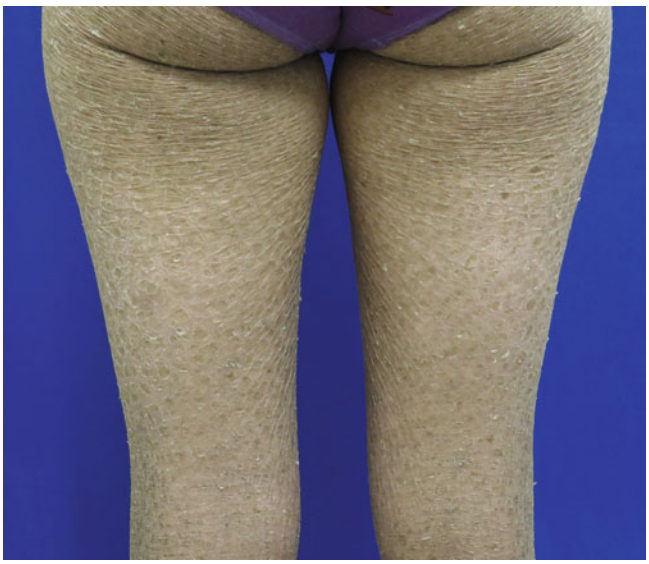

Fig. 5.2 Lamellar Ichthyosis phenotype of ARCI

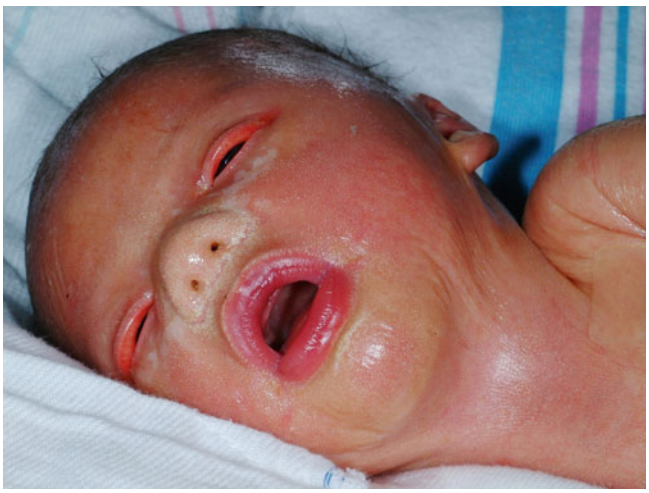

Fig. 5.3 Collodion baby

2. **Collodion baby: an update with a focus on practical management** [57]. This review summarizes the clinical characteristics, complications, outcomes, and differential diagnosis of the collodion baby, and suggests practical management.
3. **Care of the newborn with ichthyosis** [32]. This review summarizes the phenotypic presentations of ichthyosis in the neonatal period and discusses management.
4. Nine children with ichthyosis (2–17 years of age), of whom three had ARCI, applied tazarotene 0.05 % or 0.1 % cream or gel to up to 90 % of the body surface for 1 month to 2 years. In the majority, blood levels of tazarotene were undetectable, and in others, very low [58].
5. Topical tazarotene can be particularly helpful for decreasing ectropion and is a successful alternative to surgical intervention for many patients [38].
6. Ten percent N-acetylcysteine in 5 % urea is effective and safe as a topically applied cream; the odor of sulfur has recently been minimized by the addition of rosemary water [19].

1. Marked was noted in 80 % of ten patients (12 years of age and above) with ARCI who applied calcipotriol ointment (50 μg/g) twice daily for up to 12 weeks (mean 60 g/week) [59].
2. Left-right comparison trial of topical liarozole vs. placebo showed marked improvement after 4 weeks of use on the liarozole-treated side in six adult patients with ARCI. Systemic absorption occurs with widespread topical treatment and can simulate the result of oral liarozole [44].

1. Acetretin and isotretinoin are highly effective for ARCI, but have many potential side effects [41].

Table 5.5 First line therapy

Careful monitoring in the first week of life with a humidified environment and emollients
Emollients
Topical tazarotene or keratolytic agents (including N-acetylcysteine with urea)
Topical or systemic antimicrobials as needed for bacterial or fungal infection
Antihistamines if helpful for the pruritus

Table 5.6 Second line therapy

Topical vitamin D_3 analogs
Liarozole 5 % cream (not available in the US)

Table 5.7 Third line therapy

Systemic retinoids
Oral liarozole (not available in the US)

2. Oral liarozole has a similar efficacy and safety profile to oral acetretin [45].
3. Systematic review of clinical trials of treatments for congenital ichthyoses [60].

Erythrokeratodermia Variabilis

Erythrokeratodermia variabilis (EKV) is characterized by discrete red transient patches, and fixed red/brown thickened plaques with adherent yellow-brown scale (Fig. 5.4) that begin in infancy. Some patients have associated palmoplantar keratoderma. The transient red patches can be pruritic and worsened by environmental change. EKV is caused by an autosomal dominant mutations in GJBX or GJA1, encoding connexin 31 or 43, respectively. GJA1 mutation typically shows associated intense hyperpigmentation and leukonychia.

Management Strategies

As with other ichthyosiform disorders, the mainstays of treatment are emollients, keratolytics, and retinoids. EKV responds well to oral retinoids and may completely clear with low-dose treatment. Clearance is often followed by a period of remission of varying length, but sometimes can very brief. Topical retinoids can also be effective.

Investigations Recommended

- Biopsy
- Genetic testing if available

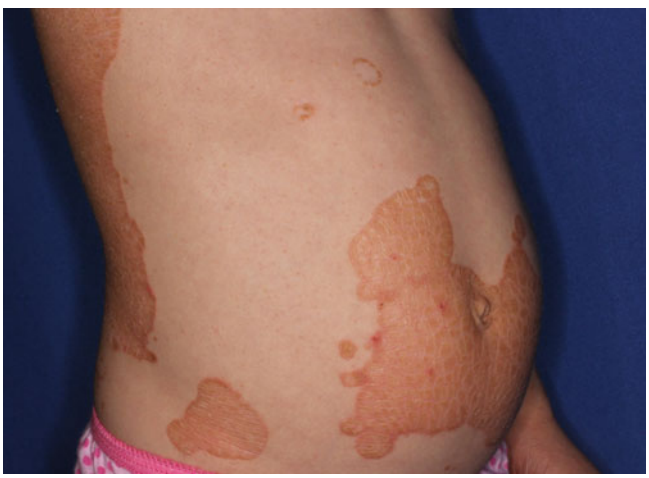

Fig. 5.4 Erythrokeratodermia variabilis

Table 5.8 First line therapy

Emollients
Topical retinoids

Table 5.9 Second line therapy

Oral retinoids (isotretinoin or acetretin)

Table 5.10 Third line therapy

Re-PUVA (retinoids + PUVA)

PUVA Psoralen and Ultraviolet A light

An 8-month-old girl was successfully treated with topical tretinoin 0.05 % cream and emollients [61].

1. A 2-year-old boy was treated with 0.5 mg/kg/day of isotretinoin and emollients. His skin, including the palms and soles, improved remarkably after only 2 weeks of treatment, and he continued treatment for at least 6 months [62].
2. A 9-year-old girl was treated with acitretin 1 mg/kg/day and noted improvement of her skin lesions in 3 weeks. The lesions rapidly recurred after discontinuation of therapy. The authors suggest that low-dose long-term therapy may be justified when EKV leads to psychosocial issues [63].

A single adult patient was treated with acetretin 10 mg/dose and PUVA for 23 treatments, with a total of 9 months of acetretin. She had good improvement in both erythematous and hyperkeratosic lesions, with almost complete normalization of her skin [64].

Syndromic Disorders: Netherton and Sjogren-Larsson Syndromes

Netherton Syndrome (NS)

Netherton syndrome is caused an autosomal recessive mutation in *SPINK5*. Skin findings include erythroderma at birth, ichthyosis linearis circumflexa (ILC, serpiginous, double-edged, migratory scale or peeling), and itching (Fig. 5.5). Trichorrhexis invaginata leads to fragile, short hair. Important associations include immunologic abnormalities (elevated serum IgE with severe allergies to foods and medications, along with other features of an impaired immune system); and nutritional deficiencies (short stature and failure to thrive). NS patients have lifelong involvement of their skin, with fluctuations in severity.

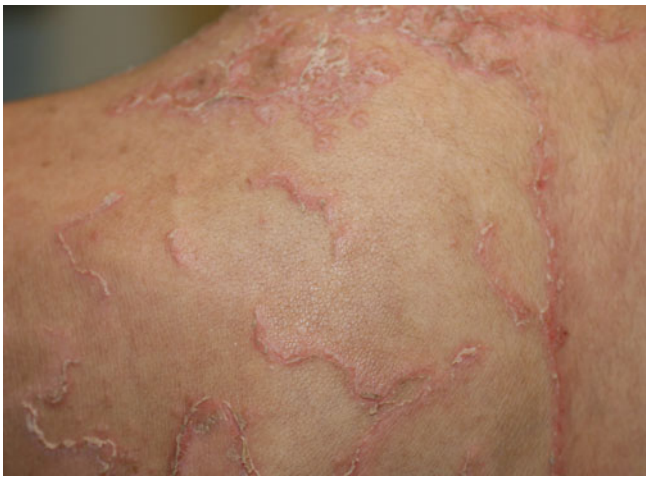

Fig. 5.5 Netherton syndrome with ichthyosis linearis circumflexa

Management Strategies

The approach to the treatment NS is complicated by potential skin irritation (e.g., from topical or oral retinoids) and increased absorption of topical medications through the impaired barrier (e.g., topical steroids and calcineurin inhibitors). These side effects are more likely in erythrodermic patients. Patients with NS, especially infants, need to be monitored for cutaneous infections and treated to prevent systemic infection. In addition to the medications listed below, first-line therapy of NS consists of bland topical emollients, and prevention of infection with bleach baths.

Investigations Recommended

- Skin biopsy
- Genetic testing if available
- Allergy/Immunology evaluation if evidence of allergy or immunodeficiency
- Bacterial, fungal, and viral swabs as appropriate to rule out secondary infection

Three children with NS applied 1 % pimecrolimus cream to up to 50 % body-surface area. Blood levels were low, but peaked in the first month of use and were higher in the patient with an erythrodermic phenotype. Disease severity and quality-of-life ratings improved significantly [65].

1. A 16-year-old patient was treated with a combination of NB-UVB, topical fluocinolone oil, and a 2-week course of prednisone to offset potential worsening of erythroderma with NB-UVB. The patient continued home

phototherapy for at least 4 years. His skin symptoms rapidly worsened with attempts to discontinue or wean the phototherapy [66].

2. Three children with NS were treated with dilute topical tacrolimus with initial good clinical effect. All three children had detectable blood levels, but no abnormalities in complete blood count, liver function tests, or renal function. All three children experienced tachyphylaxis, despite increasing concentration and frequency of application. The authors conclude that the use of dilute topical tacrolimus can be considered for short-term management of flares with monitoring of medication blood levels and other parameters [67].
3. Nine children were included in this study that extensively delineated their immunologic profiles. Five children were treated with IVIG for either of two indications: (1) abnormal response to bacteriophage; or (2) failure to thrive. Treated patients showed marked improvement in inflammation and itching, hair thickness, and weight gain. The authors suggest that Netherton syndrome can considered a primary immunodeficiency and that IVIG may improve the clinical course of NS in addition to the associated immunologic derangements [68].
4. A 9-year-old boy was treated with topical calcipotriol 005 % ointment BID every fourth day on 18–27 % BSA. Scaling and erythema improved after 3 weeks. Remission lasted 3–4 weeks. He used intermittent treatment for 9 months. He had no signs of hypercalcemia [69].

1. A young patient with NS experienced reduction of ichthyotic lesions and improved hair growth with acetretin 5 mg per day. Doses of 10 mg and 35 mg a day resulted in severe erosive dermatitis and irritation [70].
2. A 14-year-old patient was treated with 0.2 mg/kg/day of isotretinoin and slowly improved during 6 months. The authors suggest that the shorter half-life of isotretinoin may make it more useful than acitretin in the pediatric population [71].
3. A 25-year-old received 2 years' of infliximab for NS. The patient's inflammatory lesions improved, but the ichthyosis, xerosis, and allergies did not [72].

Sjogren-Larsson Syndrome

Sjogren-Larsson syndrome (SLS) is a form of ichthyosis associated with spasticity, seizures, mental disability, photophobia, and poor vision that is caused by an autosomal recessive defect in fatty aldehyde dehydrogenase. Birth as a collodion baby is rare, and the ichthyosis typically appears in the first year of life. Patients have small dark scales with limited erythema after the first year of life (Fig. 5.6). The central face is relatively spared. Itching is prominent. Early and progressive spastic paresis and speech abnormalities are prominent noncutaneous features.

Management Strategies

SLS is a multisystem disorder that requires multidisciplinary care. Skin care with emollients and keratolytics is the mainstay of treatment. Oral retinoids can also improve cutaneous manifestations. Early and aggressive speech and physiotherapy can improve function and social integration.

Table 5.11 First line therapies

Topical pimecrolimus
Topical corticosteroids
Emollients
Antimicrobials

Table 5.12 Second line therapies

Narrow band UVB
Immunoglobulin replacement (D)
Topical tacrolimus
Topical calcipotriol

Table 5.13 Third line therapies

Infliximab
Oral Acitretin (low dose)
Oral Isotretinoin

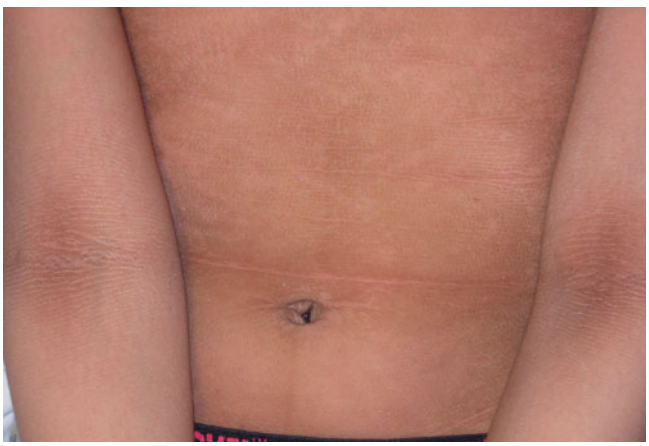

Fig. 5.6 Sjogren-Larsson syndrome

Investigations Recommended

- Genetic testing
- Developmental/Neurologic evaluation including brain imaging
- Ophthalmologic evaluation and treatment

1. Topical keratolytics—such as urea 2–10%, lactic acid, and propylene glycol—were used by all patients in this study with a frequency ranging from two times a day to one time per week. Most patients required help from nursing staff or family to apply topical creams. Patients using oral retinoids in addition to topical retinoids had lower ichthyosis scores [73].
2. Speech-language problems in SLS are based both on cognitive deficits (language pathology) and on motor deficits (pseudobulbar dysarthria). The authors recommend early speech and language therapy to improve communication and social integration [74].
3. These authors recommend physical therapy, bracing, ergonomic support, and speech-language therapy to prevent contractures and improve daily functioning. Emollients with keratolytics are the mainstay of skin treatment. Their group has had varying success with topical calcipotriol, and acitretin [75].

1. Three children were treated with acitretin (dose range 0.3–0.5 mg/kg/day). Improvement in their skin helped with PT and orthopedic management. Side effects for the SLS patients included dry skin and lips, skin fragility, and pruritus [42].
2. Retrospective study of 34 Swedish patients (5 children) with Sjogren-Larsson Syndrome. Nineteen patients were treated with oral acetretin at doses ranging from 10 to 5 mg a day, and had lower ichthyosis scores than those not treated with acetretin. Some patients reported increased itching with acetretin, which improved with a decrease in the dose [73].
3. Five patients with SLS (ages 14–21 years) were treated with zileuton (leukotriene B4 inhibitor) for 3 months, with statistically significant improvement in pruritus scores, but no change in neurologic symptoms or parameters. Leukotriene B4 degradation is impaired in SLS and has a role in the etiology of pruritus [76].
4. A 3-year-old boy with SLS was treated with montelukast sodium 10 mg a day, and had significant reduction in pruritus and improvement in behavior [77].
5. The authors treated a 15-year-old boy with SLS with calcipotriol topical (<100 g/week) with improvement in the skin thickening [78].

1. Five children with SLS aged 5 months to 8 years were given a low-fat diet with supplemental medium-chain fatty acids. Neither skin lesion symptoms nor neurological symptoms improved [79].
2. Two patients were treated with a low-fat diet with fatty acid supplementation (different from the above study). One patient who started early in infancy improved; the other did not [80].

Table 5.14 First line therapies

Topical keratolytics (D)
Physiotherapy (D)
Speech therapy (D)

Table 5.15 Second line therapies

Oral Acitretin (D, E)
Zileuton
Montelukast sodium
Topical calcipotriol

Table 5.16 Third line therapies

Dietary modification (D, E)

Other Disorders of Differentiation: Darier Disease, Palmoplantar Keratodermas

Darier Disease

Darier disease is an autosomal dominant disorder caused by a mutation in *ATP2A2*, which encodes sarcoplasmic reticulum Ca2+-ATPase (SERCA2), thereby affecting cellular calcium. Darier most commonly presents in teenage years, with greasy, keratotic papules appearing in a seborrheic distribution (Fig. 5.7). Mucosal and nail alterations, as well as psychiatric disorders, can be observed. Patients have an increased propensity toward *S. aureus* and *H. simplex* infections.

Management Strategies

The eruption of Darier can be exacerbated by sweat, heat, and infections. First-line therapy consists of controlling these modifiable external factors with gentle skin care, emollients, and infection prevention. Darier disease responds to topical and oral retinoids, although long-term therapy is required for continued control.

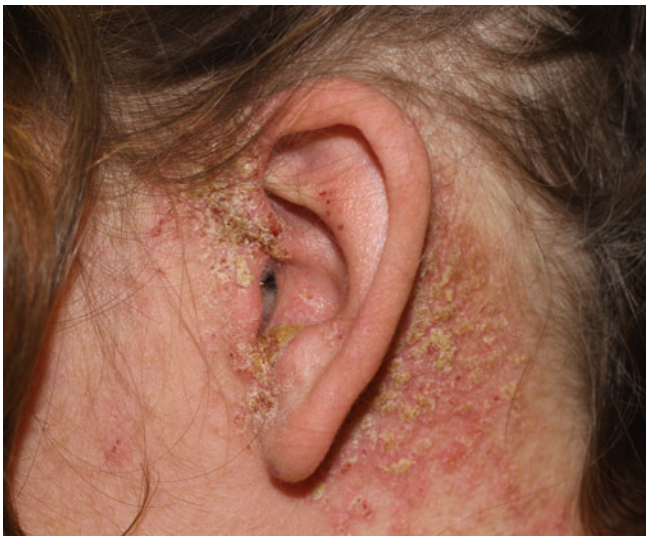

Fig. 5.7 Darier disease with hyperkeratotic papules in a seborrheic distribution

Table 5.17 First line therapies

Topical retinoids – E
Control of infections (i.e., bleach baths, chlorhexidine wash, antibiotics as needed)
Control of irritation (i.e., simple emollients, soap substitutes, cool cotton clothing)

Table 5.18 Second line therapies

Oral retinoids-A
Topical tacrolimus[a]

[a]No studies in children

Table 5.19 Third line therapies

PDT–D
Topical 5-fluorouracil[a]
Surgery + laser[a]
Prednisolone for vesicobullous variant[a]
Cyclosporine for eczematous variant[a]

[a]No studies in children

Investigations Recommended

- Biopsy
- Genetic testing if available and counseling for the patient and family
- Culture for secondary infection as appropriate

1. Adapalene 0.1 % gel was applied once daily to one side of the abdomen of a 12-year-old boy, while vitamin D3 (tacalcitol) ointment was applied to the other. After 2 months, there was marked improvement on the adapalene side and no improvement on the tacalcitol side. No adverse effects were noted [81].
2. Two teenage patients with mild Darier disease were treated once daily for 2 weeks. Their limited disease responded completely, with no side effects reported [82].
3. Lesional skin cultures were positive in 81 % of 75 adults with Darier disease; 83 % of these grew *S.aureus*. Having a positive culture in lesional skin or in the nares was associated with greater affected skin area and disease severity, as well as lower related quality of life [83].

1. This double-blind, randomized study compared the efficacy and tolerability of acitretin versus etretinate in adults and some teenagers with Darier disease. Both groups had similar rates of clearing, as well as mild mucocutaneous side effects [84].
2. In children with various disorders of keratinization (including a patient with Darier disease) on long-term acetretin therapy, side effects were mild and self-limited. Most commonly, patients reported dose-dependent mucocutaneous dryness. No irreversible toxicities were noted [42].

1. A 9-year-old girl and a 18-year-old boy achieved complete remission at 3 months after initiating topical retinoids and one course of PDT (light curettage followed by Met-ALA × 3 h + 8 min under a visible red light diode lamp). Tretinoin cream 0.05 %, once daily was started 1 week post-PDT and continued for 3 months [85].
2. A 20-year-old woman experienced almost complete clearance after 1 month of treatment of her trunk and limbs daily, and her face and flexures every other day, with 1 % 5-fluorouracil cream. Treating with 5-FU may be a safer alternative to treating with topical or oral retinoids in women of childbearing potential [86].

Palmoplantar Keratodermas

Thickening of the palms and the soles is called palmoplantar keratoderma (PPK) (Fig. 5.8). This umbrella term encompasses a wide range of heterogeneous inherited and acquired disorders, which are further categorized as diffuse, focal, or punctate. A full history and physical must be obtained in order to determine if PPK is symptomatic or part of a syndrome. Most PPKs presenting in childhood are inherited, but PPK can also be acquired (caused by infections, medications, malignancies, or systemic disease) or associated with other dermatoses.

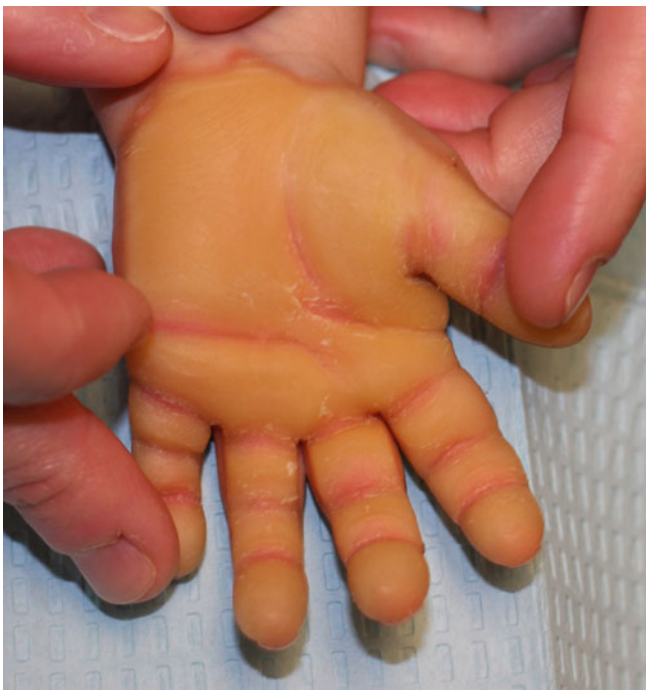

Fig. 5.8 Palmoplantar Keratoderma in a toddler

Management Strategies

Therapy can be difficult, as most treatments are short-acting, and long-term remission is almost impossible. Topical keratolytics are often first line, but oral retinoids are appropriate for patients with significant functional impairment.

Investigations Recommended

- Biopsy
- Genetic testing as appropriate
- Fungal and/or bacterial swabs if concern regarding secondary infection

1. Two children with transgrediens PPK responded partially to topical salicylic acid and glucocorticoids [87].
2. In two teenage children, the keratoderma improved with 2 weeks of high doses of vitamin A daily (100,000 IU), supplemented by 12% salicylic acid ointment in the morning and 6% coal tar and 3% salicylic acid ointment at night [88].

1. A 3-year-old girl with Papillon Lefèvre syndrome was treated with a tapering dose of acitretin for 24 weeks and then managed topically. She had mildly elevated cholesterol while on acitretin, which normalized with discontinuation [89].

Table 5.20 First line therapies

Topical retinoids – D
Topical keratolytics – E

Table 5.21 Second line therapies

Systemic retinoids – D

Table 5.22 Third line therapies

Topical calcipotriol – E
Biotin – E
PUVA – E
5-FU[a]
Surgery, dermabrasion, CO_2 laser – E

[a]No studies in children

2. Thirty-three patients (including 12 children) with a disorder of keratinization were followed for 4 months, with most showing improvement or remission. Optimal dosage in children was found to be 0.7 ± 0.2 mg/kg. Patients with Papillon-Lefèvre syndrome had better results than patients with other types of PPK [90].
3. Retrospective study of 18 young adults/children with Papillon-Lefèvre syndrome; half were treated with retinoids (mostly etretinate), while the other half served as controls. Systemic retinoids improved their skin disease, but not their periodontal health [91].

1. PPK did not improve with calcipotriol [59].
2. The PPK of one of three families with Unna-Thost PPK improved with biotin supplementation (dosage 50 mg/day) [92].
3. Two children with Olmsted syndrome and severe mutilating palmoplantar keratoderma on oral retinoids were treated with full thickness excision followed by skin grafting. Results of long-term follow up showed improvement of function of hands and feet. Hyperkeratosis recurred, but was less severe. Additional thickening was managed by CO_2 laser or mechanical removal and continuing post-operative systemic retinoid therapy [93].
4. A 5-year-old girl with severe focal PPK (possibly Huriez syndrome) was treated with tangential excision to deep dermis with delayed split-thickness skin grafting. The graft did not take and immediate disease recurrence was noted after surgery. The authors suggested deeper excision to the level of the aponeurosis, but noted the risk of growth restriction in children if the graft is placed directly on plantar aponeurosis [94].
5. An 11-year-old girl with congenital PPK showed significant improvement after 5 months of bath PUVA, and almost complete resolution by 1 year of treatment with maintenance for at least a year off therapy [95].

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Hereditary Disorders of the Dermis

6

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Ehlers Danlos Syndrome

Clinical Features

The term Ehlers-Danlos syndrome (EDS) refers to a group of inherited connective tissue disorders with different underlying genetic defects. An outdated classification of the various subtypes of EDS based on clinical presentation has been discarded in favor of the more recent molecular-based Villefranche classification. Despite the revised classification, new subtypes continue to be identified as the genetic basis of EDS subtypes is further elucidated. Of the established subtypes, the ones most commonly encountered include the classical, vascular, and hypermobile types [1–3].

Classical EDS is a dominantly inherited condition, though severity within the same family can vary significantly. It is characterized by mutations in type V collagen, resulting in marked skin hyperextensibility (Fig. 6.1), widened atrophic scars (Fig. 6.2), and generalized joint hypermobility. Additional cutaneous signs include easy bruising, subcutaneous spheroids, and molluscoid pseudotumors.

The clinical features of vascular EDS can be very subtle, and at times the diagnosis is only made after a life-threatening vessel rupture or sudden death in the third or fourth decade of life. The presenting feature in childhood is often extensive, unexplainable bruising at sites not prone to trauma. Unlike classical EDS, the skin in vascular EDS is not hyperextensible, though does tend to be thin, with visible underlying vessels, particularly on the trunk. Some patients have a characteristic facies with a thin, pinched nose, prominent eyes, lobeless ears, and a lack of subcutaneous fat. Joint hypermobility is generally restricted to the small joints of the hands. The most concerning features of vascular EDS are arterial dissection, rupture, and aneurysm. Bowel and uterine rupture may also occur. Pneumothorax may be a more common manifestation in childhood, as vessel and hollow organ rupture typically do not occur until the third or fourth decades of life. Vascular EDS is caused by mutations in type III collagen.

Hypermobile EDS remains a diagnostic challenge, as there is no diagnostic test or established genetic basis to aid in diagnosis. In addition, joint hypermobility can be dominantly inherited in many families, and it continues to be debated whether hypermobile EDS and joint hypermobility syndrome actually represent the same condition. There are no life-threatening complications associated with this form of EDS, though patients can have significant morbidity related to chronic joint pain. Patients are also more likely to develop postural orthostatic tachycardia syndrome (POTS) and other forms of autonomic dysfunction that can negatively impact quality of life.

Management Strategies

For all suspected EDS patients, a full history and physical exam are necessary, including a detailed pedigree. Clinical examination should include a full skin exam, as well as assessment of the joints. Skin biopsy may be helpful in patients where certain subtypes are being considered.

Patients with classical EDS have a wide variation in clinical severity. All patients should follow regularly with cardiology, with joint hypermobility managed by rheumatol-

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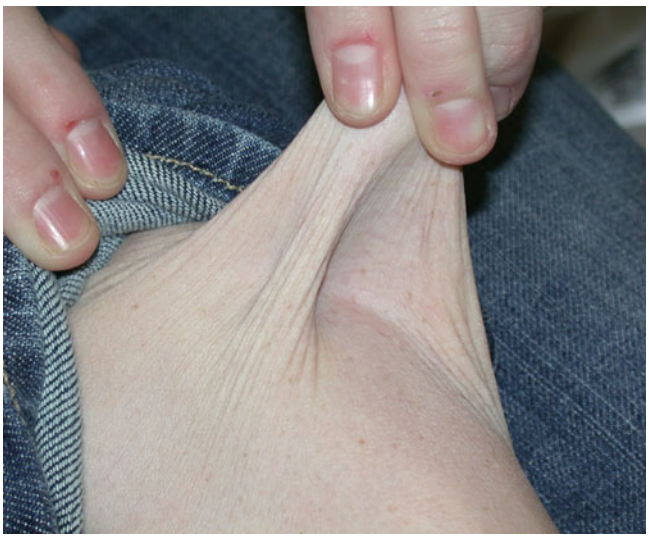

Fig. 6.1 Ehlers-Danlos syndrome. Increased skin laxity

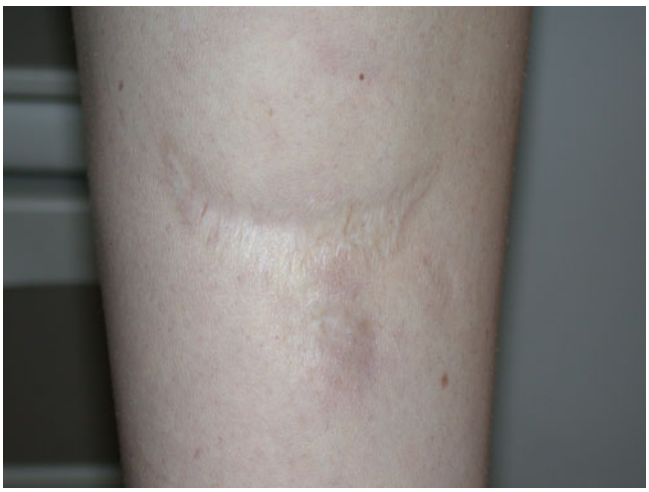

Fig. 6.2 Ehlers-Danlos syndrome. Widened fish-mouth scar with atrophic skin on the leg

ogy, physical therapy, and occupational therapy. Patients should make any surgeons aware of their condition to allow for appropriate suturing techniques.

For vascular EDS, in addition to the standard history and physical exam, baseline imaging of the arterial tree should be included. This can be accomplished with computed tomography angiography (CTA) at a young age to minimize sedation, but eventually should transition to magnetic resonance angiography (MRA). Conservative medical management is preferred when possible, as overly aggressive surgical and endovascular interventions can cause unnecessary morbidity and mortality. Patients should follow regularly with cardiology, though the role for repeat imaging and preventative medication is not well defined at this time. A recent study with a beta-blocker celeprilol found a significant decrease in arterial events, suggesting some benefit in complication prevention in these patients. Angiotensin receptor blockers have shown additional promise in delaying complications in animal models, and may play an increasing role in management of these patients in the future. For self-management, patients with vascular EDS should avoid potentially harmful activities, such as contact sports, heavy lifting, and any cause of rapid acceleration and deceleration.

Patients with hypermobile EDS should be followed by rheumatology, physiotherapy, and occupational therapy. Referral to pain clinics can be helpful to manage the significant pain that can develop over time with this condition. Connection with support groups as well as proper counseling by a psychologist or a psychiatrist can be beneficial to affected patients. The Ehlers Danlos National Foundation (EDNF) provides educational resources for patients to learn about their diseases and connect with each other.

Specific Investigations Recommended [4]

For diagnosis
Skin examination
Joint examination for hypermobility
Skin biopsies for histology, electron microscopy, and fibroblast culture
Genetic testing
Cardiology assessment including echocardiogram
Carotid duplex ultrasound (vascular EDS)
Full body MR angiography (vascular EDS)
For monitoring
Regular cardiology follow-up
Annual carotid and abdominal ultrasounds for arterial screening in asymptomatic patients (vascular EDS)
Serial MR angiography every 6–12 months with known arterial complications (vascular EDS)
DEXA scan at diagnosis especially in those at risk

First Line Therapies

As discussed above, most management of patients with EDS is directed toward appropriate monitoring and referrals for supportive care. Patients with EDS are predisposed to functional bowel disorders (i.e. gastritis and irritable bowel disease), low blood pressure, pain, temporomandibular disorder, and gum disease. Proper management of these disease manifestations by specialists is of important therapeutic consideration. Multidisciplinary clinics around the country are forming to improve management of these patients. There is limited medical treatment available currently to prevent

symptoms associated with vascular EDS. Beta-blockers and angiotensin receptor blockers show promise as possible preventative measures in patients with vascular EDS.

Celiprolol 100–400 mg twice daily (vascular EDS)	A
Losartan 2 mg/kg/day (vascular EDS)	

Marfan Syndrome

Clinical Features

Marfan Syndrome is an autosomal dominant inherited disorder of connective tissue caused by mutations in fibrillin 1, an important structural component of the microfibrils which compose elastin and other connective tissues, with a highly variable clinical presentation. The diagnosis is made clinically based on family history, mutational analysis, and hallmark criteria involving three organ systems: the ocular, skeletal, and cardiovascular systems. The National Marfan Foundation Website contains the most current diagnostic criteria necessary for a diagnosis.

Ectopia lentis or displacement of the lens from the center of the pupil affects 60 % of patients with Marfan Syndrome and is an important diagnostic feature. Other visual findings include myopia (the most common visual finding), retinal detachment, glaucoma, and early cataract formation.

Joint laxity and bone overgrowth are also characteristic findings, and the changes in the skeleton are progressive during periods of rapid growth during childhood. Overgrowth of the bones leads to extremities which are disproportionately long for the size of the body known as dolichostenomelia. Rib bone overgrowth may lead to pectus excavatum or pectus carinatum. Scoliosis is common and may become progressively worse. Assessment for the skeletal features characteristic of Marfan Syndrome is important when calculating a patient's Systemic Score, a clinical assessment tool used when establishing a diagnosis of Marfan syndrome, also available at the National Marfan Foundation Website. The different skeletal features that are considered and weighted include the following: pectus carinatum, pectus excavatum, chest asymmetry, hindfoot deformity, pes planus, scoliosis, thoracolumbar kyphosis, reduced elbow extension, a reduced ratio of the upper body segment length to the lower body segment length, an increased arm span to height ratio, and protrusio acetabulae which refers to an abnormally deep acetabulum with accelerated erosion. The thumb sign, when the thumb is noted to extend beyond the palm when the patient makes a fist, and the wrist sign, when the thumb and fifth digit are able to overlap when wrapped around the patient's other wrist, are also skeletal findings that increase a patient's Systemic Score and make a diagnosis more likely. Characteristic skeletal facial features to consider include a long narrow face, enophthalmos, downward slanting palpebral fissures, malar hypoplasia, micrognathia, and a highly arched palate with crowding of teeth.

The most serious manifestations of Marfan Syndrome affect the cardiovascular system and include progressive aortic root dilatation with a risk of aortic dissection or rupture, typically in adulthood, as well as aortic insufficiency. Other cardiac findings include mitral valve prolapse with or without mitral regurgitation and tricuspid valve prolapse with possible enlargement of the proximal pulmonary artery. Although mitral valve prolapse and mitral regurgitation is typically tolerable for the majority of patients, the leading cause of cardiovascular morbidity and mortality and the main indication for cardiovascular surgery in children with severe Marfan syndrome is mitral valve prolapse with associated ventricular dysfunction. Marfan syndrome patients are at an especially increased risk of cardiac complications while pregnant due to risk of rapid aortic root enlargement and aortic dissection or rupture during pregnancy, delivery and the postpartum period. A sufficiently dilated aortic root, calculated as a Z score which takes into account norms for patient's age and size, is used as a diagnostic criteria for Marfan syndrome while mitral valve prolapse is factored into the Systemic Score.

The only cutaneous finding in Marfan Syndrome is striae distensae. Other diagnostic findings include frequent hernias, lung bullae which may progress into spontaneous pneumothorax, and dural ectasia or stretching of the dural sac in the lumbosacral region which puts patient at risk for bone erosion, nerve entrapment, and CSF leaks. The presence of any of these findings adds to the Systemic Score.

Management Strategies

Management of Marfan Sydrome is aimed at diagnosing the condition, trying to prevent cardiovascular complications, and managing associated complications. Evaluations by specialists in ophthalmology, orthopedics, cardiology, and medical genetics who are familiar with Marfan Syndrome are necessary to establish the diagnosis, and determine the extent of disease. Management depends on severity of involvement but typically involves a multidisciplinary approach using genetics, cardiology, ophthalmology, orthopedics, and cardiovascular surgery.

The highest morbidity and mortality in affected patients is related to cardiovascular disease but the life expectancy approximates that of the general population with proper

management of the cardiovascular manifestations. Medication management with agents that reduce hemodynamic stress on the aorta are paramount with progression to cardiothoracic surgical intervention when the aorta becomes excessively dilated or when ventricular dysfunction develops from the mitral regurgitation.

Specific Investigations Recommended

For diagnosis
• Detailed medical history
• Detailed family pedigree
• Complete examination with special attention to skeletal abnormalities and striae distensae by medical genetics or physician with expertise in Marfan Syndrome
• Ophthalmologic exam including slit lamp exam looking for lens subluxation
• Echocardiogram to measure aortic root and assess cardiac valves
• Genetic testing for fibrillin 1 mutation
For treatment
• Regular evaluation by medical geneticist
• Annual ophthalmologic evaluation to assess vision acuity and the development of glaucoma and/or cataracts
• Evaluation by an orthopedist to manage scoliosis and other skeletal abnormalities
• Regular evaluation by a cardiologist; frequency of visits determined by severity of disease
• Serial echocardiogram annually to monitor aorta and cardiac valve; more frequently when aortic root diameter >4.5 cm or when the rate of aortic dilation >0.5 cm per year
• Pulmonary imaging with CXR or high resolution CT when concern for pneumothorax
• MRI of lumbosacral spine when concern for dural ectasia
• Care by a high risk obstetrician with pregnancy

First Line Therapies

- Beta blocker therapy should be initiated in all patients at time of diagnosis and continued throughout their lifetime to reduce hemodynamic stress on the aorta wall and to prevent dilatation based upon recommendations of the American Heart Association and American College of Cardiology. Atenolol is generally the preferred medication due to selectivity for beta 1 receptors although propranolol has been used as well. – A [5–7]
- Aggressive early correction of vision abnormalities with glasses to prevent amblyopia – E
- Antibiotics for prevention of subacute bacterial endocarditis prior to dental procedures in patients with valve abnormalities [8]
- Orthotics for symptomatic pes planus – E
- Palate expander and orthodontia when indicated – E
- Bracing for scoliosis when indicated – E

Second Line Therapies

- Losartan, an ACE-inhibitor, has recently been found in a randomized trial to be superior to placebo in preventing aotic root dilatation over 3 years of use. Another study comparing losartan to atenolol found a similar rate of reduction of aortic root dilatation with both medicines. Questions remain as to appropriate dosing of losartan for this indication, timing of initiation of therapy, and whether losartan and beta blockers should be used individually or together – A [9, 10]
- Hormone supplementation to accelerate puberty and limit adult height in cases where extreme adult height is predicted – E [11]

Surgical Considerations

- Surgical repair of the aorta when the maximal measurement approaches 5.0 cm in adults or older children, the rate of increase of diameter nears 1.0 cm per year, or there is progressive and severe aortic regurgitation – D
- Removal of the lens (surgical aphakia) when the lens is dislocated and mobile or interfering with vision – D
- Surgical stabilization of severe scoliosis – D
- Surgical correction of severe pectus excavatum – E
- Surgical correction of symptomatic protusio acetabulae – E
- Surgical correction of severe pes planus refractory to orthotics – E
- Pleurodesis or removal of surgical blebs if recurrent pneumothorax – E
- Use of supporting mesh when hernias are surgically repaired to prevent recurrence – E

Cutis Laxa

Clinical Features

Cutis laxa (CL) is a heterogenous group of inherited and acquired disorders characterized by abnormal elastic tissue in the skin and other organs [12]. The skin of cutis laxa tends to be hypoelastic, redundant, and hangs in folds most readily apparent in the axillae, groin, and hands (Fig. 6.3). Involvement of the face leads to a prematurely aged appearance. As opposed to the skin of Ehlers Danlos syndrome which stretches and recoils quickly, the skin of cutis laxa

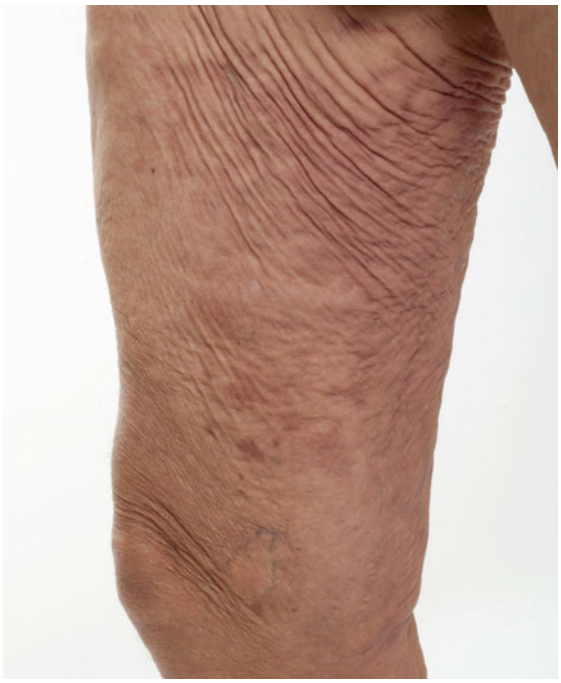

Fig. 6.3 Cutis laxa. Hypoelastic, redundant skin folds over the upper thigh and groin

pulls away easily from underlying structures but does not return to its usual position quickly when released. It also does not bruise easily and is not characterized by poor scarring.

Acquired CL typically occurs in adulthood and can follow medication use, an inflammatory process of the skin, or be associated with malignancy, autoimmune, or other systemic disease. We will focus here instead on the hereditary forms of cutis laxa, which are distinguishable based on their inheritance pattern, pathogenic mutation, and variable extracutaneous features, and present in infancy or childhood.

Autosomal dominant CL is due to a mutation in ELN resulting in a defective tropoelastin protein that is unable to bind properly to the fibrillin scaffold. It is highly variable even within families but characterized predominantly by cutis laxa of the skin that develops in childhood or early adulthood and progresses with time. Distinctive facial features include a long philtrum, high forehead, prominent ears with large lobes, and beaked nose. Patients have an increased tendancy to develop hernias. Cardiopulmonary manifestations range from mild to severe, and although many patients have a normal life span, some will develop bronchiectasis, emphysema, aortic aneurysms, and pulmonary artery disease.

The skin and ear findings of autosomal recessive cutis laxa (ARCL) type 1 are similar to those of the dominant form but are notable at birth. Other features include hernias, growth and motor delays, and a higher likelihood of systemic complications including emphysema, diaphragmatic defect, tortuous arteries, and aneurysms leading to a high risk of death from cardiopulmonary complications in childhood. Two variants of pathogenic mutations have been associated with ARCL which differ in their cardiovascular manifestations. Patients with FBLN4/EFEMP2 mutaions, also known as ARCL Type Ia are at risk of aortic aneurysm but not supravalvular aortic stenosis while those with FBLN5 mutations, also known as ARCL Type Ib, are at risk of supravalvular aortic stenosis but not aneurysm. In addition, ARCL Type Ia has characteristic retrognathia, hypertelorism, joint laxity and congenital hip dislocation, while ARCL type Ib lacks these features and has bladder diverticulae.

Autosomal recessive CL type II comes in two variants distinguished by their pathogenic mutations and clinical features. ARCL-IIA is caused by a mutation in ATP6VOA2, which leads to problems with secretion of tropoelastin, while ARCL-IIB is caused by a mutation in PYCR1 and a resulting defect in proline metabolism. While both share common features, including inelasticity of skin, retrognathia, hernias, mental retardation, intrauterine growth retardation, postnatal growth delay, and scoliosis, ARCL-IIA specifically is associated with aortic aneurysm, bladder diverticula, patent anterior fontanelle, hypotonia, and delayed motor development. On the other hand, ARCL-IIB has unique features of osteoporosis, athetoid movements, and corneal opacities.

A less known severe variant of cutis laxa is autosomal recessive CL type III (Progeroid syndrome of De Barsy or CL-corneal clouding-mental retardation syndrome) characterized by progeroid appearance, reduced subcutaneous fat, corneal opacities, athetoid movements, and mental retardation. Another rare variant known as autosomal recessive CL with severe pulmonary, gastrointestinal and urinary abnormalities (Urban-Rifkin-Davis syndrome) is distinguished by emphysema, atelectasis, tracheomalacia, diaphragmatic hernia, hydronephrosis, and diverticulae of the bladder and gastrointestinal tract, which is frequently fatal in infancy.

X-linked cutis laxa (XLCL), or Occipital Horn yyndrome, was formerly classified as a type of Ehlers-Danlos yyndrome. Allelic to Menkes disease, this variant of CL is caused by a defect in a copper transporting adenosine triphosphatase which leads to a functional deficiency of copper and impairs enzymes essential in elastic tissue production. As opposed to patients with Menkes who frequently die before age 4 due to severe neurologic defects, patients with XLCL have predominantly connective tissue abnormalities, including the hallmark downward-pointing exostoses on the occipital bone as well as inelastic skin with a droopy face at birth, occasional pili torti of hair, bladder diverticulae, urinary tract infections, inguinal hernias, and orthostatic hypotension.

Management Strategies

There is no cure for cutis laxa, and management is focused instead on making the diagnosis and then trying to prevent

and manage associated complications. Once the diagnosis is suspected, affected patients should undergo comprehensive evaluation to identify the type of cutis laxa and extent of the condition and any associated systemic manifestations. Management of the patient involves a multidisciplinary approach, which varies depending on the type and extent of disease, but may involve specialists in genetics, plastic surgery, cardiology, neurology, cardiothoracic surgery, ophthalmology, gastroenterology, and urology. Because the extracutaneous manifestations differ substantially, the individual management of a patient must be specifically tailored and the recommendations listed below may not be clinically indicated or entirely complete for every patient.

For diagnosis
• Skin biopsy with elastic stains to evaluate decreased elaunin fibers and fragmentation of elastic fibers in reticular dermis. Findings may be minimal and does not allow differentiation of subtype of cutis laxa
• Skin biopsy for electron microscopy may further elucidate abnormalities in elastic tissue production and may assist in differentiation of cutis laxa type but not widely available
• Referral to medical genetics for complete evaluation
• Genetic testing for known pathogenic mutations
• CXR
• 3-dimensional CT scan
• Pulmonary function tests
• Echocardiogram
• MRA from head to pelvis
• Kidney ultrasound
• Barium enema
• Voiding cystouretogram
For treatment
• Serial CXR, CT scan, pulmonary function tests, echocardiogram, MRA, kidney ultrasound, barium enema, and voiding cystoureterogram as clinically indicated
• Subspecialty referrals that are frequently needed: plastic surgery, pulmonary, general surgery, cardiology, urology, cardiothoracic surery, physical therapy

First Line Therapies

- Education on tobacco avoidance and sun protective measures – E
- Plastic surgery correction of redundant skin folds – E
- Symptomatic management of pulmonary emphysema with special attention prior to surgeries – E
- Serial monitoring of aortic aneurysms and other arterial abnormalities with referral for surgical management as needed – E
- Surgical management of hernias – E
- Surgical management of diverticula – E
- Consider beta blocker therapy in severe types of cutis laxa with evidence of aorta dilatation to prevent further dilatation based on evidence of benefit in Marfan syndrome but not formally studied in cutis laxa – E [13, 14]

Pseudoxanthoma Elasticum

Clinical Features

Pseudoxanthoma elasticum (PXE) is a multisystem disorder of ectopic mineralization with cutaneous, ocular, and cardiovascular manifestations. The prevalence is around 1 in 50,000, with a slight female predominance. PXE is inherited in an autosomal recessive fashion and is caused by mutations in *ABCC6*, an ABC-cassette transporter located predominantly in hepatocytes, although its exact function remains unclear. Progressive calcification of elastic fibers in target organs occurs, leading to findings within the dermis of the skin, mid-sized arteries throughout the body, and Bruch's membrane of the eye.

PXE most commonly presents with cutaneous findings, often in the first or second decade of life. Soft yellowish papules appear at the neck and other flexural areas (Fig. 6.4), with later coalescence into firmer plaques, along with the development of loose, redundant skin at the axillae and groin. Yellowish papules may also appear on mucosal surfaces, especially the lower lip, and prominent creases may be seen on the chin. Skin biopsy will reveal distorted, fragmented elastic fibers in the mid to deep reticular dermis, or in more advanced cases, calcium deposits on the elastic fibers.

Angioid streaks of the eyes develop in nearly all PXE patients by the third decade of life. This finding is caused by breaks in the calcified elastic lamina of Bruch's membrane, the innermost layer of choroid. Over time, this can lead to cho-

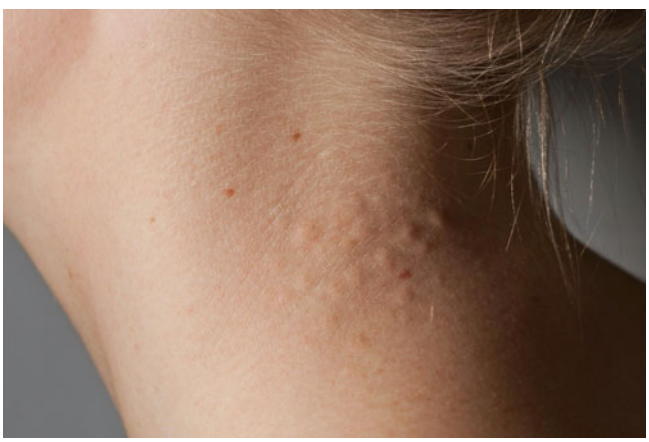

Fig. 6.4 Pseudoxanthoma elasticum. Soft, yellowish papules containing distorted fragmented elastic fibers on the neck

roidal neovascularization, followed by hemorrhage and scarring, with progressive loss of vision and even blindness. Other ocular findings may be present, including mottled, "peau d'orange" changes of the retinal pigmented epithelium.

Cardiovascular manifestations are the primary cause of premature mortality from PXE. The consequences of arterial calcifications can include intermittent claudication, loss of peripheral pulses, renovascular hypertension, angina pectoris, myocardial infarction, and stroke. Within the gastrointestinal tract, arterial calcifications can lead to gastrointestinal hemorrhage.

Management Strategies

The diagnosis of PXE requires, at a minimum, the presence of retinal angioid streaks in combination with characteristic skin lesions that show the diagnostic histopathological findings of calcified dystrophic elastic fibers. The diagnosis may be also be made via molecular genetic testing for *ABCC6* mutations, especially in patients who are too young to demonstrate the ocular or cutaneous manifestations.

Unfortunately, there currently is no proven treatment for the systemic mineralization seen in PXE. For all patients, a healthy lifestyle with diet, exercise, weight control, and avoidance of smoking and excessive alcohol should be emphasized in order to minimize other cardiovascular risk factors. Skin findings may be ameliorated by surgical excision of areas of redundant skin, or by the application of resurfacing lasers to improve the skin texture. Research on PXE has focused on elucidating the function of the ABCC6 transporter. It remains unclear what molecules are transported by the ABCC6 transporter. Recent research has shown that ABCC6 transporters in the liver mediate the cellular release of ATP, which is converted extracellularly into AMP and inorganic pyrophosphate (PPi), a mineralization inhibitor. Patients with PXE demonstrated lower plasma concentrations of PPi, suggesting that supplementation with PPi could represent a future avenue for treatment [15–18].

Studies in mouse models have shown that increasing the magnesium content fivefold that of a normal diet can prevent ectopic mineralization and, likewise, studies with magnesium-containing phosphate binders have shown similar effects. A clinical trial is currently under way to test the efficacy of supplemental dietary magnesium in human patients with PXE [19–27].

While studies in animal models have demonstrated accelerated mineralization in the setting of warfarin therapy, studies evaluating the role of supplemental vitamin K in preventing or slowing the mineralization process have been disappointing. Thus while warfarin therapy should be avoided if possible in PXE patients, supplemental vitamin K is not recommended [28–31].

In the past several years, case reports and series from the ophthalmology literature have documented the role of intravitreous injection of vascular endothelial growth factor receptor antagonists as a means to treat choroidal neovascularization and prevent loss of visual acuity and blindness. However, it should be noted that acute thromboembolic events have occurred following the administration of these medications [32–36]. Other treatments for choroidal neovascularization in patients with PXE have been attempted, including laser photocoagulation, transpupillary thermotherapy, macular translocation surgery, and photodynamic therapy, with predominantly disappointing results [37, 38].

Other areas of research include transplantation with hepatoblastic lineage cells or other pluripotent stem cells, as well as use of read-through molecules, which allow transcription of the *ABCC6* gene even in the presence of nonsense mutations. These treatments have not been studied in humans, however [39, 40].

Investigations Recommended

For diagnosis
Skin biopsy with stains for calcium (von Kossa) and elastin (Verhoeff-Van Gieson)
Genetic testing for *ABCC6* mutations for diagnosis or family planning
Complete examination by ophthalmology
For surveillance
Biannual evaluation by ophthalmology
Serial evaluation by cardiology
Baseline EKG
Baseline Echocardiogram
Baseline and serial serum lipids
Monitoring for black, tarry stools and referral to gastroenterology if necessary
Referral to other specialties such as dermatology, vascular surgery, plastic surgery, or nutrition depending on patient presentation

First Line Therapies

- Surgical excision for lax skin at neck or arms – D [41, 42]
- Fractional carbon dioxide laser for improvement in skin texture – E [43]
- Intravitreal vascular endothelial growth factor receptor antagonists (bevacizumab or ranibizumab) for patients with choroidal neovascularization – D [32–36]
- Other treatments should be tailored in consultation with specialists depending on disease presentation and severity

Second Line Therapies

- Macular translocation surgery for patients with extensive choroidal neovascularization – D [37, 38]

Elastosis Perforans Serpiginosa

Clinical Features

Elastosis perforans serpiginosa (EPS) is a rare form of perforating disorder that may be inherited or acquired. About 40 % of cases occur in conjunction with other genetic syndromes, including Down syndrome, scleroderma, Rothmund-Thomson syndrome, acrogeria, Marfan syndrome, osteogenesis imperfect, pseudoxanthoma elasticum, and Ehlers-Danlos syndrome. The medication penicillamine has also been reported to induce EPS. EPS can also be an isolated, idiopathic skin finding. Familial cases have been reported, with no consistent pattern of inheritance.

EPS presents with keratotic papules <5 mm arranged in an annular or serpiginous fashion. The lateral neck is the most common location, but lesions may occur on the upper extremities, face, or other flexural areas (Fig. 6.5). Most lesions are asymptomatic, but mild pruritus can occur. EPS often resolves spontaneously after a period of up to several years, but may leave atrophic scars. Biopsy of EPS shows transepidermal elimination of elastic fibers and inflammatory debris with overlying hyperkeratosis and surrounding epithelial hyperplasia. Verhoeff-van Gieson stain will help to identify elastic fibers both within the hyperkeratotic plug and the surrounding epidermis and superficial dermis.

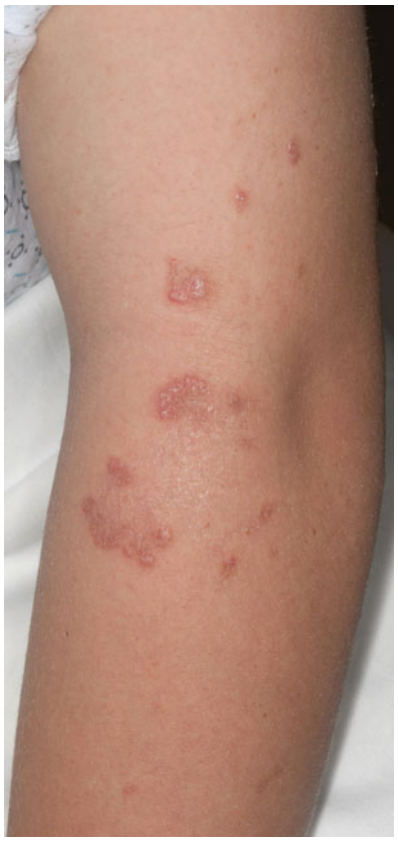

Fig. 6.5 Elastosis perforans serpiginosa. Grouped hyperkeratotic papules distributed in an annular or serpiginous fashion on the left upper arm

Management Strategies

When the diagnosis is uncertain clinically, a skin biopsy can be performed to help clarify the diagnosis [44]. A complete history and physical examination is warranted in all patients with EPS. Further testing for associated connective tissue disorders or genetic disorders should be guided by the results of the history and physical findings. Most clinicians do not routinely perform any further investigations in otherwise healthy patients.

In cases related to penicillamine therapy, the medication should be discontinued, although some case reports suggest that in susceptible patients, the damage is irreversible. There are many therapies that have been used anecdotally for EPS, but to date there have been no large studies or clinical trials, and there is no gold standard for treatment. All modalities of treatment have been associated with mixed success. In asymptomatic cases, observation may be appropriate, as the lesions do resolve spontaneously.

Specific Investigations Recommended

For diagnosis
Skin biopsy
Thorough history and physical examination

First Line Therapies

- Topical or intralesional steroids (doses vary) – E [45]
- Topical tacalcitol (applied daily) – E [46]
- Topical and systemic retinoids (doses vary) – E [47–49]
- Imiquimod 5 % cream (applied daily to three times weekly) – E [50, 51]
- Topical glycolic or salicylic acid (doses vary) – E [45]
- Cryotherapy – E [45, 52–56]
- Electrodessication and curettage – E [45]

Second Line Therapies

- Intralesional steroid (triamcinolone acetonide 40 mg/ml every 15 days for 3 months) plus topical allium cepa-allantoin-pentaglycan gel (twice daily) – E [57]

- Carbon dioxide laser, Erbium:YAG, pulsed dye laser – E [58–60]
- Aminolevulinic acid (7.6 % topical solution) with photodynamic therapy – E [61]
- Cellophane tape stripping – E [45]
- Narrow band ultraviolet B phototherapy for disseminated lesions – E [45]
- Local excision – E [45]
- Dermabrasion – E [45]

Focal Dermal Hypoplasia

Clinical Features

Focal dermal hypoplasia (FDH) is a rare, X-linked dominant condition (95 % of cases are sporadic) that primarily affects female infants, although it may be seen in males who are mosaic for mutations in the PORCN gene. Clinical features of FDH are seen at birth and may affect multiple organ systems, most commonly the skin, skeletal system, and eyes.

Cutaneous findings may occur anywhere on the skin, and consist of atrophic linear erythematous areas of skin and/or hypo- or hyperpigmentation that often follows the lines of Blaschko (Fig. 6.6). Large areas of aplasia that subsequently-heal with atrophy may also be present, accompanied by soft, yellow to brown outpouchings that are caused by herniation of fat through the dermis (Fig. 6.7). Patients commonly go on to develop erythematous papillomas at mucocutaneous junctions that can erode, ulcerate, and bleed. Hair may be sparse or absent on the scalp or other areas of the body, and nails may be dysplastic or hypoplastic. Approximately 80 % of patients will also have skeletal abnormalities. These are varied but can include syndactyly, hypoplasia or absence of digits, polydactyly, scoliosis, costovertebral abnormalities, facial asymmetry, or the rare but unique "lobster claw" deformity. Osteopathic striae may be seen radiologically and may be a helpful clue when the diagnosis is uncertain.

Eye abnormalities are seen in approximately 40 % of patients. They are usually present at birth, and can range in severity from having no impact on vision to blindness. Ocular abnormalities may include colobomas, strabismus, nystagmus, anophthalmia, microphthalmia, aniridia, heterochromia, cataracts, and hypopigmented/hyperpigmented retina. Other organ systems that may be affected include the dental, gastrointestinal, and urogenital systems.

Management Strategies

Management of FDH initially focuses on making an accurate diagnosis, and later on treating manifestations of the disease.

There is no cure for FDH, and treatment is largely supportive. For skin manifestations, care is directed at treating open wounds, preventing infection, and treating excessive granulation tissue. Excessive granulation tissue impedes wound healing in many patients. For those with skeletal manifestations, physical/occupational therapy and surgical intervention may be beneficial, but recommendations are specific to the type of manifestation and complications specific to the patient. Consultations with multiple subspecialists may be required as follows.

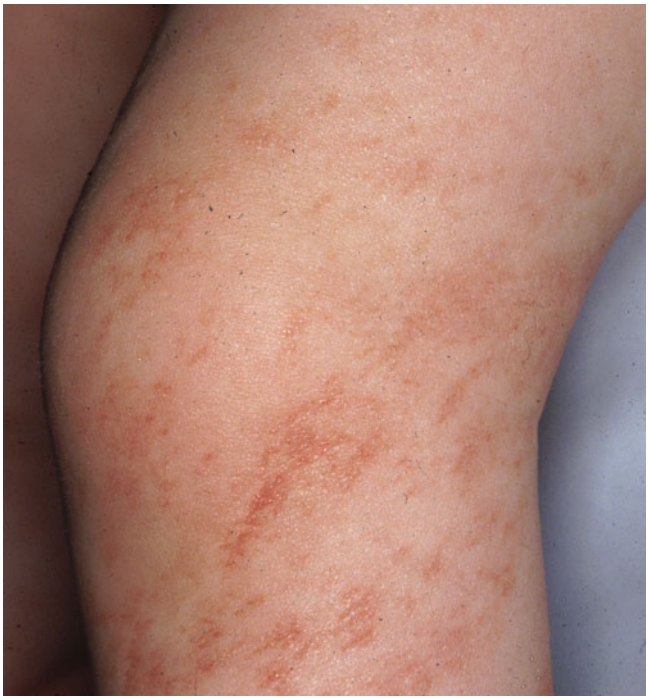

Fig. 6.6 Focal dermal hypoplasia. Linear atrophic erythematous patches on the leg follows the lines of Blaschko

Specific Investigations Recommended

- Skin biopsy of affected skin reveals a normal epidermis that overlies a hypoplastic dermis with reduced collagen. Islands of fat cells are present within the superficial dermis, clinically consistent with herniation of fatty tissue.
- Eye examination to evaluate for ocular abnormalities
- Hearing evaluation to evaluate for hearing defects
- Chest X-ray to evaluate for costovertebral defects or diaphragmatic hernia
- Renal ultrasound to evaluate for structural genitourinary abnormalities
- Genetic testing may be considered to look for PORCN gene mutations

For diagnosis
Skin biopsy
Eye examination
Hearing evaluation
Chest X-ray

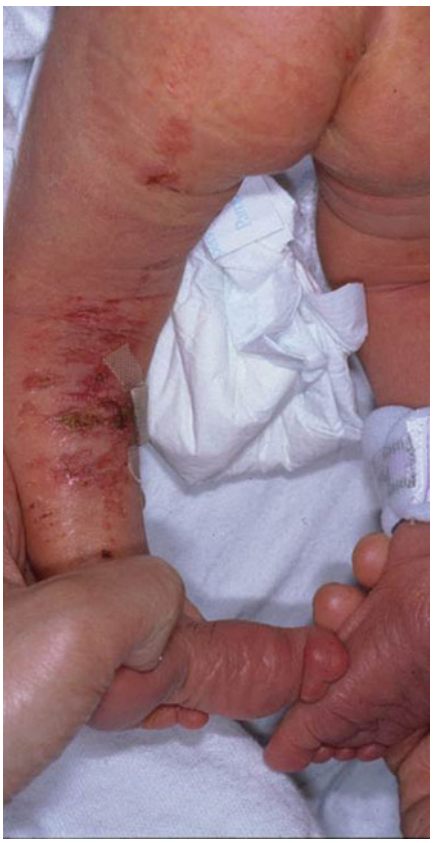

Fig. 6.7 Focal dermal hypoplasia. Large areas of linear patches of aplasia that subsequently healed with atrophy. These areas may also be seen with soft, yellow to brown outpouchings that are caused by herniation of fat through the dermis

Renal ultrasound	
Genetic testing	
For surveillance	
Orthopedic surgery- if skeletal abnormalities present; regular exams to evaluate for scoliosis	
Dental specialties- regular exams are recommended	
Ophthalmology- baseline evaluation and continued follow-up if abnormalities present	
Pediatric surgery- if diaphragmatic hernia or abdominal wall defects present	
Otorhinolaryngology- particularly prior to general anesthesia to evaluate for the presence of oral or airway papillomas that could complicate intubation [62, 63]	
Urology- if abnormalities present	

First Line Therapies

- Wound care and topical antibiotics: for those with significant erosions and areas of aplasia, wound care with topical antibiotics to prevent secondary infection, and use of occlusive dressings until epidermal healing occurs is recommended [64].
- Physical/occupational therapy is recommended for those with impaired function due to their skeletal abnormalities [64].

Topical antibiotics	E
Wound care	E
Physical/occupational therapy	E

Second Line Therapies

Excessive granulation tissue can be very problematic for patients with FDH. Each of the following therapies are generally regarded as conventional treatments for excessive granulation tissue in patients with FDH. (Evidence level E) [64–66]

- Silver nitrate
- Topical or intralesional steroids
- Cryotherapy/curettage
- Surgical excision

Third Line Therapies

- Pulsed dye laser- treatment of the cutaneous lesions of FDH can be difficult to treat. One report described successful decrease in the erythema associated with one patient's atrophic lesions of FDH (Evidence level E) [65]. Photodynamic therapy: Excessive granulation tissue in FDH can be very refractory to conventional means of treatment. Two patients – one adult, and one child – have had successful treatment of excessive granulation tissue refractory to conventional modalities with photodynamic therapy (Evidence level E) [66].

Buschke-Ollendorff Syndrome

Clinical Features

Buschke-Ollendorff syndrome is a rare autosomal dominant genetic connective tissue disorder that is caused by loss-of-function mutations in LEMD3 and is characterized by the presence of connective tissue nevi and osteopoikilosis. Connective tissue nevi generally present in early childhood, but may be present at birth. While the connective tissue nevi can be composed of either elastin or collagen, most are elastomas. When composed of collagen, findings are consistent with dermatofibrosis lenticularis disseminate. They connective tissue nevi are typically asymptomatic, firm flesh-colored to yellow papules and nodules that may coalesce into plaques (Fig. 6.8). They are most commonly asymmetrically present on the trunk or extremities, but may also be present in other areas of the skin, such as the skin folds. They typi-

cally grow in proportion to the child, and the number of lesions present may increase with age.

The other characteristic finding in Buschke-Ollendorff syndrome is osteopoikilosis. Osteopoikilosis consists of asymptomatic "spotting," or skeletal dysplasia, in the bones. This most commonly affects the carpals, tarsal bones, phalanges of hands and feet, pelvis, and epiphyses and metaphyses of long bones. It is typically discovered incidentally if a diagnosis of Buschke-Ollendorff is not initially suspected. While it does not require treatment and does not predispose the patient to fractures, it is important to be aware of these bony changes to avoid confusion with malignant changes and to avoid unnecessary work-up. Although osteopoikilosis may be present early in life, often it may not develop until puberty.

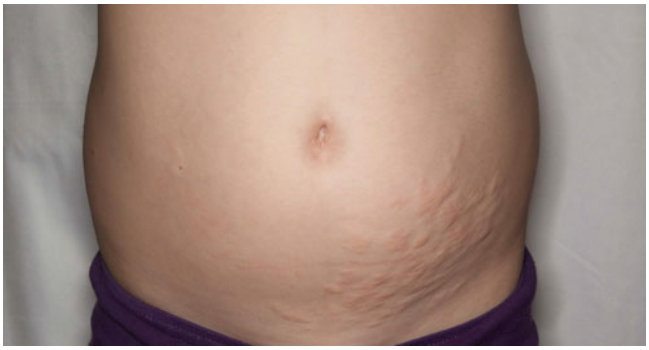

Fig. 6.8 Buschke-ollendorff syndrome. Asymptomatic connective tissue nevi presented as firm flesh-colored to yellow papules on the abdomen

Management Strategies

There is no treatment for Buschke-Ollendorff syndrome. Management focuses on making the correct diagnosis and evaluating the patient for the possibility of osteopoikilosis so that unnecessary concern and work-up is not undertaken. Genetic counseling may also be indicated in affected persons.

Specific Investigations Recommended

- Skin biopsy of affected lesions demonstrate normal to thickened collagen bundles with an increased number of elastic fibers as demonstrated with an elastic fiber stain, such as Verhoeff-van Gieson or orcein.
- Radiographs show small, disseminated, well-circumscribed areas of increased radiodensity located in the epiphyses and metaphyses of long bones, as well as the pelvis, scapula, hands, and feet [67].
- Genetic testing for low-of-function mutations in LEMD3 may be undertaken, but is often not necessary [68].

For diagnosis
Biopsy
X-rays
Genetic testing
For treatment
None

Hutchinson-Gilford Progeria Syndrome

Clinical Features

Hutchinson-Gilford Progeria Syndrome (HGPS) is an extremely rare genetic disorder characterized by premature aging of the skin, bones, and cardiovascular system. The incidence is about one in four million births. Most cases occur due to sporadic autosomal dominant mutations in the *LMNA* gene, although rarely the disorder may be inherited in cases of parental mosaicism. Mutations lead to abnormal transcription of the nuclear membrane protein lamin A, which when mutated is known as progerin. This protein undergoes farnesylation as part of normal post-transcriptional modification, but in its altered form, the farnesyl group is unable to be removed. This causes persistent attachment to the inner nuclear membrane, leading to disruption of normal nuclear shape and function, and ultimately, genetic instability, decreased cellular proliferation, and premature cell death.

Affected infants are usually healthy at birth, although mild sclerodermatous skin changes may be present. Within the first few years of life, patients develop worsening sclerodermatous skin findings, typically on the abdomen and lower extremities. Growth retardation, alopecia, and lipodystrophy usually become apparent, along with the characteristic prominent nose and prematurely senile features, leading to the "plucked bird" appearance. The skin is atrophic and translucent with visible veins, particularly on the scalp. With time, hearing loss and joint contractures may develop, and radiographic studies will reveal diffuse osteopenia and skeletal dystrophy. The teeth are often overcrowded, with delayed or failed eruption of primary or secondary teeth and increased caries. Hypertension, decreased high-density lipoprotein levels, and arteriosclerosis develop. Some phenomena of aging, such as increased malignancy and cataract development, are absent from this syndrome. The affected individuals usually have normal intelligence. The average survival is around 14 years, with early death due to cardiovascular or cerebrovascular disease.

Management Strategies

A comprehensive handbook detailing the care of children with HGPS, published by the Progeria Research Foundation, is available at http://www.progeriaresearch.org/patient_care.

html [69]. This handbook provides an excellent resource for both families and medical professionals caring for children with HGPS. The diagnosis may be made based on clinical features, but often in combination with genetic testing for LMNA mutations.

Multidisciplinary care is ideal for children with HGPS, and consultations with genetics, cardiology, neurology, ophthalmology, dentistry, dermatology, audiology, physical therapy, occupational therapy, and podiatry should be considered. Particular attention should be paid to maintaining adequate caloric intake, with the recognition that children with HGPS will gain weight at a much slower rate than their peers.

Cardiovascular testing with measurement of fasting lipids and glucose, blood pressure, electrocardiogram, echocardiogram, and carotid duplex ultrasound is recommended at baseline and on an annual basis. Low-dose aspirin (2–3 mg/kg/day) is often given as a preventative measure [70]. Dietary and lifestyle modifications, along with statin medications, may be added if lipid abnormalities develop. Magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA) should also be performed at baseline to evaluate risk of stroke, and may be repeated regularly to track disease progress. Patients may require sedation to undergo these procedures, and the anesthesiologist should be aware of a higher risk of complications related to anesthesia and airway management [70].

Recent research has centered on the use of farnesyl transferase inhibitors (FTIs), with the goal of blocking the persistent farnesylation of progerin [71]. Early mouse models showed improved phenotype and survival, but HGPS fibroblasts in these studies exhibited potential for activation of alternative prenylation pathways that likewise lead to early morbidity and mortality [72–74]. The first human single-arm clinical trial administered the FTI lonafarnib for 2 years, with improvement in disease phenotype, including markers such as weight gain, vascular stiffness, bone structure, and hearing loss. Reported adverse effects included gastrointestinal complaints, fatigue, and depressed serum hemoglobin [75]. A second ongoing trial added a statin and a bisphosphonate with the goal of inhibiting other steps along the protein prenylation pathway [71, 76]. Post-trial analysis conducted to date showed a mean survival of 14.6 years in untreated patients, with patients treated with lonafarnib surviving an additional 1.6 years, after a median follow-up of 5.3 years [71]. Further research is needed with an even longer follow-up period, along with studies to assess the impact on survival of patients who receive treatment starting at an early age.

Rapamycin has been investigated due to its ability to enhance clearance of progerin from cells [77, 78]. Similarly, sulforaphane, an antioxidant compound found in cruciferous vegetables, has been found to enhance progerin clearance [79]. Neither of these has been studied in humans.

Investigations Recommended

- Genetic testing for LMNA mutations (may be available at no cost through the Progeria Research Foundation, http://progeriaresearch.org/diagnostic_testing.html)
- Consultations with genetics, cardiology, neurology, ophthalmology, dentistry, dermatology, audiology, physical therapy, occupational therapy, and podiatry
- Measurement of fasting lipids and glucose at baseline and annually
- Blood pressure at baseline and annually
- Electrocardiogram (ECG) at baseline and annually
- Echocardiogram at baseline and annually
- Carotid duplex ultrasound at baseline and annually
- MRI/MRA of head and neck at baseline and repeated as needed for monitoring
- Dual-energy X-ray absorptiometry (DEXA) of hip and lumbar spine
- Hip X-ray or other radiographic studies at baseline and repeated as needed

First Line Therapies

- Farnesyl transferase inhibitor (lonafarnib) 115 mg/m^2/dose increased to 150 mg/m^2/dose after 4 months administered every 12 h – B [71, 75]
- Low-dose aspirin 2–3 mg/kg/day – E [70]
- Other treatments should be tailored in consultation with specialists, depending on disease presentation and severity

Second Line Therapies

- Dietary or lifestyle modifications if lipid abnormalities are noted – E [70]

Werner Syndrome

Clinical Features

Werner syndrome (WS), also referred to as "adult progeria," is a rare, autosomal recessive disorder of premature aging and increased malignancy. The prevalence in the United States is thought to be around 1:200,000, but the prevalence is higher in some populations, namely in Japan and Sardinia, due to founder mutations. WS is caused by mutations in the *WRN* gene, which encodes a protein in the RecQ family of DNA helicases. Normally, the WRN protein is thought to be involved in the unwinding of DNA, necessary for various

nuclear functions such as DNA repair, recombination, replication, and transcription. Mutations lead to genomic instability through mechanisms that are not completely understood, but some evidence points to telomeric dysfunction as the main etiology of the premature aging and high rate of cancers seen in WS.

Most patients with WS develop normally until adolescence, when the lack of a normal growth spurt may be noted. Over the next decade, premature canities and thinning of the hair, hoarseness, and sclerodermatous skin findings develop. Around 30 years of age, most patients will start to develop bilateral ocular cataracts, diabetes mellitus type 2, hypogonadism with depressed fertility, and osteoporosis. The most prominent dermatologic features are the characteristic "bird-like" facies and the development of deep chronic ulcers around the ankles. The mean age at death is 54 years, with premature morbidity due to accelerated arteriosclerosis and malignancy. WS patients may develop many forms of carcinomas, but sarcomas and acral lentiginous melanoma are noted to appear at a particularly high rate in this population.

Management Strategies

The diagnosis of WS may be made based on clinical findings. Molecular genetic testing for WRN mutations can also be used to confirm or make the diagnosis. An international registry is maintained at the University of Washington, with genetic testing available free of charge to eligible patients (www.wernersyndrome.org) [80].

Patients with WS should undergo a complete history and physical examination annually, with particular attention paid to cancer surveillance. The dermatologic examination should include examination of the legs and feet to assess for ulcerations, as well as the palmoplantar surfaces and nail beds to assess for concerning pigmented lesions. Screening for diabetes mellitus type 2 and fasting lipid profile should be performed at baseline and annually. If neurologic signs or symptoms are present, brain MRI is indicated to evaluate for meningioma.

Referrals should be made to ophthalmology and genetics, with consultations to other specialties, such as cardiology or hematology-oncology, pursued depending on the patient's presentation. Associated conditions such as diabetes, cardiovascular disease, osteoporosis, and malignancy are treated with the same modalities as the general population. All patients should be counseled regarding lifestyle measures to reduce the risk of cardiovascular disease, such as smoking cessation, dietary measures, and exercise. Patients should avoid trauma to the lower extremities, and wounds should be treated early and aggressively to prevent progression to chronic ulceration.

While at this time there is no targeted treatment for WS, the disease often is studied as a model of the normal aging process, with the underlying goal of finding methods to slow this process both in WS patients and the general population. Small molecule inhibitors such as SB203580, an experimental anti-inflammatory drug that acts by modulating the p38 mitogen-activated protein (MAP) kinase pathway, are being studied in the laboratory as a potential therapy for WS [81, 82] Other dietary compounds thought to have antioxidant properties, such as resveratrol and vitamin C, have been investigated for potential use, but so far no studies in humans are available [83–86].

Statin medications and pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist that improves insulin sensitivity with further anti-inflammatory effects, are used for treatment of cardiovascular and metabolic disease in patients with WS, but some researchers have noted that these medications also may have effects on telomere function that provide additional benefits in WS [87–92]. The addition of testosterone replacement therapy may provide additional benefits on insulin sensitivity for males with WS [89]. With regard to osteoporosis, one patient treated with recombinant human insulin-like growth factor (IGF)-1 showed improvement in bone density at the lumbar spine [93].

Treatment of leg ulcerations is difficult and involves standard wound care with debridement, topical dressings, infection control and, in some cases, surgical skin grafting. Isolated case reports detail the use of topical platelet derived growth factor (PDGF)-BB to improve granulation tissue and allow for successful skin grafting, as well as the use of oral bosentan, an endothelin receptor antagonist that has been used in the treatment of severe skin ulcers in other disorders such as systemic sclerosis [94, 95].

Specific Investigations Recommended

- Comprehensive history and physical examination
- Referral to genetics
- Genetic testing for *WRN* mutations can be considered if necessary for diagnosis or family planning
- Diabetes screening at baseline and annually
- Serum lipids at baseline and annually
- Dual-energy X-ray absorptiometry (DEXA) of hip and lumbar spine
- Brain MRI if neurologic signs or symptoms are present
- Referral to ophthalmology
- Referral to other specialties such as dermatology, wound care, cardiology, or hematology-oncology depending on patient presentation

First Line Therapies

- Pioglitazone 7.5–30 mg/day for insulin resistance – E [88–92]

- Statins (doses vary) for cardiovascular disease – E [87]
- Other treatments should be tailored in consultation with specialists depending on disease presentation and severity

Second Line Therapies

- Bosentan 125–250 mg/day for refractory leg ulcers – E [95]
- Recombinant human IGF-1 30–75 μg/kg subcutaneously daily for osteoporosis – E [93]
- Topical PDGF-BB for refractory leg ulcers – E [94]
- Testosterone replacement therapy 250 mg intramuscularly every 4 weeks for insulin resistance – E [89]

Lethal Restrictive Dermopathy

Clinical Features

Lethal restrictive dermopathy is a rare genodermatosis caused by abnormal skin growth and differentiation in the fetal period, leading to death in utero or within days to weeks after birth. Similar to progeria, lethal restrictive dermopathy is one of the laminopathies, a group of inherited disorders that result from a genetic mutation interfering with the post-translational modification of prelamin A to lamin A, an essential part of the nuclear envelope. Affected neonates are born at 30–33 weeks gestation due to premature rupture of the membranes, following a pregnancy characterized by intrauterine growth retardation, decreased fetal movements, and polyhydramnios. Characteristic skin findings are generally diagnostic at birth and include thin, extremely taut skin of the entire body with increased visibility of vessels that is frequently eroded at the joints, and the mouth fixed with an "o" appearance. Other facial features include micrognathia, down-slanting palpebral fissures, hypertelorism, a small pinched-appearing nose, neonatal teeth, and low-set, posteriorly rotated ears. Clinical features also include generalized anklylosis, rocker bottom feet, narrow chest, and pulmonary hypoplasia, leading to respiratory insufficiency and early death.

Management Strategies

There is no cure for restrictive dermopathy, and at this point, all cases have been fatal. Management is directed at supportive and symptomatic care in the neonatal period. Genetic testing and prenatal testing for the known genetic mutations can be offered to affected families [96–98].

Specific Investigations Recommended

For diagnosis
Clinical examination
Skin biopsy
Genetic testing for one of the known mutations in LMNA or ZMPSTE24

Stiff Skin Syndrome

Clinical Features

Stiff skin syndrome, also known as congenital fascial dystrophy, is a rare scleroderma-like condition that presents in infancy or early childhood with progressively worsening rock-hard, bound-down induration of the skin that can feel tumor-like, usually involving areas of prominent fascia including the buttocks, lower back, and thighs, but can less commonly involve the upper extremities as well (Fig. 6.9). Mild hypertrichosis and hyperpigmentation of affected areas are variable features. Restriction of joint mobility, gait disturbance, scoliosis and other postural abnormalities, and thoracic abnormalities limiting respiratory capacity may occur. The proximal involvement of skin findings, the absence of systemic findings, and lack of serologic evidence of autoimmune disease are key to making the diagnosis. An autosomal dominant inherited form of the condition exists and is due to a causative mutation in fibrillin 1 that is distinct from the causative mutation in Marfan syndrome [99, 100].

Management Strategies

There is no cure for stiff skin syndrome, but the prognosis is generally good, and patients are able to lead productive lives. Management should be directed at improving joint mobility through early initiation of physical therapy and exercise. Immunosuppressant therapies that are useful in scleroderma are not helpful in stiff skin syndrome [101].

Specific Investigations Recommended

- Skin biopsy shows variable findings, possibly related to stage of disease. Lack of inflammation, increased dermal mucin, increased dermal fibroblasts, increased subcutaneous sclerosis and a thickened fascia with or without sclerosis

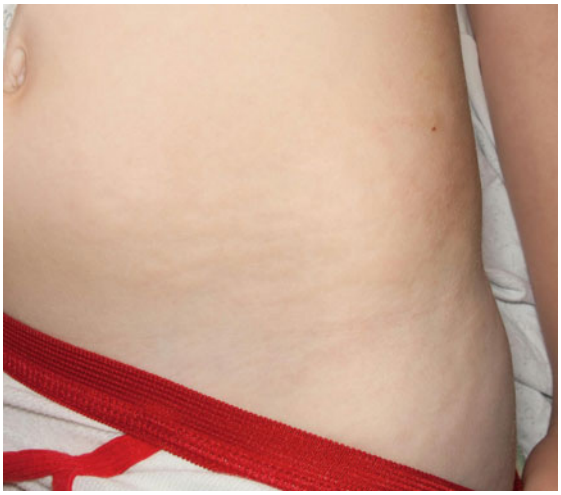

Fig. 6.9 Stiff skin syndrome. Progressively hardening and induration of the skin on the abdomen

have all been noted. A horizontal orientation of the collagen in the subcutaneous tissues with a lattice-like or basketweave appearance has been specifically associated with stiff skin syndrome by one author [102].

For diagnosis
Skin biopsy
Serologies to exclude autoimmune disease
Genetic testing for causative mutation in fibrillin 1

First Line Therapies

- Physical therapy to improve mobility – E

Lipoid Proteinosis

Clinical Features

Lipoid proteinosis, also known as Hyalinosis cutis et mucosae, or Urbach-Wiethe disease, is a rare autosomal-recessive genetic disorder caused by homozygous loss-of-function mutations in extracellular matrix protein 1 gene (ECM1). Hoarseness is the first clinical sign, usually developing soon after birth, and is due to thickening of the vocal cords. Cutaneous signs follow soon thereafter over the first few years of life.

Generalized cutaneous findings develop over two overlapping stages; in the first stage, there are vesicles and hemorrhagic crusts of the face, mouth, and extremities that develop with trauma and resolve with scarring. In the second stage, the skin becomes diffusely yellow, thickened, and waxy from hyaline deposits within the dermis. The pathognomonic finding is of beaded eyelid papules, with a "string of pearls" sign (Fig. 6.10) and loss of cilia [103]. Hyperkeratosis may be found in areas exposed to mechanical friction. The hair and mucosa may also be affected with patchy alopecia, and thick, woody infiltration of the tongue, making it bound to the floor of the mouth and difficult to extrude. This may be accompanied by infiltration of the lips and oropharynx.

Patients with lipoid proteinosis may have other extracutaneous findings including dysphagia, seizures, tooth abnormalities such as hypoplasia or aplasia of some teeth, and ocular problems [104].

Management Strategies

There is no cure for lipoid proteinosis. Current management is directed at making the correct diagnosis and at symptomatic and supportive care. Patients should be managed in conjunction with an otorhinolaryngologist. If symptomatic, neurology and dental involvement may be necessary. Gene therapy may be an option in the future.

Specific Investigations Recommended

For diagnosis
• Skin biopsy to evaluate deposition of concentric layers of laminated or amorphous PAS-positive material around blood vessels, at the dermal-epidermal junction, around the adnexal epithelium, and in the connective tissues. Basement membrane thickening is seen
• Immunofluorescence to examine perivascular as well as epidermal-dermal junctional labeling via anti-collagen IV, VII antibodies
• Brain MRI to evaluate temporal lobe and/or hippocampal calcifications
• Genetic testing for mutations in the ECM1 gene
For treatment
• LFTs, lipid profile, creatinine if starting systemic retinoids

First Line Therapies

- Topical/oral corticosteroids- symptom improvement with topical or oral steroids has been anecdotally reported (Evidence level E) [105, 106].
- CO2 laser has been successfully used to treat the beaded eyelid papules and the laryngeal involvement in lipoid proteinosis (Evidence level E) [107, 108].
- Systemic retinoids, most commonly acitretin, have been used in several patients with lipoid proteinosis, including one series of ten patients, resulting in improvement

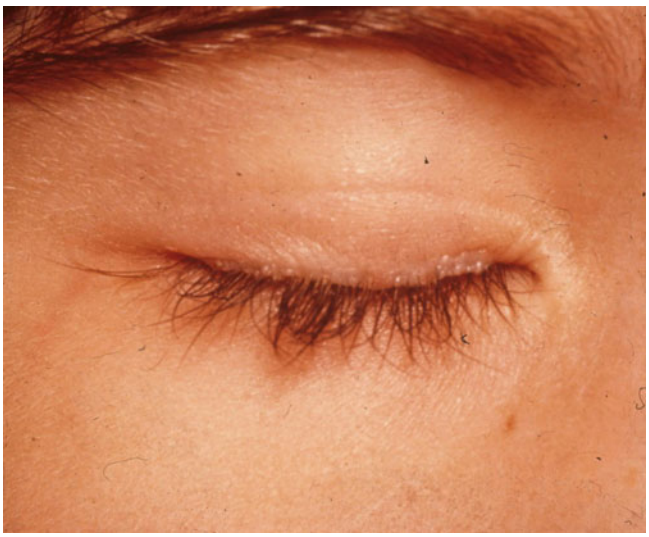

Fig. 6.10 Lipoid proteinosis. "String of pearls" sign on the eyelid, beaded papules along the lid margin with loss of cilia

ranging from some regression and softening of skin lesions to complete resolution of skin lesions and improvement of hoarseness (Evidence level D) [106, 109, 110].

Topical/oral corticosteroids	E
CO2 laser	E
Systemic retinoids	D

Second Line Therapies

- D-penicillamine: One teenaged patient reported resolution of hoarseness and improvement of cutaneous lesions when treated with D-penicillamine (Evidence level E) [111].
- Dimethylsulfoxide (DMSO): Reports of use of DMSO in lipoid proteinosis have been conflicted. One patient experienced improvement in hoarseness and in cutaneous lesions, however, its use in three other cases reported in a different series did not show any improvement (Evidence level E) [112].
- Surgical procedures such as correction of vocal cords, tracheostomy, blepharoplasty, and dermabrasion as indicated in patients refractory to other treatments (Evidence level E) [113].

Infantile Systemic Hyalinosis and Juvenile Hyaline Fibromatosis

Clinical Features

Infantile systemic hyalinosis and juvenile hyaline fibromatosis appear to be disorders along the spectrum of hyaline fibromatosis syndrome. These are rare, autosomal recessive disorders that are caused by a mutation of the gene that encodes capillary morphogenesis protein-2 (CMG2). The infantile form of the disease presents at birth or within the first 6 months of life. The cutaneous manifestations typically include hyperpigmented thickened skin overlying bony prominences, perianal nodules, and small papules on the face around the nose and mouth. The juvenile form presents in early childhood, and commonly manifests as large nodules on the scalp [114].

Oral manifestations such as thickening of the oral mucosa, gingival hyperplasia, and feeding difficulties may be seen. Joint contractures are preset in some patients, and in juvenile hyaline fibromatosis, osteolytic bone lesions may be seen. Other manifestations of infantile systemic hyalinosis are more severe and may include hyaline deposits in internal organs, failure to thrive from protein-losing enteropathy and diarrhea, and recurrent infections.

Management Strategies

There is no cure for infantile systemic hyalinosis and juvenile hyaline fibromatosis. Nutritional support and supportive care are the mainstays of treatment. Prognosis is poor, with death usually by 2 years of age in infantile systemic hyalinosis, and by the second or third decade of life in juvenile hyaline fibromatosis.

Specific Investigations Recommended

For Diagnosis

- Skin biopsy shows PAS+ homogeneous deposits of fibroblasts in hyalinized connective tissue stroma, intracytoplasmic and extracellular eosionophilic globules, osteoclast-like giant cells perivascularly, and CD68+ mononuclear cells. In JHF, accumulation of type IV collagen may be seen within fibromas.
- Electron microscopy shows fine fibrillar material with a banding pattern identical to type VI collagen [115].
- Genetic testing for mutations in the gene encoding CMG2 may be done.

For diagnosis
Biopsy
Electron microscopy
Genetic testing

First Line Therapies

- Surgical excision of nodules and gingival hypertrophy is often done as supportive care of problematic areas (Evidence level E) [116].

- Due to risk of protein-losing enteropathy, diarrhea, and failure-to-thrive, nutritional support is indicated for all patients (Evidence level E) [116].
- Cardiovascular evaluation is recommended due to risk of cardiomyopathy from hyaline deposit deposition in the heart (Evidence level E) [116, 117].

Second Line Therapies

- Penicillamine has been used anecdotally to improve mobility with variable success (Evidence level E) [116].
- Physical therapy may improve mobility (Evidence level E) [117].

Osteogenesis Imperfecta

Clinical Features

Osteogenesis imperfecta (OI) is a condition characterized by increased bone fragility and decreased bone mass. Various classification systems have been used to further subdivide OI based on genetic and phenotypic heterogeneity, although there is a recent move to limit the classification to five subtypes based on phenotype only, as the number of genes has expanded over recent years.

OI type I is the most common, and mildest, form of the disease, characterized by blue sclera (Fig. 6.11) and recurrent fractures, but minimal long-bone or spinal deformity [118]. Hearing loss may occur as patients age. OI type II is the most lethal form, with most cases not surviving beyond the perinatal period. It presents with multiple fractures and bony deformities, but the long-term survival is determined by the extent of pulmonary hypoplasia, which causes significant respiratory distress. OI type III is the most severe form of OI surviving past the perinatal period. Neonates often have multiple long-bone, rib fractures, and limb deformities at birth from injuries sustained in utero. They often are wheelchair-dependent from a young age and have ongoing bone fragility throughout life. Other features include blue sclera, triangular facies, and dentinogenesis imperfecta. OI type IV is similar to the OI type I phenotype, though lacks the blue sclera and deafness. There is bone fragility, however, and the majority of these patients have short stature.

Types I through IV may all be caused by mutations in collagen type 1 protein and are autosomal dominantly inherited. Other genes continue to be discovered for types II–IV, with varying modes of inheritance, but present phenotypically similar to the descriptions above. OI type V was the first noncollagen OI type to be identified, and is characterized by bone fragility, hypertrophic callus formation, and early calcification of the interosseous membrane between the bones of the forearm.

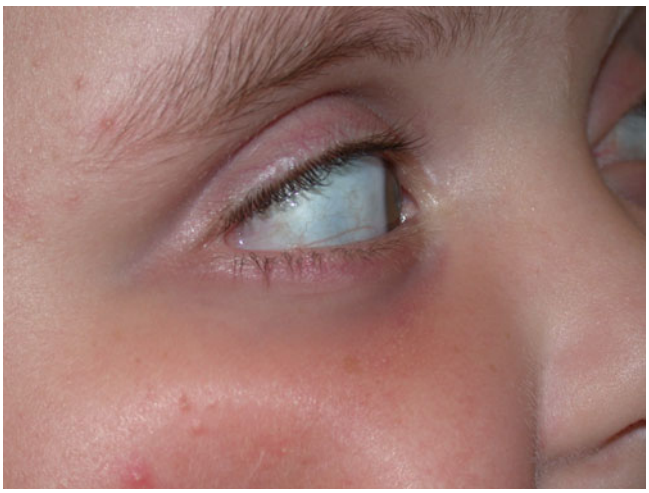

Fig. 6.11 Osteogenesis imperfect (OI). Blue sclera in a patient, the most common finding in OI

Management Strategies

Management of patients with OI requires a multidisciplinary approach involving pediatricians, endocrinologists, rehabilitation specialists, orthopedic surgeons, geneticists, and psychologists [118]. The goal of treatment is to maximize motor function and improve functional outcome. These goals can be achieved through a combination of medical and surgical treatment options, and some novel therapies targeting specific proteins are being explored for their use in OI.

Investigations Recommended

For diagnosis
Antenatal ultrasound (types II and III)
Skeletal survey
Dental exam
Genetic testing [119]
For treatment
Calcium levels following first bisphosphonate infusion
Dental review with necessary extractions and reparative work prior to bisphosphonate treatment
Pregnancy test prior to each bisphosphonate treatment cycle
For surveillance
Dental exams every 6 months if dentinogenesis imperfecta identified
Hearing evaluation for OI type I throughout adulthood

First Line Therapies

Bisphosphonate therapy is the mainstay of medical treatment for OI. Pamidronate and zoledronate are the most widely used agents [120]. For moderate to severe disease, intrave-

nous bisphosphonates are recommended, though oral bisphosphonates may be used as part of the maintenance regimen or as the initial treatment for more mild disease. There is no consensus on an optimum treatment regimen. Treatment is best begun for all moderate to severe OI, or in children with mild OI with two or more long-bone fractures in 1 year or vertebral compression fractures.

Intravenous bisphosphonates (moderate to severe OI)	A
Pamidronate 1 mg/kg/day for 2 days every 3–4 months	
Zoledronate 0.025–0.05 mg/kg/day for 2 days every 3–4 months	
Oral bisphosphonates (mild OI)	A
Risedronate 0.2–2 mg/kg/week, 2.5–5 mg daily	
Opadronate 10 mg/m^2 daily	
Alendronate 5–10 mg daily	
Intramedullary telescopic rod insertion	D

Second Line Therapies

Oral bisphosphonates	A
Orthotics	D

Third Line Therapies

Whole body vibration therapy	E

Winchester Syndrome

Clinical Features

Winchester syndrome is one of several inherited osteolysis disorders characterized by destruction and resorption of affected bones with resultant skeletal deformities and functional impairment. Many of these disorders have overlapping clinical features, though discoveries of genetic mutations in several have allowed improved classification of previously reported cases. Winchester syndrome is a rare, autosomal recessive, disorder with fewer than 12 cases reported since its description in 1969. With a novel genetic mutation discovered in 2012 in membrane type-1 metalloproteinase (MT1-MMP), some of the previously reported cases have been re-classified as other inherited osteolysis disorders.

Winchester syndrome presents with severe osteolysis of the carpals and tarsals, with generalized osteoporosis and bone thinning. Other features that are variably found include a gradual coarsening of the facies, corneal opacities, gum hypertrophy, and electrocardiogram (EKG) changes. Cutaneous findings are likewise variable, and include thickened, hyperpigmented, and hypertrichotic skin. Patients with Winchester syndrome are not thought to have painful subcutaneous nodules, as they may in other inherited osteolysis disorders.

Management Strategies

With the few cases reported, there are no established guidelines for managing patients with Winchester syndrome. It is important, when approaching a patient with signs suggestive of an inherited osteolysis disorder, to first exclude other potential causes of such features. Genetic testing is available for Winchester syndrome and can help differentiate it from other similarly presenting conditions [121]. Unfortunately, there are not any treatments to prevent progression of the disease. The management largely lies in ensuring appropriate initial evaluation, and follow-up with specialists who may aid in symptomatic treatment and supportive care.

Investigations Recommended

For diagnosis
X-rays
Urine and plasma mucopolysaccharide tests
Rheumatoid factor
EKG/echocardiogram
Eye exam
Renal ultrasound
Skin and gum biopsy
Genetic testing
For treatment
Consultation with ophthalmology, orthopedics, rheumatology, genetics
Referral for physiotherapy

First Line Therapies

- No reported treatments

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Disorders of Hair and Nail

7

Brian J. Simmons and Antonella Tosti

Congenital Non-scarring Alopecias with Fragility

Overview

Congenital hair shaft disorders are usually evident at birth or within the first months of life. The alopecia is most commonly limited to the scalp, but may involve other terminal hair, particularly eyebrows or eyelashes, and rarely body hair. Scalp areas exposed to friction are more affected and the alopecia is therefore more severe on the occipital scalp due to repetitive friction while sleeping on a pillow.

Investigations Recommended

For Diagnosis

- Dermoscopy and microscopic examination of the hair shaft provide diagnosis in most cases. Dermoscopy offers the advantage of being non-invasive and allowing fast examination of a large number of hair shafts, including eyebrows, eyelashes and body hairs (Table 7.1).

For Treatment

- There is no specific treatment for hair shaft fragility except for gentle handling of hair to minimize breakage. In most patients fragility improves with aging. Early identification and treatment of patients with Menkes kinky hair disease is paramount. By administering copper injections early, longer-term survival approaches 92 % [1]. Parenteral copper can prevent development of neurological abnormalities in some patients, but response to treatment depends on specific ATP7A mutations.

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Trichorrhexis Invaginata (Bamboo Hair)

Clinical Features

The hair shaft shows multiple knots along its length. The knots consists of a proximal cup-shaped portion and a distal ball-shaped portion resembling the ball and cup joint of bamboo. Hair breakage occurs at the nodes. Hair of patients with trichorrhexis invaginata is dry, dull, fragile, and short due to hair breakage. Trichorrhexis invaginata frequently affects eyelashes, eyebrows and secondary sexual hair. The eyebrows usually show multiple bamboo nodes, and may present the abnormality even when the scalp hair, which improves with age, appears normal [2].

Trichorrhexis invaginata may be isolated, but most commonly is part of Netherton disease (MIM 256500). A rare autosomal recessive genodermatosis, which combines ichthyosis, bamboo hair and atopic dermatitis [3].

Monilethrix (Beaded Hair; MIM158000, 177750, 252700)

Clinical Features

The hair is dull, fragile, breaks easily at 0.5–2.5 cm from the scalp, and breakage is prominent in the nape and occipital areas (Fig. 7.1a). The severity of the alopecia may vary considerably from almost complete hair loss to very mild thinning. Even members of the same family can be differently affected. Follicular keratosis of the affected scalp and keratosis pilaris are typical.

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Table 7.1 Evaluation for diagnosis of congenital non-scarring alopecias with fragility

Trichorrhexis invaginata
Microscopic examination of hair shaft: bamboo hair. Hair shaft with multiple knots resembling the ball-and-cup joint of bamboo
Dermoscopy: nodular swellings at irregular intervals, ball-shaped knots similar to match sticks, and hair breakages
Prenatal chorionic villus testing for SPINK5
Monilethrix
Microscopic examination of hair shaft: beaded hair. Hair shaft with elliptical nodes of normal hair and are medullated, regularly separated by internodes which are narrow, devoid of medulla, and are the site of fracture
Dermoscopy: beading and breakage at the internode level, with affected hairs bending in different directions
Menkes kinky hair syndrome
Microscopic examination of hair shaft: pili torti. The shafts are flattened and present twisting through 180° at irregular intervals
Dermoscopy: pili torti
Labs for serum copper, ceruloplasmin, and urine homovanillic/vanillylmadelic acid ratio
Prenatal diagnosis: placental copper levels are threefold to fivefold higher in pregnancies
Trichothiodistrophy
Microscopic examination of hair shaft: tiger tail hair. Under polarized microscopy the affected hair has a banded or "tiger tail" pattern because of alternating birefringence due to the presence of transverse dark and bright bands. Analyze proximal shaft to avoid changes due to weathering
Dermoscopy: useful to select the hairs to be examined under the microscope, as they present a dishomogeneous structures resembling grains of sand

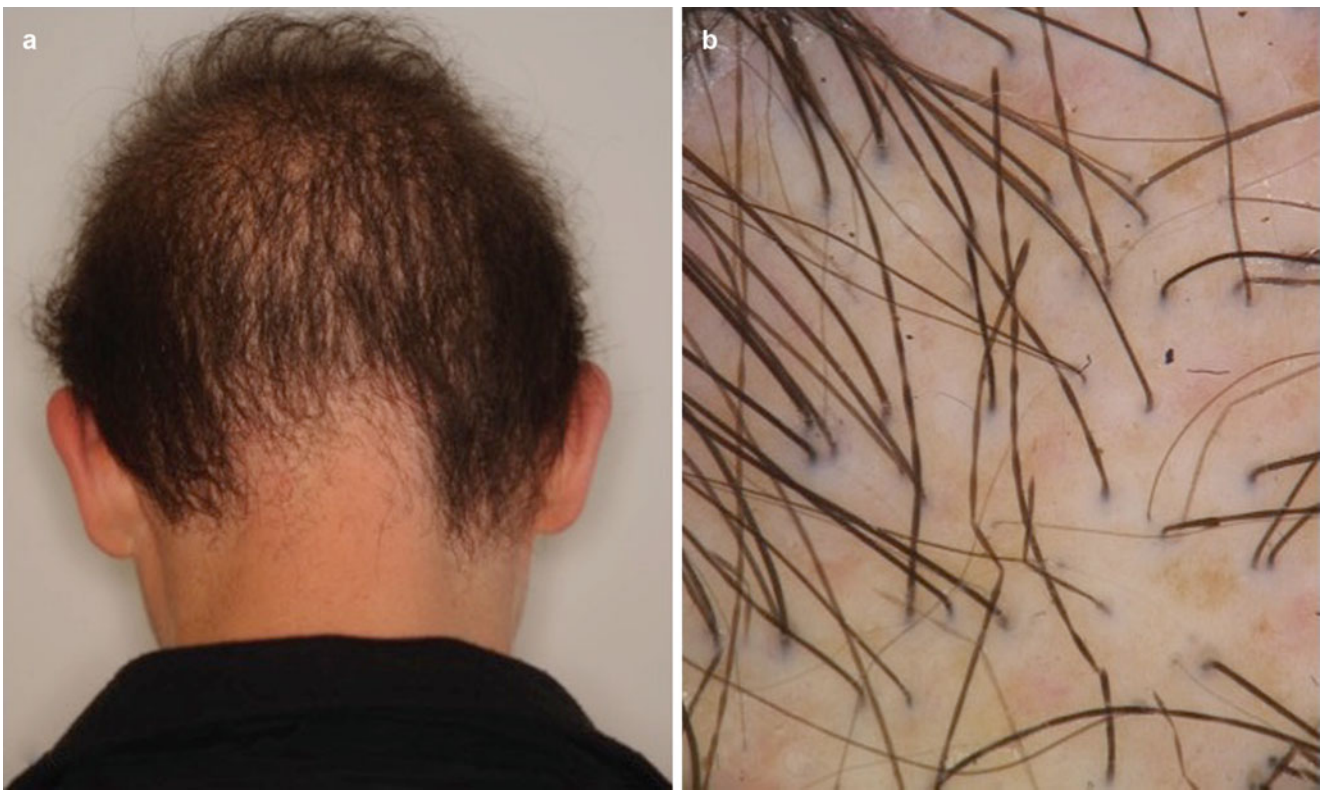

Fig. 7.1 (**a, b**) Monilethrix. (**a**) Diffuse hair thinning with pronounced loss in the occipital region. Hair is dull and short. (**b**) Characteristic beading of hair seen on dermoscopy

Monilethrix does not affect lanugo hair and usually becomes evident with growing of mature hair. At birth the scalp hair is either normal or absent; in the latter case the scalp has a shaved appearance. Scraping of the scalp may show the typical beads resulting from broken monilethrix hairs. Hair fragility improves with age. Monilethrix can occasionally affect eyebrows and eyelashes.

Monilethrix is most commonly inherited as an autosomal dominant condition with variable expression. Several mutations in the human basic hair keratins (hHb1 and hHb6) have

been reported [4, 5] with the most frequent mutation E413K occurring in hHb6 [6]. Linkage to the type II keratin cluster is on 12q13. Recessive monilethrix is rare and has been linked to mutations in desmoglein 4 (*DSG4)* [7].

Investigations Recommended

For Diagnosis

Diagnosis is made by clinical examination utilizing dermoscopy and in some instances microscopic examination of the hair shaft (see Table 7.1).

- **Microscopic examination of the hair shaft:** the hair shaft has a beaded appearance due to the presence of elliptical nodes, which have the diameter of normal hair and are medullated, regularly separated by internodes which are narrow, devoid of medulla and are the site of fracture.
- **Dermoscopy**: Beading and breakage at the internode level with affected hairs bending in different directions are very evident with dermoscopy (Fig. 7.1b), which aids in rapid diagnosis [8].

Menkes Kinky Hair Syndrome (MIM 309400)

Clinical Features

The hair is fine, silver or white, fragile and has a kinky/wiry appearance. The abnormal hair is usually not present at birth, but becomes evident around 4–5 months of age. Menkes kinky hair syndrome is an X-linked neurodegenerative disorder of copper metabolism, which combines pili torti and progressive neurological dysfunction [9]. The Menkes gene mutation has been mapped to Xq13.3 affecting the ATP7A gene. Pili torti in the hair of the mother of a patient with Menkes kinky hair disease is considered definitive proof of her status as a gene carrier.

Trichothiodystrophy (MIM 601675)

Clinical Features

Trichothiodystrophy is due to a reduction in the sulfur and cystine content of hair. The hair is brittle, sparse, dry, unruly and short. Eyebrows and eyelashes can also be affected. Brittle nails are often associated with trichothiodystrophy. The condition is autosomal recessive. The presence of associated features allows for distinguishing several syndromes (see Table 7.2). Photosensitivity, with mutations of the XPD, XPB or TTDA gene is present in about 50 % of cases. However, there is no predisposition to skin cancers in these patients [10].

Congenital Hair Shaft Disorders Without Fragility

Diffuse Partial Woolly Hair (DPWH)

Clinical Features

Diffuse partial woolly hair is a rare condition characterized by the presence of two distinct hair populations (strait long pigmented hairs and short, fine, hypopigmented and curly hairs). The disease is restricted to the scalp where 20–30 % of hairs are abnormal.

The condition may be inherited as an autosomal dominant trait and most commonly affects females. Patients typically complain of hair thinning, which is thought to occur from progressive follicular miniaturization [11] and thus represents a mild form of androgenic alopecia. The woolly hair is short, with variations in caliber and is hypopigmented [12].

DPWH should be distinguished from acquired progressive kinking of the hair (APKH), which is also characterized by development of curly hairs, most commonly on androgen-dependent scalp, and sometimes curling of the eyelashes [13, 14].

Investigations Recommended

For Diagnosis

- **Scalp biopsy:** pathology shows increased number of intermediate hairs as in early androgenetic alopecia [15, 16].

For Treatment

First Line Therapies

- Gentle handling of hair, minimizing physical and chemical trauma, is important due to the fragility of the hair. With time some patients' hair becomes darker and less curled [17]. Thinning of the hair in DPWH is due to follicular miniaturization and 2 % or 5 % topical minoxidil may be useful [18].

Pili Annulati (MIM 180600)

Clinical Features

Pili annulati is a rare hair shaft abnormality that is usually diagnosed coincidentally. The hair shaft presents with alternating light and dark bands that are visible even with the

Table 7.2 Classification of trichothiodistrophy

Type	MIM	Findings	Eponym/acronym
A		Hair ± nail involvement	
B	211390	Hair ± nails + mental retardation	Sabinas
C	275550	Hair, mental retardation, folliculitis, retarded bone age ± caries and ± nail involvement	Pollitt
D	234050	Brittle hair, infertility, developmental delay, short stature and ± nail involvement	BIDS
E	242170	Ichthyosis + BIDS. Brittle hair, ± nail involvement, mental retardation, short stature, ± decreased gonadal function, ± lenticular opacities/cataracts, failure to thrive, microcephaly ± ataxia, ± calcifications of the basal ganglia, erythroderma and scale	Tay + BIDS
F	278730	Photosensitivity + IBIDS	PIBIDS
G	258360	TTD with immune defects. Hair +/âˆ' mental retardation + chronic neutropenia or immunoglobulin deficiency	Itin
H		Trichothiodistrophy with severe intrauterine growth retardation (IUGR). Hair + severe IUGR and failure to thrive + developmental delay + recurrent infections + cataracts + hepatic angioendotheliomas	

Fig. 7.2 Pili annulati. Characteristic alternating white bands on dermoscopy

unaided eye, especially in blond or white hair. Axillary, beard, and pubic hair can also be affected.

The condition is autosomal dominant with variable expression. The affected hair has lower cystine content in comparision to normal hair [19]. Pili annulati usually does not produce hair fragility, but affected hairs are more susceptible to weathering [20]. The increased susceptibility to weathering is due to the air-filled cavities of the hair cortex that are seen as dark bands with microscopy, and as white bands at dermoscopy (Fig. 7.2). Although pili annulati has been reported to occur in patients with alopecia areata, the association is most likely coincidental [21].

Table 7.3 Evaluations for diagnosis of Pili Annulati

For diagnosis
Microscopic examination of hair shaft: the hair shaft presents alternating dark patches, which corresponds to air spaces in the cortex
Dermoscopy: air-filled cavities appear as white areas. Trichorrhexis nodosa in frequently present
Scanning electron microscopy: shows damaged cuticle and cortex structures adjacent to cavities within the hair shaft

Investigations Recommended

For Diagnosis

- Diagnosis is based on hair shaft examination with a variety of methods (see Table 7.3).

For Treatment

- No specific treatment exists. Gentle handling of the hair helps to decrease hair weathering

Woolly Hair

Clinical Features

Woolly hair resembles African hair. The hair is extremely curly, does not group in locks, and does not lie flat on the scalp [22]. The condition is rare and can be subdivided into three types based on clinical features and mode of inheritance (see Table 7.4).

Table 7.4 Subtypes of woolly hair

Type	Key characteristics
Hereditary woolly hair (HWH)	Hair is normal in color
	Grows at normal rate, but may be short due to reduced duration of anagen phase
	Autosomal dominaint inheritance
Familial woolly hair/woolly hair hypotrichosis (FWH/WHH)	Hair is lighter than unaffected family members
	Very short due to reduced anagen phase
	Autosomal recessive inheritance
Woolly hair nevus (WHN)	Patch of abnormally curly hair, often lighter in color that surrounding hair
Naxos syndrome (MIM 601214)	Woolly hair, palmoplantar keratoderma, and arrhythmogenic right ventricular cardiomyopathy
Carvajal syndrome (MIM 605676)	Woolly hair, palmoplantar keratoderma, and dilated cardiomyopathy

Hereditary woolly hair (HWH) is autosomal dominant inherited, and not associated with hair thinning or fragility [17]. The hair color is variable and the manageability improves with age.

Woolly hair is associated with palmoplantar keratoderma and cardiac abnormalities [23] in the Naxos syndrome (MIM 601214). The syndrome is autosomal recessive and caused by mutations in plakoglobin genes [24]. Mutations of desmoplakin cause Carvajal syndrome, which is characterized by woolly hair, palmoplantar keratoderma, and dilated cardiomyopathy.

Familial woolly hair (FWH) is autosomal recessive and associated with hair thinning. This condition, also known as woolly hair hypotrichosis, can be caused by mutations in either lipase H (*LIPH*) or lysophosphatidic acid receptor 6 (*LPAR6*) gene, encoding an LPA-producing enzyme PA-PLA$_1\alpha$ and an LPA receptor LPA$_6$, respectively. The hair is hypopigmented, sparse, thin, and short (Fig. 7.3) [25].

Woolly hair nevus (WHN) is present at birth or may develop during adolescence. The lesion presents as an isolated patch of woolly hair among normal hair. The condition is frequently associated with epidermal or melanocytic nevus of the neck or arm [26, 27].

Investigations Recommended

For Diagnosis

- Diagnosis of woolly hair is based on clinical examination and the boiling water test. When immersed in boiling water, woolly hairs form regular spirals [28].
- Microscopic examination of hair shaft is not useful for diagnosis.
- On dermoscopy, woolly hair can demonstrate a short wavy "crawling snake" appearance [29].

For Treatment

- Topical minoxidil can improve woolly hair hypotrichosis [30].

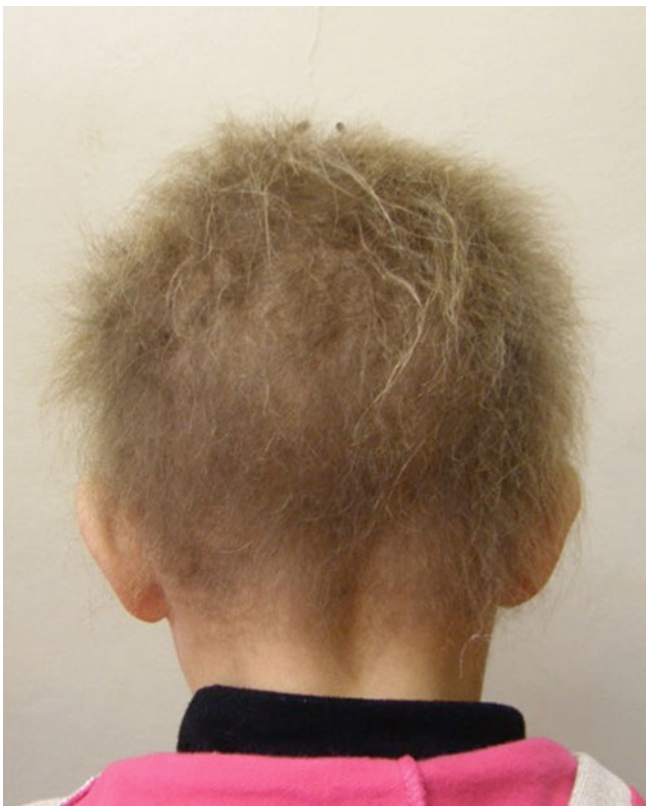

Fig. 7.3 Woolly hair hypotrichosis. Note sparse, short, blond wooly hair

Uncombable Hair Syndrome (Pili Trianguli et Canaliculi, Spun Glass Hair)

Clinical Features

Uncombable hair syndrome presents with blond, dry, and unruly hair that resists all efforts of styling. The overall appearance resembles synthetic doll hair. Eyebrows and eyelashes are normal and unaffected.

The condition usually appears during the first years of life and considerably improves with age when the hair becomes longer. Inheritance is known to be autosomal-dominant, but shows both complete and incomplete penetrance. The syndrome affects males and females equally. Besides the classic form, there is an acquired and partial form, where the abnormality is limited to the frontal or occipital area [31]. The condition is usually an isolated finding, but has been reported to occur with congenital abnormalities. Unruly hair similar to uncombable hair can be seen in Rapp-Hodgkin and loose anagen hair syndromes [32].

Investigations Recommended

For Diagnosis

- Diagnosis requires dermoscopy or scanning electron microscopy [32]. The affected hair has a typical triangular or reniform-shape with longitudinal grooving and flattening.

For Treatment

- The natural course of UHS is to resolve by adolescence.
- Biotin supplements have also been advocated and shown in at least some reports to improve hair strength, combability, and rate of growth after 4 months' of treatment [32, 33].

Acquired Hair Shaft Disorders Without Fragility

Acquired Progressive Kinking of the Hair (APKH)

Clinical Features

APKH includes a variety of conditions (see Table 7.5) characterized by acquired curly, frizzy, and lusterless hair that resembles secondary sexual hair.

Table 7.5 Conditions described as acquired progressive kinking of the hair

Condition
Whisker hair; kinking of the hair over preauricular areas of the scalp
Acquired progressive kinking of androgen-dependent hair associated with thinning
Rapidly progressive kinking of most or all the scalp hair without associated hair thinning
Acquired reversible hair kinking before or after puberty
Acquired hair kinking involving a localized non-androgen dependent area of the scalp
Hair kinking after anagen/telogen effluvium (alopecia areata/drugs)

Whisker hair is APKH over periauricular areas of the scalp. Whisker hair is short and curly and resembles hair of the beard. The condition is strongly associated with severe androgenetic alopecia [34]. Acquired progressive kinking of androgen-dependent hair represents a type of androgenetic alopecia that is associated with poor prognosis in most cases [35].

Rapidly progressive kinking of most or all the scalp hair without associated hair thinning has been reported, albiet rare. APKH has been shown to be reversible in patients before and after puberty in certain instances [34, 36]. Acquired hair kinking can also be localized to non-androgen dependent areas of the scalp [37].

Trauma, ionizing radiation, [38] and drugs can also induce hair kinking. Sometimes hair regrowth after alopecia areata or chemotherapy show hair kinking. Some drugs that have been implicated include etretinate [39] and isotretinoin, [40] which may or may not be reversible.

Investigations Recommended

For Diagnosis

- APKH is a variation of AGA. Diagnosis can be confirmed principally with dermoscopy that shows more than 20% variability or via scalp biopsy.
- **Microscopic Examination of Hair Shaft:** Under light microscopy irregular twisting and periodic redution in hair shaft diamter can be observed.
- **Scanning Election Microscopy:** Partial longitudinal grooves and longitudinal twisting of the hair shaft can be observed [41].

For Treatment

First Line Therapies

- Since APKH is a variation of AGA, treatment options include finasteride 1 mg (E) [14] and topical minoxidil. However, minoxidil is not always effective.

Alopecia Areata (AA)

Clinical Features

Alopecia areata is a common non-cicatricial alopecia, characterized by patchy hair loss in the absence of inflammatory signs. The condition is an autommune T-cell mediated disorder, which leads to disruption of the normal hair cycle [42]. The disease affects both sexes at any age, but severe forms are more frequent in males, and often start during childhood.

The disease usually starts abruptly with one or multiple patches of hair loss that usually enlarge in a centrifugal way. Although AA frequently resolves spontaneously, relapses occur in a high percentage of patients. Diffuse shedding may or may not be present in the surrounding scalp. Peribulbar inflammation leads to interruption of the anagen phase with loss of dystrophic anagen roots [42]. AA may involve any hair-bearing skin, but is more common on the scalp (Fig. 7.4) and on bearded areas. Rarely, it may exclusively affect the eyelashes and/or the eyebrows [43].

Severity of AA may be evaluated according to percentage of scalp involvement. Severe forms affect the entire scalp (AT, alopecia totalis) or all body hair (AU, alopecia universalis). Involvement of the scalp margin (ophiasis) is associated with a poor prognosis [44]. The affected scalp may be completely devoid of hair or may be covered by vellus, unpigmented, short hair. Acute AA is characterized by the presence of exclamation point and cadaverized hair. AA may also present with diffuse hair thinning without typical patches. The genetic inheritance of AA is polygenic. The condition affects first-degree relatives in about 20% of cases, and monozygotic twins 42% of the time [45, 46]. AA can be associated with a wide array of disorders, including various autoimmune diseases, nail abnormalities, and genetic syndromes (see Table 7.6).

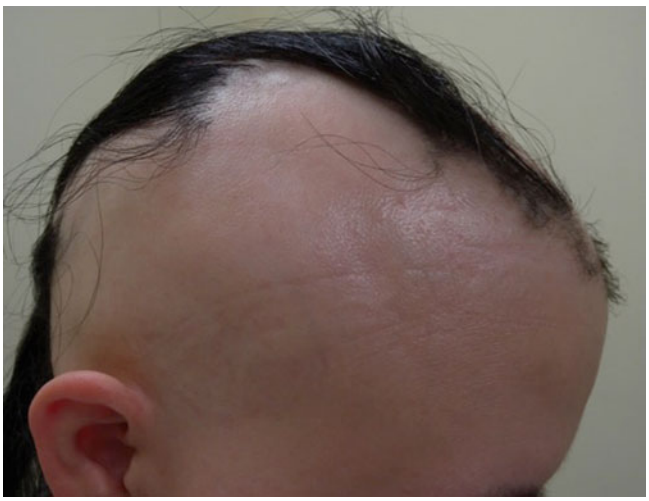

Fig. 7.4 Alopecia areata. Ophiasis pattern of hair loss

Investigations Recommended

For Diagnosis

- Diagnosis in most cases is based on clinical examination by the presence of smooth discrete areas of hair loss and exclamation mark hairs.
- **Pull Test:** The pull test is very positive if the disease is rapidly progressing.
- **Microscopic Examination:** Microscopic examination shows telogen and dystrophic hair roots.
- **Dermoscopy:** Dermatoscopic examination of the scalp may show a wide array of findings including exclamation mark hair, yellow dots, broken hairs, and black dots.
- **Histopathology:** Is dependent on the chronicity of the disease. Acute AA has peribulbar lymphocytic infiltrates around anagen follicles described as "a swarm of bees." Biopsy in chronic stage of AA shows follicular miniaturization, shift toward catagen and telogen follicles, vellus hair, and variability of inflammatory infiltrates [50].

For Treatment

- Treatment of AA in children can be challenging and is based primarily on the use of topical agents in children under age 10.
- In children over 10 years old, treatment is based on the same treatments as adults, which is based on extent of disease. Topical treatments and intralesional steroids are used in patients that have less than 50% scalp involvement (Fig. 7.5).

Table 7.6 Associated disorders of alopecia areata

Associated disease	Findings
Nail abnormalities	
Superficial pitting with geometric pattern	Findings are especially prevalent in children
Twenty-nail dystrophy (trachyonychia)	Nails are rough due to excessive longitudinal ridging
Autoimmune disease	
Thyroid autoimmune disease	Clinical/subclinical thyroiditis in up to 30% of patients
Celiac disease	Uncommon finding, but removing gluten does not change course of AA
Vitiligo	3–8% of patients present with concurrent disease [47]
Atopic disorders	
Atopic dermatitis	Higher risk for development of AA; up to 31% seen to develop [48]
Genetic syndromes	
Down syndrome	Prognosis with AA is unfavorable
Polyglandular autoimmune syndrome type 1	Rare condition; but reported in up to 33% of patients [49]

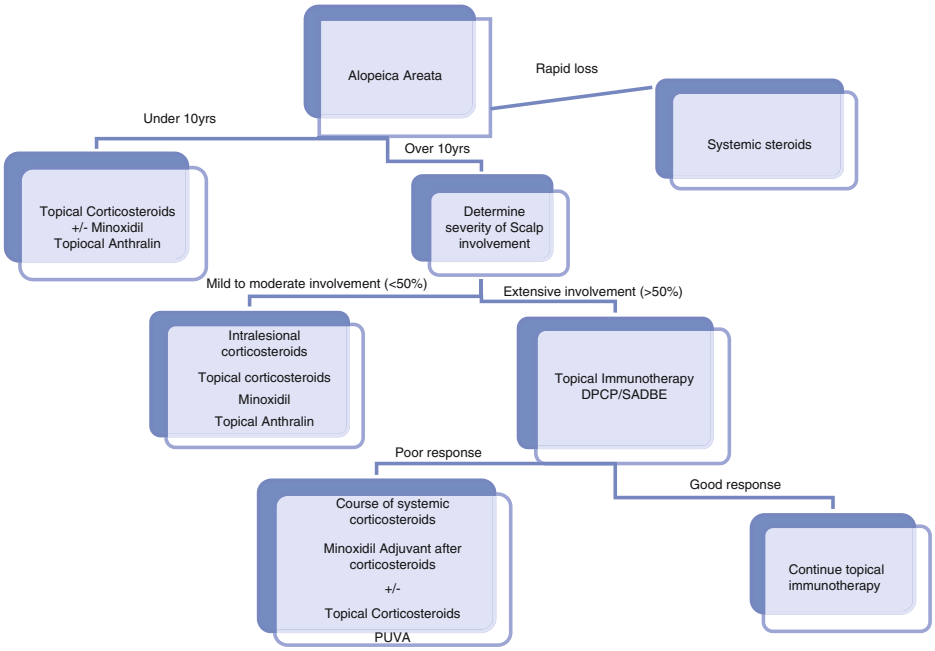

Fig. 7.5 Treatment algorithm for alopecia areata

- In patients with more extensive scalp involvement, topical immunotherapies and oral corticosteroids can be considered [51].
- In patients with extensive AA, wigs and tattooing of affected eyebrows can help mask the disease (see Table 7.7).

First Line Therapies

- In patients who present with patchy alopecia or alopecia affecing the eyebrows, intralesional steroids are the preferred treatment (age >10 years). Triamcinolone acetonide should be diluted in saline solution at 5–10 mg/ml for injection in the scalp and 2.5–5 mg/ml for eyebrow and beard involvement. Maximum dosage should not exceed 40 mg per session. Treatement should be repeated every 4–6 weeks, but if no response is seen after 6 months, discontinue treatment and seek alternative treatment options [52].
- In extensive disease (>50 % scalp involvement), topical immunotherapy with agents that induce allergic contact dermatits is preferred. These treatments have been shown to be superior to intralesional corticosteroids [53]. The two currently used sensitizers are diphenylcyclopropenone (DPCP) and squaric acid dibutyl ester (SADBE). Sensitization is obtained using a 2 % acetone SADBE or DPCP under closed patch test for 48 h. Treatment is performed with weekly application of the allergen diluted in acetone at a concentration that is able to induce mild scalp contact dermatitis. The concentration to achieve contact dermatitis can vary among different patients and even in the same patient during the treatment period. Acceptable regrowth (75 % or more) is seen in 38–63.8 % of patients [54, 55]. Moreover, hair regrowth can be achieved in 20 % of patients with alopeica totalis/universalis (AT/AU).
- Clobetasol propionate 0.05 % applied under occlusive dressing nightly can improve hair growth significantly. However, in the authors' experience this treatment is not a good option in children younger than 14 due to the risk of absorption and adrenal suppression [56]. Clobetasol propionate foam once a day has been shown to be effective in alopecia areata and can be utilized in children 10 years and older [57].

Second Line Therapies

- Topical minoxidil 5 % solution or foam can be used in combination with topical or intralesional steroids. However, studies on efficacy of minoxidil are conflicting [58]. Minoxidil has been show to be useful to prevent relapses after interruption of systemic steroids [59].
- Topical anthralin upto 1 % applied daily for 2 h or less can be used. Treatment induces mild erythema and irritation of the scalp. This treatment is an alternative option for children and mild forms of AA. However, effectiveness data is limited to case series [60].
- Phototherapy can be used in the treatment of AA. Topical PUVA has been reported to regrow hair in 50–70 % of patients. However, studies are not RCTs and results have not been confirmed [61]. Topical PUVA using a 0.0001 % 8-MOP solution is applied using a soaked cotton towel at 37 °C for 20 min, followed by UVA irradiation three to four times a week, with cumulative UVA dose ranging between 60.9 and 178.2 J/cm^2. Narrowband UVB is an option for patients with AT/AU, but efficacy rates are low,

Table 7.7 Treatments for alopecia areata

First line treatment	**Level of evidence**
Triamcinolone acetonide 5–10 mg/ml scalp, 2.5–5 mg/ml beard/eyebrow monthly (10 years and up)	B
Clobetasol propionate 0.05 % applied under occlusive dressing 6 days per week for 3 months (preferred treatment over age of 14)	A
Clobetasol propionate 0.05 % foam (10 years and up)	A
Sensitization to DPCP or SADBE (preferred treatment for >50 % scalp involvement)	A
Second line treatment	**Level of evidence**
Topical anthralin; 0.5–1 %, short contact therapy (up to 2 h)	B
Topical PUVA 0.0001 % 8-MOP solution, three to four times weekly	B
Topical minoxidil 5 % foam or solution, daily to scalp	B
Third line treatment	**Level of evidence**
Oral prednisolone 200 mg once weekly for 3 months	B
Methylprednisolone iv 500 mg/day for 3 days a month for 3 months (10 mg/kg/day in children)	B
Oral prednisone 300 mg/month (5 mg/kg in children)	B
Oral dexamethasone 40 mg/month (5 mg/day for 2 consecutive days every week)	B

with 20 % responding to treatment [62]. Moreover, presence of hair limits UV penetration, and thus maintainance of hair regrowth is difficult.

Third Line Therapies

- Systemic steroids can be used for acute severe AA. Various systemic steroid treatment protocols exists, but pulse steroids are perferred because of side effect profile (see Table 7.7). Studies have shown that pulse steroids are effective in acute progressive disease, but not in long-standing AT/AU. However, a high likelihood of relapse exists after discontinuation of systemic steroids [63]. Future promising treatments look at targeting the STAT1 pathway, including simvastatin and JAK-kinase inhibitors, which have shown promise in case reports and small studies [64, 65].

Loose Anagen Hair Syndrome (LAHS)

Clinical Features

LAHS is a benign, sporadic, or familial hair disorder that primarily affects children [66]. The condition is due to a defective anchorage of the hair shaft to the follicle, resulting in easily and painless pluckable hair. LAHS is more frequent in females than in males, occuring most commonly between the ages of 2 and 6. The typical patient is a young girl with short, blond hair that does not grow long. The condition usually improves spontaneously when the child grows up.

Three different varieties of LAHS have been catergorized by Olsen (see Table 7.8). Mutations in the gene encoding for the companion-layer keratin have been reported in some families with LAHS.

LAHS can cause diffuse thinning and irregular bald patches due to traumatic painless extraction of hair tufts. The hair is often dull, unruly, or matted (Fig. 7.6) [67]. LAHS is usually isolated, but may occur in association with hereditary or developmental disorders.

Investigations Recommended

For Diagnosis

Diagnosis is pricipably based on clinical features, pull test and trichogram.

- **Microscopic examination of hair shafts:** LAH presents as anagen hair devoid of sheets; its bulb is often misshapen and its proximal portion often shows a ruffled cuticle.
- **Pull Test/Trichogram:** Presence of LAH at pull test or trichogram may occur in controls. Thus, the diagnosis of LAHS should be made only if the trichogram shows at least 70 % LAH [68]. A negative pull test does not exclude the diagnosis.

Short Anagen Hair Syndrome

Clinical Features

This is a rare condition, which is characterized by a short hair cycle with an inability to grow long hair, and recurrent episodes of telogen effluvium [69]. The condition is usually diagnosed in childhood, and patients complain of short hair that does not grow and/or increased hair shedding (Fig. 7.7). The condition has also been reported in African Americans [70] and is usually sporadic [71]. However, familial cases have been reported, suggesting an autosomal dominant inheritance [69].

Table 7.8 Variants of loose anagen hair syndrome

Type	Major differences
Type A	Characterised by decreased hair density
Type B	Characterised by mainly unruly hair
Type C	Characterised by increased hair shedding

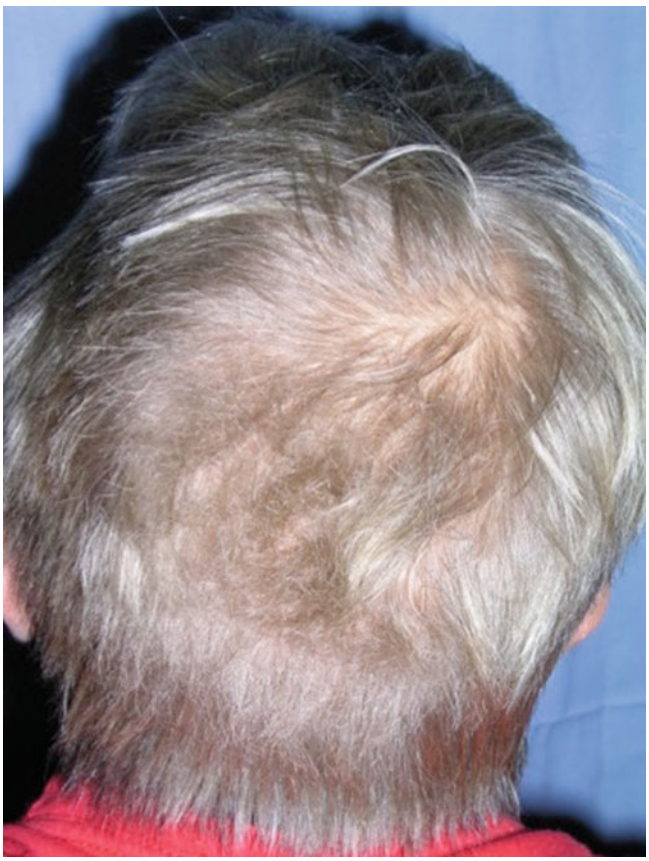

Fig. 7.6 Loose anagen hair syndrome. The hair is blond, short, and unruly

Investigations Recommended

For Diagnosis

- The diagnosis is made by the characteristic clinical features and the finding of short (less than 6 cm long) telogen hair with a tipped point on pull test or trichogram [70].
- The chief differential diagnosis is loose anagen syndrome.

For Treatment

Treatment for short anagen hair syndrome is not necessary because the condition usually improves after puberty, but increase in the hair length has been reported with minoxidil and cyclosporine [72].

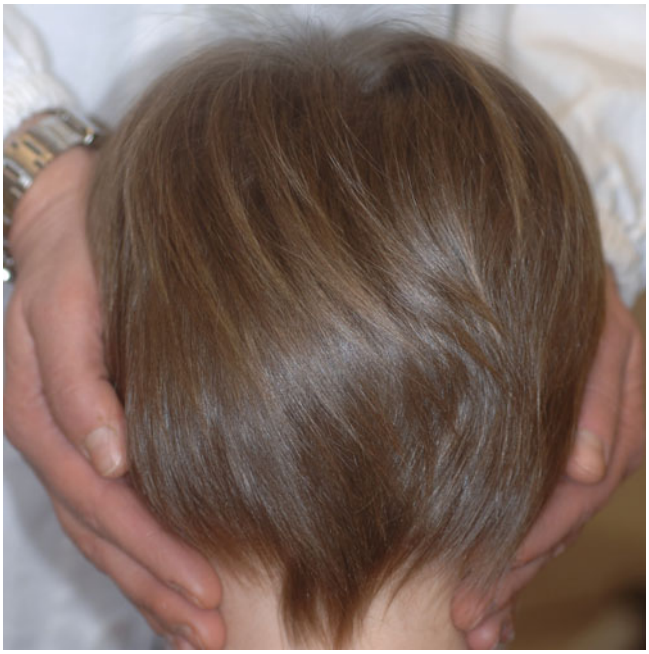

Fig. 7.7 Short anagen hair syndrome. The scalp hair is very short (less than 6 cm)

Scarring Alopecia

Keratosis Follicularis Spinulosa Decalvans (MIM 308800)

Clinical Features

Keratosis follicularis spinulosa decalvans is a rare scarring alopecia that shows X-linked inheritance that has been mapped to Xp21-p23 [73]. This inherited condition usually becomes evident in infancy. The scalp presents with follicular keratotic papules and pustules that produces progressive cicatricial alopecia (Fig. 7.8a). Follicular papules are also evident on the eyebrows, eyelashes, and cheeks. The disease is slowly progressive and can produce severe alopecia.

Investigations Recommended

For Diagnosis

- The diagnosis is based primarily on characteristic clinical findings of scarring alopecia with papules and pustules.
- Dermoscopy shows loss of follicular openings and peripilar casts (Fig. 7.8b). Findings are similar to those observed in lichen planopilaris.

For Treatment

- No specific treatment exists. All treatments are minimally effective and the disease is slowly progressive.

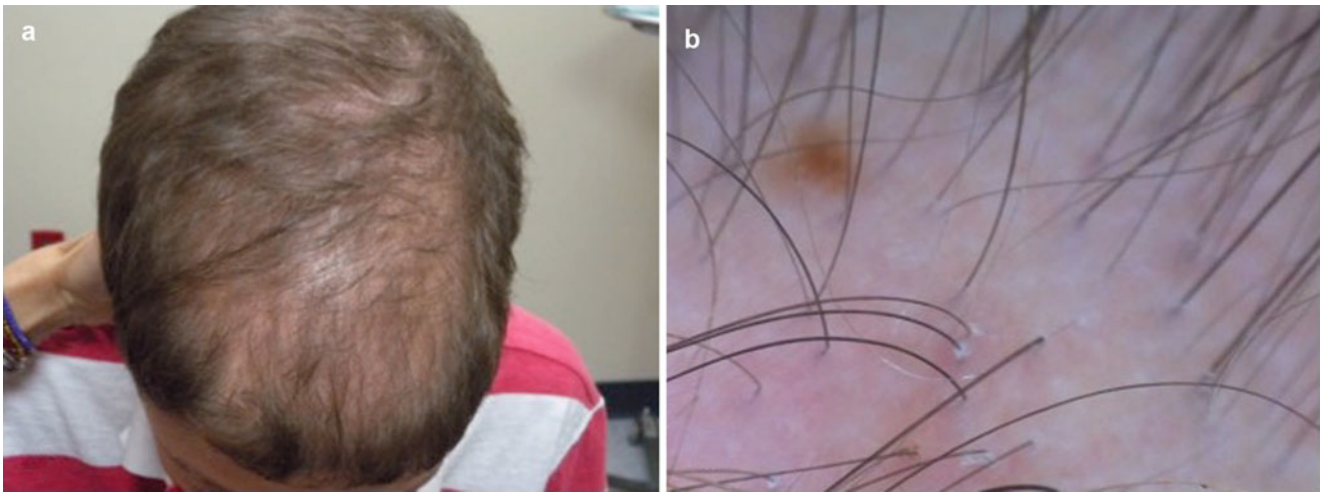

Fig. 7.8 (**a**, **b**) Keratosis follicularis spinulosa decalvans. (**a**) Scarring alopecia (**b**) Dermoscopy shows loss of follicular openings and peripilar casts

- Emollients, topical steroids and keratolytic agents can provide symptomatic relief.
- Case reports reported improvement with oral retinoids, dapsone, and tetracyclines.

Eruptive Vellus Hair Cysts (EVHC)

Clinical Features

Eruptive vellus hair cysts are rare benign neoplasms that present as multiple smooth or umbilicated papules, predominately on the chest and abdomen [74]. They primarily occur in children and young adults, and have been noted to occur concurrently with steatocystoma multiplex. Most cases are sporadic, but an autosomal dominant pattern has been reported [75]. EVHC has been associated with paronychia congenita, trichostasis spinulosa, hidrotic ectodermal dysplasia, and anhidrotic ectodermal dysplasia [76].

Investigations Recommended

For Diagnosis

Although clinical examination can provide clues to the diagnosis, definitive diagnosis is made with biopsy or incision into top of the lesion, followed by expression of cystic material.

- **Dermoscopy:** On Dermoscopy, EVHCs have well-defined white to yellow round structures with erythematous brownish halos. A central gray/blue color can be seen that corresponds to the melanin in the hair shaft of the cyst [77]. Dermoscopy is helpful because it can aide in differentiation of EVHCs from molluscum contagiosum, which has a polylobular white to yellow amorphous center with a crown of hairpin vessels at the periphery [75].
- **Histopathology:** EVHC have small epidermoid cysts, which contain multiple vellus hairs.

For Treatment

EVHC present a cosmetic problem and can be bothersome when occurring on the face. A variety of medical and surgical treatment options have been used with variable success (Table 7.9). However, 25 % of lesions spontaneously regress without treatment.

Hypertrichosis

Clinical Features

The term hypertrichosis describes the presence of an excessive amount of hair in non-androgen dependent area (Fig. 7.9). Hypertrichosis can be congenital or acquired, and is further characterized as localized or generalized (see Table 7.10). In both cases, hypertrichosis can be an isolated symptom or occur in association with other abnormalities. Hypertrichosis can also be a feature of numerous genetic syndromes. Hypertrichosis should be differentiated from hirsutism, which is characterized by excessive growth of terminal hairs in androgen-dependent areas, and represent an underlying endocrine disorder (Fig. 7.10).

Generalized Hypertrichosis

Congenital Hypertrichosis Universalis (MIM 145701)

This variety of hypertrichosis is a dramatic rare autosomal dominant familial disorder. The entire body is covered with long vellus-type hair, leading to an appearance that has been

Table 7.9 Treatments for eruptive vellus hair cyst

Treatment	Level of evidence
12 % lactic acid daily	E
10 % urea cream ± dermabrasion	E
Tazarotene cream 0.1 % daily	C
CO2 laser: face; 2-mm spot size, 5 W power, 160 J/cm^2 0.2 s pulse	E
Er: YAG laser; 2-mm spot size, 250 μs pulse duration, and 60.5–63.7 J/cm^2	E

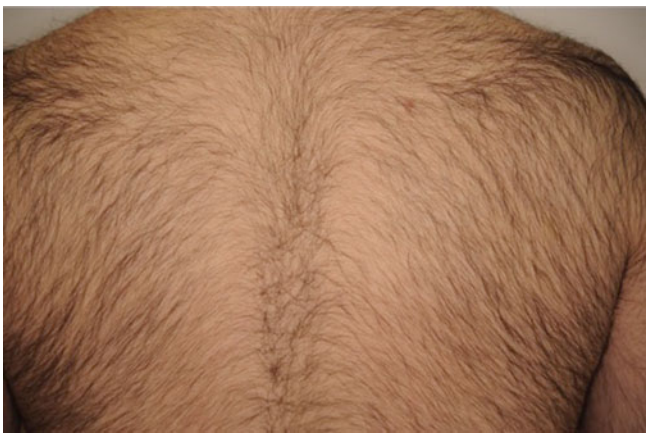

Fig. 7.9 Generalized hypertrichosis

Table 7.10 Types of hypertrichosis

Congenital generalized
Universal congenital hypertrichosis aka as Ambras syndrome (MIM 145701)
Congenital hypertrichosis lanuginosa (MIM 145700)
Prepuberal hypertrichosis
Congenital localized
Nevoid hypertrichosis
Hypertrichosis pinnae (MIM 139500, 425500)
Hypertrichosis nasi (MIM 139630)
Familial hypertrichosis cubiti (MIM 139600)
Hairy palms and soles (MIM 139650)
Anterior cervical hypertrichosis
Posterior cervical hypertrichosis
Lumbosacral hypertrichosis
Acquired generalized
Drug-induced hypertrichosis
Acquired hypertrichosis lanuginosa
Acquired localized
Acquired circumscribed hypertrichosis

likened to that of a werewolf. Individuals remain hairy throughout life. The condition can be associated with various abnormalities and syndromes.

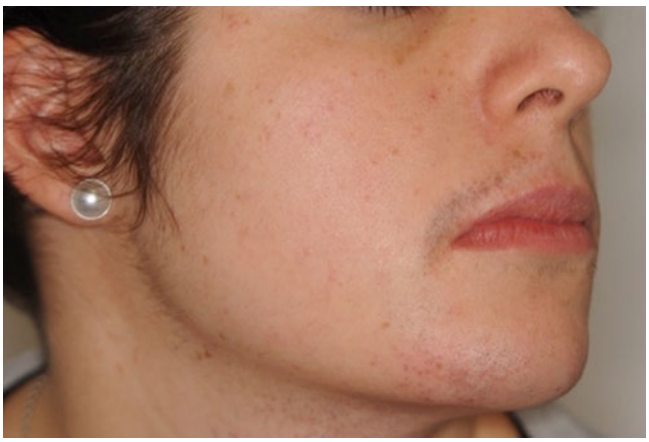

Fig. 7.10 Clinical presentation of hirsutism demonstrating clear male pattern of facial hair

Congenital Hypertrichosis Lanuginosa (MIM 145700, 307150)

Hypertrichosis lanuginosa is an exceedingly rare disorder that is most commonly transmitted as an autosomal dominant trait [78] and has been associated with an inverse mutation on chromosome 8q [79]. Hypertrichosis is present at birth and affects all skin surfaces except for the palms, soles, lips, glans penis, and distal phalanges. The abnormal hairs may be blond to black in color, and are lanugo type hairs that continue to grow. The hair may reach a length of 5–10 cm. In some families the hairs are lost in childhood, and in others they persist into adult life. The condition is associated with congenital glaucoma, pyloric stenosis, tetralogy of Fallot, and growth/developmental delay [80].

The hypertrichosis associated with gingival hyperplasia, although similar, represents a different condition (MIM135400), even though the distribution and appearance of the hypertrichosis is similar to that of hypertrichosis lanuginosa. Gingival hyperplasia appears in early childhood and progresses to completely obscure the teeth [81].

Prepubertal Hypertrichosis

Hypertrichosis of the limbs and/or the back is common in young children. The condition differs from other forms of congential hypertrichosis because the hair is of the terminal type. The etiology is unknown, and it is not clear if it is an abnormal entity or an extreme form of the normal range of hair growth, such as racial hirsutism. This form of hypertrichosis continues into adulthood.

Localized Hypertrichosis

Congenital Melanocytic Nevi

These lesions can present with large, coarse, terminal hairs in up to 95% of congenital giant melanocytic nevi [82]. However, the presence of hair is not an indicator of possible malignant transformation.

Becker's Nevus

Becker's nevus is an epidermal nevus characterized by irregular macular pigmentation with hypertrichosis, [83] which appears in 0.25–5% of the population [84, 85]. The pigmentation, which is light brown in color, usually develops in childhood or at puberty, most commonly involving the trunk or the upper arm. Hypertrichosis always appears after puberty, usually 2–3 years after the onset of pigmentation in about 50% of cases. Hypertrichosis of Becker's nevus appears to be androgen-dependent, and androgen receptors have been found in the nevus [86].

Although Becker's nevus is reported to occur much more frequently in males than in females (10:1), Becker's nevus in females is often undiagnosed since it is not associated with hypertrichosis. Becker's nevus can occur as part of a syndrome (Becker's nevus syndrome) that includes unilateral breast hypoplasia and/or other cutaneous, muscular, or skeletal defects.

Hypertrichosis Cubiti (Hairy Elbows Syndrome)

This condition is usually sporadically inherited, but may have a familial inheritance. Lesions are characterized by the presence of lanugo hair on the extensor surface of the elbows, extending from mid humerus to mid forearm. Hypertrichosis cubiti is typically bilateral and is usually present in the first few months of life, becomes more evident during childhood, and may disappear in adult life. There is a potential association with short stature and other abnormalities, but reports are conflicting [87].

Cervical Hypertrichosis

Cervical hypertrichosis may be localized to the anterior or posterior side of the neck and is present since birth. In anterior cervical hypertrichosis, "hairy throat" which is a tuft of terminal hair, is present 1–4 cm above the sternal notch. The mode of inheritance appears to be autosomal recessive and, in some cases, X-linked [88]. It can be associated with neurological and ocular abnormalities, of which peripheral sensory and motor neuropathies are most common. Posterior cervical hypertrichosis presents with a tuft of terminal hair present over the cervical vertebras.

Faun Tail (Lumbosacral Hypertrichosis; Spinal Hypertrichosis)

Faun tail describes the presence of a tuft of long terminal hair on the lumbosacral area. A full neurological and radiological workup is mandatory in all children with faun tail, as this can be associated with spina bifida, diastematomyelia, tethered cord, intraspinal lipomas, dermal sinuses, cutaneous aplasia, lipomenigomyelocele, and hemangiomas [89].

Hypertrichois in Porphyria

Congenital or erytropoietic porphyria are typically associated with hypertrichosis of the face and limbs [90].

Trichomegaly

Elongation and thickening of the eyelashes can occur in the setting of congenital syndromes such as Oliver-McFarlane and Cornelia de Lange syndrome. Moreover, the condition has been reported to occur in HIV patients, patients with atopic dermatitis, and those with uveitis [91].

Acquired Hypertrichosis

Drug-Induced Hypertrichosis

Several drugs are known to cause significant generalized hypertrichosis, but phenytoin, cyclosporine, and minoxidil are the most common agents. Phenytoin-induced hypertrichosis occurs after 3 months, affecting girls more than boys, preferentially occurring over the extensor surfaces of the limbs. Cyclosporine A can induce hypertrichosis in over 60% of patients in the first 6 months [92]. Topical minoxidil can cause generalized hypertrichosis due to systemic absorption in children [93]. Overall, identification of the offending agent and discontinuation leads to resolution of hypertrichosis.

Postinflammatory/Post-traumatic Hypertrichosis

Chronic inflammation, scratching, and mechanical friction (cast wearing) can also induce localized hypertrichosis and hyperpigmentation.

Investigations Recommended

For Diagnosis

- A through history and physical examination are paramount to rule out any underlying manifestations of general medical problems on syndromes that occur. This includes characterization of type of hair involved, pattern of growth, age on initial presentation, drugs/systemic disorders, family history, and physical exam abnormalities.
- Acquired hypertrichoses are most commonly iatrogenic, metabolic, nutritional, or paraneoplastic. Thus, labs and imaging are helpful to determine the underlying etiology.

For Treatment

- A wide array of treatment options exist to treat hypertrichosis—from hair bleaching, trimming, and shaving to plucking, waxing, etc.
- Several depilation (removal of hair at some point along its shaft) and epilation (removal of entire hair shaft) techniques can be utilized depending on site, sverity, and patient's age. Epilation lasts longer than depilation, and may cause enough damage to follicle to provide partial long-term permanent removal.

First Line Therapies

- Trimming is the recommended modality for treating children with hypertrichosis, which makes the hair less noticeable while not increasing hair growth [92]. Shaving is an alternative to trimming, however there is a higher propensity for skin irritation.
- Laser hair removal offers an alternative modality for rapid hair removal, which targets melanin within the hair follicle of darker hair (Ruby, Alexandrite, Diode). The Q-switched Nd: YAG is less effective, but suitable for light hair, and can be used in darker skin types with less risk for post-inflammatory hyperpigmentation. Regardless of laser type, all systems have been shown to reduce hair growth and decrease hair count by 20 % with each treatment. Moreover, significant hair reduction can be achieved in 85 % of patients using alexandrite or diode lasers at 12 months. Dark hair over fair skin is the most amenable to lead to long-term hair removal after a single treatment session, while blond, red, or white-haired patients are unlikely to obtain permanent reduction in hair [94].
- Eflornithine cream is suitable for facial hypertrichosis that works by inhibiting ornithine-decarboxylase, which is essential for cell growth. Efficacy is moderate and can reduce hair growth in up to 70 % of patients [95]. Moreover, eflornithine can be used in laser-resistant hirsutism or laser-induced hypertrichosis.

Second Line Therapies

- Plucking and waxing allow for longer hair-free periods between treatment of 2 weeks or more. However, these methods are painful in children and can lead to skin irritation or folliculitis.
- Chemical depilatories are based on thiols that destroy the keratin of the hair, but have a high propensity for skin irritation. Furthermore, they can lead to allergic contact dermatitis, and if the solution comes in contact with the eyes, it can lead to corneal alkali burns [96]. Thus, thioglycolate depilatories should be avoided in children, but can be used in adolescents.
- Electrosurgical epilation can be used to permanently remove hair. Galvanic electrolysis is one particular modality that works by destroying the hair follicle. However, this modality requires multiple treatments and long treatment sessions, and thus is not an ideal method for the treatment of children [92].

Hirsutism

Clinical Features

Hirsutism describes excessive terminal hair with a male pattern of distribution in a female (Fig. 7.10). Hirsutism is a common condition, which affects between 5 % and 15 % of women [97]. Prevalence of hirsutism is influenced by genetic and racial factors. It is frequent in Hispanic and Mediterranean women, but rare in Asiatic and African women. Hirsutism may or may not be associated with hyperandrogenism, and the magnitude of androgen excess is not well correlated with hirsutism severity. However, even in mild cases of hirsutism, one should look for underlying endocrine abnormalities (see Table 7.11). In general, idiopathic hirsutism accounts for about 15 % of cases [98]. The clinical evaluation of hirsutism is based on the Ferriman and Gallwey score.

Table 7.11 Etiologies of hirsutism

Condition	Incidence
Polycystic ovary syndrome (PCOS)	70 %
Idiopathic hyperandrogenism	15 %
Idiopathic hirsutism	10 %
Hyperandrogenism, insulin resistance, acanthosis nigricans (HAIR-AN)	3 %
Non-classical congenital adrenal hyperplasia (CAH)	3 %
Exogenous sources	0.3 %
Hyperprolactinemia	Rare
Acromegaly	Rare
Cushing's disease	Rare
Gestational hyperandrogenism	Rare
Glucocorticoid resistances	Rare

The most common cause of hirsutism is polycystic ovarian syndrome (PCOS). PCOS is defined as clinical and/or biochemical hyperandrogenism, ovulatory dysfuction, and polycstic ovarian morphology. However, hirsutism that is moderate to severe or rapidly progressive should not be overlooked due to the increased propensity for the development of metabolic syndrome, cardiovascular disease, infertility, etc. that can occur with disorders causing hirsutism. Moreover, there is a signifiacnt social stigma with hirsutism that can lead to depression, and impacts on quality of life [99].

Investigations Recommended

For Diagnosis

- Once excessive terminal hairs are identified in a male pattern in a woman, a baseline level of total testosterone, sexual hormone binding globuline (SHBG), and dehydroepiandrosterone sulfate (DHEAS) should be done.
- Futher laboratory work-up is useful to evaluate the underlying etiology of hirsutisim, which can require multiple tests and/or imaging (see Table 7.12) in combination with phyiscal exam.
- Diagnosis of idiopathic hirsutism requires demonstration of normal ovulatory cycles and normal androgen levels.

For Treatment

Treatment for hirsutism is centered on treating the underlying cause leading to hyperandrogenism. However, in the case of idiopathic hirsutism, similar physical, topical and light modalities used for hypertrichosis can be utilized.

Table 7.12 Test commonly used to determine etiology of hirsutism

For diagnosis
Total testosterone, steroid hormone binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS)
Dexamethasone suppression test
Plasma cortisol
ACTH stimulation test
17-a-hydroxyprogesterone
Pelvic ultrasound

Table 7.13 Treatments for hirsutism

Treatment	Level of evidence
Oral contraceptive pill (OCP)	A
3rd generation low-dose OCPs	
Spironolactone 100 mg/day and daily OCP [101]	A
Finasteride 5 mg/day and daily OCP [102]	A
Flutamide 125 mg/day and daily OCP [103]	A

First Line Therapies

- Antiadrogen therapy is usally combined with an oral contraceptive pill (OCP). The prefered OCP is a 3rd generation low-dose antiandrogenic medication.
- OCP treatment is necessary to avoid pregnancy as antiandrogens can interfere with genitalia development of the male fetus [100].
- A variety of anti-androgenes have been used (see Table 7.13). In most patients treatment should be prolonged for 3–4 years.

Nail Disorders

Twenty-Nail Dystrophy (TND, Trachyonychia)

Clinical Features

Twenty-nail dystrophy causes excessive longitudinal ridging of the nail plate with a distinctive rough, sandpaper-like appearance (Fig. 7.11). The condition often occurs in children and can be idiopathic or associated with other conditions; most commonly alopecia areata [104]. Pathological studies show that TND can be spongiotic, caused by nail lichen planus or nail psoriasis. Spongiotic TND can be idiopathic or associated with AA. However, the idiopathic form is almost exclusively seen in children. TND has also been associated with ichthyosis vulgaris, vitiligo, hemolytic abnormalities, incontinentia pigmenti, and lichen planus [105].

Two clinical variants of TND exist: opaque and shiny. Both varieties may occur in association with AA or may be idiopathic. In opaque TND, the affected nails show excessive longitudinal striations with loss of nail luster (vertically

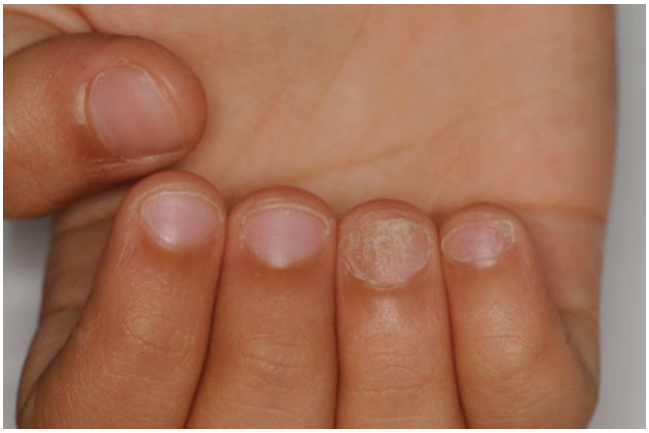

Fig. 7.11 Twenty-nail dystrophy (trachyonychia). The affected nails are rough due to excessive longitudinal striations. Despite the term TND, the condition is often limited to a few nails

striated sandpapered nails). In shiny TND, the nails show longitudinally distributed small pits. Koilonychia may also be present. The disorder is symptomless, and patients only complain of brittleness and cosmetic discomfort. Despite the term TND, the nail changes do not necessarily involve all 20 nails (Fig. 7.11).

Investigations Recommended

For Diagnosis

Diagnosis is clinical. A nail biopsy is not recommended, as TND is a benign condition that does not require a specific treatment, even when it is caused by nail lichen planus.

For Treatment

Reassurance is the best modality for the management of the condition. No first line treatments exist. Although systemic steroids improve TND, the nail abnormalities usually relapse after discontinuation.

Pachyonychia Congenital (PC)

Clinical Features

Pachyonychia congenita (PC) defines an autosomal dominant disorder characterized by severe nail thickening due to nail bed hyperkeratosis. Mutations in one of five keratin genes (KRT6A, KRT6B, KRT6C, KRT16, or KRT17) are responsible. Different phenotypes of PC have been recognized, depending on the clinical features and genetic mutations (see Table 7.14). Nail abnormalities, keratoderma, and plantar pain are present in 90 % of cases, [107] with nail abnormalities developing during childhood. All the nails are thickened, difficult to trim, and show an increase in the lateral curvature of the nail plate.

Investigations Recommended

For Diagnosis

- Diagnosis is based principally off clinical examination, with over 75 % developing painful plantar keratoderma and nail dystrophy before 5 years old.
- Genetic testing can be performed to identify specific keratin mutations, which may help in predicting the prognosis of disease.

For Treatment

- No specific treatment exits. Treatment is directed toward mitigating bothersome manifestations of the condition, in particular the palmoplantar keratoderma and associated pain.
- Redistribution of weight using orthotic inserts, insoles, and protective socks and gloves can help to decrease pain.
- Mechanical pairing down of keratotic nails and calluses have been shown to improve appearance, pain and quality of life. Alternatively, softening of the nails and calluses can be done using urea, salicylic acid or propylene glycol.
- Retinoids such as isotretinoin and acitretin can be used to decrease keratoderma and follicular keratosis. However, caution should be taken due to thinning of skin, which can lead to increased pain and blistering [108]. Alternatively, topical Sirolimus is an approved orphan drug that can be used to treat keratoderma.
- Treatment of painful foot blistering secondary to hyperhidrosis can be treated with botulinum toxin A. Studies have shown response in up to 75 % of patients, with results lasting 3 months [109].
- Short interfering RNA (siRNA) therapies have been developed to treat local plantar callouses in keratin 6a (K6a) type PC [110].

Congenital Malalignment of the Big Toenail

Clinical Features

Congenital malalignment of the big toenail occurs when the nail plate of the big toenail deviates laterally from the longitudinal axis of the distal phalanx (Fig. 7.12). The etiology is thought to occur secondary to tension from extensor tendon of the hallux. The condition affects girls more than boys. The condition is almost always complicated by the development of lateral or distal nail embedding.

The affected nail frequently shows dystrophic changes due to repetitive traumatic injuries: the nail plate may be

Table 7.14 Mutation-based classification of pachyonychia congenita and incidence of associated findings

	Keratin gene mutation				
Clinical findings	K6a	K6b	K6c	K16	K17
Thick toenails	99 %	98 %	56 %	95 %	99 %
Thick fingernails	99 %	51 %	0 %	61 %	87 %
Plantar pain	89 %	98 %	94 %	100 %	80 %
Plantar keratoderma	96 %	100 %	100 %	97 %	89 %
Palmar keratoderma	54 %	41 %	19 %	81 %	51 %
Cysts	68 %	71 %	25 %	26 %	92 %
Follicular hyperkeratosis	62 %	47 %	0 %	14 %	68 %
Natal or prenatal teeth	2 %	0 %	0 %	0 %	77 %
Oral leukokeratosis	88 %	31 %	19 %	41 %	27 %

Based on the International Pachyonychia Congenita Research Registry (IPCRR) 2010 proposed symposium classification [106]

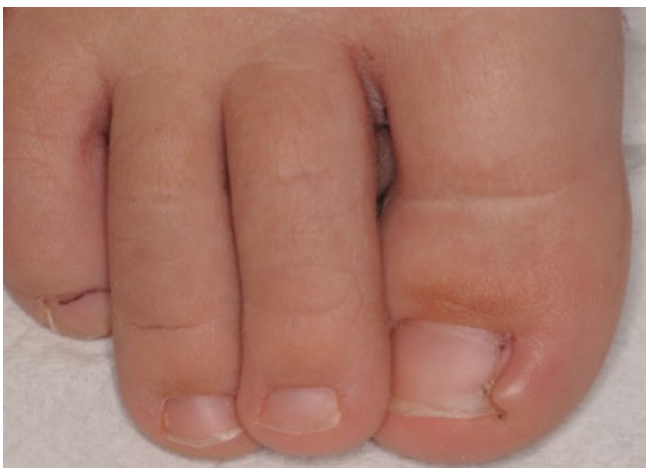

Fig. 7.12 Congenital malalignment of the big toenail, with hypertrophy of the lateral nail fold

thickened, yellow–brown in color, and present transverse ridging due to intermittent nail matrix damage. Onycholysis is frequent [111].

Investigations Recommended

For Diagnosis

Diagnosis is based principally on clinical exam findings of lateral hallux nail displacement that often occurs bilaterally.

For Treatment

- Correction of the nail plate deviation is reported to occur in up to 50 % of patients spontaneously [111].
- If the patient remains asymptomatic, no further treatment is necessary. However, with severe deviation or complaints, surgical correction of the nail is indicated. Best surgical results are obtained if surgery is performed before the age of 2 [112].

Ingrown Nails (Unguis Incarnates, Onychocryptosis)

Clinical Features

Ingrown nails are a common complaint, and usually affect the great toe of teenagers and young adults. Predisposing factors include congenital malalignment of the great toenails and congenital hypertrophy of the lateral nail folds. In the latter condition, the periungual soft tissues of the great toe are hypertrophic and partially cover the nail plate, favoring nail ingrowing. Improper nail trimming, traumatic injuries, excessive sweating, and occlusive footwear favor the development of ingrown nails.

Newborns can develop multiple ingrown fingernails with paronychia as a result of the grasp reflex [113]. The pathogenesis of the condition is the repeated compression of the soft tissues of the lateral nail fold by the lateral edges of the nails during grasping. The condition regresses spontaneously when the grasp reflex disappears, at about 3 months of age.

The clinical manifestations of ingrown toenails can be divided into four stages according to the Mozena classification (see Table 7.15), which accounts for the lateral nail fold involvement [114, 115].

Investigations Recommended

For Diagnosis

- Diagnosis is based off clinical exam findings, which allows for classification of nail severity. Various findings can be seen, such as lateral nail fold hypertrophy, formation of granulation tissue, erythema etc.
- The importance of staging ingrown nails is that it provides for a treatment algorithm.

Treatment

- Stage 1 treatment is principally conservative, with extraction of the embedded specula and placement of cotton under the lateral corner.
- In stage 2, topical application of high-potency steroid under occlusion for a few days can reduce the overgrowth of nail fold. Chemical partial matricectomy with phenol can also be considered.
- In stage 3, the granulation tissue becomes covered by newly formed epidermis of the lateral nail fold (Fig. 7.13). This stage always requires selective destruction of the

Table 7.15 Mozena classification for ingrown toenails

Stage	Findings
Stage 1 inflammatory stage	Erythema, mild edema, pain when pressure is applied to lateral fold
Stage 2 (2a/2b) abscess stage	2a; increase stage 1 symptoms with drainage and infection nail fold <3 mm
	2b; increased stage 1 symptoms with drainage and infection nail fold ≥3 mm
Stage 3 hypertrophic stage	Magnified stage 2 symptoms, presence of granulation tissue and nail fold hypertrophy
Stage 4 distal hypertrophic stage	Serious chronic deformity that involves lateral and distal folds, with hypertrophic tissue completely covering lateral, medial, and distal nail plate

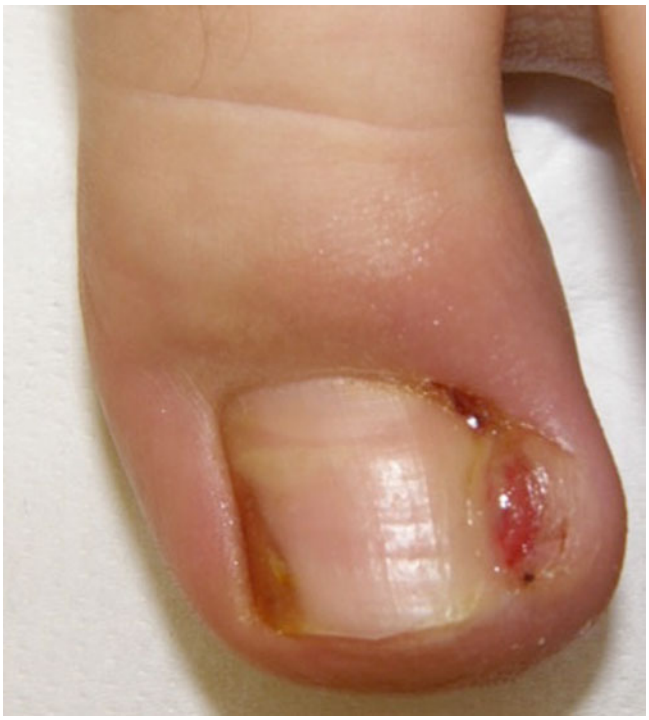

Fig. 7.13 Ingrown toenail of the hallux

lateral horn of the nail matrix. Chemical matricectomy using phenol is preferred by most authors.

- Stage 4 has serious nail dystrophy, and hypertrophic tissue completely covers the nail, which requires surgical treatment using a wedge technique or super U procedure [116].

Beau's Lines

Clinical Features

First described by Beau in 1846, these lines are transverse depressions of the nail plate surface that result from a temporary interruption of the mitotic activity of the proximal nail matrix. The depth of the depression indicates the extent of the damage within the matrix; the width of the depression (along the longitudinal axis) indicates the duration of the insult. Beau's lines grow distally with the nail plate, with multiple lines indicating repeated damage (Fig. 7.14). Most commonly, Beau's lines are caused by mechanical trauma (e.g. manicures, onychotillomania) or dermatologic disease of the proximal nail fold (e.g. eczema, chronic paronychia) [117]. The presence of Beau's lines at the same level in all nails suggests a systemic cause, such as severe or febrile illness, erythroderma, drugs etc. [118].

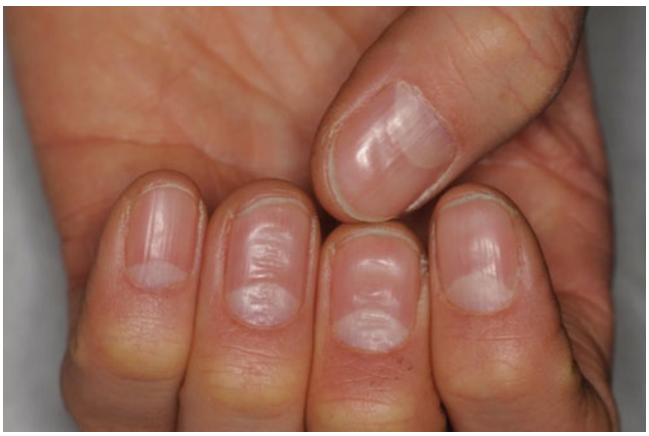

Fig. 7.14 Clinical presentation of Beau's lines, demonstrating transverse depressions in the nail plate

Investigations Recommended

For Diagnosis

Diagnosis is based on clinical exam. Determine the underlying cause, which has been documented to occur with severe systemic illness, chemotherapy, malnutrition, zinc deficiency, trauma, paronychia, pemphigus, and Kawasaki disease.

For Treatment

Treat the underlying cause to prevent development of new lesions.

Onychomadesis (Nail Shedding)

Clinical Features

Onychomadesis is characterized by separation of the nail plate from the matrix, with persistent attachment to the nail bed that usually leads to nail shedding. Onychomadesis occurs due to a severe insult that produces a complete arrest of nail matrix activity. Onychomadesis occurs due to the same reasons that Beau's lines form (see Table 7.16).

Table 7.16 Causes of onychomadesis [119]

Associations	Causes
Autoimmune	Alopecia areata, pemphigus vulgaris
Severe medical illness	Guillain-Barré syndrome, major depressive disorder, Stevens-Johnson syndrome, Cronkite-Canada syndrome, peritoneal dialysis, immunodeficiency, meningitis, mycosis fungoides, Kawasaki disease
Drug induced	Chemotherapy agents, penicillin, antiepileptics, azithromycin, retinoids, lead, lithium
Loss in neonatal period	Trauma of birth
Infectious causes	Hand-foot and mouth disease, *Varicella zoster*, *Candida albicans*, *Fusarium solani*, *Trichophyton tonsurans*
Idiopathic	Hereditary (autosomal dominant pattern)

Investigations Recommended

For Diagnosis

Diagnosis is based principally on physical exam findings of proximal detachment of the nail. In cases of multi-digit involvement, the underlying cause is most likely systemic.

For Treatment

No specific treatment exists. Treatment centers on treating the underlying inciting illness, or withdrawal of medication causing insult.

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Disorders of the Sebaceous and Sweat Gland

8

Karen A. Chernoff and Andrea L. Zaenglein

Clinical Features of Acne Vulgaris and Its Variants

Acne Vulgaris

The clinical presentation of acne vulgaris consists of open and closed comedones as well as inflammatory erythematous papules and pustules. It is typically categorized as mild, moderate, or severe in terms of severity (see Figs. 8.1, 8.2, and 8.3). Nodular acne signifies the presence deeper inflammatory nodules. Both non-inflammatory and inflammatory lesions are often seen in the same patient. While its age of onset is typically in adolescence, acne may begin in the pre-adolescent child beginning around 8 years of age. Upon resolution of acne lesions, patients may develop hyperpigmented or erythematous macules, as well as variable degrees of scarring.

Acne Fulminans

Acne fulminans is the most severe form of acne, and primarily affects adolescent boys. It is characterized by the abrupt development of nodular and suppurative acne lesions in the background of mild to moderate acne. Lesions affect the face, neck, chest, back, and trunk, and often develop into painful, friable ulcerated plaques with overlying hemorrhagic crust. Significant scarring is common. Systemic manifestations include fever, arthralgias, myalgias, hepatosplenomegaly, and malaise. The systemic findings of acne fulminans overlap with ***s***ynovitis, ***a***cne, ***p***ustulosis, ***h***yperostosis, and ***o***steitis (SAPHO) syndrome.

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Acne Conglobata

Acne conglobata is a severe form of nodular acne with eruptive onset in the absence of systemic manifestations. It can be seen as part of the follicular occlusion tetrad, along with dissecting cellulitis of the scalp, hidradenitis suppurativa, and pilonidal cysts. It may also be seen as part of PAPA syndrome, an autosomal dominant disorder caused by mutations in the *PSTPIP1* gene, characterized by sterile ***p***yogenic ***a***rthritis, ***p***yoderma gangrenosum, and ***a***cne conglobata. PAPASH syndrome includes sterile ***p***yogenic ***a***rthritis, ***p***yoderma gangrenosum, ***a***cne and ***s***uppurative ***h***idradenitis. Novel mutations in the *PSTPIP1* gene are also implicated [1].

Drug-Induced Acne

Drug-induced acne typically presents as monomorphous papules and pustules, and can be secondary to several medications. In the pediatric population, the most common cause is systemic or ultrapotent topical corticosteroids, and less often lithium, isoniazid, and phenytoin. Other possible agents include cyclosporine, azathioprine, and phenobarbital, as well as accidental exposure secondary to testosterone-containing agents.

Specific Investigations

For diagnosis
Endocrine evaluation (in children under 7 years and adolescents when other signs of hyperandrogenism are present)
For treatment
With isotretinoin: liver function tests, lipid profile, β-hCG (females of childbearing age)
With dapsone: complete blood count (CBC) with differential, glucose-6-phosphate dehydrogenase (G6PD) level

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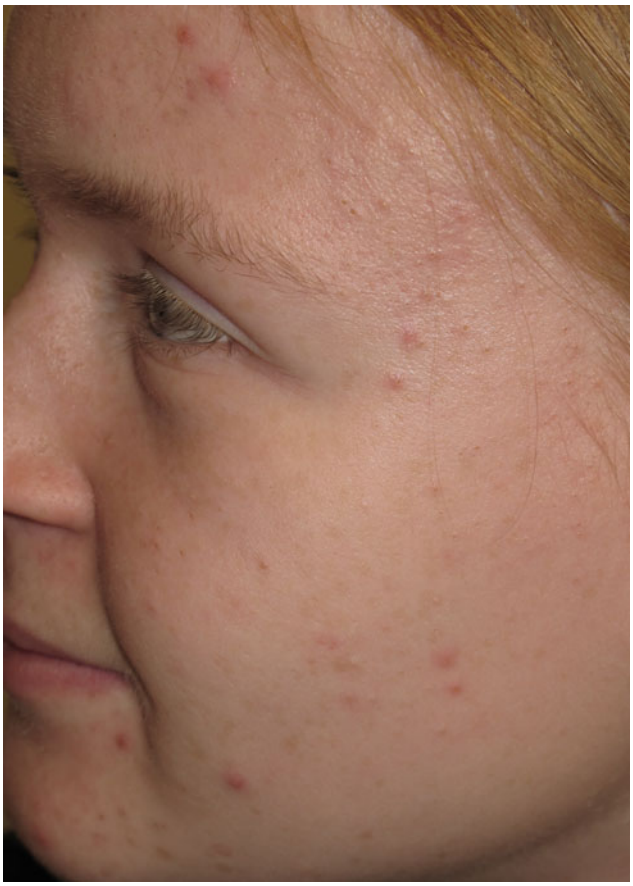

Fig. 8.1 A patient with papules and closed comedones consistent with mild acne

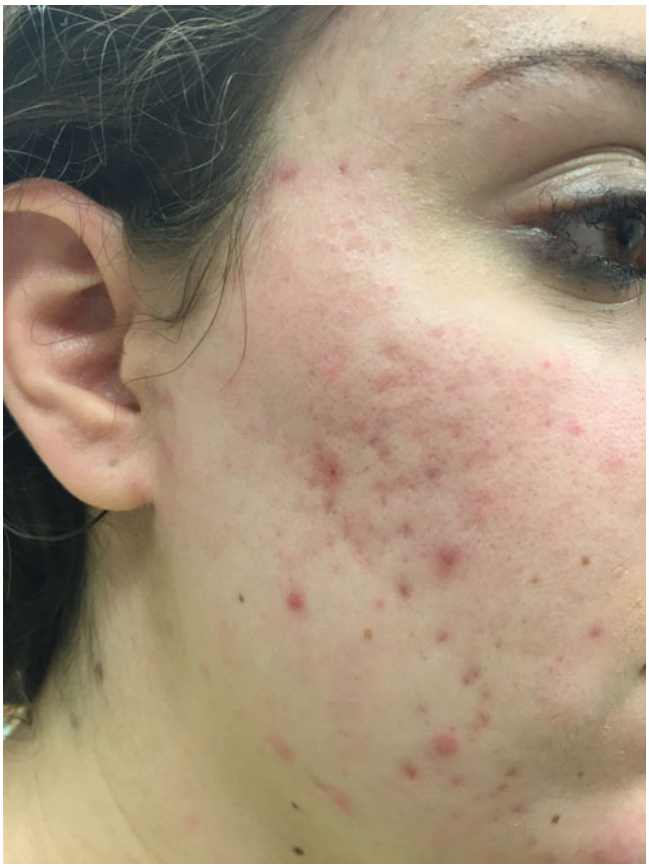

Fig. 8.2 Combined inflammatory papules with closed comedones and scarring in a patient with moderate acne

Laboratory evaluation is not required in the majority of patients with acne. In patients with a suspected endocrine abnormality, such as polycystic ovarian syndrome (PCOS), congenital adrenal hyperplasia, an adrenal or gonadal tumor, baseline evaluation should be performed. Screening tests include serum total and free testosterone, dihydroepiandrosterone-sulfate (DHEA-S), and 17-hydroxyprogesterone. Lutenizing hormone (LH) and follicle-stimulating hormone (FSH) may be obtained as well. In females with PCOS, serum free testosterone typically ranges from 100 to 200 ng/dl, and may be associated with an increased LH/FSH ratio (>2–3:1). Congenital adrenal hyperplasia is usually associated with 17-hydroxyprogesterone levels of >3 ng/ml [2]. Serum testosterone >200 ng/dl raises concern for an ovarian tumor, while serum DHEA-S levels of >8,000 ng/ml may be secondary to an underlying adrenal tumor.

In patients undergoing treatment with isotretinoin, baseline laboratory tests include liver function tests and a serum lipid panel. Repeat laboratory testing should be performed at monthly intervals when the lipid response to isotretinoin is established [3]. Females of childbearing potential must have two negative pregnancy tests within a month prior to starting isotretinoin therapy, then monthly during treatment and for 1 month after cessation of therapy.

Oral dapsone therapy can cause hemolytic anemia and, uncommonly, agranulocytosis, thus warranting periodic CBCs. Its use is contraindicated in those with G6PD deficiency, and levels of the enzyme should be checked prior to starting treatment with dapsone.

Discussion of Treatment Modalities

Topical Retinoids

Topical retinoids are first-line agents in acne treatment. They should be applied to the entire acne-prone area in order help prevent future acne lesions. The most common side effect is skin dryness and irritation, especially when used in combination with other topical agents. To minimize irritation, the retinoid can be applied every 2–3 days, and increased to daily as tolerated. Additionally, moisturizer can be applied directly over top of the medication.

Three topical retinoids are available; tretinoin, adapalene, and tazarotene. Tretinoin is photolabile and susceptible to oxidation by benzoyl peroxide. It should be applied at night and should not be used at the same time of day as benzoyl peroxide. Microsphere formulations do not have these restrictions, nor does adapalene or tazarotene.

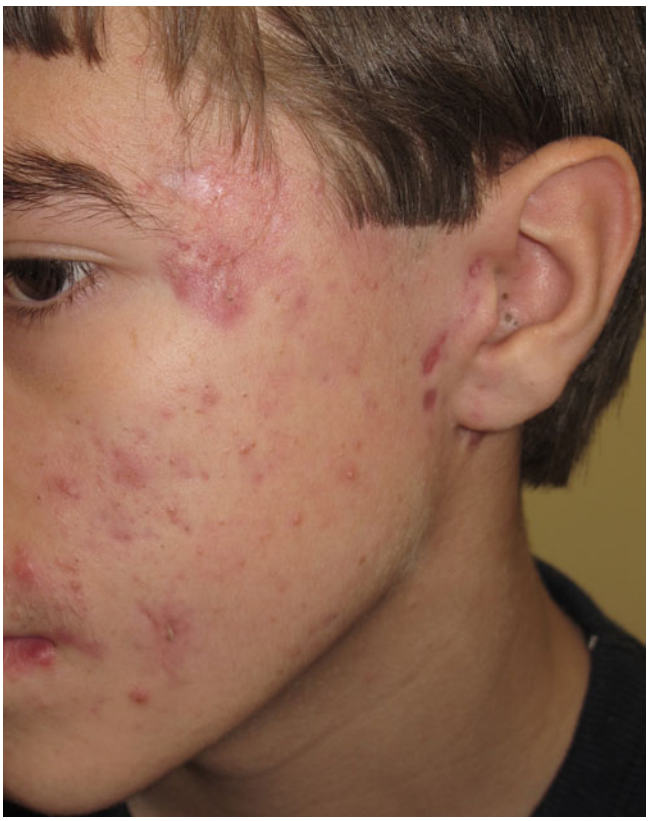

Fig. 8.3 Severe acne in a patient with numerous nodules, scarring, as well as open comedones in the ears

Table 8.1 First line therapies

Acne type	Treatment
Mild	Benzoyl peroxide or
	Topical retinoid or
	Topical combination therapy[a]
Moderate	Topical combination therapy[a] +/– oral antibiotic
Severe	Topical combination therapy[a] +/– oral antibiotic or
	Isotretinoin (if severe nodular or scarring)+/– oral steroid

Prescribe separate products or fixed dose combinations including adapalene/BP, clindamycin/BP, clindamycin/tretinoin + BP, erythromycin/BP, tretinoin + BP
BP benzoyl peroxide
[a]Topical combination therapy = retinoid + BP +/– topical antibiotic

Tretinoin and adapalene are labeled pregnancy category C, while topical tazarotene is pregnancy category X, and patients of childbearing potential should be counseled accordingly.

Topical Antimicrobials

Benzoyl peroxide is an effective treatment alone or when used in combination therapy. Unlike other antimicrobials, microbial resistance has not been reported to benzoyl peroxide. It is available in concentrations from 2.5 % to 10 % and

Table 8.2 Second line therapies

Acne type	Treatment
Mild	Add topical retinoid or BP (if not already using) or
	Alternate topical combination therapy* or
	Azelaic acid or salicylic acid or dapsone gel
Moderate	Alternate oral antibiotic + alternative retinoid
	+/– BP or
	Combined oral contraceptive or spironolactone (for females) or
	Isotretinoin
Severe	High-dose oral antibiotic + alternate topical retinoid + BP or
	Combined oral contraceptive (for females) or
	Dapsone or
	Etanercept or systemic immunosuppressive (rarely used)

Level of evidence	
Topical retinoids	A
Benzoyl peroxide (BPO)	B
Combination topical retinoid + BPO	A
Topical dapsone 5 % gel	A
Topical azelaic acid	B
Oral antibiotics	A
Isotretinoin	A
Oral contraceptives	A
Spironolactone	A
Oral dapsone	A
Oral corticosteroids	C

Table 8.3 Third line therapies

Chemical peels – A (level of evidence)
Laser therapy – B (level of evidence)
Intralesional steroid injections – E (level of evidence)

in several formulations, including washes, creams, gels, lotions, soap, foams, and pads. Benzoyl peroxide can bleach towels, sheets, and clothing, and cause skin erythema and irritation. A combination adapalene 0.1 %/benzoyl peroxide 2.5 % topical gel is available.

Other topical antibiotics include clindamycin and erythromycin, which are available as gels, solutions, and pledgets. However, antibiotic resistance to these agents is increasing, so monotherapy with these agents is not recommended.

Other Topical Agents

Azelaic acid cream or gel has inhibitory properties against *P. acnes* and can be used to treat inflammatory acne. It has the additional benefit of providing modest improvement to the post-inflammatory hyperpigmentation from prior acne lesions.

Topical dapsone 5 % gel has anti-inflammatory and antimicrobial properties and can also be used for inflammatory acne. The most common adverse event is skin irritation or dry-

ness, and it can cause a temporary orange-yellow discoloration of the skin and hair if used concurrently with benzoyl peroxide. Studies have shown minimal absorption of topical dapsone, and it is safe in those with G6PD deficiency [4]. There is one report of methemoglobinemia attributed to topical dapsone use [5].

Salicylic acid is present in many over-the-counter acne treatments. It can be effective in mild comedonal acne. Several formulations in concentrations up to 2% exist, including gels, creams, lotions, foams, solutions, and washes. It is typically well tolerated, but can cause erythema and xerosis.

Oral Antibiotics

Oral antibiotics are used in combination with topical agents as first-line therapy for moderate papulopustular acne. Doxycycline and minocycline are used most commonly, and given at doses of 100 mg daily to twice daily. Once-daily extended-release formulations are available. The most common side effect is gastrointestinal upset, especially with doxycycline. Esophagitis can also occur. Doxycycline can cause phototoxicity. Pseudotumor cerebri has been associated with all of the tetracyclines, especially if combined with isotretinoin. Tetracyclines can also cause permanent discoloration of developing teeth. Doxycycline and tetracycline are thus contraindicated in children under the age of 8 years. Minocycline is indicated for those 12 years and older. It can cause dizziness, or accumulate in the skin, leading to bluish pigmentary changes. Minocycline can uncommonly lead to hypersensitivity reactions as well as various autoimmune conditions, including drug-induced lupus.

Macrolides are second-line antibiotics for inflammatory acne. Azithromycin is most often used, as *Propionibacterium acnes* resistance to erythromycin is exceptionally high. Azithromycin is variably dosed for acne, from 250 to 500 mg three times weekly to daily. In younger children, 5 mg/kg daily to three times weekly is used. Macrolides have many drug interactions, and a thorough medication history is warranted prior to treatment. Erythromycin is dosed at 500 mg twice daily. For younger children, a dose of 30–50 mg/kg/day, divided twice daily, is used. Gastrointestinal upset is very common, and an often limiting side effect.

Trimethoprim-sulfamethoxazole is sometimes used for recalcitrant acne or to treat secondary gram-negative folliculitis. Due to the numerous potential serious side effects, it is generally regarded as third-line treatment among antibiotics, and use should be limited. Dosing is weight-based in children, and patients are given 6–12 mg/kg of trimethoprim every 12 h up to the adult dose of one double-strength tab twice daily.

Isotretinoin

Oral isotretinoin is approved for patients with severe, nodulocystic acne refractory to treatment including oral antibiotics. It may also be used as first-line therapy in those with severe nodular acne at risk for scarring, or those with significant scarring.

Patients may start at a lower dose of isotretinoin (0.25–0.5 mg/kg daily) and titrated up to 1 mg/kg/day after 1 month. Treatment is continued until a cumulative dose of 120–150 mg/kg is reached. When used to treat acne fulminans, it is typically started concurrently with oral steroids to prevent flaring, with tapering of the steroids over a few weeks.

Isotretinoin is a potent teratogen, and females of childbearing potential must receive proper counseling and use two forms of contraception during therapy. Common side effects include xerosis, cheilitis, epistaxis, and myalgias. Dry eyes or blurred vision is sometimes reported. Isotretinoin can cause elevations in triglycerides and liver enzymes. Two possible associations link isotretinoin to inflammatory bowel disease and depression, although recent data does not support causality.

Oral Dapsone

In patients with recalcitrant nodular acne, or with contraindications to isotretinoin, oral dapsone is sometimes used at a dose of 100 mg daily.

Hormonal Therapy

Hormonal therapy is considered second-line therapy in female patients with acne, but can be used initially in those with noted perimenstrual flares or irregular periods. Oral contraceptives are the mainstay of hormonal therapy, and contraceptives containing progestins with lower androgen activity or anti-androgen activity are most effective. They are commonly used in adolescent girls, ideally after they have established menstrual cycles.

The most common side effects include nausea, vomiting, menstrual irregularities, weight gain, and breast tenderness. Rare adverse events include hypertension and thromboembolism. This rate is higher in smokers and in those >35 years of age. Decreased bone density is a concern, so low-dose estrogen contraceptives are not recommended.

Spironolactone is a second-line hormonal treatment for acne, which has additive effects when combined with oral contraceptives. Doses range from 25 to 200 mg/day divided into twice-daily dosing. The most common side effects include breast tenderness, headache, and menstrual irregularities. Postural hypotension is uncommon, and hyperkalemia is usually not seen in healthy females. It is not commonly used in younger adolescents.

Table 8.4 Third-line therapies

Third-line therapies
Third-line acne treatments include chemical peels (usually with glycolic or salicylic acid) [6] and laser therapy. Individual nodular lesions can be injected with triamcinolone in concentrations up to 2.5 mg/cc

Neonatal Acne

Neonatal acne, considered by some to be synonymous with neonatal cephalic pustulosis, is seen up to 20 % of healthy newborns. It is characterized by small, inflamed papules and pustules in the absence of comedones, favoring the cheeks and nasal bridge, but often extending to the forehead, chin, neck, and upper trunk. Lesions usually appear by 2 weeks of age and resolve within the first few months of life. While some support a pathogenetic role of *Malassezia* yeast, this remains unproven and debated.

Specific Investigations

- None

Table 8.5 First-line therapies

First-line therapies
Observation

Neonatal acne is a self-limited condition and treatment is usually not required, unless extensive or persistent.

Table 8.6 Second-line therapies

Second-line therapies
Topical imidazole – E (level of evidence)

When treatment is required, the most commonly used agents are topical imiadazole creams, including econazole and ketoconazole [7]. These agents have anti-inflammatory properties and target the *Malassezia* yeast, which may provide additional improvement.

Table 8.7 Third-line therapies

Third-line therapies
Low potency topical steroids – E (level of evidence)

Improvement of neonatal acne with low-potency topical steroids has been reported and can be tried in those who fail topical imidazole therapy.

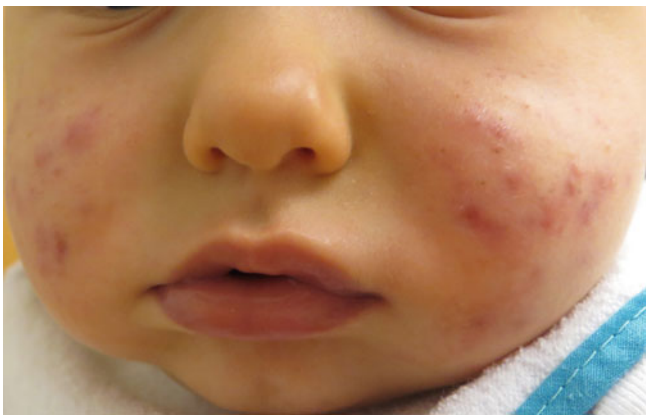

Fig. 8.4 Infantile acne with many inflammatory papules and open comedones on the cheeks

Infantile Acne

Infantile acne typically presents later than neonatal acne, at 3–12 months of age. It is most often characterized by prominent comedones with variable inflammatory lesions (see Fig. 8.4). Deep nodules are occasionally seen. Even with a minimal inflammatory component, infantile acne commonly results in scarring, up to 25 %. Infantile acne typically resolves within 1–2 years.

Specific Investigations

- None

No workup is typically required for infantile acne, unless secondary signs of hyperandrogenism are noted, and then a complete hormonal workup is indicated. Testing includes a serum total and free testosterone, DHEA-S, 17-OH progesterone, LH and FSH, and bone age.

Table 8.8 First-line therapies

Topical retinoid – E (level of evidence)
Topical antimicrobial – E (level of evidence)

Infantile acne is often treated, due to the potential for scarring. Mild comedonal acne is usually treated with tretinoin cream or adapalene gel. When present, mild inflammatory lesions are treated with a topical antimicrobial agent, such as benzoyl peroxide, erythromycin, or clindamycin. While not specifically studied in younger children, standard acne treatments have been reported to be safe and effective in infants [8]. Topical agents should be applied sparingly, and started thrice weekly to avoid excess irritation.

Table 8.9 Second-line therapies

Second-line therapies
Oral antibiotic – E (level of evidence)

Infants with more severe acne, especially those with a prominent inflammatory component, may be treated with an oral antibiotic, usually erythromycin.

Table 8.10 Third-line therapies

Third-line therapies
Oral isotretinoin – E (level of evidence)

In infants with severe nodular acne or with significant scarring, oral isotretinoin can be used, although this is rarely warranted.

Mid-childhood Acne

The onset of acne in mid-childhood (between 1 and 7 years of age) is unusual due to the minimal androgen production at this time. Its presence raises concern for possible pathologic hyperandrogenism, as can be seen in congenital adrenal hyperplasia, central precocious puberty, polycystic ovarian syndrome (PCOS), and gonadal or adrenal tumors. A thorough physical examination for signs of virilization and careful review of growth charts and bone age are required. If any abnormalities are noted, a complete endocrine evaluation is indicated.

Specific Investigations

- Serum total and free testosterone
- DHEA-S
- 17-OH progesterone
- LH and FSH
- Bone age

As noted above, screening tests for an endocrinologic abnormality include serum total and free testosterone, dihydroepiandrosterone-sulfate (DHEA-S), and 17-hydroxyprogesterone [9]. Lutenizing hormone (LH) and follicle-stimulating hormone (FSH) may be obtained in females with suspected hyperandrogenism. In mid-childhood acne, a bone age should be obtained to screen for precocious puberty.

Table 8.11 First-line therapies

Management of any underlying endocrine abnormality
Topical retinoid – E (level of evidence)
Topical benzoyl peroxide – E (level of evidence)

In young children with an underlying endocrine abnormality, treatment should first be directed at hormone regulation through an endocrinologist. In treatment of the acne, first-line therapy for mid-childhood acne is similar to infantile acne. Mild comedonal lesions can be treated with a topical retinoid, while mild inflammatory acne can be treated with topical benzoyl peroxide [8].

Table 8.12 Second-line therapies

Second-line therapies
Oral antibiotic – E (level of evidence)

Children with moderate inflammatory acne in childhood can be treated with an oral macrolide such as erythromycin or azithromycin. Tetracyclines are contraindicated in this age group.

Table 8.13 Third-line therapies

Third-line therapies
Oral isotretinoin – E (level of evidence)

In children with a prominent nodular component or with significant scarring, oral isotretinoin can be considered.

Preadolescent Acne

Acne occurring at the onset of adrenarche, ages 7–12, is designated preadolescent acne. The incidence of acne in this age group may be on the rise due to an overall earlier onset of puberty in children, and more prolonged and irregular pathways through puberty. Lesions are typically confined to the T-zone of the central face, and comprised of closed comedones, although all lesions types can be seen. Endocrinologic workup is generally not indicated unless other abnormal clinical findings are present.

Specific Investigations

- None

Table 8.14 First-line therapies

Topical retinoid – A (level of evidence)
Topical benzoyl peroxide – B (level of evidence)
Combination topical retinoid + benzoyl peroxide – A (level of evidence)

Treatment of preadolescent acne is similar to that of typical adolescent acne. Since the majority of patients in this age range have mild comedonal acne, a topical retinoid is first-

line therapy. Of note, preadolescents are often not self-motivated to treat their acne, and so any treatment plan should take this into consideration and remain simple.

Table 8.15 Second-line therapies

Alternative topical retinoid – E (level of evidence)
Salicylic acid – E (level of evidence)

Second-line options for preadolescent acne include the use of an alternative topical retinoid or using a salicylic acid-containing product.

Table 8.16 Third-line therapies

Oral antibiotics – E (level of evidence)
Oral isotretinoin – E (level of evidence)

For patients with an early onset of moderate-to-severe acne, oral antibiotics and oral isotretinoin can be considered and used in a similar fashion as described for adolescent acne.

Periorificial Dermatitis

Periorificial dermatitis is an acneiform eruption that commonly occurs in infants and young children. The rash is characterized by small inflammatory papules and pustules grouped around the mouth, nose, and eyes, which may coalesce into scaling patches or plaques. Extrafacial involvement involving the trunk, extremities, and vulvar skin is occasionally observed. The rash is typically asymptomatic, but itching and burning can be associated. Some patients have a granulomatous form of periorificial dermatitis characterized by small pink or skin-colored flattened papules and micronodules, which can coalesce into plaques with a striking perioral demarcation. Some experts believe periorificial dermatitis is a form of childhood rosacea. Topical, systemic, or inhaled corticosteroids are often a precipitating factor [10, 11].

Specific Investigations

- History regarding prior topical and oral steroid use

Workup for perioral dermatitis involves obtaining a thorough history regarding prior corticosteroid use. Patients should be asked about topical, inhaled, and oral steroids, as all forms may be implicated. Biopsy is rarely required for diagnosis.

Table 8.17 First-line therapies

Discontinue topical steroids, when applicable
Topical metronidazole – A (level of evidence)
Topical clindamycin – B (level of evidence)

First-line treatment for perioral dermatitis first involves discontinuation of any steroids, if possible. Changing from a mask inhaler to a chamber inhaler for pulmonary steroids may help as well. Initial treatment also typically involves a topical antimicrobial or anti-inflammatory agent, including metronidazole cream or gel, or clindamycin gel or lotion [12, 13]. Mild cases may resolve simply by discontinuing the corticosteroid.

Table 8.18 Second-line therapies

Oral macrolide antibiotic – D (level of evidence)
Oral tetracyclines – A (level of evidence)

Second-line therapy is generally indicated for patients who do not respond to topical therapy after approximately 6–8 weeks of treatments, and involves the use of oral antibiotics [13]. Macrolide antibiotics, particularly erythromycin and azithromycin, are the most commonly used agents in younger children [14]. Tetracycline-class antibiotics can be used in older children. Long-standing cases may take several months to resolve, with periods of waxing and waning, requiring a more prolonged treatment course.

Table 8.19 Third-line therapies

Pimecrolimus cream – A
Tacrolimus ointment – E
Sodium sulfacetamide lotion – E

Topical tacrolimus ointment and pimecrolimus cream have also been used to treat periorificial dermatitis, especially when there is a prominent dermatitis component, with mixed reports of efficacy. Sodium sulfacetamide lotion or wash was reported to be of use in one case, although was used concurrently with a low-potency topical steroid [15].

Childhood Rosacea

Rosacea is most commonly seen in adults, and is generally considered rare in young children. However, its true incidence may be higher, as other conditions more commonly seen in children, such as periorificial dermatitis and idiopathic facial aspeptic granuloma, may actually be variants of rosacea. Four subtypes of rosacea have been described: papulopustular, telangiectatic, granulomatous, and ocular. The papulopustular variant is most common in children.

Specific Investigations

- Ophthalmologic exam if ocular rosacea is suspected

A diagnosis of childhood rosacea is typically made clinically without further workup required. However, patients with ocular complaints such as dryness or redness should be referred to ophthalmology for evaluation and treatment.

Table 8.20 First-line therapies

Topical antibiotics – A (level of evidence)
Azelaic acid cream – A (level of evidence)
Niacinamide – B (level of evidence)

Treatment of childhood rosacea is similar to that of perioral dermatitis. First-line therapy includes topical antimicrobial and anti-inflammatory agents such as metronidazole and azelaic acid [16, 17]. Topical niacinamide can also be used for its effect on the associated erythema of rosacea [18]. Of note, while numerous studies have shown the efficacy of various treatments for rosacea in adults, these studies have not been reproduced in the pediatric population, likely due in part to the uncommon incidence of rosacea in children.

Table 8.21 Second-line therapies

Oral macrolide antibiotics – B (level of evidence)
Oral doxycycline– A (level of evidence)

Second-line treatment for resistant or extensive cases includes oral antibiotics. In younger children, erythromycin or azithromycin is typically used and has been shown to be effective [19]. Tetracyclines, such as doxycycline, are often used in children 9 years of age and older [20].

Keratosis Pilaris

Keratosis pilaris is a common disorder affecting up to 20 % of children [21]. Small, dry, rough, follicular-based papules with variable erythema are distributed symmetrically, most commonly over the extensor surface of the upper arms and cheeks, with lesser involvement of the thighs, buttocks, distal extremities, calves, and trunk. Lesions are typically asymptomatic, except for the pruritus noted when lesions are dry and inflamed. The disorder is often associated with ichthyosis vulgaris and atopy. Improvement with age occurs in a minority of patients, particularly in regard to facial involvement.

Specific Investigations

- None

Table 8.22 First-line therapies

First-line therapies
Emollients

Treatment for keratosis pilaris is often ineffective and does not change the natural course of the disorder. First-line therapy consists of emollients, which may result in some textural improvement of the skin.

Table 8.23 Second-line therapies

Topical keratolytics – D (level of evidence)
Topical retinoids- B (level of evidence)

In older children, second-line therapy consists of topical retinoids or keratolytics, including urea, glycolic acid, ammonium lactate, and salicylic acid, although they may all cause skin irritation [22, 23]. Those who experience improvement typically experience recurrences when medication is discontinued.

Table 8.24 Third-line therapies

Topical steroids – D (level of evidence)
Laser therapy – B (level of evidence)

Topical steroids should be reserved for inflamed lesions and used for short periods of time only. Parents must be counseled regarding the inability of topical steroids to clear the skin lesions, and importance of avoiding prolonged use.

In older teenagers who are particularly bothered by keratosis pilaris, laser therapy can be considered [24].

Pseudoacne of the Nasal Crease

Pseudoacne of the nasal crease is characterized by milia, cysts, and comedones along the transverse nasal crease, a horizontal anatomical demarcation line between the alar and triangular cartilages at the lower third of the nose. It typically affects pre-pubertal children and is more common in those with atopy and an "allergic salute."

Specific Investigations

- None

Table 8.25 First-line therapies

First-line therapies
Surgical expression – E (level of evidence)

Table 8.26 Second-line therapies

Topical retinoids – E (level of evidence)
Benzoyl peroxide – E (level of evidence)

While no treatment is required, first-line therapy involves surgical expression of open comedones.

Second-line therapy consists of topical retinoids and benzoyl peroxide, which are not consistently effective [25].

Demodicosis

Demodex (*D. folliculorum* and *D. brevis*) are commensal mites residing in the pilosebaceous units of humans. Young children typically have few, if any, mites, with increasing colonization with age. However, immunocompromised children are at increased risk of develop demodex colonization and subsequent folliculitis. There are also rare reports of this entity in healthy children. Demodex folliculitis presents as small erythematous papules and fine scale on the face, which can resemble periorificial dermatitis.

Specific Investigations

- Direct microscopy

Diagnosis can be established by direct microscopy of the follicular contents scraped onto a glass slide and examined under immersion oil. Biopsy is occasionally required for diagnosis.

Table 8.27 First-line therapies

Permethrin cream – E (level of evidence)
Metronidazole gel – E (level of evidence)
Sodium sulfacetamide – E (level of evidence)

First-line treatment options include permethrin 5 % cream, metronidazole 1 % gel, and sodium sulfacetamide 10 % – sulfur 5 % formulation [26].

Table 8.28 Second-line therapies

Alternative topical agent – E (level of evidence)
Combination therapy – E (level of evidence)

Response to therapy of demodex folliculitis is variable. Oftentimes, one must try multiple different modalities among permethrin cream, metronidazole gel, and sodium sulfacetamide to obtain a response, although children tend to respond faster than adults [26]. Combination therapy with these agents may also be required.

Table 8.29 Third-line therapies

Third-line therapies
Oral ivermectin – E (level of evidence)

In patients who fail to respond to multiple topical agents, or who have extensive involvement, oral ivermectin may be required at either a single dose of 200 μg/kg or with weekly doses until resolution [27].

Idiopathic Facial Aseptic Granuloma

Idiopathic facial aseptic granuloma (IFAG; aka pyodermite froide du visage) is characterized by one or more persistent, asymptomatic, inflammatory nodules, most commonly located on the cheek in young children. Lesions are typically red to purple, slightly rubbery in consistency, ranging widely in size from 3 to 25 mm. Lesions are most commonly solitary, although some patients have two or three lesions. It can be associated with chalazion, and some consider this entity a variant of rosacea.

Specific Investigations

- Biopsy

Diagnosis is primarily made upon skin biopsy, which will rule out other possible entities including acne, Spitz tumor, pyogenic granuloma, pilomatricoma, and infections such as leishmaniasis and cat scratch disease. Histologic findings include granulomatous inflammation in the dermis comprised of lymphocytes, histiocytes, neutrophils, and giant cells.

Table 8.30 First-line therapies

Observation
Refer to ophthalmology if chalazion noted

Treatment is often unnecessary, as lesions tend to resolve spontaneously, although this may take several months.

Table 8.31 Second-line therapies

Oral antibiotics – E (level of evidence)
Topical metronidazole cream – E (level of evidence)

When treatment is initiated, macrolide antibiotics such as azithromycin, erythromycin, and clarithromycin are most often used. Topical metronidazole cream has also been used. Efficacy for all treatments is variable [28].

Table 8.32 Third-line therapies

Incision and drainage
Excision

Third-line therapy includes incision and drainage, or surgical excision for persistent cases.

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Cutaneous Tumor and Tumor Syndromes

9

Amy J. Theos, Patricia A. Treadwell, and Nancy Cheng

Pigmented Lesions: Congenital Melanocytic Nevus

Clinical Features

Congenital melanocytic nevi (CMN) are benign proliferations of nevomelanocytes (nevus cells) that appear at birth or within the first year of life. CMN present as well-defined hyperpigmented patches or plaques that can vary significantly in color (tan to black), thickness, surface topography, size, and amount of hypertrichosis (Fig. 9.1a–c).

CMN are classified according to the maximum diameter the nevus is expected to obtain in adulthood: small <1.5 cm; medium ≥1.5–19.9 cm; and large ≥20 cm. In newborns, the projected adult size can be obtained by multiplying the diameter by the following factor determined by location: 1.7 (head); 2.8 (torso or upper extremities); or 3.5 (lower extremity).

Patients with CMN are at a higher risk of malignant melanoma and neurocutaneous melanosis. The exact lifetime incidence of melanoma in CMN remains to be determined, but is estimated to be <1 % in small and medium-sized nevi, and 2–5 % for large nevi [1–3]. The risk of melanoma in small- and medium-sized CMN increases after puberty, and superficial spreading melanoma is the most common presentation. In contrast, half of melanomas occurring in large CMN appear before the age of 5 and are dermal or subcutaneous in origin; these patients are also at risk for extracutaneous melanoma. The risk of melanoma is greatest in patients with giant nevi (>40 cm) in a posterior axial location.

Neurocutaneous melanosis (NCM) refers to the abnormal deposition of nevomelanocytes along the leptomeninges of the brain or spinal cord. Three percent to 10 % of patients with high-risk large CMN develop symptomatic NCM [4]. Symptoms of NCM include seizures, hydrocephalus, developmental delay, and focal neurologic deficits. Symptomatic NCM most commonly presents by the age of 3 and is associated with a poor prognosis. Risk factors for NCM are: (1) >40 cm CMN in a posterior axial location; (2) >20 satellite nevi; and (3) patients with ≥3 medium-sized CMN [5].

The diagnosis of CMN is usually straightforward, but a biopsy can be performed if necessary. Histological examination reveals nests of nevus cells at the epidermal-dermal junction and dermis, often with extension into the deeper dermis and subcutis, around adnexal structures, and single file between collagen bundles. Dermoscopy can be a useful diagnostic tool and typically shows reticular, globular, reticuloglobular, or homogeneous patterns.

Management Strategies

The approach to the management of CMN is individualized and dependent on many factors; including the age of the patient, size and location of the CMN, ease of monitoring for malignant changes, risk of melanoma and NCM, and psychological impact. Surveillance is a reasonable option, given the low absolute risk of melanoma, especially when surgical excision is not feasible due to unacceptable cosmetic or functional outcomes.

Small- and medium-sized CMN can be observed or excised, depending on the above factors. Parents and patients should be counseled on periodic examination and bring to attention any abrupt focal changes in size, color, border, new growths, or new onset symptoms, such as pain or pruritus. Any suspicious changes should be biopsied.

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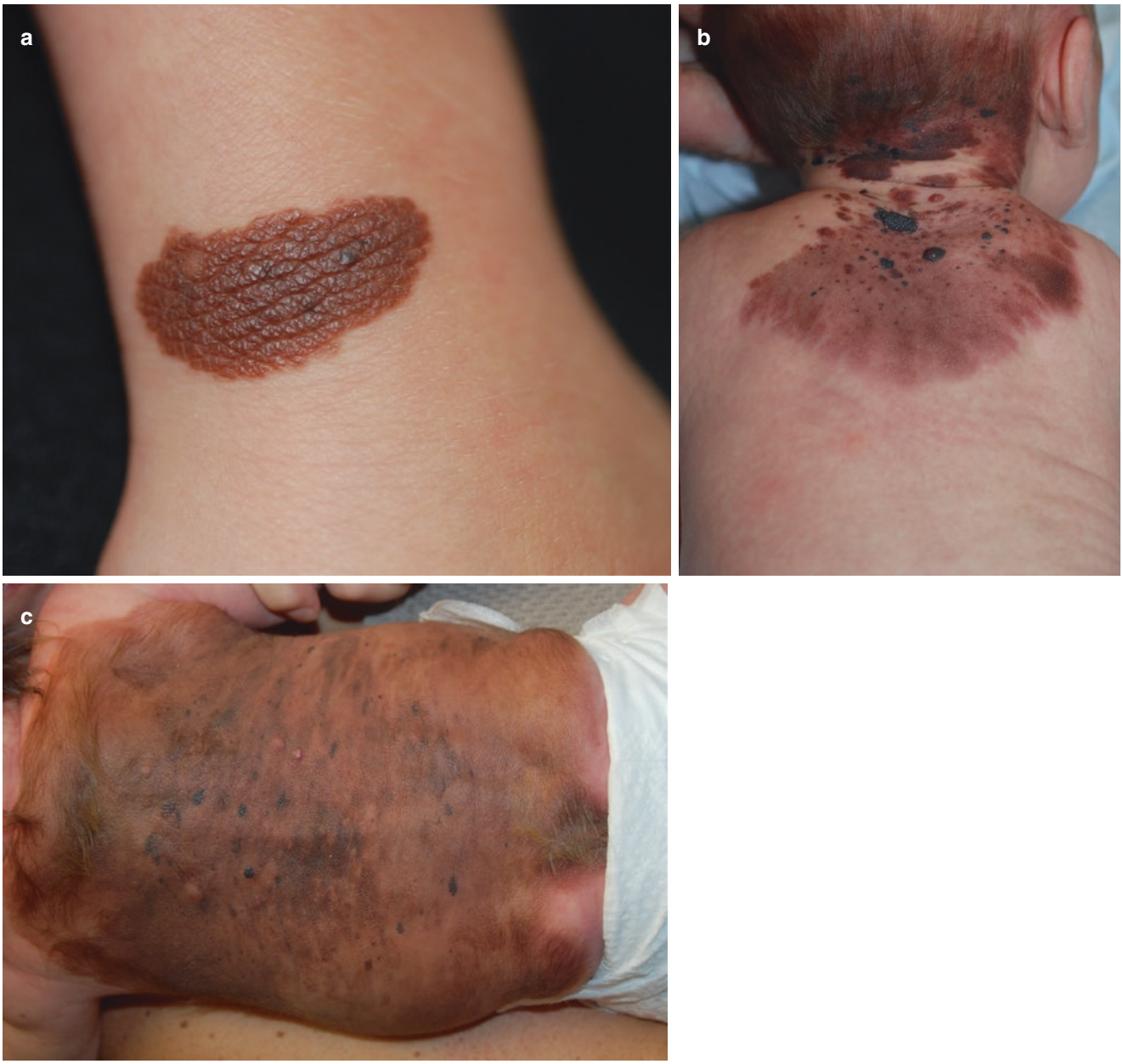

Fig. 9.1 Varying clinical appearances of congenital melanocytic nevi. (**a**) A medium-sized, evenly pigmented congenital melanocytic nevus on the arm. (**b**) A large heterogeneous congenital melanocytic nevus on the scalp and upper back. (**c**) A giant posterior axial congenital melanocytic nevus

Patients with large CMN require closer monitoring. More frequent examinations, typically every 3–12 months, are necessary for patients with large or giant CMN. Examination should include visual inspection along with palpation for firm, subcutaneous nodules. Any suspicious changes should be evaluated with biopsy. Referral to a surgeon experienced in the removal of CMN should be offered to the family. Excision is thought to decrease, although not eliminate, the risk of melanoma. Regardless of excision, patients need lifelong follow-up and evaluation of scars and any residual nevi.

All patients with CMN should be counseled on the importance of UV protection and self-examination. Some patients may benefit from psychological counseling or support groups.

Investigations Recommended

A biopsy can be done to confirm the diagnosis or to exclude malignant transformation. Baseline and serial photographs and dermoscopy are useful noninvasive tools for monitoring

Table 9.1 Specific investigations recommended for CMN

For diagnosis
Biopsy, confirmation of diagnosis or exclusion of malignancy
Baseline photographs
Baseline dermatoscopic evaluation
MRI of brain and/or spine
In patients with large CMN and neurological symptoms
Midline lumbosacral location to rule out tethered spinal cord
Consider baseline in asymptomatic patients with high-risk lesions: giant CMN (>40 cm, posterior axial location) or >20 satellite nevi or ≥3 medium CMN
Neurodevelopmental assessment
Referral to neurologist, if indicated
Pet scan, if MRI suspicious for deep or extracutaneous melanoma
For surveillance
Periodic examination by physician (large CMN every 3–12 months, small or medium CMN more important after puberty)
Serial photographs and dermoscopy
Monthly self-examination by family and/or patient

Table 9.2 First line therapies for CMN

Therapy	Evidence level
Observation	B
Full thickness excision	D

CMN. A MRI of the brain and spinal column should be done in all patients with a large CMN or ≥3 medium-sized CMN, and neurological symptoms to evaluate for NCM, CNS melanoma or other CNS malformations.

Additionally, baseline MRI can be considered in asymptomatic individuals with LCMN >40 cm or >20 satellite nevi or ≥3 medium-sized CMN, although this is debatable. Ideally, MRI screening is best done between 4 and 8 months of age. If the patient has neurological symptoms or the MRI is abnormal, referral to a neurologist is warranted. See Table 9.1 for specific investigations recommended.

First Line Therapies

Observation is appropriate for the majority of lesions. If treatment is desired for aesthetic reasons, symptoms, or malignancy concerns, full thickness excision is the treatment of choice. For most lesions it is recommended that excision be carried down to the fascia. For larger lesions this may require serial excisions, skin grafts, or the use of tissue expanders. See Table 9.2.

Second Line Therapies

Laser therapy may be an option to improve cosmesis in lesions not amenable to surgical excision. Various lasers, both pigment specific and nonselective, have been used with widely variable efficacy, ranging from poor to excellent. Scarring and dyspigmentation are potential complications and recurrence is very common. Multiple treatment sessions are necessary. There is some concern that laser treatment of CMN may mask the development or even increase the risk of melanoma, but this has not been proven in studies [6–8].

Curettage and dermabrasion have been advocated as procedures to remove the superficial portion of CMN, thereby lightening the lesion and decreasing the nevus cell burden. Results have been variable. Both of these procedures are done in the newborn period to take advantage of the natural cleavage plane between the epidermis and dermis. Recurrence and hypertrophic scarring are potential complications. There is some concern that the scarring induced by these procedures may mask the detection of melanoma (Table 9.3).

Spitz Nevus

Spitz nevi, or Spitz tumors, typically present in children and adolescents as pink or red well-circumscribed, dome-shaped papules on the face or lower extremities (Fig. 9.2). In adults, Spitz nevi more commonly manifest as brown or black papules. Spitz tumors are most often solitary, though groups of lesions may occur. These lesions may grow rapidly for several months and then stabilize. Composed of large epithelioid and/or spindled cells, they can be difficult to distinguish histologically from melanoma [9–12].

Spitz tumors most often develop before 20 years of age and occur in all ethnic groups, with slightly higher predominance among young females. Benign Spitz tumors are usually seen in children younger than 10. Spitz tumors that

Table 9.3 Second line therapies for CMN

Therapy	Evidence level
Laser therapy	
Nonselective ablative lasers: CO_2 laser and erbium:YAG	D
Pigment selective lasers: Q-switched ruby, Nd:YAG and alexandrite	B
Dermabrasion	D
Curettage	D

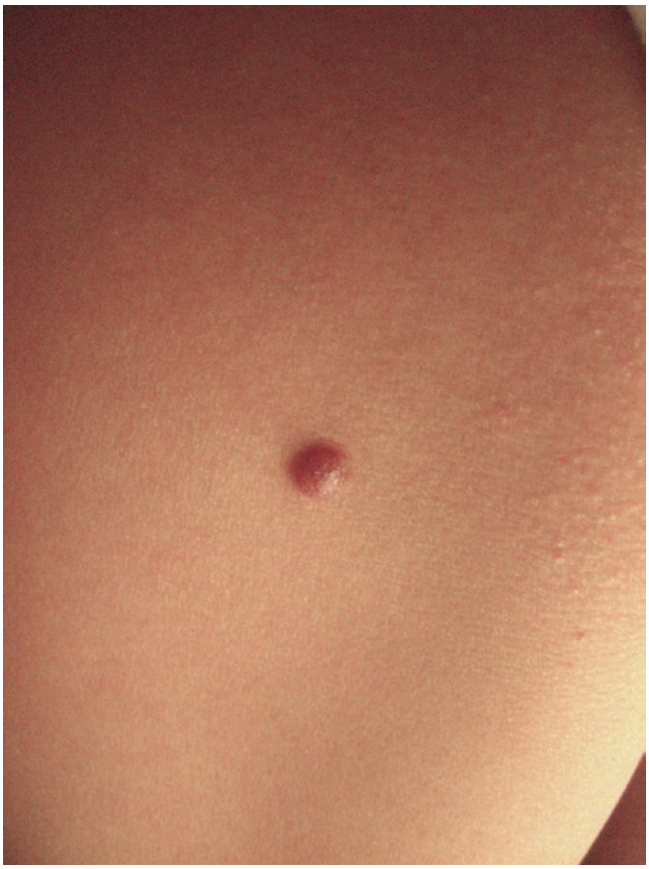

Fig. 9.2 Spitz nevi

develop in patients older than 20 years of age carry increased malignancy risk [10–14].

Spitz tumors are classified along a histological and clinical continuum, from conventional benign Spitz tumors to malignant Spitz neoplasms, with pleomorphic features impossible to differentiate from melanoma. Between these extremes exists a range of atypical Spitz tumors, with varying degrees of cytologic atypia and clinical behavior [11].

Conventional Spitz tumors are generally less than 6 mm in diameter, symmetric, and sharply defined. Atypical Spitz tumors are usually 6–10 mm in diameter and may show asymmetry, color variegation, and irregular topography. It is rarely possible to clinically distinguish atypical Spitz tumors from melanoma, as both may contain atypical findings such as large diameter (greater than 1 cm), asymmetric border, and color variegation. This distinction is sometimes made retrospectively after adverse events such as metastasis or death [11–16]. Cases of multiple Spitz nevi have been reported, but they have not been associated with any increased risk of malignancy [17, 18].

Management Strategies

Spitz tumors are diagnosed based on clinical and/or histologic features. Ancillary immunohistochemical and genetic studies exist though without the sensitivity or specificity necessary to distinguish atypical Spitz tumors from melanoma.

Lesions without atypical features should be monitored every 3–12 months. Patients should return if the lesion changes appearance. Lesions concerning for atypical Spitz tumors or melanoma should be removed by simple excision with margins of 3–5 mm (Table 9.4). Atypical Spitz tumors with positive margins should be re-excised with clear margins of 1 cm if cosmetically feasible. Severely atypical Spitz tumors should be managed as melanomas. Sentinel lymph node biopsy in the case of atypical Spitz tumors is controversial, as there is no data to suggest this improves prognosis (Table 9.5).

Specific Investigations

For diagnosis
Dermoscopic exam
Skin biopsy for histologic evaluation
Molecular and cytogenetic testing if histologically indicated
For treatment
Monitor every 3–12 months for lesions without atypical features
Simple excision of atypical Spitz tumors (3–5 mm margins)
Re-excision of atypical Spitz tumors with + margins (1 cm if possible)

- **Dermoscopic Features**: Conventional Spitz tumors show little to no pigmentation with a dotted vascular pattern. A "starbust" or "peripheral globular pattern" may occur in pigmented lesions [16].
- **Histological Features**: Conventional Spitz tumors show maturation, a uniform cell population, and rare or no mitoses. Atypical Spitz tumors may show asymmetry, significant cytologic atypia, and dermal mitoses. There are no firm histologic features that distinguish atypical Spitz tumors and melanoma, though melanomas often show greater cytologic pleomorphism and higher mitotic rate [11, 19, 20].

Table 9.4 First line therapies

Observation. Monitor every 3–12 months for lesions without atypical features	E
Simple excision of atypical Spitz tumors with 3–5 mm margins especially in those over 12 years of age	C [21]

A retrospective review of 89 Spitz tumors found that biopsy or excision with less than 3 mm margins was associated with positive margins in greater than 20 % of cases [21].

*A retrospective analysis of ten recurrent Spitz tumors using comparative genome hybridization found that two cases yielded results consistent with melanoma, rather than Spitz nevi [11].

Table 9.5 Second line therapies

Re-excision of atypical Spitz tumors with positive margins of 1 cm if possible	C [11]
Treat atypical Spitz tumors as melanoma in place of sentinel lymph node biopsy	C [15]

*A meta-review of 24 observational studies and 541 patients found that sentinel lymph node biopsy followed by lymph node dissection did not improve prognosis in patients with atypical Spitz tumors [15].

Halo Nevus

Clinical Features

A halo nevus is a melanocytic nevus surrounded by a zone of depigmentation, often resulting in spontaneous regression of the nevus [22]. This halo phenomenon is most often associated with acquired benign melanocytic nevi, but has been reported to occur around congenital nevi (Fig. 9.3), Spitz nevi, blue nevi, and melanoma. Halo nevi can be single or multiple, and most frequently occur on the trunk. They are common in children and young adults, with an estimated prevalence of 1 %; but occur at higher rates in patients with vitiligo and Turner syndrome [23, 24].

The diagnosis is usually evident clinically. Dermatoscopic examination most commonly shows a globular and/or homogeneous pattern encircled by a white structureless area [25]. Histological examination shows a dense, often band-like, infiltrate of lymphocytes in the papillary dermis intermingled with nests of nevus cells.

Management Strategies

Because the majority of halo nevi in children are benign and typically regress over months to years, observation of halo nevi is usually sufficient [22, 26]. If the central nevus is atypical or the halo is asymmetrical, a biopsy of the nevus is indicated.

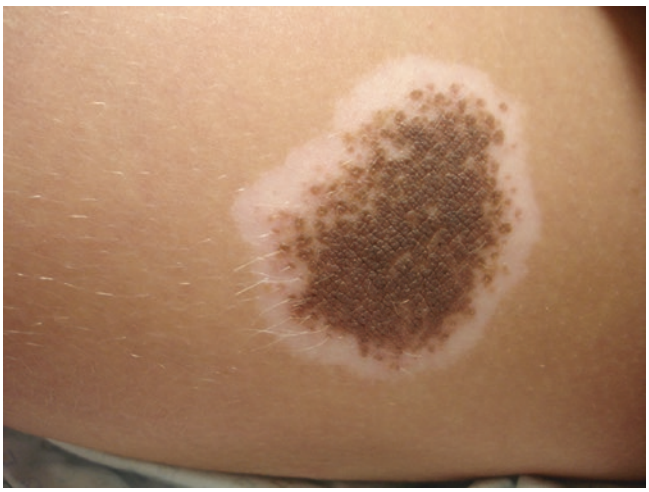

Fig. 9.3 A depigmented halo surrounding a medium-sized congenital melanocytic nevus

Investigations Recommended

The central nevus should be carefully evaluated using the "ABCD" diagnostic criteria for melanoma. Dermatoscopic examination is also recommended. A full skin examination is useful for evaluating all of the patient's nevi. A skin biopsy of the central nevus is indicated if there are worrisome clinical and/or dermatoscopic features. See Table 9.6 for a summary of recommended investigations.

Table 9.6 Specific investigations recommended for Halo Nevi

For diagnosis
Close clinical evaluation of the central nevus and halo
Dermatoscopic examination
Full skin examination
Biopsy, if the central nevus or halo has atypical clinical or dermatoscopic features

First Line Therapies

Observation is generally sufficient for halo nevi. Most are benign and spontaneously regress over time. If the central nevus or surrounding halo has any concerning features, a biopsy is indicated and further treatment is based on the histological findings. See Table 9.7.

Table 9.7 First line therapies for Halo Nevi

Therapy	Evidence level
Observation	D
Biopsy, if central nevus or halo atypical	D

Becker's Melanosis

Clinical Features

Becker's melanosis (also known as Becker's nevus) is a cutaneous hamartoma which often develops in the peripubertal period, although has been noted in some cases to be present at birth [27]. Clinically, this benign hamartoma is typically hyperpigmented and unilateral with an irregular border and surface (Fig. 9.4). Common locations are the shoulders, scapula or anterior chest. In many cases increased overlying hair and/or acne are present. The hypertrichosis and acne tend to be more prominent in males because of androgen mediated effects [28]. Becker's nevus syndrome has been described which is characterized by associated abnormalities including breast hypoplasia, limb asymmetry, scoliosis, and supernumerary nipples [29].

Management Strategies

Observation is the primary approach to the lesions. Excision of overgrowths may be recommended if they are symptomatic. See Tables 9.8 and 9.9 for management options.

Investigations Recommended

For diagnosis
Biopsy: The histopathologic findings are acanthosis, papillomatosis and increased pigmentation of the basal layer
Thorough history and physical to assess for signs of Becker's nevus syndrome

Becker's melanosis is a benign hamartoma often identified in the peripubertal period. Identification of the lesion should trigger consideration of Becker's nevus syndrome. The lesion typically requires no therapy unless it becomes symptomatic.

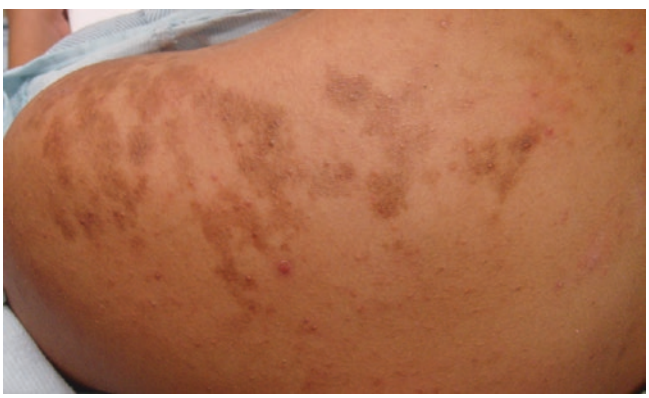

Fig. 9.4 Becker's melanosis containing acne inflammatory papules

Tumor of the Epidermal Appendages: Nevus Comedonicus

Clinical Features

Nevus comedonicus is a hamartoma involving the pilosebaceous unit. It consists of grouped dilated follicular openings containing central keratotic plugs, resembling open comedones. Pustules, cysts, abscesses, secondary bacterial infection and scarring can occur. Lesions can be localized or extensive.

Nevus comedonicus syndrome refers to a neurocutaneous disorder that consists of nevus comedonicus with associated skeletal (scoliosis, fused vertebrae, spina bifida), ocular (cataracts), limb defects (absent fifth finger, polydactyly), or neurological abnormalities [31].

A variety of benign epithelial tumors, including trichoepithelioma, syringocystadenoma papilliferum, hidradenoma papilliferum, and keratoacanthoma, have been reported to occur in nevus comedonicus. Malignant tumors are rare, but basal cell and squamous cell carcinoma have been reported [32].

The diagnosis is usually evident clinically. Histological examination shows hairless dilated follicular ostia filled with lamellar keratin, epidermal invaginations, rudimentary sebaceous glands, and absent arrector pili muscles.

Management Strategies

Nevus comedonicus is a benign lesion, therefore treatment is not required, unless desired for aesthetic purposes or for lesions complicated by recurrent inflammation and/or infection. The only definitive treatment is surgical excision. Numerous medical and surgical treatments have been reported, with incomplete responses. The treatment of extensive lesions is very challenging and often disappointing.

Table 9.8 First line therapies

Observation
Lightening hair
Lightening pigmentation
Treat acne

Table 9.9 Second line therapies

Laser: YAG vs Nd:YAG	Evidence level B	[28]
Intense pulsed light	Evidence level E	[30]

Investigations Recommended

A skin biopsy can be done if the diagnosis is uncertain. Patients with extensive lesions should be evaluated carefully for the existence of nevus comedonicus syndrome. See Table 9.10 for specific investigations.

First Line Therapies

Complete surgical excision is curative and is the treatment of choice for lesions that are bothersome and amenable to surgical excision. Various topical therapies, including emollients, topical keratolytics (ammonium lactate 12 %, salicyclic acid), topical retinoids (tretinoin, tazarotene), topical vitamin D analogs (calcipotriene, talcalcitol), alone or in combination may improve cosmesis in some patients [31–33]. Commercial pore remover strips may be helpful for removing keratin plugs [34]. Inflammatory lesions may respond to treatment with topical or intralesional corticosteroids. Oral antibiotics are indicated if secondary infection is present. Incision and drainage or excision of localized abscesses or cysts is effective (See Table 9.11) [35].

Table 9.10 Specific investigations recommended for nevus comedonicus

For diagnosis
Biopsy, if diagnosis uncertain
Exclude nevus comedonicus syndrome in patients with extensive lesions
Physical examination, with focus on skeletal, ocular, digital and nervous system
Ophthalmologic evaluation, if indicated
Roentgenogram of spine, if indicated
Neurology referral, if indicated

Second Line Therapies

Laser treatment with various lasers, including 1,450 nm diode laser, ultrapulsed CO_2 laser, and erbium:YAG laser, have been reported to be effective in adults. Laser therapy can be considered for bothersome lesions not amenable to surgical excision or for extensive lesions [36, 37].

Isotretinoin has been reported to be helpful for decreasing the number of cystic flares associated with inflammatory lesions, but has not been effective as a therapy for non-inflamed lesions (Table 9.12) [34].

Third Line Therapies

Dermabrasion, shave excision, and manual comedone extraction have poor efficacy and often produce unacceptable scarring and recurrence (Table 9.13).

Nevus Sebaceous

Clinical Features

Nevus sebaceous (NS) is a hamartoma of the pilosebaceous unit. NS occurs in approximately 0.3 % of newborns and is usually evident at birth as an oval or linear, hairless, yellow-brown plaque on the scalp (Fig. 9.5a) or less frequently on the face and neck. At puberty, NS becomes more papillomatous or verrucous, due in part to androgen stimulation of the aberrant sebaceous glands (Fig. 9.5b).

It is estimated that approximately 20 % of lesions will develop secondary, mostly benign, tumors. The most common tumor is trichoblastoma, followed by syringocystadenoma papilliferum. Basal cell carcinoma is estimated to occur in approximately 1 % of lesions and is extremely unlikely to appear before puberty. Squamous cell carcinoma,

Table 9.11 First line therapies for nevus comedonicus

Therapy	Evidence level
Localized lesions	
Surgical excision, curative and best treatment if lesion amenable to surgery	E
Topical keratolytics (ammonium lactate 12 %, salicylic acid)	E
Topical retinoids (tretinoin, tazarotene)	E
Topical vitamin D analogs (calcipotriene, talcalcitol), alone or in combination with topical retinoids	E
Commercial pore remover strips	E
Extensive lesions	
Topical keratolytics, retinoids, vitamin D analogs	E
Inflamed lesions (pustules, cysts, abscesses)	
Topical or intralesional corticosteroids	E
Oral antibiotics	E
Incision and drainage or excision of localized abscesses or cysts	E

Table 9.12 Second line treatment for nevus comedonicus

Therapy	Evidence level
Localized or extensive lesions	
Laser therapy (1,450 nm diode laser, ultrapulsed CO_2 laser, erbium:YAG)	E
Inflammatory lesions	
Isotretinoin (1 mg/kg), may decrease cystic lesions, otherwise ineffective	E

Table 9.13 Third line treatment for nevus comedonicus

Therapy	Evidence level
Dermabrasion	E
Shave excision	E
Manual comedone extraction	E

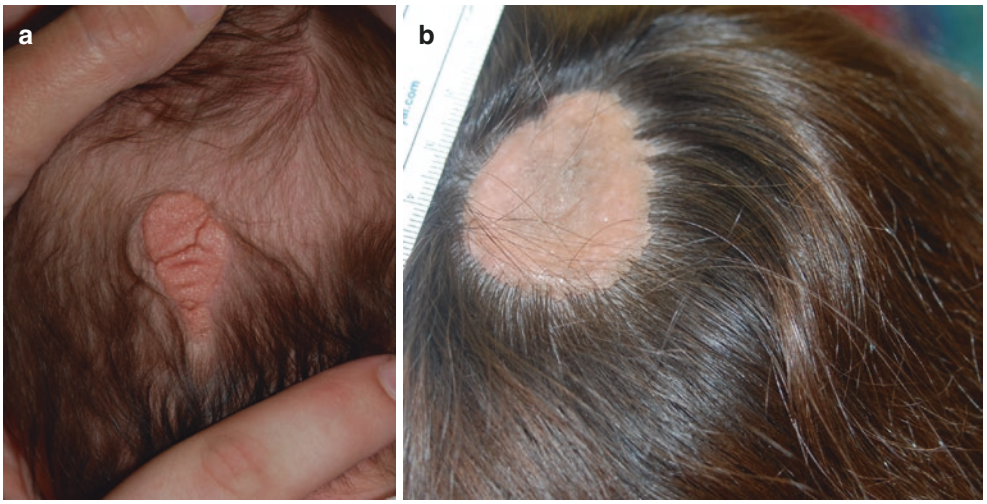

Fig. 9.5 Nevus sebaceous. (**a**) A nevus sebaceous on the scalp at birth. (**b**) A nevus sebaceous on the scalp in an adolescent that has become more verrucous

adenocarcinoma, and sebaceous carcinoma have also been reported [38–40].

Nevus sebaceous syndrome (Schimmelpenning syndrome) refers to the association of an extensive linear nevus sebaceous that follows the lines of Blaschko with neurological (seizures, developmental delay, hemimegalencephaly), ocular (lipodermoid, coloboma), and skeletal (skull deformity, scoliosis, short stature) anomalies. Patients with nevus sebaceous syndrome are also at risk for Vitamin D-resistant hypophosphatemic rickets, which should be suspected in patients with an extensive nevus sebaceous along with growth retardation, bone pain, fractures or bone deformities [41].

The diagnosis of nevus sebaceous can usually be made clinically. A biopsy can be done if the diagnosis is uncertain. In prepubertal children, histopathology reveals mild epidermal acanthosis and papillomatosis with immature sebaceous glands and pilosebaceous units. After puberty, there is more prominent acanthosis and papillomatosis of the epidermis, prominent sebaceous glands often located high in the dermis, immature hair follicles and ectopic apocrine glands in the lower dermis.

Management Strategies

Historically, excision prior to puberty was recommended due to the perceived high rate of basal cell carcinoma. Given that the rate of malignant transformation is actually quite low, especially in children, prophylactic excision of all lesions before puberty is no longer recommended. However, lesions should be observed for suspicious changes, and new localized growths or ulceration should be biopsied and completely excised if necessary. Prophylactic removal may be desirable in some cases for cosmetic concerns, and the timing of such excision should be evaluated on an individual basis.

Investigations Recommended

A skin biopsy is indicated if the diagnosis is uncertain or to exclude malignancy. Patients with an extensive nevus sebaceous should be evaluated carefully for the occurrence of nevus sebaceous syndrome. See Table 9.14 for specific investigations recommended.

Table 9.14 Specific investigations recommended for nevus sebaceous

For diagnosis
Biopsy, to confirm diagnosis or exclude a secondary malignant neoplasm
Exclude nevus sebaceous syndrome in patients with extensive linear NS
Ophthalmologic examination
MRI of brain, as indicated in patients with suspected neurologic abnormalities
Skeletal radiographs, if indicated
Serum and urine calcium and phosphorous levels, parathyroid hormone levels, vitamin D levels, in patients with suspected hypophosphatemic rickets

First Line Therapies

Full thickness excision, when feasible, with 2–3 mm margins, is the treatment of choice for lesions that are symptomatic or cosmetically concerning. Staged excision or tissue expansion can be done if necessary. The timing of excision is dependent on the age of the child, size and location of the lesion, and the risks and benefits of general anesthesia versus local anesthesia later in life (see Table 9.15) [40].

Table 9.15 First line therapy for nevus sebaceous

Therapy	Evidence level
Full thickness excision with 2–3 mm margins	D

Second Line Therapies

Nonsurgical options for the treatment of NS include photodynamic therapy and various lasers. These treatments produce variable results and should be reserved for extensive lesions or lesions not amenable to surgical excision. Photodynamic therapy using various photosensitizers (aminolevulinic acid 20 % or methylaminolevulinate) and light sources (light emitting diodes device, 630-nm argon tunable dye laser, intense pulsed light), have resulted in cosmetic improvement in a small number of patients with facial NS. Laser ablation or curettage of thicker lesions or nodules was done prior to photodynamic therapy in some patients [42, 43]. Different lasers, including continuous wave CO_2 laser, fractional CO_2 laser, and erbium:YAG laser, have been reported to be useful in single case reports [40, 44]. Multiple treatment sessions were necessary for all of these modalities (Table 9.16). It is important to realize that these modalities do not completely remove the lesion, leaving a risk for recurrence and development of secondary neoplasms; therefore continued monitoring is necessary.

Other Adnexal Tumors

Clinical Features

Adnexal tumors are a diverse group of benign neoplasms originating from adnexal epithelium. The most common adnexal tumors in children include pilomatricomas, trichoepitheliomas, and syringomas [45]. These tumors are often solitary, but can be multiple, especially when associated with an underlying syndrome (Table 9.17).

Pilomatricomas are most common on the head and extremities and present as hard, mobile subcutaneous nodules, often with a pink or blue hue. Due to calcification in the tumor, they may show a "teeter-totter" sign or "tent" sign when the overlying skin is stretched. Trichoepitheliomas appear as skin-colored papules with a predilection for the central face. Syringomas present as small, yellow-white translucent papules most commonly on the lower eyelids, neck, upper chest and genitalia (Fig. 9.6). They may occur in an eruptive manner. The clinical presentation of other adnexal tumors is summarized in Table 9.18.

Management

Adnexal tumors are benign and therefore treatment is not necessary, but may be desired for aesthetic or symptomatic reasons. Solitary lesions are best treated by surgical excision.

Treatment of multiple adnexal tumors is often difficult, but electrodessication, electrosurgery, cryosurgery, dermabrasion, chemical peels and laser ablation have been reported with variable success.

Investigations Recommended

A skin biopsy may be necessary for definitive diagnosis. If multiple tumors are present, or there is a positive family history of similar lesions, further work-up to rule out an underlying

Table 9.16 Second line therapies for nevus sebaceous

Therapy	Evidence level
Photodynamic therapy	D
Laser therapy (CO_2 laser, fractional CO_2 laser, erbium:YAG laser)	E

Table 9.17 Syndromes associated with multiple adnexal tumors

Adnexal tumor	Clinical appearance	Associated syndrome
Trichoepithelioma	Firm, flesh-colored papules in central face	Brooke-Spiegler syndrome
		Multiple familial trichoepitheliomas
Cylindroma	Pink, firm plaques or nodules most common on the scalp	Brooke-Spiegler syndrome
		Familial cylindromatosis
Trichilemmoma	Small flesh colored, sometimes verrucous papules, in central face	PTEN hamartoma—tumor syndrome (includes Cowden and Bannayan-Riley-Ruvalcaba syndromes)
Pilomatricoma	Firm, subcutaneous nodule with pink or blue hue; "teeter-totter" or "tent" sign	Myotonic dystrophy, Gardner syndrome, Rubenstein-Taybi syndrome
Syringoma	Small flesh-colored to yellow translucent papules	Down syndrome
Sebaceous adenoma	Yellow, lobulated papules on face	Muir-Torre syndrome

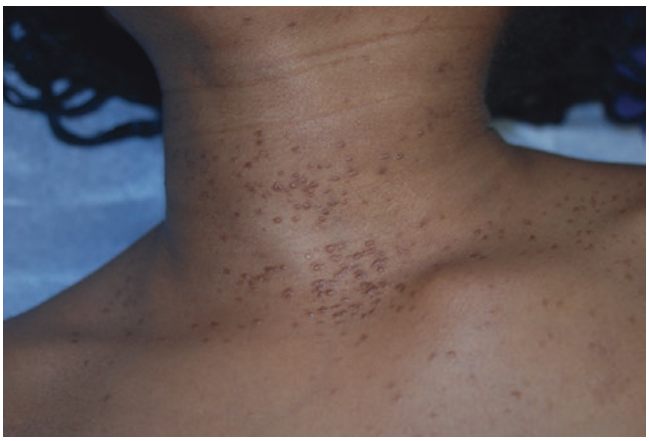

Fig. 9.6 Multiple eruptive syringomas on the neck and upper chest in an adolescent

Table 9.18 Specific investigations recommended adnexal tumors

Skin biopsy, if needed for diagnosis
Evaluation for potential syndrome in patients with multiple adnexal tumors

syndrome may be necessary. See Table 9.18 for specific investigations recommended.

First Line Therapies

Surgical excision is the treatment of choice for isolated lesions. The recurrence rate after complete excision is extremely low (Table 9.19) [46].

Table 9.19 First line therapies for adnexal tumors

Therapy	Evidence level
Surgical excision	D

Second Line Therapies

Laser ablation using various CO_2 lasers (continuous wave, pulsed, fractional) or erbium:YAG has been reported for patients with multiple syringomas or trichoepitheliomas (see Table 9.20). Several treatment sessions may be necessary, and recurrence and scarring are potential complications [47]. Other destructive methods have also been reported in small numbers of patients.

Table 9.20 Second line therapies for adnexal tumors

Therapy	Evidence level
Laser ablation (CO_2, fractionated laser, erbium:YAG)	B
Electrodessication	E
Electrosurgery	E
Cryosurgery	E
Trichloroacetic acid, various strengths	E

Tumor of the Epidermis: Mastocytosis

Clinical Features

Mastocytosis is characterized by infiltration of mast cells in the dermis. Maculopapular cutaneous mastocytosis lesions

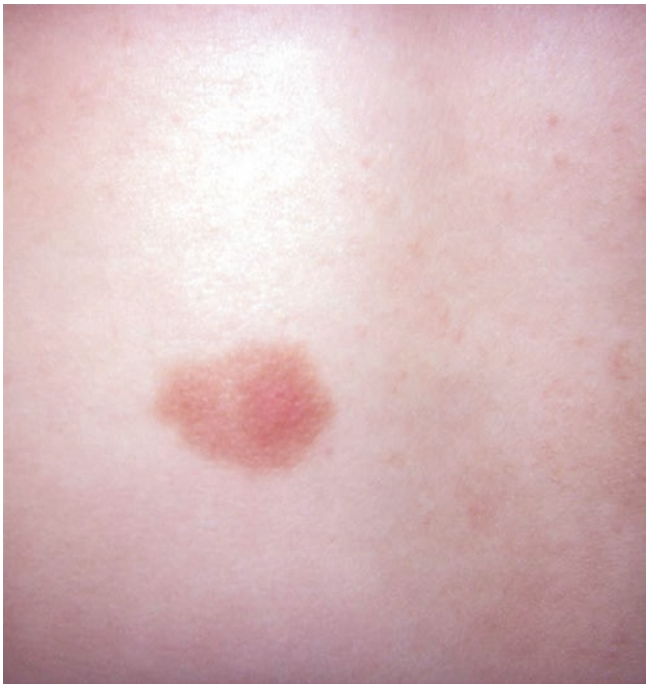

Fig. 9.7 Solitary mastocytoma with "peau d'orange" appearance

(MPCM) have a "peau d'orange" clinical appearance (Fig. 9.7). The lesions urticate and become reddened with rubbing (positive Darier's sign) and some may become vesicular. Cutaneous lesions of mastocytosis may present as: (1) a single lesion (Solitary mastocytoma); (2) multiple maculopapular lesions (maculopapular cutaneous mastocytosis-MPCM aka Urticaria pigmentosa); or (3) diffuse infiltrative lesions [48].

The lesions are often present before 2 years of age and may affect any area of the body. Spontaneous resolution of hyperpigmentaiton is often seen by 10–12 years of age, although urticarial changes are usually difficult to elicit after 4 years of age [49].

Familial mastocytosis are rare, with fewer than 100 cases reported in the literature [50]. Individual lesions are clinically similar between different subtypes of cutaneous mastocytosis, however, familiar mastocytosis often persist into adulthood. Over 90 % of patients with mastocytosis have mutations of the *c-kit* gene that often occur spontaneously. Mutations have been found on exons 8, 9, 10, 11, 13, 17, and 18 of *c-kit*.

Childhood-onset mastocytosis has a better prognosis than adult-onset disease and has less systemic involvement that is mastocytosis related [48].

Management Strategies

- Initiate measures to minimize blistering or discomfort.
- Avoid triggers. Some triggers include: vigorous rubbing, hot baths, aspirin, alcohol, ibuprofen, and codeine. A very complete list of potential triggers can be found at the website Mastokids website-www.mastokids.org [51].
- Mastocytosis is a condition which is characterized by increased mast cells present in the dermis. The lesions may produce a variety of cutaneous findings and symptoms. Therapies are varied for the different presentation types. See Tables 9.21–9.23 for recommendations regarding management.

Investigations Recommended

For diagnosis
Biopsy—shows mast cell infiltration in the dermis and around the blood vessels. Giemsa stain and toluidine blue can stain the granules in the mast cells
Genetic test for *c-kit* mutations
Tryptase can be elevated in the presence of systemic disease [49, 50]

Basal Cell Nevus Syndrome

Clinical Features

Basal cell nevus syndrome (BCNS; also known as Gorlin syndrome) is an autosomal dominant multi-system disorder caused by mutations in the *PTCH1* gene. The main features are: (1) multiple basal cell carcinomas (BCCs); (2) odontogenic keratocysts of the jaw; (3) palmar/plantar pits; (4)

Table 9.21 First line therapies

Solitary Mastocytoma		
Avoid triggers		
Topical corticosteroids	Evidence level E	[52]
Excision	Evidence level E	[53]
MPCM		
Avoid triggers		
Cyproheptadine, H1 blockers	Evidence level B [54]	

Table 9.22 Second line therapies

H2 blockers	Evidence level C	[54]
Pimecrolimus cream and antihistamine	Evidence level E	[54]

Table 9.23 Third line therapies

Biologics	Evidence level E	[55]

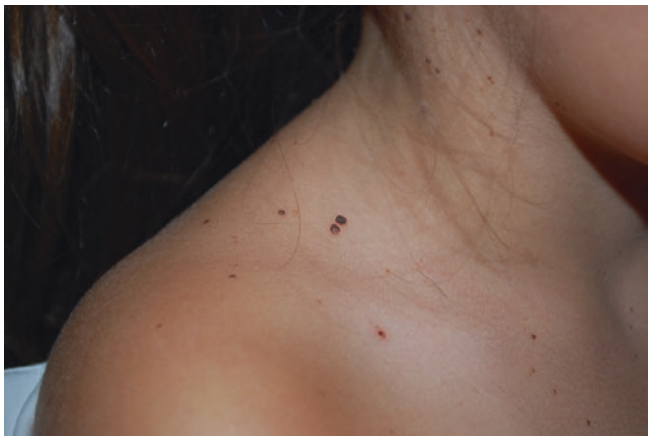

Fig. 9.8 Multiple basal cell carcinomas resembling nevi in a young child with basal cell nevus syndrome

skeletal abnormalities (most commonly of the ribs and spine); (5) ectopic calcification of the falx cerebri; (6) ocular abnormalities; and (7) medulloblastoma. Macrocephaly and typical facial features, including frontal bossing and hypertelorism, are frequent and early findings. Young children often have multiple facial milia and skin lesions that resemble nevi ("basal cell nevi") or skin tags, but with the typical histological appearance of BCC (Fig. 9.8) [56]. These lesions generally lack aggressive behavior in childhood. Invasive BCC usually presents during late teens and early adulthood and becomes more frequent with age. Crusting, ulceration, and enlargement are signs of invasion. The diagnosis of a BCC before the age of 20 should signal an evaluation for BCNS.

Management

The management of BCNS requires a multidisciplinary and individualized approach, which entails appropriate surveillance for complications, minimizing exposure to radiation, treatment of tumors, and genetic counseling. Several surgical and nonsurgical options exist for the treatment of BCCs. Often a combination of treatment modalities is necessary and the choice of treatment is dependent on many factors, including the age of the patient, location, size and number of BCCs, as well as the histological subtype. Aggressive treatment of BCCs in younger children may not be necessary, as most of these lesions will not become invasive. The optimal treatment of BCCs in patients with BCNS remains to be defined.

Exposure to radiation should be minimized as much as possible as soon as the diagnosis is suspected. Approximately 5–10 % of children develop medulloblastoma and treatment with radiation therapy should be avoided, if feasible, because of the high numbers of BCCs that may develop in the field of radiation. All patients should be counseled on the importance of strict sun protection. This involves the use of protective clothing and

Table 9.24 Specific investigations recommended for basal cell nevus syndrome

For diagnosis
AP and lateral radiographs of the skull, chest, and spine
Orthopantogram (by 8 years of age)
Ophthalmologic examination, baseline
Echocardiogram (in first year of life)
Skin examination, biopsy suspicious skin lesions
Plotting of head circumference
MRI (if indicated by enlarging head circumference or abnormal neurologic examination; some experts recommend a routine baseline MRI)
Molecular genetic testing
Referral to geneticist for counseling
For surveillance
Orthopantogram, every 12–18 months
Ophthalmologic examination, only if indicated
Skin examination at least yearly then every 3–6 months after diagnosis of first BCC, biopsy any suspicious skin lesions
Plotting of head circumference
MRI (some experts recommend yearly MRI until age 8)
Pelvic ultrasound, prior to pregnancy or as indicated for symptoms

glasses, SPF 30+ sunscreens, and avoidance of sun during midday hours. Radiographs should be minimized as much as possible and performed only as needed for diagnosis or management of valid medical issues.

Investigations Recommended

The diagnosis of BCNS is made based on diagnostic criteria. A thorough clinical examination and radiographs of the jaw, skull, chest, and spine are usually necessary to confirm the diagnosis. Modalities utilizing non-ionizing radiation, such as MRI, ultrasound or digital technology, are preferred [57]. Molecular genetic testing is commercially available and is useful for diagnostic confirmation in patients with suspected BCNS not fulfilling diagnostic criteria or in at-risk asymptomatic family members (i.e. child of a parent with BCNS). Skin biopsy is indicated if invasive BCC is suspected. See Table 9.24 for specific investigations recommended for diagnosis and surveillance.

First Line Therapies

A recent Cochrane review concluded that excision was the most effective treatment for sporadic BCC, and that Mohs micrographic surgery (MMS) offered the highest cure rate for high-risk facial BCC [58]. Electrodessication and curettage (ED&C) is appropriate for smaller lesions located in low-risk areas (neck, trunk, and extremities). Cryosurgery also offers an acceptable cure rate for small nodular or superficial low-risk BCC [59, 60].

Photodynamic therapy (PDT) is useful for larger areas containing multiple lesions. Success has been reported with topical methylaminolevulinate, aminolevulinic acid, and systemic photosensitizers. The clearance rates range from 31 to 100 %, with superficial lesions responding better than nodular ones. PDT has been used successfully in children, but tumescent anesthesia was necessary to control pain. There is also evidence emerging that PDT may decrease the development of new BCC. More frequent treatment sessions are often necessary in patients with BCNS [61].

Imiquimod 5 % cream is FDA approved for the treatment of sporadic superficial BCC in adults and has been used in patients with BCNS. Reported regimens have varied with application frequency ranging from three to seven nights a week for 6–14 weeks. Clearance rates range from 50 to 100 %, with the best response in superficial lesions (see Table 9.25).

Table 9.25 First line therapies for basal cell nevus syndrome

Therapy	Evidence level
Surgical excision	E
Mohs micrographic surgery	D
Electrodessication and curettage	E
Cryosurgery	E
Photodynamic therapy	B
Imiquimod 5 % cream	E

Second Line Therapies

Laser ablation with CO_2 or erbium:YAG resurfacing offers the advantage of treating multiple BCCs in a single session. The evidence is limited to a few case reports.

Topical retinoids, including tretinoin and tazorotene, have been reported in case reports as an effective treatment for BCC. However, a recent randomized controlled trial found that it was not effective for treating or preventing BCC in patients with BCNS [62].

Topical 5-fluorouracil 5 % cream applied twice daily has been used with variable results as monotherapy, or in combination with tretinoin 0.1 % cream or cryosurgery (see Table 9.26).

Table 9.26 Second line therapies for basal cell nevus syndrome

Therapy	Evidence level
Ablative laser therapy	E
CO2 laser	
Erbium:YAG laser	
5-fluoruracil 5 % cream BID × 12 weeks or longer	E
Topical retinoids	
Tretinoin 0.1 % cream	E
Tazorotene 0.1 % cream	A

Third Line Therapies

Oral retinoids may be partially effective at treating and inhibiting BCC, but higher doses (e.g. isotretinoin 3 mg/kg) are often necessary, and its use is limited by the development of adverse effects. Vismodegib was recently approved to treat metastatic or advanced BCC and has been used in patients with BCNS [63]. It is not recommended for use in pediatric patients, as potential adverse effects, especially on bone growth, are not known (see Table 9.27).

Table 9.27 Third line therapies for basal cell nevus syndrome

Therapy	Evidence level
Oral retinoids	D
Vismodegib	A

Epidermal Nevus and Epidermal Nevus Syndrome

Clinical Features

Epidermal nevi are hamartomas of epidermal or appendageal origin that present at birth or early in life. Keratinocytic nevi are the most common type and are commonly called linear (verrucous) epidermal nevi (LEN). They vary in size and extent and appear as hyperpigmented papillomatous to verrucous papules that coalesce into plaques (Fig. 9.9a, b). A characteristic feature of LEN is the distribution along the lines of Blaschko [64]. Malignant degeneration is rare, but basal cell carcinoma, squamous cell carcinoma, and keratoacanthoma have been reported.

Inflammatory linear verrucous epidermal nevus (ILVEN) is a unique variant of LEN that is characterized by inflammation, severe pruritus, and a poor response to therapy.

Epidermal nevus syndrome (ENS) refers to the association of an epidermal nevus with extracutaneous anomalies, most often of the central nervous system, eye, cardiovascular, and skeletal systems. It is now clear that ENS doesn't represent a single entity, but instead encompasses a variety of syndromes. The best known is nevus sebaceous syndrome, which is discussed separately. Keratinocytic nevi have been reported in Proteus syndrome, type 2 segmental Cowden syndrome, CHILD syndrome, and CLOVES syndrome, as well as a number of less well-defined syndromes [41].

The diagnosis of LEN is usually clinically apparent, but a skin biopsy can be done for confirmation, and shows varying degrees of hyperkeratosis, epidermal acanthosis, and papillomatosis. A number of histological patterns, including epidermolytic hyperkeratosis and acantholytic dyskeratosis, have been reported to occur within LEN. The presence of epidermolytic hyperkeratosis, at least in some cases, represents somatic mosaicism for a keratin 1 or 10 mutation. There are reports of patients with extensive epidermolytic LEN having children with bullous congenital ichthyosiform erythroderma [65]. Genetic counseling is important for patients with widespread epidermolytic LEN. At least some cases of ILVEN mimic psoriasis on histology.

Management

LEN are benign lesions that do not require treatment. If treatment is desired for aesthetic or symptomatic reasons, numerous surgical and nonsurgical treatments have been reported in the literature. Surgical excision is the only definitive treatment. ILVEN is generally resistant to most therapies other than complete surgical excision.

Investigations Recommended

A skin biopsy can be done if needed for diagnostic confirmation, or to evaluate for the presence of epidermolytic hyperkeratosis in patients with extensive LEN. Patients with extensive LEN should be evaluated carefully for an associated syndrome. Patients with extensive epidermolytic LEN should receive appropriate genetic counseling regarding the slight risk of transmission of bullous congenital ichthyosiform erythroderma to offspring. See Table 9.28 for specific investigations recommended.

First Line Therapies

Full thickness surgical excision, when feasible, is the treatment of choice. One study showed an excellent response with cryotherapy for small, focal LEN [66]. Superficial destructive methods, such as curettage, dermabrasion, and electrodessication, may provide temporary improvement, but recurrence is likely. Ablative lasers, including CO_2

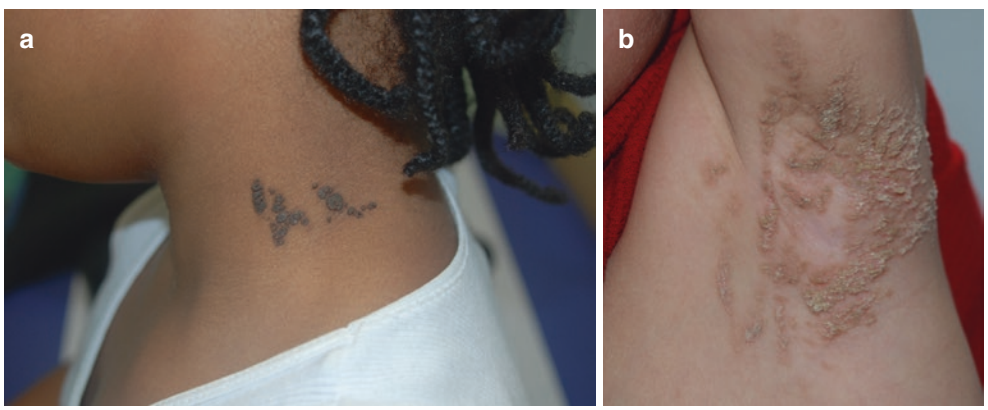

Fig. 9.9 Linear epidermal nevi. (**a**) A linear epidermal nevus on the neck. (**b**) A linear verrucous epidermal nevus in the axillae that showed epidermolytic hyperkeratosis on histology

Table 9.28 Specific investigations recommended for linear epidermal nevi

For diagnosis
Biopsy, diagnostic confirmation
Exclude ENS in patients with extensive LEN, if indicated
Neurologic examination
EEG
Skeletal survey
Ophthalmologic evaluation
ECHO
EKG
Genetic counseling for patients with extensive epidermolytic LEN

Table 9.29 First line therapies for linear epidermal nevi

Therapy	Evidence level
Surgical excision	E
Cryotherapy	D
Superficial destructive methods (curettage, dermabrasion, electrodessication), high rate of recurrence	E
Ablative laser resurfacing, for lesions not amenable to surgical excision	
CO_2 (continuous wave or pulsed)	D
Erbium:YAG (variable-pulsed or dual-mode)	B
Topical or intralesional corticosteroids, for pruritus or inflammation	E
Topical calcipotriene or calcipotriol, for ILVEN phenotype	E
Topical keratolytics or retinoids, may provide temporary improvement in thickness and symptoms	E
Topical 5 % 5-fluorouracil with topical tretinoin 0.1 % under occlusion	E

(continuous wave and pulsed) and erbium:YAG (variable-pulsed or dual-mode), have been used to treat LEN, with variable results [67, 68]. The best outcomes were seen with smaller, less hyperkeratotic lesions located on the face and neck. Scarring and pigmentary changes were seen in some patients, and the recurrence rate was about 30 %. ILVEN located in the vulvar area seemed to have a particularly good response to treatment with CO_2 laser. Topical or intralesional corticosteroids may provide temporary relief of pruritus and erythema. Topical preparations, including retinoids, keratolytics, calcipotriene, and 5-fluorouracil, alone or in combination, have provided temporary improvement in some patients, but long-term therapy is necessary (see Table 9.29).

Second Line Treatments

Oral retinoids (acitretin, isotretinoin) have been effective in patients with extensive LEN or ILVEN, but maintenance therapy is necessary (see Table 9.30) [69].

Table 9.30 Second line therapies for linear epidermal nevi

Therapy	Evidence level
Oral retinoids (isotretinoin, acitretin)	E

Dermal Tumor: Angiofibroma

Clinical Features

An angiofibroma typically presents as a firm papule. Although they may develop anywhere on the body, they are often found on the face [70]. Facial angiofibroma is one of the major clinical diagnostic features of tuberous sclerosis complex (TSC), a hereditary condition affecting 1:5000–1:10,000 children born [71]. Approximately 80 % of patients with TSC will have facial angiofibromas (Fig. 9.10). They sometimes coalesce to form fibrotic plaques. In dark-skinned individuals they may be hyperpigmented (Fig. 9.11). Associated genetic mutations have been identified in TSC-*TSC1* gene on chromosome 9q34 and *TSC2* on chromosome 16p13.3 [71]. More than 70 % of the cases are the result of spontaneous mutations, while the remaining are inherited in an autosomal dominant manner.

Facial angiofibromas may also occur in other genetic diseases such as multiple endocrine neoplasia syndrome 1 (MEN 1) and Birt-Hogg-Dube syndrome [72]. Histologically, cutaneous angiofibromas are characterized by stellate fibroblasts located around blood vessels and adnexa.

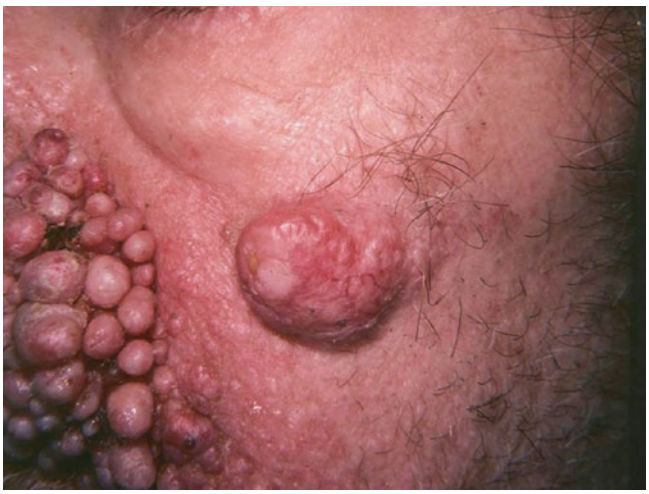

Fig. 9.10 Large angiofibromas in a patient with TSC

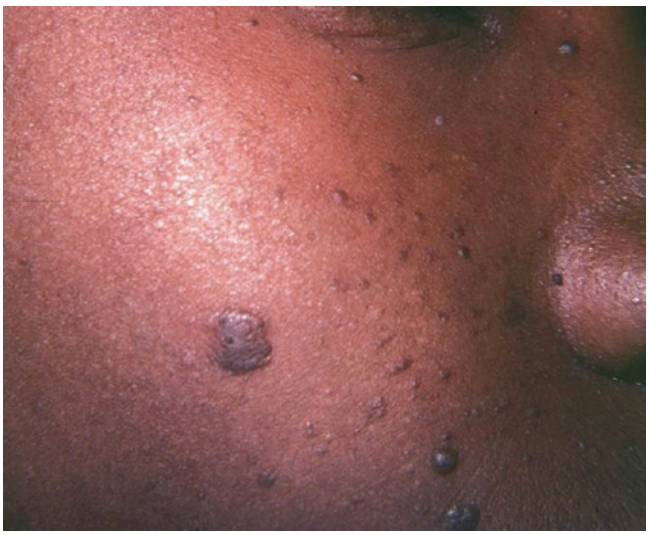

Fig. 9.11 Hyperpigmented angiofibromas in a patient with TSC

Management Strategies

Observation is recommended if the lesions are cosmetically acceptable and clinically asymptomatic. For widespread, disfiguring, or symptomatic angiofibromas (bleeding or obstructing vital structures), several therapies have been prescribed (Tables 9.31 and 9.32).

Investigations Recommended

For diagnosis
Skin Biopsy
Full skin exam should be performed to evaluate for other cutaneous findings of TSC
Genetic testing for *TSC1* and *TSC2* may be indicated especially when a patient has limited cutaneous finding(s) but does not meet diagnostic criteria
Any family history or clinical features of MEN 1 should prompt further workup in order to initiate appropriate monitoring

Table 9.31 First line therapies

Topical rapamycin	Evidence level B	[73, 74]
Other topical mTOR inhibitors	Evidence level E	[74]
Lasers	Evidence level D	[75–77]

Table 9.32 Second line therapies

Systemic everolimus	Evidence level E	[78]

Angiofibromas are papules and/or plaques that are often present in the context of a diagnosis of tuberous sclerosis complex. Newer therapies continue to be developed to address these lesions.

Connective Tissue Nevus

Clinical Features

Connective tissue nevi are typically skin-colored plaques with normal overlying epidermis. The nevi can occur anywhere on the body. A shagreen patch (typically noted on the lower back) is one of the major clinical diagnostic criteria of the TSC (Fig. 9.12). A shagreen patch is a subtype of connective tissue nevus that contains excess amount of collagen fibers. Northrup et al. updated the TSC criterion to specifically note shagreen patch in TSC, since connective tissue nevi can also occur in MEN 1, Birt-Hogg-Dube syndrome, and Cowden syndrome [72].

Management Strategies

Connective tissue nevi are benign lesions. Observation is the primary approach (Table 9.33). Since the presence of a Shagreen patch is one of the major diagnostic criteria for the diagnosis of TSC, exploring the possibility of a diagnosis of TSC is appropriate. Other syndromes should be considered as indicated by any additional findings.

Table 9.33 First line therapies

First line therapies
Observation

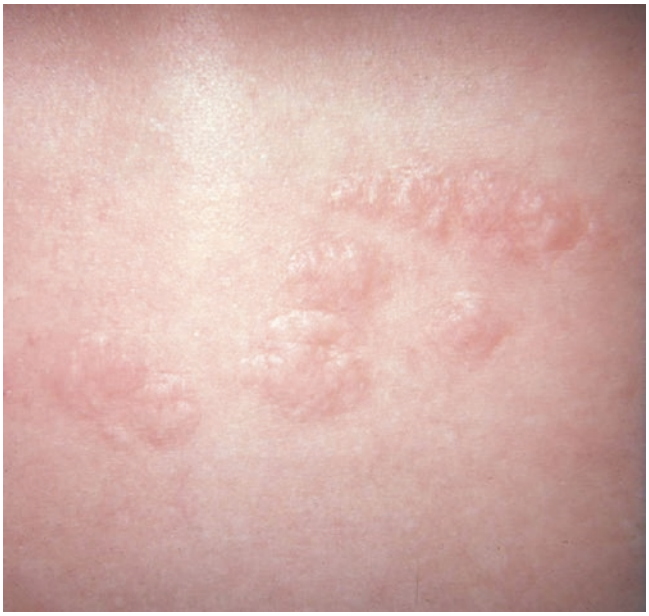

Fig. 9.12 Shagreen patch of the lower back with TSC

Investigations Recommended

For diagnosis
Biopsy shows increased collagen fibers and fragmented elastic fibers [79]
Full skin exam to evaluate for other cutaneous findings of TSC or other genetic disorders

Granuloma Annulare

Clinical Features

Granuloma annulare (GA) in children most often presents clinically as annular lesions with a raised border (Fig. 9.13) [80]. GA occurs more often in females than males, especially near sites of trauma (minor or otherwise), such as the wrists and ankles. Less typical locations include the trunk and face [81]. Other than annular lesions, GA can present as diffuse papules or subcutaneous nodules (SGA). The subcutaneous nodules are often found in the pretibial region or scalp [82]. Localized GA lesions commonly resolve spontaneously in 1–2 years. Generalized GA (GGA) is uncommon in children.

Differential diagnoses of GA include tinea corporis and erythema migrans associated with Lyme disease. Although in adults there is a speculated association of GA with diabetes and rheumatic disorders, this association has not been established in children [83]. However, some anecdotal cases with an association with diabetes can be found in the literature [84].

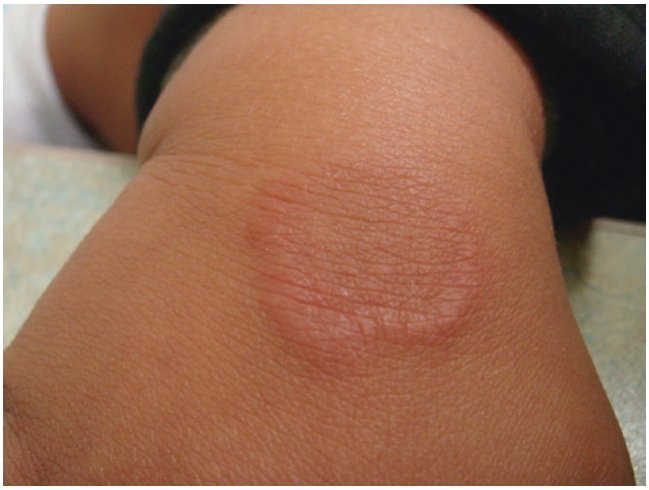

Fig. 9.13 Annular nodular lesion of the dorsal hand (granuloma annulare)

Management Strategies

Observation and reassurance is recommended in most cases. A thorough history about signs of diabetes should be obtained.

Investigation Recommended

For diagnosis
Clinical evaluation
Biopsy
Histology usually show palisaded granuloma, with lymphocytes, histiocytes, and multinucleated histiocytic giant cells [84]
Histology of SGA may be interpreted as pseudorheumatoid nodule
Ultrasound of SGA shows an ill-defined hypoechoic mass confined to the subcutaneous tissues
MR imaging shows ill-defined mass extending to but not traversing the underlying fascia, hypointense T1-wieghted and hyperintense T2-weighted images with variable enhancement after gadolinium administration [82]

GA is a benign cutaneous disease that often resolve spontaneously. The reported marked association with diabetes in adults has not been documented in children. See Tables 9.34–9.36.

Table 9.34 First line therapies

Observation	Evidence level D	[81]
Excision	Evidence level D	[81]

Table 9.35 Second line therapies

Corticosteroids	Evidence level D	[85]
Intralesional, topical, systemic		

Table 9.36 Third line therapies

Third line therapies
A wide variety of therapeutic modalities have been tried in GGA, randomized clinical trials in children have never been conducted [85]

Neurofibroma

Clinical Features

Cutaneous neurofibroma may occur as single lesion, or associate with genetic disorder such as neurofibromatosis (NF). Type 1 NF is an autosomal dominant RASopathy that is caused by mutation in the neurofibromin gene and characterized by many specific cutaneous findings. Some cutaneous findings present early in life; therefore are recognized as important part of the diagnostic criteria [86].

Neurofibromas are tumors developed from localized disorderly proliferation of Schwann cells. The lesions are usually soft and may be raised, subcutaneous, or exophytic at times. The "Buttonhole sign" (Fig. 9.14) is an important diagnostic feature of cutaneous neurofibroma. When the tumor is pressed with a digit the surrounding skin can feel like a buttonhole. Four subtypes have been identified: (1) focal or diffuse cutaneous; (2) subcutaneous; (3) nodular or diffuse plexiform; and (4) spinal [86].

Plexiform neurofibroma is a subtype that usually present at birth, and is noted in approximately 30–50 % of patients diagnosed with neurofibromatosis 1. Plexiform neurofibroma often grow along the length of the nerve and involve multiple nerve branches or plexuses; therefore they are associated with increased risk of morbidity. Compared to neurofibroma, the plexiform lesions are usually larger and more proliferative. Neurofibromas are generally benign, although plexiform neurofibromas have potential risk for transformation into malignant peripheral nerve sheath tumors (MNPST) [87].

Management Strategies

Observation of cutaneous neurofibromas is the most typical approach. If the lesions are causing pain or cosmetic issues, they can be surgically removed. In light of the possible malignant transformation associated with plexiform neurofibromas, close monitoring of the plexiform neurofibromas is recommended. See Tables 9.37–9.39.

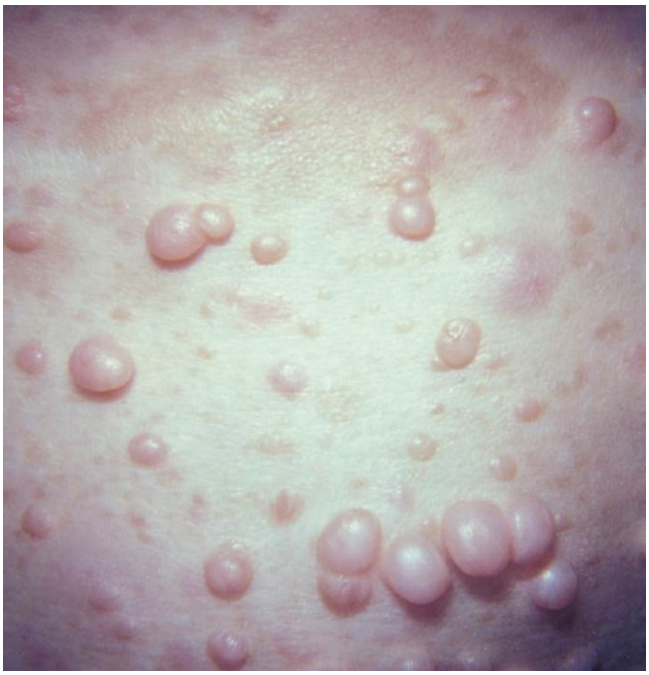

Fig. 9.14 Multiple neurofibromas in a patient with NF1

Investigations Recommended

For diagnosis
Skin biopsy
MRI for plexiform neuroma—"bag of worms" appearance as they extend along the nerve braches [88]
Genetic testing for gene map locus 17q11.2

Table 9.37 First line therapies

Observation if not symptomatic
Excision

Table 9.38 Second line therapies

Second line therapies
Rapamycin (mTOR) and mitogen-activated protein kinase inhibitors Evidence level B [89]

Table 9.39 Third line therapies

For Plexiform Neuromas:	
Phase 1 trial interferon alpha 2b [antiviral cytokine]	[86]
Phase 2 trial imatinib [tyrosine kinase inhibitor]	[86]

Dermatofibrosarcoma Protuberans

Clinical Features

Dermatofibrosarcoma protuberans (DFSP) is a cutaneous soft tissue sarcoma of fibrohistiocytic origin and intermediate malignant potential. It is characterized by slow growth, local invasion, and high risk of recurrence after excision. Metastasis is uncommon. DFSP typically presents in adults between the second and fifth decades and is rare in children, with fewer than 200 cases reported in the literature, some of which were present at birth. As in adults, pediatric DFSP begins as a fibrous papule or plaque, or sometimes atrophic plaque that may slowly become multinodular and protuberant over the course of several years, and tends to present on the trunk or proximal extremities [90, 91]. It has been proposed that acral locations are more commonly affected in children than in adults [91, 92]. DFSP may be misdiagnosed in children as a vascular malformation or tumor, keloid, dermatofibroma, scar, or epidermal cyst. Atrophic presentations may be clinically indistinguishable from morphea.

Management Strategies

Immunohistochemistry of DFSP demonstrates a characteristic staining profile, with the most helpful marker being CD34, which stains positive in over half of all cases and is notably negative in dermatofibroma. In 70–90 % of cases, DFSP has been associated with the chromosomal translocation t(17:22), which fuses the gene for collagen type 1, alpha 1 (*COL1A1*) next to that of platelet derived growth factor beta (*PDGFB*) [90]. As such, genetic studies can be a powerful supplementary diagnostic tool. The main goal of treatment is to achieve complete surgical excision, as tumors excised with negative margins lend a survival rate close to 100 %. Mohs micrographic surgery is preferred over wide local excision in children for its superior cure rates with smaller surgical margins (Tables 9.40 and 9.41). For larger lesions, it has been proposed that preoperative magnetic resonance imaging (MRI) may be a valuable tool for evaluating the extent of involvement and planning the surgical approach [92]. For very large, unresectable, or multiple DFSPs, clinical trials have shown effectiveness of imatinib mesylate in adults and may help shrink tumor size prior to surgery [93]. Radiation therapy may also aid in this regard and is now included in the National Comprehensive Cancer Network (NCCN) guidelines for DFSP, although radiation is rarely used in children (Table 9.42).

Investigations Recommended

For diagnosis
Biopsy
Immunohistochemistry
Positive: CD34, vimentin, apolipoprotein D
Negative: S100, factor XIIIa, smooth muscle actin, desmin
Detection of chromosomal translocation t (17:22)
Polymerase chain reaction (PCR)
Fluorescence in situ hybridization (FISH)
MRI for larger lesions

Table 9.40 First line therapy

Mohs micrographic surgery	D

Table 9.41 Second line therapy

Wide local excision	D

Table 9.42 Third line therapy

Imatinib mesylate (Gleevec) 600 mg PO daily for at least 6 weeks or until surgery with negative margins	C
Radiation therapy	E

Fibromatoses: Recurring Digital Fibroma of Childhood

Clinical Features

Recurring digital fibroma of childhood (RDFC), also known as recurring infantile digital fibromatosis, is a rare condition presenting most commonly at birth or during infancy as a flesh-colored to erythematous exophytic papule or nodule on the dorsal or lateral fingers or toes. Of note, it tends to spare the thumbs and halluces [94]. Lesions may grow up to 2 cm in size, and involvement of underlying structures may affect joint integrity and function. Histology demonstrates characteristic eosinophilic inclusion bodies.

Management Strategies

Treatment of RDFC remains a subject of debate. The progressive growth and functional impairment that may be seen with larger lesions often prompts surgical excision. However, excision is commonly followed by recurrence, may not improve any existing joint disease, and may not be necessary, as spontaneous regression has been reported [94–96]. Current thinking suggests smaller tumors that remain

asymptomatic may be closely followed and managed conservatively (Table 9.43).

Investigations Recommended

For diagnosis
Biopsy: characteristic eosinophilic inclusion bodies

Table 9.43 First line therapy

Close monitoring (small, asymptomatic lesions)	E
Surgical excision (large lesions with functional impairment)	E

Infantile Myofibromatosis

Clinical Features

Though rare overall, infantile myofibromatosis (IM) is among the more common benign fibrous tumors of infancy, characterized by slow-growing, solitary or multicentric, flesh-colored to purple firm nodules of the skin, subcutaneous tissue, muscle, or bone [97]. Presentation is most often in the first 2 years of life. For solitary lesions and some multicentric cases, prognosis is generally excellent. Some lesions have been described to regress spontaneously within 24 months, perhaps from massive apoptosis or factors modulating angiogenesis. However, generalized forms of IM, defined as having both skin and visceral involvement, warrant ongoing clinical evaluation [98]. The presence of visceral involvement carries a high risk of complications and mortality of up to 76% despite aggressive measures. Recently, autosomal dominant IM has been associated with mutations in the gene for platelet-derived growth factor receptor beta (PDGFRB) on chromosome 5q31-q32, which promotes growth of mesenchymal cells including blood vessels and smooth muscle, and the gene for NOTCH3, which is involved in cell differentiation [99].

Management Strategies

Histopathologic evaluation has been recommended for definitive diagnosis, as the clinical presentation may be nonspecific. In addition, various imaging modalities may be helpful in determining the extent of involvement and for surgical planning. Given the relatively small number of reported cases of generalized IM, no formal treatment guidelines have been proposed. However, available literature indicates some success with low-intensity chemotherapy, with the understanding that chemotherapy has suboptimal effect on benign tumors with low mitotic rates and carries well-known risks for adverse events [97, 100]. For children who are deemed not to be surgical candidates, tumors that remain asymptomatic with no immediate life-threatening developments may be monitored closely (Tables 9.44–9.46).

Investigations Recommended

For diagnosis
Biopsy: deep-seated proliferation of spindle-shaped cells arranged in short fascicles at periphery and vascular proliferation in center
Immunohistochemistry
Positive: smooth muscle actin
Imaging (optional)
Ultrasound: well-defined lesion with central hypoechogenicity
Computed tomography: mass with peripheral enhancement and calcifications
Magnetic resonance imaging: low intensity on T1, high or low intensity on T2

Table 9.44 First line therapy

Close monitoring (solitary or asymptomatic lesions or non-surgical candidates)	D

Table 9.45 Second line therapy

Conservative excision	D

Table 9.46 Third line therapy

Low-dose chemotherapy (high-risk lesions)	D
Methotrexate and vinblastine	
Dactinomycin and vincristine	

Tumors of the Oral Mucosa: Congenital Granular Cell Tumor

Clinical Features

Congenital granular cell tumor (CGCT), also termed congenital epulis, congenital myoblastoma, or Neumann's tumor, is a rare benign neoplasm of the soft tissue. It is typically found on the alveolar ridge and can grow as large as several centimeters, causing obstruction with breathing and feeding. Lesions are more common in females, possibly due to maternal hormonal influence, and may appear in multiplicity in about 10% of cases [101–103].

Management Strategies

Small, asymptomatic lesions may be monitored closely for possible spontaneous regression. Larger lesions interfering with breathing or feeding may be surgically excised

(Table 9.47). Reports have also demonstrated effective results with ablative lasers including carbon dioxide and erbium, chromium: yetrium-scandium-galliumgarnet (Er,Cr:YSGG) (Table 9.48) [103]. In emergent situations of life-threatening airway obstruction by CGCT at birth, the ex utero intrapartum (EXIT) strategy has been described as a way of accessing and securing the airway under placental circulation prior to surgical resection [104].

Investigations Recommended

For diagnosis/treatment
Biopsy/excision: large sheets of closely packed cells with abundant granular cytoplasm

Table 9.47 First-line therapy

Observation (if asymptomatic)
Excision

Table 9.48 Second-line therapy

Second-line therapy
Ablative laser

Mucocele

Clinical Features

Mucocele is a common benign oral neoplasm that arises from disruption of a minor salivary duct, allowing mucus to escape into the surrounding connective tissue [105]. It presents as a soft, painless, dome-shaped nodule with translucent bluish hue that may undergo multiple cycles of rupturing and refilling. The most common location is the lower labial mucosa, but mucocele may also develop on the ventral tongue, buccal mucosa, and posterior hard palate. When present on the floor of the mouth, it is termed a ranula [106]. A variant, plunging ranula, arises from the sublingual gland and may herniate through the soft tissues of the inferior, lateral, or posterior pharynx and neck, resulting in its frequent misdiagnosis as thyroglossal duct cyst, dermoid cyst, vascular malformation, or cystic hygroma [107]. In one study, mucocele was significantly associated with positivity of human immunodeficiency virus (HIV) in teenagers and young adults, suggesting an increased risk with HIV infection [108].

Management Strategies

Small or asymptomatic lesions may be monitored closely for possible spontaneous regression. Simple excision of the mucocele and adjacent minor salivary glands achieves effective resolution with low rates of recurrence (Table 9.49) [105]. Other reported modalities include marsupialization, electrodessication, intralesional steroid injection, cryosurgery, and ablative laser. While marsupialization has been proposed to carry a higher risk of recurrence, carbon dioxide laser has been reported to be equally effective to surgery with the additional benefits of less bleeding, no sutures, and shorter operative time (Table 9.49) [106]. Preoperative imaging for larger or deeper lesions, such as plunging ranula, may be indicated to confirm the diagnosis and plan the surgical approach. Ultrasound is preferred as the initial study, as it allows dynamic assessment for active herniation, with magnetic resonance imaging (MRI) to be considered for recurrent lesions after surgery or for more specific localization. Computed tomography (CT) yields lower resolution and is less useful for soft tissue processes than MRI [107].

Investigations Recommended

For diagnosis/treatment
Biopsy/excision: large sheets of closely packed cells with abundant granular cytoplasm
Ultrasound
MRI

Table 9.49 First-line therapy

Observation (if asymptomatic)	
Excision	D
Ablative laser	D

Miscellaneous: Epidermal Cyst

Clinical Features

Epidermal cysts, also known as epidermoid cysts or epidermal inclusion cysts, are the most common cutaneous cyst. They present most commonly on the face or upper trunk as well-defined flesh-colored to yellowish dermal papules or nodules, sometimes with an appreciable central punctum. The misnomer "sebaceous cyst" is used primarily by non-dermatologists; true epidermal cysts are derived from the follicular infundibulum. Multiple cysts may be seen in patients with a history of significant acne vulgaris, Gardner syndrome, pachyonychia congenita, or basal cell nevus syndrome [109, 110]. Epidermal cysts are typically asymptomatic but may become inflamed or rupture, resulting in pain at the site.

Management Strategies

Treatment for this benign entity is optional and symptomatic. Simple excision is curative. Incision and drainage of non-inflamed epidermal cysts may provide temporary relief, but without complete removal of the epithelial lining, recurrence is likely (Table 9.50) [111]. Inflamed, fluctuant, or painful cysts are more concerning for infection. While intralesional triamcinolone is a widely used initial therapy, the Infectious Disease Society of America recommends incision and drainage as the first-line treatment for inflamed epidermal cysts. Oral antibiotics directed against *Staphylococcus aureus* should be added if the patient meets systemic inflammatory response syndrome (SIRS) criteria, with coverage for methicillin-resistant *S. aureus* (MRSA) in those previously unresponsive to antibiotic therapy or with a history of impaired immune function (Table 9.51). Notably, Gram stain and culture from inflamed epidermal cysts is not recommended [112].

Investigations Recommended

For diagnosis/treatment
Biopsy/excision: cystic space filled with laminated keratin, filled with stratified squamous epithelium with granular layer

Table 9.50 First line therapy

Observation
Simple excision or punch excision
Incision and drainage (inflamed lesions)

Table 9.51 Second line therapy

Second line therapy
Antibiotics covering *S. aureus*

Steatocystoma Multiplex

Clinical Features

Steatocystoma is a benign cyst derived from the sebaceous gland. When solitary, they may be termed steatocystoma simplex, and in multiplicity, steatocystoma multiplex. These asymptomatic dermal cysts present most commonly on the chest, axillae, and groin, and drain oily fluid when punctured [113]. Rare facial, acral, and congenital linear variants have been described. An autosomal dominant form of steatocystoma multiplex has been attributed to mutations in keratin 17 (*KRT17* gene) and may be associated with eruptive vellus hair cysts and pachyonychia congenital type 2 [113, 114].

Management Strategies

As with epidermal cysts, treatment is optional and may be desired for cosmetic reasons. Lesions may be excised, such as by a punch tool, with removal of the cyst wall (Table 9.52). Numerous other treatment modalities have been reported, including cryosurgery, electrocautery, ablative lasers, aspiration, extirpation with a vein hook or Volkmann's spoon, and incision using a radiofrequency instrument [115–117].

Investigations Recommended

For diagnosis/treatment
Biopsy/excision: cystic space filled with laminated keratin, filled with stratified squamous epithelium with granular layer

Table 9.52 First-line therapy

Observation
Simple excision or punch excision

Calcinosis Cutis

Clinical Features

Calcinosis cutis is comprised of deposits of insoluble calcium compounds in the dermis and subcutaneous tissue. Clinically they are seen as very firm, whitish papules (Fig. 9.15). Classification of the four subtypes of calcinosis cutis is delineated as following: [118].

A. Dystrophic calcification—Following tissue inflammation and/or damage (e.g. CREST syndrome, infection etc.)
B. Metastatic calcification—Seen with abnormal calcium and phosphorous metabolism
C. Idiopathic
D. Iatrogenic (e.g. following medical procedures)

The calcified material can induce local inflammation that results in ulceration or extrusion. The presence of calcium may also predispose the individual to form contractures.

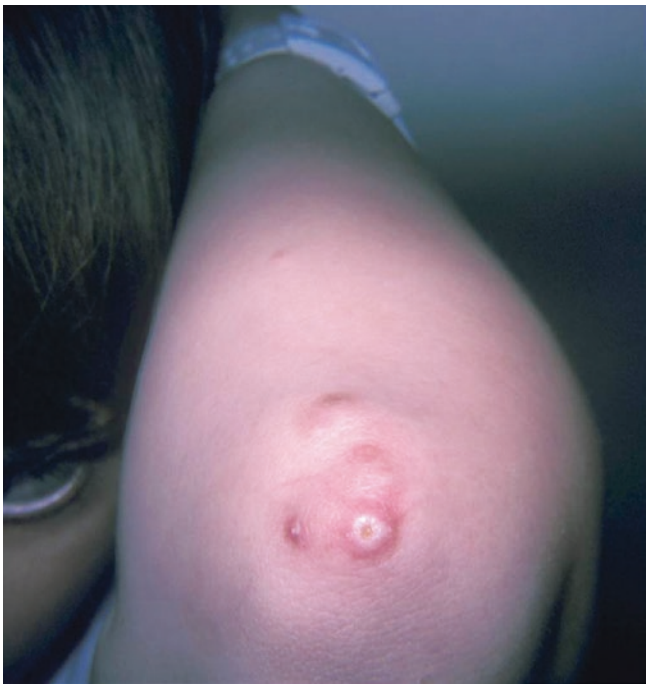

Fig. 9.15 Whitish nodule noted in calcinosis cutis

Management Strategies

See Tables 9.53–9.55 for a summary of treatment options.

- Observation
- Debridement

Investigations Recommended

For diagnosis
Biopsy shows globules of calcium (tiny granules in the dermis or larger deposits in the subcutaneous tissue). Possibly a foreign body reaction will be seen
X-rays-show radiopaque lesions
Laboratory tests
Check calcium and phosphorus -may be abnormal in the metastatic form
Evaluate for Vitamin D poisoning
Work-up to look for collagen vascular disease if indicated by history, physical examination, or family history

Table 9.53 First line therapies

Treat any underlying cause identified		
Phosphate binders (magnesium or aluminum antacids) if hyperphosphatemia is present		
Excision (but may recur) if painful		
Diltiazem Evidence level B [119]		

Table 9.54 Second line therapies

Intralesional corticosteroids for inflammation	Evidence level E	[118]
Decrease calcium and vitamin D intake	Evidence level E	[118]
Probenecid and colchicine	Evidence level E	[118]
Warfarin	Evidence level E	[118]

Table 9.55 Third line therapies

Biologics	Evidence level E	[119]
IV immunoglobulin	Evidence level E	[119]

Osteoma Cutis

Clinical Features

Osteoma cutis denotes the abnormal development of bone in the skin. It can occur de novo or secondary to skin injury [120]. The term refers to a group of ossifying disorders and approximately 14 % of cases are primary. When the lesions are primary, they may be associated with Albright hereditary osteodystrophy, progressive or non-progressive osseous heteroplasia due to GNAS mutations [121]. There have been very rare reports of extramedullary acute leukemia arising in osteoma cutis lesions [122]. Clinically, the lesions may present as firm papules, nodules, or plate-like lesions (Fig. 9.16).

Management Strategies

- Treat any underlying cause if present and relieve symptoms (Tables 9.56–9.58).

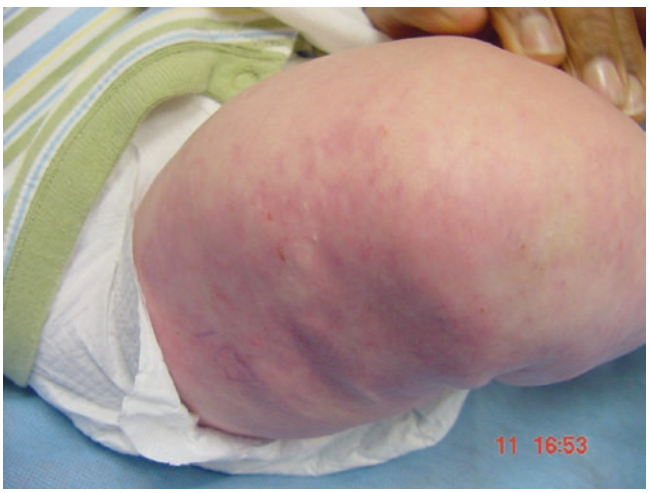

Fig. 9.16 Firm plaques and papules of the right upper lateral thigh

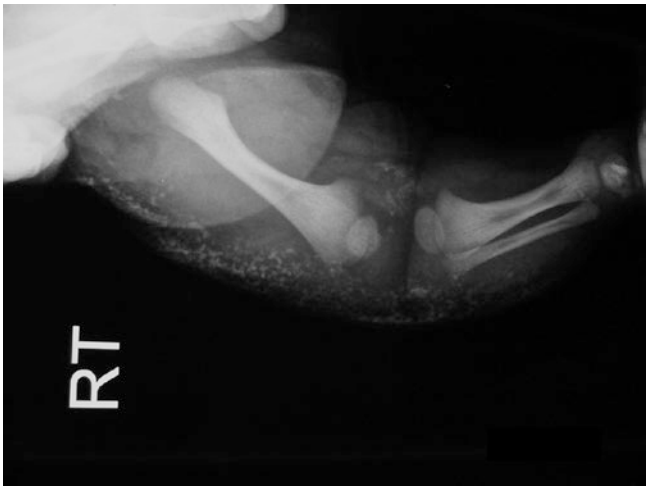

Fig. 9.17 X-ray of a patient with osteoma cutis showing calcifications

Investigations Recommended

- Biopsy shows bone formation with osteoblasts, osteoclasts, lacunae and sclerotic bodies.
- X-ray demonstrates calcifications (Fig. 9.17)
- Assess parathyroid hormone levels and calcium and phosphorus levels [123]
- Molecular studies to look for GNAS mutation

Table 9.56 First line therapies

Excision
Topical tretinoin Evidence level D [120]
Treat any underlying condition

Table 9.57 Second line therapies

Yag laser	Evidence level D	[120]

Table 9.58 Third line therapies

Bisphosphonate pamidronate	Evidence level E	[124]

Summary

Osteoma cutis is a rare disorder that is characterized by cutaneous bone formation. When the diagnosis is made, further work-up for associated conditions may be indicated.

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Histiocytoses and Malignancy

10

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Langerhans Cell Histiocytosis

Clinical Features

Langerhans cell histiocytosis (LCH) is a rare clonal proliferative disease of CD1a+, CD207+ (Langerin) dendritic cells with a broad spectrum of clinical manifestations that can involve skin, bone, viscera, and the central nervous system. The proliferative dendritic cells share many phenotypic features of the epidermal Langerhans cell, including demonstration of Langerin-associated Birbeck granules on electron microscopy [1]. Nevertheless, recent gene expression profiling has implicated LCH as arising from a myeloid precursor rather than from differentiated epidermal Langerhans cells [2]. The recent discovery that approximately 50% of LCH cases involve somatic activating mutations in the proto-oncogene BRAF supports a neoplastic origin for the condition and has raised possibility of more targeted therapies [1]. The estimated incidence of LCH is 8.9 cases per million children younger than 15 years, with a median age of diagnosis of 3 years old [3]. Skin and bone are the most commonly affected organ systems [4]. The majority of cases (65%) affect only one organ system, with isolated skin involvement representing 11% of single-system disease [5, 6]. In patients with multi-system LCH, skin involvement is common and is seen in 53% of such patients [7]. Diagnosis is challenging and is ideally made by excisional biopsy of an involved skin lesion or lymph node to allow for histopathologic and immunophenotypic evaluation. The differential diagnosis can often include seborrheic dermatitis, herpetic infection, diaper dermatitis, and other proliferative disorders of lymphocytes, mast cells, or non-langerhans cell histocytes.

LCH presents with a broad spectrum of clinical manifestations and variable disease course, ranging from benign self-resolving or self-limited disease to fatal multi-organ involvement. The field has moved away from differentiation into specific variants given significant overlap between the previously described entities. Classically described presentations include development of asymptomatic, solitary, or multiple osteolytic lesions (previously referred to as eosinophilic granulomas), the clinical triad of exophthalmos, diabetes insipidus, and multiple osteolytic lesions of the skull (previously termed Hand-Schuller-Christian Disease), or more acute, life-threatening eruptions including disseminated involvement of the skin, liver, and spleen (originally described as Abt-Letterer-Siwe, or Letterer-Siwe, disease) [3, 4]. Skin findings, when present, are highly variable and include crusted or scaly red-brown to erythematous or purpuric papules, vesiculopustular lesions, solitary papules or nodules with central necrosis, and even hypopigmented macules, with common sites of involvement being the scalp, postauricular skin, trunk, and intertriginous areas of the neck, axillae, and perineum [8]. Keratotic palmoplantar lesions and mucosal involvement are sometimes observed. Within the dermatologic literature, congenital self-healing reticulohistiocytosis, first described by Hashimoto and Pritzker, [9] refers to a benign clinical variant of LCH that presents at birth with red-brown papules and nodules that could have a central craterifom like ulceration. This variant often lacks systemic symptoms, but do require long-term follow up for potential reports of diabetes insipidus after resolution of skin symptoms and potential systemic involvement. Skin lesions often self-resolve over a few months and have involuted by 1 year of age. The extent of LCH involvement cannot be predicted with certainty based on the degree or type of skin involvement observed, therefore multi-organ work-up with close serial follow-up is required to accurately risk stratify patients.

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Management Strategies

Treatment is determined based on the extent of disease and whether there is involvement of high-risk sites such as the hematologic system, spleen, and liver, which are associated with higher mortality. Referral to a pediatric hematology/oncology specialist is strongly recommended for all cases for complete systemic evaluation. One expert center has reported that 40 % of cases referred for apparently skin limited disease were ultimately found to have multisystem involvement [10]. If baseline studies fail to identify extracutaneous involvement, close surveillance alone is appropriate for asymptomatic skin lesions given the approximately 60 % chance of self-resolution of the involved skin lesions [3]. Although prognosis is considered good in skin-limited disease, surveillance is requisite as the true rate of progression to systemic disease is still unclear with conflicting reports ranging from 0 to 60 % [10]. Treatment of symptomatic skin lesions in skin-limited disease is appropriate and includes topical steroids, imiquimod, and phototherapy. Evidence to support these treatments is limited to few case reports and case series. Systemic therapy can be considered for skin lesions that are causing pain, are deeply ulcerated, or are leading to secondary infections. Solitary bone lesions can be treated with curettage, oral NSAIDs, or intralesional corticosteroids. Management of multisystem or multifocal bone-involvement LCH should occur at an expert center to enable access to investigational protocols. Current treatment regimens include vinblastine/prednisone for 1 year for non-high risk and vinblastine/prednisone/mercaptopurine for 1 year for high-risk disease [11]. Other treatments for multisystem LCH include cladribine, cytaribine, and stem cell transplantation [4, 11, 12]. Vemurafenib is under investigation as an additional therapeutic option [4]. These regimens are subject to change based on ongoing research.

For the purposes of this text, treatment recommendations will focus on management of cutaneous LCH lesions. The Histiocyte Society website (http://www.histiocytesociety.org/) provides an excellent resource for those interested in up to date recommendations for treatment of multisystem involvement or high risk disease.

Investigations Recommended

Diagnostic
Skin Biopsy, preferably excisional sent for: Histology Immunohistochemistry
Evaluation
Baseline studies of complete blood count (CBC), complete metabolic panel (CMP), gamma glutamyl transferase (GGT), INR/PT, APTT/PTT, fibrinogen, early morning urine specific gravity and osmolality, abdominal ultrasound, chest radiograph, and skeletal survey. PET scan useful for scanning for extracutaneous lesions if available
Specialized testing including MRI, high resolution CT, bone marrow biopsy, and lung biopsy as indicated based on results of baseline evaluation and clinical scenario. Multispecialty involvement recommended in such circumstances
Treatment
Methotrexate: Pregnancy test (for women of child-bearing potential), CBC, CMP, tuberculosis testing at baseline, monitor CBC and hepatic panel during treatment
Retinoids: Pregnancy test (for women of child-bearing potential), CBC, AST, ALT, fasting lipids at baseline and during treatment
Thalidomide: Pregnancy test (for women of child-bearing potential), CBC. Monitor CBC and pregnancy tests during treatment
Azathioprine: Thiopurine methyltransferase (TPMT), pregnancy test (for women of child-bearing potential), CBC, CMP, tuberculosis testing at baseline. Monitor CBC and CMP during treatment

Diagnosis requires histologic and immunophenotypic identification of the characteristic CD1a+, CD207+ langerhans cells in the appropriate clinical setting, and is greatly aided by biopsy of an involved skin lesion. Referral for curettage of the center of an involved bone lesion may also yield the diagnosis.

Prior to initiating treatment, a complete history and physical examination should be performed, with attention paid to a review systems of pain, swelling, rashes, otorrhea, irritability, fever, loss of appetite, diarrhea, weight loss or poor weight gain, growth failure, polydipsia, polyuria, change in energy level, and behavioral or neurological changes. Baseline staging studies recommended by expert consensus panel include laboratory and radiologic studies to evaluate for systemic involvement [12]. PET scan can be helpful for baseline identification of extracutaneous LCH lesions, though availability may be limited due to cost. More specialized testing can be pursued based on the results of the screening studies and clinical scenario.

Table 10.1 First line therapies [12]

Close observation	D
Topical steroids, moderate and high potency	E[a]

[a]Based on adult data (used due to lack of pediatric data)

Given the often self-resolving or limited course of skin-limited disease, close observation alone is recommended unless skin lesions are symptomatic. In children with a more rash-like eruption, moderate- to high-potency topical steroids may be used, though benefit is typically marginal [12].

Table 10.2 Second line therapies [12–15]

Nitrogen mustard therapy Mechlorethamine hydrochloride 20 mg dissolved in 40 ml water applied daily × 14 days, then taper	D
Narrow-band UVB (nbUVB)	E
Imiquimod 5 % cream, 5×/week for 2 months	E[a]
Surgical excision	E

[a]Based on adult data (used due to lack of pediatric data)

Nitrogen mustard has been shown to be effective in treatment of cutaneous LCH lesions in children [13]. Treatment may be limited by contact dermatitis to the agent, and treatment must be weighed against potential mutagenic effect, though fortunately there have been no reports of secondary tumors developing secondary to nitrogen mustard use in LCH [12]. One recent nitrogen mustard regimen reported to be effective was 20 mg mechlorethamine hydrochloride dissolved in 40 ml water applied once daily for 14 days, followed by taper to daily use for 1 week per month and subsequently twice per month as lesions regressed [13]. Other treatments that have been reported to offer benefit include nbUVB and topical imiquimod cream [10, 14]. In the adult literature, imiquimod applied five times/week for 2 months was beneficial in one reported case [15]. For symptomatic nodules, surgical excision may be appropriate in some circumstances, though radical excision should be avoided.

Table 10.3 Third line therapies [10–12, 16–20]

Methotrexate 20 mg/m^2 weekly	D
Oral steroids	D
Thalidomide 50 mg daily	C
Azathioprine	E[a]
Psoralen plus UVA (PUVA)	E[a]
Photodynamic therapy	E
Interferon alpha	E[a]
Oral retinoids	E[a]
Radiation therapy	D

[a]Based on adult data (used due to lack of pediatric data)

For symptomatic skin involvement causing significant morbidity that is refractory to local treatment modalities, oral corticosteroids and low-dose methotrexate can be considered. A reported pediatric methotrexate regimen is 20 mg/m^2 weekly, and the successful combination of this with alternating day dosing of prednisone 40 mg/m^2/day has been reported [11, 16]. Thalidomide at a dose of 50 mg daily for children has been shown to be effective in low-risk skin disease, though it must be weighed against a significant toxicity profile including fatigue, neutropenia, peripheral neuropathy, and increased risk of deep-vein thrombosis and thromboembolism [17]. Successful use of photodynamic therapy with methylaminolevulinate has been reported in an infant [18]. Oral retinoids, such as acitretin, azathioprine, interferon alpha 2, and PUVA therapy have been anecdotally reported to be effective in adults, and can be considered in children in severe cases [10, 12, 19]. Radiation therapy is generally not recommended given concern for long-term sequelae in children, though it is very effective for treatment of painful ulcerated lesions refractory to other treatments [20].

Juvenile Xanthogranuloma

Clinical Features

Juvenile xanthogranuloma (JXG) is the most common non-Langerhans cell histiocytosis. It is benign, self-limited, and presents in infants and children more commonly than adults. JXG is derived from dermal dendrocytes and presents in normolipemic individuals without abnormalities in lipid metabolism. Cutaneous lesions often present on the head, neck, and trunk and can be divided by their size into 'micronodular' (lesions <1 cm) and 'macronodular' (lesions >1 cm) forms. Giant JXG lesions are also rarely seen, and can be up to 5–10 cm in size. The lesions are often asymptomatic, but can ulcerate and bleed. Clinically, they present as solitary to numerous firm, round papules or nodules. The solitary presentation is more common, occurring in up to 90% of all patients with JXG. Early on they present as more erythematous papules with minimal yellow-orange color. As they mature they become more characteristically yellow in color and may develop overlying telangiectasias. This correlates histologically to earlier lesions showing monomorphic nonlipid containing histiocytes with more mature lesions containing foamy cells and Touton giant cells with positive fat immunohistochemical staining. Extracutaneous involvement can occur, with ocular involvement being the most common, presenting in approximately 0.4% of patients [21]. Other sites that have been reported include lungs, bone, kidneys, pericardium, colon, testes, ovaries, and liver [22]. Mucous membranes can be involved, but very rarely. JXG may be present at birth (30%), but most cases present during the first year of life (75%), with rare onset in adulthood reported. Onset is often abrupt with lesions continuing to persist or erupt for years, followed by spontaneous regression in 3–6 years time [23].

There has been as association seen between patients with JXGs and neurofibromatosis type 1 (NF1) [24] and JXGs and childhood leukemia, most commonly juvenile chronic myelogenous leukemia (JCML) [25]. In the majority of cases the JXG precedes or occurs at the same time as the leukemia is diagnosed and often multiple JXGs are present. There is also a triple association between JXG, NF1, and JCML in which individuals with JXG and NF1 are at a 20- to 32-fold higher risk of developing JCML than an individual with NF1 and no JXGs [26].

Investigation Recommendations

Diagnostic
Skin biopsy for:
Histopathology
Immunohistochemistry
Electron microscopy
Evaluation
Complete full body skin examination
Complete review of systems
Ophthalmology examination (if multiple JXGs)

Diagnosis can be made clinically and can be confirmed by skin biopsy if needed. Skin biopsy and specific immunohistochemical stains show the following:

- Histology: Nodular histiocytic infiltrate in the dermis sometimes with extension to upper subcutis. Early lesions are monomorphic and have few lipid-laden cells, where as more mature have foamy histiocytes and Touton giant cells ('wreath' of nuclei surrounded by foamy cytoplasm) and interstitial fibrosis. They can also be scattered neutrophils, rare plasma cells, and few eosinophils.
- Immunohistochemical stains: Negative CD1a and S100 and positive Factor XIIIa and CD68
- Electron microscopy: Reveals histiocytes with lipid-laden vacuoles, lysosomes, cholesterol clefts and myeloid bodies. Absence of Birbeck granules

A complete skin examination must be performed to determine the number of JXGs and rule out co-existent NF1. Patients that are 2 years of age or younger with multiple JXGs (2 or more) require an ophthalmology examination to rule out ocular involvement [21]. A complete review of systems should be performed to determine whether further evaluation should be undertaken to look for the rare circumstance of extracutaneous involvement.

Management Strategies

Juvenile xanthogranuloma is benign condition with spontaneous resolution of cutaneous and visceral lesions within 3–6 years. Cutaneous lesions can leave behind residual anetoderma, mild atrophy, and/or hyperpigmentation. Treatment is generally not indicated for cutaneous lesions given spontaneous resolution. However, treatment can be pursued in symptomatic cases or where there is significant cosmetic disfigurement.

On the other hand, in cases where there is intraocular involvement, there is high risk of morbidity that can result in spontaneous hyphema, glaucoma or blindness if left untreated [21]. Therefore, early treatment of ocular lesions is warranted.

Cutaneous Disease

Table 10.4 Potential Treatment Options [27, 28]

Surgical excision (partial or complete)	D

Treatment of cutaneous lesions with partial or complete excision is only pursued for diagnostic considerations, if there is significant cosmetic disfigurement, or if the JXG is symptomatic [27]. Recurrence of lesions after excision has been reported [28].

Table 10.5 First-line treatment options [27, 29–32]

Surgical resection (localized disease)	E
Topical or systemic corticosteroids	E
Carbonic anhydrase inhibitors	E
Pilocarpine	E

Ocular Disease

Treatments that have been tried for ocular involvement, which can occur in the presence or absence of skin disease, include surgical resection for localized disease [29, 30], topical or systemic corticosteroids [29, 31], carbonic anhydrase inhibitors [29, 32], pilocarpine [29], and when medical management has failed radiation therapy [27, 29, 32].

Table 10.6 Second-line treatment options [27, 29, 32, 33]

Radiation therapy	E
Bevacizumab	E

As stated above, radiation therapy is generally recommended when medical management has failed [27, 29, 32]. There was also one case report of use of intraocular bevacizumab [33].

Visceral Lesions

Table 10.7 Potential treatment options [27, 34, 35]

Chemotherapy	D
Corticosteroids	E
Cyclosporine	E
Radiotherapy	E

Visceral lesions do not usually need to be treated, as they do spontaneous resolve, unless there is interference with organ functionality or if they are causing symptoms. Treatments that have been used include chemotherapy, [27] corticosteroids, [27, 34] cyclosporine, [27] and radiotherapy [27, 34, 35].

Benign Cephalic Histiocytosis

Clinical Features

Benign cephalic histiocytosis (BCH) is a cutaneous, self-healing, non-Langerhans cell histiocytosis. Clinically, it is characterized by 2–6 mm small, asymptomatic, yellow-brown or red-brown macules or slightly elevated papules classically located on the face, less commonly located on the

neck and trunk, and rarely on the extremities, buttocks, or genital region. Mucous membranes and acral surfaces are spared. BCH typically occurs prior to 6 months of age and generally before 3 years of age. Average age of onset is approximately 15 months. Onset of regression on average has been reported at about 23 months (range 8–48 months), with complete regression on average by 50 months (9–108 months) [36]. BCH may be considered to lie along a spectrum with other non-Langerhans cell histiocytosis such as juvenile xanthogranuloma (JXG) and generalized eruptive histiocytosis, with overlapping clinical and histologic features. There have been cases of BCH that have showed transformation to JXG after initial biopsy and diagnosis [37]. Some even consider BCH a variant of micronodular juvenile xanthogranuloma.

Investigation Recommendations

Diagnostic
Skin biopsy for:
Histopathology
Immunohistochemistry
Electron microscopy

Diagnosis can be made clinically and can be confirmed by skin biopsy if needed. There can be overlap between the various histiocytic conditions. Some features that may help differentiate BCH from other histiocytoses that may have internal involvement and a more insidious course are as follows:

- Histology: Well circumscribed histiocytic infiltrate in the superficial to mid-reticular dermis
- Stains: Negative CD1a and S100 (can sometimes be weakly positive) and positive Factor XIIIa and CD68
- Electron microscopy: Reveals intracytoplasmic comma-shaped or worm like bodies, coated vesicles, and desmosome like structures. Absence of Birbeck granules

Management Strategies

No treatment is necessary, as BCH runs a benign course with spontaneous healing. There can be residual macular dyspigmentation or atrophic scars. Since there can be overlap with other histiocytic entities, clinical follow-up for progression, review of systems, and physical examination for any internal involvement is recommended. Systemic disease has not been reported with BCH, but there has been one case of diabetes insipidus [38] and one case of insulin-dependent diabetes mellitus in a child with BCH [39].

Xanthoma Disseminatum

Clinical Features

Xanthoma disseminatum (XD) is a rare mucocutaneous non-Langerhans cell histiocytosis that occurs in both children and adults. There is predominance in males, and most cases have their onset prior to 25 years of age. XD can be classified into three forms by its evolution and prognosis: a self-healing form with spontaneous resolution; a more common persistent form in which lesions may never resolve; and a very rare progressive form with systemic involvement, organ dysfunction, and potential central nervous system (CNS) involvement [40].

Most patients have no alteration in lipid metabolism and have normal lipid profiles. Clinically, patients present with numerous small ovoid yellow-red to brown papules, plaques and nodules that occur predominantly on the face, flexural and intertriginous areas, around the umbilicus, perineum, and genital region. On the face the most prominent location is the eyelids. Approximately 30–50 % of cases have mucosal involvement including the oropharynx and gastrointestinal tract, conjunctiva and cornea, and upper respiratory tract (epiglottis, larynx, and trachea) [41]. Depending of the location, involvement of mucosal surfaces can result in dysphagia, dysphonia, visual impairment and blindness, respiratory distress, and intestinal obstruction. XD may also rarely manifest itself in the central nervous system, bone, liver, and within other ocular structures. Diabetes insipidus has been reported in about 40 % of patients with XD and tends to be transient, mild, and desmopressin responsive.

Investigation Recommendations

Diagnostic
Skin biopsy for:
Histopathology
Immunohistochemistry
Electron microscopy
Evaluation for systemic involvement:
MRI
F-fluorodeoxyglucose PET/CT scan

Diagnosis can be made by skin biopsy in conjunction with history and clinical appearance. Systemic involvement can rarely occur, therefore thorough physical examination, review of systems, and possible further imaging studies may be warranted to determine disease extent.

There can be overlap between the various histiocytic conditions. Some features that may help differentiate xanthoma disseminatum from other histiocytoses are as follows:

- Histology: Histiocytic infiltrate in the dermis with presence of Touton and foreign body giant cells admixed with a mild inflammatory cell infiltrate of lymphocytes, plasma cells, and neutrophils.
- Immunohistochemical Stains: Negative CD1a and S100 and positive for Factor XIIIa and CD68.
- Electron microscopy: Lipid-laden histiocytes with prominent endoplasmic reticulum and fat droplets. Absence of Birbeck granules.

Given higher risk of systemic involvement, imaging is also recommended, including MRI. Recent data also supports the use of F-Fluorodeoxyglucose positron emission tomography/computed tomography (F-FDG PET/CT), which detects increased glucose metabolism, correlating to cell proliferation; this may detect systemic involvement earlier than MRI [42].

Management Strategies

Patients with XD should be followed for progression of disease or symptoms. There are no curative treatments for XD. Various treatment modalities have been reported in the literature as monotherapy or in combination; however, given the minimal data with these treatment modalities, there are none that are recommended as first-line, second-line, or third-line. As such, we will list them below as potential treatment options.

Table 10.8 Potential treatment options [43–52]

Surgery	E
Ablative carbon dioxide laser	E
Non-ablative diode laser	E[a]
Radiotherapy	E
Corticosteroids	E[a]
Cyclophosphamide	E
Azathioprine	E
Chemotherapy (various regimens)	
Lipid-lowering agents: combination of rosiglitazone, simvastatin, and acipimox or fenofibrate	E[a]
2-chlorodeoxyadenosine (cladribine)	D[a]
Anakinra	E[a]

[a]Based on adult data (due to lack of pediatric data)

Various treatment modalities have been reported in the literature as monotherapy or in combination ranging from use of localized therapies such as surgery, ablative carbon dioxide lasers, [43] non-ablative, 1,450 nm laser, [44] and radiotherapy [45] directed at cutaneous and accessible lesions, lipid lowering medications, immunosuppression, and chemotherapy. The decision to pursue treatment is dependent of the extent of disfigurement, symptoms, anatomical location, and potential morbidity and mortality. Response rates to various treatment modalities are quite variable with no one modality showing consistent and successful results. Localized treatments are shown to be effective at treating individual lesions often without reoccurrence in the treated area, but they do not keep new lesions from developing and are limited by use for extensive disease. Corticosteroids have shown partial response in some cases, [46] but response has not been durable, with recurrence of lesions and progression of disease once corticosteroids were discontinued. Cyclophosphamide and azathioprine have been noted to have improvement in disease state in few cases [47]. There have been various chemotherapy regimens with variable response. Lipid-lowering agents have shown some effect, even in individuals with normal lipid profiles [48]. In particular, a regimen of rosiglitazone, simvastatin, and acipimox or fenofibrate have been used, which has shown some partial remission and stabilization of disease [49]. Use of 2-Chlorodeoxyadenosine (Cladaribine) has also shown some promising results in a case series of eight patients [50, 51]. 2-Chlorodeoxyadenosine is a purine analogue which inhibits adenosine deaminase enzyme and has been successfully used to treat numerous hematological malignancies and used in other systemic histiocytoses. Doses of 0.14 mg/kg/day for 5 days per month are repeated monthly for five to eight cycles. After three to five cycles, cessation of new lesions with significant improvement was noted in old lesions in all patients. Treatment was well tolerated without development of new lesions over follow-up period of 3 months to 8 years. There has also been a recent case report suggesting the use of a interleukin-1 receptor antagonist, Anakinra, with complete resolution of disease in a patient with cutaneous and CNS involvement [52]. This medication has been successfully used in other histiocytic disorders, such as multicentric reticulohistiocytosis and Erdheim-Chester disease.

Spontaneous resolution of XD lesions has also been reported, but most patients have the lesions lifelong. There have not been any reports of malignant transformation of cutaneous lesions.

Necrobiotic Xanthogranuloma

Clinical Features

Necrobiotic xanthogranuloma (NXG) is a rare disorder that is predominantly reported in adults. Clinically, it is characterized by asymptomatic or pruritic, well demarcated, yellow-orange to red-brown papules and nodules that coalesce to form an indurated plaque, often with overlying telangiectasias. Lesions have a predilection for periorbital areas, trunk, and the extremities. Ulceration, atrophy, and scarring can occur. Periorbital lesions and ocular involvement are very common and occur in 80–85 % of patients [53]. Systemic involvement can also occur

in the heart, bone marrow, liver, spleen, larynx, pharynx, kidney, skeletal muscle, ovary, and intestine [54]. Oral mucosal erosions may also be present. There is often an associated underlying lymphoproliferative disorder, myelodysplastic disorder, or a paraproteinemia [53]. Paraproteinemia is found in 80–90 % of cases, with IgG kappa monoclonal gammopathy being the most common [55]. Lymphoproliferative and myelodysplastic disorders include multiple myeloma, chronic lymphocytic leukemia, and Hodgkin's and non-Hodgkin's lymphoma. NXG can occur an average of 2.5 years prior to the onset of the myeloma or myelodysplastic disorder.

Investigation Recommendations

Diagnostic
Biopsy of skin or other affected organ
Evaluation
Laboratory evaluation: CBC with differential, comprehensive metabolic panel, lipid panel, serum protein electrophoresis, ESR and CRP
Bone marrow biopsy
Echocardiogram
CT or MRI
Ophthalmology examination

Diagnosis can be confirmed by skin biopsy or biopsy of another affected organ in addition to clinical presentation.

- Histology: Granulomatous inflammation located in the dermis with extension to the subcutaneous fat with large zones of necrobiotic collagen with characteristic cholesterol clefts with multinucleated and Touton giant cells and foreign body type cells with surrounding lymphocytic and plasma cell infiltrate.
- Laboratory evaluation looking for lymphoproliferative disorders, other organ involvement, bone marrow dysfunction, and paraproteinemia should be performed. This may include CBC with differential, comprehensive metabolic panel, lipid panel, serum electrophoresis, ESR and CRP (often significantly elevated) [56].
- Bone marrow biopsy may be indicated if there is a paraproteinemia or lab abnormalities. An echocardiogram should be done at baseline to determine whether there is cardiac involvement. Finally, imaging, including CT or MRI, may be indicated to evaluate the soft tissues, other organ involvement, or the orbit and ocular structures

Management Strategies

Patients with NXG should have regular continued follow-up to evaluate for systemic involvement and development of an underlying myelodysplastic syndrome, as these can occur an average of 2.5 years after the onset of the NXG. Follow-up should also include routine ophthalmologic evaluation. The course of NXG is chronic and indolent. The prognosis is generally good, with reports of 100 % patient survival at 10 years and 90 % survival at 15 years [57]. Prognosis of NXG largely depends on the extent of extracutaneous involvement.

There have been numerous reports of various treatments that have been tried, with variable outcomes. There are no consensus guidelines in regards to treatment due to the rarity of the disorder and lack of clinical and randomized control trials.

Table 10.9 Potential treatment options [58–61]

Topical corticosteroids	D[a]
Intralesional corticosteroids	D[a]
Ablative CO2 laser	E[a]
Surgical excision	D[a]
Topical nitrogen mustard (mechlorethamine)	E[a]
PUVA	E[a]
Localized radiation therapy	E[a]

[a]Based on adult data (due to lack of pediatric data)

For limited cutaneous disease potent topical corticosteroids have shown little effect, but intralesional corticosteroids have proved to be more effective [58]. Ablative laser treatment with carbon dioxide (CO2) laser has been trialed, in addition to surgical excision for small localized lesions [58, 59]. With laser and surgical excision there have been reported recurrence of lesions. Other therapies that have been tried for cutaneous lesions are topical nitrogen mustard (mechlorethamine) [60], phototherapy (Psoralen ultraviolet A [PUVA]), [61] and localized radiation therapy [58] with some reported success.

Often this disorder does not present only with cutaneous disease, therefore systemic therapies are needed to help control and treat the disease. Numerous medications have been tried, with variable results. These are beyond the scope of this chapter, and thus will be briefly change to listed here. The main classes of treatment are chemotherapy (chlorambucil, [62] low-dose melphalan, interferon alpha, methotrexate, cyclophosphamide); immune modulators (intravenous immunoglobulin, [63] azathioprine, and systemic corticosteroids); and then few reports of other medications (dapsone, [64] clofazimine, thalidomide, [65] lenalidomide, acitretin). Medically refractory cases have also been treated with extracorpeal photopheresis with IVIG [66]. If there is an underlying paraproteinemia or lymphoproliferative disorder (i.e. multiple myeloma) then treatment has been aimed at the underlying disorder with specific chemotherapy protocols, antimyeloma protocols, or plasmapheresis.

Generalized Eruptive Histiocytoma

Clinical Features

Benign Cephalic Histiocytosis (BCH) Generalized eruptive histiocytoma (GEH) is a rare subtype of non-Langerhans cell histiocytosis that is often seen in adults, but has been reported in children as young as 1 month of age [67]. Clinically, it is characterized by asymptomatic, self-healing, recurrent crops of multiple, widespread, small tan to red-brown papules that often present symmetrically on the face, trunk, and proximal extremities. The mucous membranes are rarely involved, and the viscera are spared. Lesions appear in crops and subside spontaneously. GEH is thought to lie along a spectrum with other histiocytic disorders, and can represent the early undifferentiated stages of other non-Langerhans cell histiocytoses that share clinical and histologic characteristics, such as xanthoma disseminatum, [68] juvenile or adult xanthogranuloma, multicentric reticulohistiocytosis, and progressive nodular histiocytosis [69]. Many of these histiocytoses can have systemic involvement and can be more serious.

Investigation Recommendations

Diagnostic
Skin biopsy for:
Histopathology
Immunohistochemistry
Electron microscopy

Diagnosis can be made by skin biopsy in conjunction with history and clinical appearance. There can be overlap between the various histiocytic conditions. Some features that may help differentiate GEH from other more serious histiocytoses are as follows:

- Histology: Dense, monomorphic histiocytic infiltrate within the upper and mid dermis with a normal epidermis. Histiocytic cells have vacuolated cytoplasm. Absence of foamy histiocytes and touton cells.
- Immunohistochemical stains: Negative CD1a and S100 and positive Factor XIIIa and CD68.
- Electron microscopy: Reveals various nonspecific cytoplasmic organelles such as comma-shaped or worm like bodies, laminated body, dense bodies, dark lipid bodies, myeloid bodies, and popcorn or eyeball bodies. Absence of Birbeck granules.

Management Strategies

No treatment is necessary for this disorder as it is self-limited and there is no systemic involvement reported. Since there can be significant overlap with other more severe forms of non-Langerhans cell histiocytoses that can have systemic involvement, clinical follow-up is warranted to monitor for any development of systemic signs or symptoms or transformation of the disease. The course of GEH has been noted to last anywhere from 1 month to 12 years, with either complete disappearance of lesions, or residual hyperpigmented brown macules. Potential treatment options have been reported to hasten resolution and minimize recurrence.

Table 10.10 Potential treatment options [70, 71]

PUVA	E[a]
Isotretinoin	E[a]

[a]Based on adult data (due to lack of pediatric data)

There have been case reports in the literature of use of PUVA [70] and isotretinoin [71] in adults with GEH. PUVA therapy showed partial regression of lesions after 10 treatments, and complete resolution without recurrence after 20 treatment sessions. Isotretinoin use showed complete resolution of lesions for 8 months, but then recurrence of lesions after this period.

Progressive Nodular Histiocytoma

Clinical Features

Progressive nodular histiocytoma (PNH), also known as progressive nodular histiocytosis, is an extremely rare mucocutaneous, non-Langerhans cell histiocytosis that occurs in normolipemic individuals with no abnormalities in lipid metabolism. Onset in both childhood and adulthood have been described. PNH does not resolve spontaneously, and has an unremitting course. Clinically, it is characterized by the progressive appearance of numerous lesions of two distinct morphologies, one being widespread yellow-brown to yellow-pink papules ranging from 2 to 10 mm in size, presenting throughout the body, but sparing the flexural areas. The second morphology is large red-brown subcutaneous nodules ranging from 10 to 50 mm in size, with overlying telangiectasias often located on the trunk and/or over areas of pressure [72]. Mucosal involvement of the conjunctiva, oral mucosa, pharynx, and larynx [73] can also occur. Cutaneous lesions are benign, but can be significantly disfiguring, painful, and pruritic. Ulceration and bleeding of the papules and nodules can occur. Lesions of PNH most commonly affect the face, where they are so densely grouped that they can result in the typical appearance of leonine facies and can cause ectropion. Overall, patients are generally in good health, there is no joint involvement, and very rarely any systemic involvement [74].

Investigation Recommendations

Diagnostic
Skin biopsy for:
Histopathology
Immunohistochemistry
Electron microscopy

Diagnosis can be made by skin biopsy in conjunction with history and clinical appearance.

- Histology: Histiocytic infiltrate within the dermis with spindle-cell appearance and vacuolated clear cytoplasm, Touton-like giant cells, lymphocytes, plasma cells, and 'collagen trapping,' which is a result of splaying of collagen bundles at edge of the infiltrate. In older lesions there is more fibrosis present and absence of Touton-like giant cells.
- Immunohistochemical staining: Negative CD1a and S100 and positive Factor XIIIa and CD68
- Electron microscopy: Histiocytes with large indented nuclei and scant cytoplasm. Cytoplasm is rich with endoplasmic reticulum, Golgi bodies, lysosomes, and comma shaped bodies. Absence of Birbeck granules.

Management Strategies

Table 10.11 First line treatment options [75, 76]

Surgical excision	E

The course of PNH is progressive and disfiguring. Surgical excision of large, disfiguring, or symptomatic nodules is the best therapeutic option for individual lesions, and in many cases did not show evidence of recurrence [75]. Surgical excision has been recommended in at least one article to be the only treatment option available, [76] as none of the other treatments reported in case reports have been shown to be effective.

Carbon dioxide laser has been reported in one case to remove cutaneous lesions, but showed recurrence within the scars [74]. Medical treatments that have been tried include intralesional and systemic corticosteroids, [77, 78] cyclophosphamide, [79] and vincristine, [78] but these treatments were not curative and did not alter the course of disease.

Multicentric Reticulohistiocytosis

Clinical Features

Multicentric reticulohistiocytosis (MCRH) is a rare non-Langerhans cell histiocytosis with systemic involvement. It is seen predominantly in adults, primarily in middle-aged white women, with rare pediatric cases reported [80, 81]. The hallmark features of this disorder are cutaneous lesions and arthritis. Cutaneous lesions present as firm skin-colored to red-brown papules and nodules most often located on the hands, and face (lips, ears, and nose). Along the cuticle there can be a chain of papules referred to as the "coral bead" sign, which may cause nail dystrophy. Nodules over extensor surfaces of the arms, elbows, and knees can also occur, resembling rheumatoid nodules. Ulceration of cutaneous lesions can occur. Development of leonine facies with cartilaginous destruction can also occur.

Approximately one-third of patients have hypercholesterolemia and xanthelasma. Mucous membranes are involved in up to 50 % of patients with involvement of the lips, buccal mucosa, nasopharynx, larynx, tongue, palate, gingiva, and sclera. Joint involvement is the presenting sign in the majority of cases, and can be rapidly progressive and destructive leading to long-term disability. Any joint can be involved, often with synovitis due to infiltration of histiocytes. Joint involvement tends to be symmetric, inflammatory, and polyarticular. The joints of the hands and wrists are most commonly affected, with the DIP joint being most affected [82]. Viscera may also be involved. Including bone, muscle, lymph nodes, liver, myocardium, pericardium, lungs, pleura, and stomach.

Systemic symptoms of weight loss and fever can occur in approximately one-third of patients. There are numerous associated conditions seen with MCRH (Table 10.11) [83]. Twenty-five percent of cases have an associated malignancy that can occur after or concomitantly with cutaneous lesions. There is no predominant type of malignancy reported in association with MCRH. About 15 % of patients have associated autoimmune disorder and an underlying myopathy has also been described in a few patients.

Table 10.12 Conditions associated with multicentric reticulohistiocytosis

Autoimmune disease	Vitiligo, primary biliary cirrhosis, systemic sclerosis, systemic lupus erythematous, Sjorgren disease, dermatomyositis, hypothyroidism, celiac disease
Malignancy	Carcinoma (breast, ovary, endometrium, stomach, cervix, pleura, lung, ovary, colon, pancreas, penile, primary undetected)
	Mesothelioma, melanoma, sarcoma, lymphoma, leukemia
Pregnancy	Increased risk of preeclampsia
Infection	Tuberculosis
Other	Hyperlipidemia, diabetes mellitus, vasculitis, thyroid disease, ulcerative colitis

Investigation Recommendations

Diagnostic
Skin or synovial tissue sent for:
Histopathology
Immunohistochemistry
Laboratory evaluation: rheumatoid factor, anti-CCP, ANA, ESR, CRP, CBC
Hand radiographs
Age-appropriate malignancy screen
Screening for underlying autoimmune disorder with thorough physical examination, review of symptoms, and laboratory evaluation
Intradermal PPD and/or quantiferon gold

Diagnosis can be made by skin or synovial tissue biopsy in addition to clinical presentation. Cutaneous lesions are not always present at time of joint involvement. When they are, and biopsy is performed, findings include:

- Histology: Histiocytic infiltrate in the mid dermis with presence of giant cells and polymorphous inflammatory infiltrate of lymphocytes, neutrophils, eosinophils, and plasma cells. Histiocytes have abundant eosinophilic granular cytoplasm or a "ground glass" appearance. The epidermis is thinned and there is a presence of a Grenz zone, separation of epidermis from dermis by a narrow zone of collagen.
- Immunohistochemical stains: Negative CD1a and S100 and positive for CD68. Positive for osteoclast markers of tartrate-resistant acid phosphatase (TRAP) and cathepsin K.

Radiographs of hands should be performed to evaluate for arthritis, especially in symptomatic patients, but can also be considered for asymptomatic patients as well. Characteristic changes include marginal erosions and joint space narrowing in early cases that can progress to telescopic changes of phalangeal resorption or DIP and PIP joint destruction called "opera glass deformity." There is no osteopenia, osteoporosis, or periosteal new bone formation, as seen in other forms of inflammatory arthritis.

There are no specific laboratory findings for MCRH. Rheumatoid factor, anti-CCP, and ANA often negative. ESR or CRP elevated in 50 % of cases. Normocytic anemia is seen in some cases [84].

Given the potential underlying associations with MCRH, age-appropriate malignancy screening should be performed, as should screening for an underlying autoimmune disorder, with thorough physical examination, review of symptoms, and laboratory evaluations if needed. Finally, patients should be screened for tuberculosis infection with intradermal PPD and/or Quantiferon gold.

Management Strategies

MCRH can have a relapsing and remitting course and may regress spontaneously over 6–8 years, but for patients with articular involvement, the joint destruction is permanent and nonreversible. Eleven percent to 45 % of patients progress to severe arthritis. Although there is no consensus on how to treat MCRH due to the fact that the same treatment produces variable and inconsistent results, there is consensus to treat early and aggressively to avoid the permanent disfiguring and debilitating long-term sequelae of the disease. Numerous treatment modalities have been tried as monotherapy or in combination. Prior to starting treatments, screening for an underlying malignancy, infection (e.g. tuberculosis), or autoimmune condition should be completed, as they could be masked or worsened by immune suppressing therapies. There have also been reports that treatment of the underlying malignancy can result in improvement in skin and joint symptoms of MCRH.

Cutaneous Disease

Table 10.13 Potential treatment options [85, 89]

Topical nitrogen mustard	E[a]
PUVA	E[a]
Methotrexate	E
Hydroxychloroquine	E[a]
TNF-alpha inhibitors: Entanercept, Adalimumab, Infliximab	E (infliximab)
	E[a] (etanercept, adalimumab)
Bisphosphonates: Zoledronate, Pamidronate, Aledronate	E[a]

[a]Based on adult data (due to lack of pediatric data)

For cutaneous disease, treatment is not necessarily needed as remission does occur, but for symptomatic or disfiguring lesions, treatment can be pursued. Therapeutic options that can be empirically tried include topical nitrogen mustard, PUVA, low-dose methotrexate, hydroxychloroquine, TNF alpha inhibitors, and bisphosphonates. In addition, sunscreen and sun-protective clothing have been recommended to prevent koebnerization of lesions via ultraviolet light.

Joint Disease

Table 10.14 First-line therapies [80, 85–87, 89]

Corticosteroids	
Systemic	E
Intraarticular	E[a]
NSAIDs	E
Bisphosphonates: Zoledronate, pamidronate, aledronate	E[a]

[a]Based on adult data (due to lack of pediatric data)

For mild joint disease, many reports have started with a combination of corticosteroids and NSAIDS. For moderate or severe joint disease, DMARDs, bisphosphonates, and biologic agents have been used as monotherapy, or more often in various combinations and sometimes with corticosteroids [86]. Bisphosphonates have been suggested in MCRH due to the infiltrating cells having osteoclastic activity [87].

Table 10.15 Second-line therapies [88, 89]

Methotrexate	E
Azathioprine	E[a]
Cyclosporine	E[a]
Anti-TNF alpha inhibitors: Entanercept, adalimumab, infliximab	E (infliximab) E[a] (etanercept, adalimumab)
Hydroxychloroqine	E[a]
Cyclophosphamide	E[a]

[a]Based on adult data (due to lack of pediatric data)

Though medication results have been inconsistent, there are trends in which medications seem to be most effective: prednisone, methotrexate, azathioprine, cyclosporine, bisphosphonates, and anti-TNF medications [88]. The combination and sequence of therapies still remains to be an individual and empiric choice.

Table 10.16 Third-line therapies [90–92]

Arthrodesis	E[a]
Tocilizumab	E[a]
Anakinra	E[a]

[a]Based on adult data (due to lack of pediatric data)

More recently, the roles of cytokine-mediated therapy have been discussed, given the fact that skin and synovial fluid has shown overexpression of interleukin 6, TNFa, and interleukin 1B. With the use of anti-TNF medications there have been reports that if a particular anti-TNF medication is ineffective, switching to another anti-TNF may lead to dramatic improvement in symptoms. There has been one case report of use of tocilizumab, [90] which targets IL-6, and a case report of use of Anakinra, an IL-1 receptor antagonist. Anakinra was shown to stop the development of new lesions, aid in regression of old lesions, complete remission of disease at 12 months, and no relapse after 2-year follow-up [91]. For medically refractory cases, there has been on case report of use of arthrodesis of the MCP, DIP, and PIP joints. Arthrodesis has shown to increase range of motion and halt disease progression [92].

Sinus Histiocytosis with Massive LAD (Rosai-Dorfman Disease)

Clinical Features

Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease, is a rare disorder that occurs predominantly in children. It has a relapsing and remitting course and is characterized by reactive proliferation of histiocytes in the sinuses of lymph nodes. Patients present with massive lymphadenopathy, most often in the head and neck region, which can be accompanied by fevers, leukocytosis, anemia, elevated ESR, and polyclonal hypergammaglobulinemia. Lymphadenopathy presents as large, painless, and bilateral, and is most common in the cervical region. Extranodal involvement can occur, with the skin being the most common site, but also can involve the kidney, adrenal gland, testes, bone, cranium, and meninges [93]. Some patients can present with cutaneous-only disease, which occurs in about 3% of cases, and is more likely to occur in adults. Cutaneous lesions occur in about 10% of patients, and present as a few to diffuse red to red-brown papules, nodules, or macules [83]. Large annular lesions that can look like granuloma annulare have also been reported.

Investigation Recommendations

Diagnosis
Biopsy of affected organ for:
Histopathology
Immunohistochemistry
Electron microscopy
Laboratory evaluation: CBC, ESR, quantitative immunoglobulins
Viral serologies for: EBV, HHV6, HHV8, CMV, HIV
Imaging studies: CT, MRI, ultrasound, radionuclide bone scan

There is no protocol for the evaluation and management of SHML. Given the broad differential, including diagnoses with significant morbidity would consider thorough physical examination, laboratory evaluations, imaging, and biopsy to confirm diagnosis.

Diagnosis is confirmed by histology of the affected organ in addition to physical exam. Cutaneous lesions are not always present.

- Histology: superficial and deep perivascular infiltrate of lymphocytes and plasma cells, with diffuse nodular infiltration of foamy histiocytes in the dermis. Emperipolesis, finding of intact lymphocytes within the cytoplasm of the histiocytic cells, is present and a specific finding for SHML. Histologic findings can be more specific in lymph nodes or in other involved organs than the skin.
- Immunohistochemical stains: positive for CD4, Factor XIIIa, and S-100.
- Electron microscopy: absence of Birbeck granules.

Laboratory studies are recommended to evaluate for leukocytosis, anemia, elevated ESR, and polyclonal hypergammaglobuliemia. SHML has been associated with

bloodline malignancies and with viral infections or reactivation of viruses, therefore can consider screening for Epstein-Barr virus (EBV), human herpesvirus-6 (HHV6), human herpesvirus-8 (HHV8), human immunodeficiency virus (HIV), and cytomegalovirus (CMV). Imaging studies include CT, MRI, ultrasound, and/or radionuclide bone scan.

Management Strategies

SHML has a usually benign clinical course, with relapsing and remitting course followed by eventual spontaneous resolution [94]. Treatment is usually not needed, unless there is compromise or compression of a vital organ or structure, or if the disease becomes symptomatic [94, 95].

Table 10.17 Potential treatment options [95–106]

Cryotherapy	E[a]
Topical corticosteroids	E[a]
Intralesional corticosteroids	E[a]
Surgery	E
Localized irradiation	E
Systemic corticosteroids	E[a]
Methotrexate	E
Thalidomide	E[a]

[a]Based on adult data (due to lack of pediatric data)

For cutaneous disease only, multiple therapy modalities have been tried with variable success including cryotherapy, [96] topical corticosteroids, [97] and intralesional corticosteroids [98, 99]. Surgery has been used for resection or debulking of lesions that are accessible and have become symptomatic; localized irradiation has also be used in similar circumstances [97, 100]. Medical treatments that have been used include systemic corticosteroids that have shown to be helpful in many cases, but their effect seems to wane after cessation of therapy [95, 101]. In some cases, methotrexate has been added to corticosteroids for improved effect, and has also been used as monotherapy for successful treatment of some cases of SHML [102–104]. Thalidomide has also been reported to be helpful in a few cases of SHML [105]. Radiation, chemotherapy, and interferon have also been used with variable success and for more severe or medically refractory cases. There have been case reports of patients having both SHML and lymphoma, [106] therefore, some regimens of chemotherapy that have been used have been those that have been used for Hodgkin's lymphoma.

Leukemia Cutis

Clinical Features

Leukemia cutis refers to the direct infiltration of the epidermis, dermis, or subcutis with neoplastic leukocytes or their precursors. Leukemia cutis can be seen with any type of leukemia, but is more common with leukemias of myeloid origin (3–30 % of patients), specifically those of monocytic differentiation rather than lymphoblastic origin (1–3 %) [107]. In congenital leukemia, defined as leukemia that is present at birth or within the first month of life, leukemia cutis is present in 25–30 % of cases [108]. Clinically, patients with leukemia cutis may present with single or multiple flesh-colored, erythematous, red-brown, or violaceous papules, nodules, or plaques of varying size that often are purpuric or hemorrhagic [109]. Other clinical presentations of leukemia cutis that have been described are eccyhmoses, petechiae, bullae, urticarial lesions, panniculitis resembling erythema nodosum, eczematous eruption, [110] seborrheic dermatitis like presentation, erythroderma, and mastocytoma-like lesions with positive Darier's sign [111]. The leukemic infiltrate tends to occur at sites of previous or current skin trauma, inflammation, or cutaneous infection. The legs are most commonly involved, followed by the arms, back, chest, scalp, and face [112].

Other possible clinical findings include gingival hypertrophy and oral petechiae, leonine facies, and penile or scrotal ulcers. Most cases of leukemia cutis occur after the diagnosis of systemic leukemia has been made, and in about 30 % of cases, concomitant cutaneous and systemic involvement has been seen. Less commonly, the presentation of leukemia cutis can precede the development of leukemia, sometimes by years, and this phenomenon is termed aleukemic leukemia cutis [113]. Aleukemic leukemia cutis occur predominantly in patients with AML, and are often widespread and papulonodular in morphology [114].

Congenital leukemia cutis presents as multiple red-brown to violaceous papules or nodules that can be referred to as "blueberry muffin" baby due to malignant infiltration of the skin or causes of extramedullary hematopoiesis. Patients that have leukemoid reactions or transient myeloproliferative disease can also present clinically with a pustular or vesiculopustular skin eruption that self resolves as the hematologic disorder resolves, but there are cases where these patients can go on to develop true leukemia. Therefore, long-term follow-up is warranted in these patients.

Investigation Recommendations

Diagnostic
Skin biopsy for:
Histopathology
Immunophenotyping
Complete blood count with differential
Peripheral blood smear with immunophenotyping
Bone marrow aspiration

Diagnosis can be made by skin biopsy with immunophenotyping in correlation with examination of peripheral blood and bone marrow aspirates. Skin biopsy reveals a nodular/diffuse pleomorphic mononuclear cell infiltrate, often with perivascaular and/or periadnexal involvement located predominantly within the dermis and subcutis, with sparing of the upper papillary dermis (Grenz zone). There is often single arraying of neoplastic cells between collagen bundles and presence of atypical mitotic figures. Histology alone cannot determine lineage of leukemia, therefore immunophenotyping is needed. A complete blood count with differential and peripheral blood smear with immunophenotyping and bone marrow aspirate are also essential parts of the work-up of leukemia cutis.

Management Strategies

In general, leukemia cutis is often associated with a poor prognosis. One study reported that 88 % of patients with leukemia cutis died within 1 year of diagnosis [109]. The exception to this is congenital leukemia cutis, where prognosis is also poor, but involvement of the skin does not tend to worsen prognosis. There have been cases of congenital leukemia cutis with spontaneous remission, [115, 116] often without involvement of the blood or bone marrow. In these cases late relapses have been reported, therefore long-term follow-up is warranted. Leukemia cutis is a cutaneous manifestation of an underlying leukemia or myeloproliferative disorder. Therefore, treatment is often an intensive multiagent systemic chemotherapy aimed at the specific type of leukemia. Use of radiation therapy and hematopoietic stem cell transplantation can also be considered, based of type and cytogenetic profile of the leukemia. Patients with this diagnosis should be immediately referred to a pediatric hematology/oncology specialist, if one does not already follow them.

Cutaneous T-Cell Lymphomas

Clinical Features

Primary cutaneous T-cell lymphomas (CTCL) are rare diagnoses within the pediatric population, representing approximately 1 case per 1,000,000 person years [117]. CTCL is composed of a heterogeneous group of diseases. Mycosis fungoides (MF), which accounts for more than half of all cases, is the most commonly encountered condition. Patients with MF typically present with pruritic, erythematous scaling patches, often with associated poikilodermatous change, and a distribution that favors sun-protected skin such as the buttock, flanks, thighs, and peri-axillary areas. Children have a greater tendency than adults to present with hypopigmented lesions [118, 119]. Numerous series have shown that children are also more likely to present with early patch stage MF, which is associated with an excellent prognosis, and a mortality rate comparable to the general population [120, 121].

Rarely, the lesions can progress to plaque stage with the development of infiltrated, erythematous plaques, and to a tumor stage characterized by nodules and ulcerating tumors. Sezary syndrome is an aggressive form of MF characterized by erythroderma and the presence of circulating peripheral malignant T-cells (Sezary cells) which is extremely uncommon in children. Other variants of MF include pagetoid reticulosis (Worringer-Kolopp disease), which presents as a solitary scaling patch or plaque of the distal extremities; and granulomatous slack skin disease, which demonstrates characteristic erythematous cutis-laxa-like changes of the skin folds. The latter can be associated with the diagnosis of a second lymphoma. In general, MF typically takes an indolent course in children, with diagnosis delayed due to its mimicry of common dermatoses such as atopic dermatitis or seborrheic dermatitis. Diagnosis is made through clinical and histopathologic correlation, with skin biopsy demonstrating epidermotropic, atypical lymphocytes in the setting of a supportive clinical presentation.

Primary cutaneous CD30+ lymphoproliferative disorders (CD30+ LPD) represent the other most significant group of CTCL diagnoses, accounting for nearly 25 % of cases [121]. Primary cutaneous anaplastic large cell lymphoma (PALCL) presents as solitary, large ulcerated tumors and nodules. Biopsy of the skin lesions demonstrate large, pleomorphic, anaplastic cells with >75 % expressing CD30. PALCL is associated with a good prognosis, with 5 to year survival ranging from 76 % to 96 % [122]. Lymphomatoid papulosis

(LYP) is a CD30+ LPD that typically presents with recurrent crops of papules and nodules that heal over weeks to months. It is characterized by an indolent course lasting years to decades. In one series, the median age of pediatric patients with LYP was 12 years old, though it has been reported in a child as young as 11 months old [121]. LYP has no effect on mortality risk, but patients with the condition are at higher risk of developing a second cutaneous or lymphoid malignancy like MF, cutaneous or nodal ALCL, or Hodgkins lymphoma.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) most commonly occurs around ages 12–16 years in children and presents with subcutaneous nodules suggestive of a panniculitis [121]. Biopsy demonstrates either an alpha-beta T-cell receptor phenotype or gamma-delta phenotype. SPTCL expressing the latter is associated with a more aggressive course, while alpha-beta disease is typically more indolent. Patients who experience systemic symptoms such as fevers, fatigue, and weight loss may ultimately develop a hemophagocytic syndrome, which is rapidly progressive.

Management Strategies

As children account for only 4–11 % of all CTCL cases, [120] there are few large studies available to guide management of pediatric CTCL patients. Treatments are largely extrapolated from adult studies. Referral to a dedicated CTCL clinic is helpful for confirmation of the diagnosis, staging, and access to investigational protocols. Treatment of CTCL is dependent upon staging, which involves assessing the involvement of the skin, lymph nodes, viscera, and blood. The National Comprehensive Cancer Network (http://www.nccn.org) provides updated guidelines for TNMB staging of MF, CD30+ LPDs, and SPTCL, and can be a useful resource.

Given that the majority of MF patients present with early patch stage disease, skin-directed therapy is often appropriate. The mainstay of treatment is currently moderate- to high-potency topical steroids. In more refractory disease, nitrogen mustard topicals, narrowband UVB, and PUVA have been shown to be effective. Surgical excision and local radiation may be appropriate for a solitary nodule or tumor.

For more aggressive cases of CTCL, systemic therapies such as the oral retinoid bexarotene, methotrexate, extracorporeal photophoresis, electron beam radiation, systemic steroids, multi-agent chemotherapy, and alpha and gamma interferon can be considered, though involvement of a dedicated CTCL center is strongly recommended in such cases. These treatments are listed for interest, though for the purposes of this text, emphasis will be placed on skin-directed therapies.

Investigations Recommended

Diagnostic
Biopsy required for diagnosis, often multiple
TCR rearrangement studies of biopsy specimens to evaluate for clonality
Sezary cell count, assessment of peripheral T-cell populations by flow cytometry, peripheral blood clonality studies, Chest XR, PET-CT, lymph node biopsies as indicated based on clinical concern for extracutaneous involvement
CBC, CMP, lactate dehydrogenase (LDH). Consider HTLV-1/2 or HIV testing if appropriate

Diagnosis is challenging, and typically requires multiple biopsies, preferably of lesions that have not been treated by topical steroids for more than 4 weeks. Histopathologic features can be subtle, and diagnosis can be aided by TCR rearrangement studies such as PCR or high throughput sequencing (if available) in an attempt to identify a dominant clone that is ideally present in multiple tissue specimens. There are currently no standard recommendations available regarding baseline studies for CTCL in pediatric patients, though CBC, CMP, and LDH are appropriate. HIV and HTLV-1/2 serological testing can be considered in appropriate patients. In patients with lymphadenopathy or exam or laboratory findings concerning for extracutaneous systemic involvement, Sezary cell counts, assessment of circulating T cells and clonality, PET-CT scan, and lymph node biopsy should be considered.

Table 10.18 First line therapies [118, 119, 123–125]

Topical steroids, moderate and high potency	B[a]/C
Narrow-band UVB (nbUVB)	D
Topical and oral antimicrobials	D

[a]Based on adult data (used due to lack of pediatric data)

Moderate to high potency topical steroids with twice daily application are the mainstay for early patch stage MF, and have been shown to achieve a 94 % total response rate in stage I disease in a predominantly adult population [123]. For more diffuse involvement, or if compliance is a concern, phototherapy with narrowband UVB has also been repeatedly reported to be beneficial for early stage pediatric MF [118, 124]. Given that pediatric MF tends to have a frequently relapsing course, cumulative UV exposure must be weighed in the decision to treat. Narrowband UVB also led to improvement in six of seven treated patients with LYP in one series [125]. Patients with erythrodermic skin involvement tend to tolerate phototherapy poorly, and alternate therapies should be sought in such cases. Frequently culturing any crusted, eroded, or ulcerated lesions and treating any active staphylococcal infection can improve lesion clearance as *S. aureus* superantigens can trigger T cell proliferation [119].

Table 10.19 Second line therapies [126–128]

Nitrogen mustard topicals	A[a]/D
Mechlorethamine hydrochloride ointment (0.01–0.04 %) applied twice daily, compounded	
Mechlorethamine hydrochloride 0.02 % gel	
Surgical excision	D
Local radiation therapy	D

[a]Based on adult data (used due to lack of pediatric data)

In patients for whom topical steroids or nbUVB prove ineffective, nitrogen mustard topicals can be considered. Application of compounded mechlorethamine hydrochloride ointment (ranging in strength from 0.01 to 0.04 %) applied twice daily achieved a total response rate of 93 % in T1 disease, and 72 % in T2 disease in a predominantly adult trial population [126]. Approximately 10 % of patients experienced skin hypersensitivity reactions, which was an improvement over older aqueous formulations. The six pediatric patients in the study were routinely monitored with CBC and CMPs, and there was no evidence of systemic absorption or toxicity related to the nitrogen mustard. More recently, mechlorethamine hydrochloride 0.02 % gel has been shown to be non-inferior to compounded 0.02 % ointment in an adult trial, with a similar toxicity profile [127]. The decision to treat with nitrogen mustard must be weighed against the relatively higher rate of skin hypersensitivity reaction, contact dermatitis, and theoretical risk of skin carcinogenesis when compared to topical steroids. For solitary tumors in PALCL, successful treatment with surgical excision of the lesion with or without local radiation has been reported [128].

Table 10.20 Third line therapies [118, 129]

Psoralen plus UVA (PUVA)	D
Photodynamic therapy	E

For children with MF refractory to phototherapy and topicals, psoralen plus UVA (PUVA) has been reported to be effective [129]. PUVA treatments can be complicated by phototoxic erythema, nausea, and itch, and extensive prolonged use can lead to increased risk of skin cancer. Methylamino-levulinic photodynamic therapy has also been effective in one case of a child with a unilesional plaque of MF that was refractory to topical steroids, UVA1, and topical PUVA [118]. Other treatments that have been successfully used in adults and may be considered in children with severe or refractory disease include methotrexate, the oral retinoid bexarotene, combination chemotherapy, local and total skin electron beam radiation, alpha and gamma interferon, and others. Safety and efficacy data in pediatric populations for these treatments are scarce, and again, referral to a dedicated CTCL clinic is appropriate once these treatments are being considered.

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Generalized Eruptive Histiocytoma

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Disorders of Pigmentation

11

Candrice Heath and Nanette Silverberg

Introduction

The skin contains approximately 1,000 melanocytes per mm^2 which doesn't vary much by race [1]. Melanocytes produce melanin, the human pigment, storing the melanin in packets called melanosomes. Pigment production is a complex multi-step process involving enzymes and co-factors. Melanosomes are released from the dendritic melanocyte and taken up by keratinocytes in the epidermis. There are approximately 36 keratinocytes that are supplied by each melanocyte. Because of the complexity of pigment production in the skin, alterations in pigmentation occur frequently. These disorders range from congenital disorders with localized to generalized alterations in pigment production in isolation or associated with other anomalies to acquired disorders of pigmentation which can occur locally or generally, depending on the causative factors involved.

This chapter provides an overview of the disorders of pigmentation that are most commonly seen by pediatricians and highlights those conditions specifically requiring additional laboratory screening. The chapter is divided into four sections: congenital localized alterations in pigmentation, congenital generalized alterations in pigmentation, acquired localized alterations in pigmentation and acquired generalized alterations in pigmentation. The first two categories are separated from the latter two by onset before the age of 2 years, in most cases [2].

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Congenital Localized Alterations in Pigmentation

The congenital localized alterations in pigmentation are generally noted in the first 2 years of life. Although some are present at birth, some of the conditions do not become notable until pigmentation has developed more fully. Pigmentary disorders may involve excess (hyperpigmentation), reduced (hypopigmentation), or no (depigmentation) pigment locally. Many of these conditions are diagnosed clinically and do not require biopsy for confirmation. Wood's lamp evaluation can demonstrate enhancement with localized loss of pigmentation. Biopsy can be performed in cases where diagnosis is not clear to identify number and placement of pigment cells and/or associated inflammation.

Mongolian Spot

For diagnosis
Clinical evaluation
Biopsy rarely needed for confirmation
Genetic screen for mucopolysaccharidoses in extensive cases
For treatment
Tincture of time—most lesions resolve by age 6 years

The most common hyperpigmentation is the Mongolian spot (Fig. 11.1), which can be noted at birth or shortly thereafter [3]. The Mongolian spot is a bluish coloration noted with immature pigment cell placement in the skin, usually in infants of color who are full term and full-size. The bluish color comes from the Tyndall effect, an optical alteration noted when melanocytes are in the dermis. The leading location is the sacrum and gluteal region, but eccentric placement can be seen anywhere on the body. The Mongolian spot is seen in 9.5–18.9 % of Caucasian infants, 46 % of

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Hispanic/Latino infants, 62.2 % of Indian infants, 83.6 % of East Asians, and 96 % of Black newborns [4, 5]. Extensive lesions can be associated with mucopolysaccharidoses and may need genetic screen [6].

Most Mongolian spots will disappear with time, and no therapy is needed [7].

Café au Lait Macules

Café au lait macules (Fig. 11.1) are common localized areas of excess pigmentation that are generally round or oval, but may follow a segmental pattern. Although the classic lesion seen in light-skinned individuals or in association with neurofibromatosis is the color of light coffee, lesions can vary from nearly imperceptible in Caucasian infants to dark brown in Black children. It is estimated that 22 % of Black children and 11 % of Caucasian children have a solitary lesion. The lesions are most concerning when found in larger number [8].

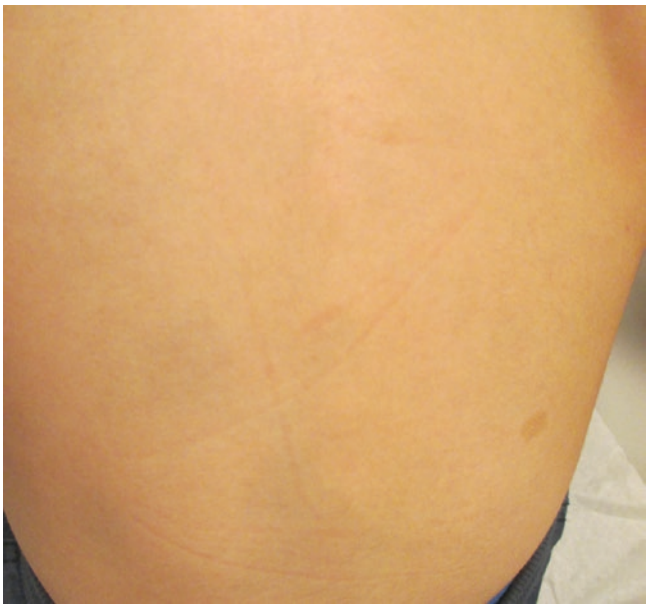

Fig. 11.1 Mongolian spot on the lower back of an 8-year-old Asian boy with a solitary café au lait macule off to the right side of the back

The presence of six or more café au lait macules of 5 mm or greater in childhood or 1.5 cm in adulthood is a criterion for the diagnosis of neurofibromatosis type I, a multi-system autosomal dominant genetic disorder associated with tumor development [9]. Of 44 children in a neurofibromatosis type I clinic who had 6 or more café au lait at presentation, 34 went on to meet criteria for the disease—32 of whom met criteria by 72 months [10]. The vast majority of patients will be diagnosed by age 8 years, and 46 % of spontaneous cases by age 1 year [9].

Large segmental café au lait over the trunk may be associated with McCune Albright Disease seen with macrocephaly and precocious puberty. In the setting of multiple café au lait macules, clinical evaluation for the other criteria of neurofibromatosis includes an ophthalmology examination every 6 months, dermatologic evaluation every 6 months, and neurological, orthopedic and/or genetic screen where appropriate. Criteria for neurofibromatosis type 1 and the average timing of onset are listed in Table 11.1 [9].

For diagnosis
Clinical confirmation/ examination (benign vs. in the setting of a systemic genetic syndrome)
Biopsy in atypical lesions may help
Full body skin examination every 6 months
Ophthalmology examination every 6 months

Table 11.1 Diagnostic criteria for neurofibromatosis type I

Criterion	Clinical appearance	Timing of onset
Café au lait	Six or more tan to brown ovoid macules and patches	Most children will meet this criteria by age 6 years
	>5 mm childhood	
	>1.5 cm adulthood	
Optic nerve gliomas	Tumor of the optic nerve visualized on dilated examination	10 % by age 3 years
Lisch nodules (smooth muscle hamartomas of the iris)	Pigmented papules on the iris visualized with slit lamp examination	Age 6 or later; 68 % by age 10 years
Osseous lesions	Pseudoarthrosis, sphenoid wing dysplasia, and dysplastic vertebrae seen on x-rays	30 % at birth
Relative	First degree relative with neurofibromatosis	About half are sporadic and half have a first-degree relative
Neurofibromas	Two or more neurofibromas, which are soft tumors that indent with pressure, or plexiform neuroma, which is described as a bag of worms	Meet criteria:
		10 % at birth
		48 % by age 10 years
		84 % of 20 year olds
Freckling	Pinpoint tan macules of the axillary and or inguinal folds	90 % by age 6 years; rare after age 7 years

For treatment
Laser may reduce appearance in some cases
Excision of tumors that are causing functional impairment in the setting of neurofibromatosis type 1
Developmental and neurological evaluation in multiple lesions
Ophthalmic examination every 6 months
For treatment
No therapy needed. Most cases cause limited cosmetic disfigurement
Cosmetic camouflage

Nevus Depigmentosus (Fig. 11.2)

This misnomer represents a localized reduction in pigmentation seen at birth in children of Asian, Indian, and Hispanic/Latino descent [11]. The areas represent a localized increase in the ratio of pheomelanin to eumelanin and reduced melanosomes (melanin storage organelles). Fifty percent will be seen at birth and almost all lesions are noted by age 1 year.

Wood's lamp examination will demonstrate partial highlighting and better define lesions. Nevus depigmentosus needs no therapy, but judicious sun protection to avoid enhancement of the color differential from normal skin is cosmetically beneficial [12].

For diagnosis
Wood's lamp equivocal
Biopsy for hematoxylin and eosin stain or electron microscopy
In cases of multiple lesions, full-body exam every 6 months with Wood's lamp for highlighting

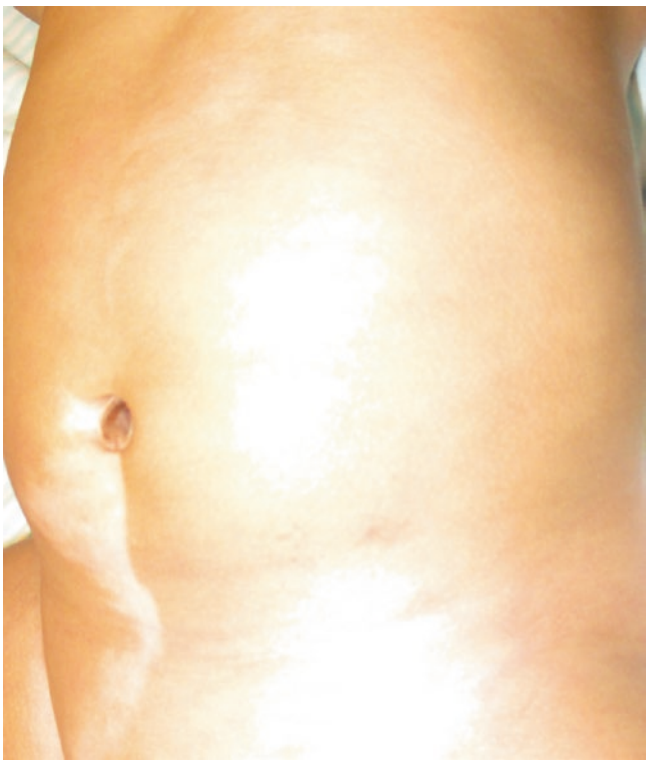

Fig. 11.2 Nevus depigmentosus on the lower abdomen in a Hispanic male infant

Tuberous Sclerosis

Multiple areas of hypopigmentation can be noted in systemic genetic disease such as tuberous sclerosis, presenting early on with confetti macules and thumbprint macules, and later with the botanically reminiscent ash leaf macules. The current criteria for tuberous sclerosis are listed in Table 11.2. Diagnosis requires ophthalmologic, neurologic, and genetic screens accompanied by frequent dermatologic follow-up (every 6 months) and imaging of the head, which may identify UBOs (unidentified bright objects) or intracranial tubers [13–16].

For diagnosis of tuberous sclerosis	
Criteria evaluation, coordinated multidisciplinary evaluation—ophthalmology, dermatology, neurology, renal, pulmonary, genetics, dental, and cardiology	
Skin and oral evaluation every 3–6 months	
Biopsy for confirmation of growths which are not clinically typical, including fibrous forehead plaque	
In cases of multiple lesions, full-body exam every 6 months with Wood's lamp for highlighting	
Chest X ray, EKG, echocardiography, abdominal ultrasound, CT scan head, MRI abdomen	
Ophthalmic examination every 6 months	
For treatment	
	Level of evidence
Coordinated multidisciplinary care—ophthalmology, dermatology, neurology, renal, pulmonary, genetics	
Cosmetic camouflage	
Cosmetic therapies are available to reduce facial lesions, including topical rapamycin	C
Topical rapamycin for facial angiofibromas	C
MTOR inhibitors (e.g. sirolimus)	A

Nevoid Melanosis or Blaschkoid Pigmentation

Nevoid hypermelanosis or hypomelanosis (Fig. 11.3) (synonyms hypomelanosis of Ito, linear and whorled nevoid hypermelanosis, nevus depigmentosus, cutis tricolor or Blaschkoid dyspigmentation) is the appearance of tan to brown (slightly hypopigmented to hyperpigmented) lesions in a Blaschkoid pattern, usually on limbs with trunk and abdomen trailing as locations [17]. A

Table 11.2 Diagnostic criteria for tuberous sclerosis (two major or one major and two minor)

Criteria	Dermatologic clinical appearance	Frequency
Major		
Angiofibromas or Fibrous forehead plaque	Flesh-colored papules perinasal	32.1–100 %
	Similar to Shagreen but facial forehead localization (Both begin in toddler to early childhood years)	2.5–55 %
Hypomelanotic macules (≥3, at least 5-mm diameter)	Ovoid hypopigmented lesions, usually truncal	55.5–95 %
Ungual fibromas (> or =2)	Flesh-colored to brown narrow spicules of skin originating in the cuticle and overhanging the nail	20 % overall; 80 % of older patients
Shagreen patch	Thick or indurated flesh-colored plaque, usually lower back; onset first decade	12.3–83 %
Multiple retinal hamartoma	Noted on ophthalmology exam	30–50 %
Cortical dysplasias	Tubers and cerebral white matter migration lines	
Subependymal Nodules	Noted on brain scans; tubers and cerebral white matter migration lines	
Subependymal giant cell astrocytoma	Noted on brain scans	
Cardiac Rhabdomyoma	Noted in utero/at birth on ultrasound/echocardiography; self-resolving	12 % have cardiac issues as a result
Lymphangioleiomyomatosis (LAM)	Noted within the bones and lungs of the chest cavity with imaging	38 % adults
Angiomyolipomas	Noted mostly within the kidneys on imaging	
Minor "Confetti" skin lesions	Scattered hypopigmented areas a few mm wide across the back	3–58 %
Dental enamel pits (>3)	Noted on dental evaluation	100 %
Intraoral fibromas (> or =2)	Noted on dental evaluation	20–50 %
Retinal achromic patch		1.2–15 %
Multiple renal cysts		6.2–28 %
Non renal hamartomas		

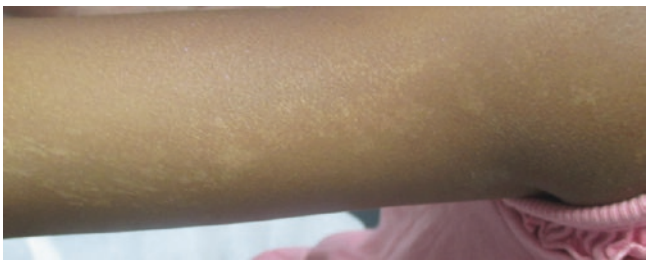

Fig. 11.3 Congenital hypopigmentation along the lines of Blaschko

Blaschkoid pattern means they follow the Lines of Blaschko, which are noted at birth or within the first 2 years of life, and represent localized cutaneous mosaicism in association with either a normal child (majority of cases) or neurologic (e.g. seizure and mental retardation), skeletal and multi-system abnormalities. When hypopigmented streaks are paired with neurologic abnormalities, the complex is often termed hypomelanosis of Ito. In two chart reviews, of 36 patients and 54 patients, only 13.9 % and 30 % of patients had extracutaneous manifestations, respectively [17, 18]. The majority of patients with Blaschkoid pigmentation were otherwise normal.

Neurologic and ophthalmologic screen is indicated [19]. Gross skeletal evaluation of children with Blaschkoid dyspigmentation and limb measurement (assessment for symmetry or anomaly) and appropriate orthopedic evaluation where indicated. Genetic testing for chimerism is reasonable, with cutaneous genotyping of the two different tones of skin (from biopsy) being an optional screen for mosaicism, though unnecessary in the general setting. Where the underlying diagnosis is hard to establish, biopsy can be performed.

For diagnosis of syndromic cases
Repeat cutaneous evaluation every 6–12 months in the first few years of life with Wood's lamp for highlighting looking for anomalies, localized alterations in hair growth, overgrowth or atrophy of limb and associated cutaneous changes (e.g. palmoplantar keratoderma)
Referrals to ophthalmology, neurology and genetics
Biopsy for confirmation of diagnosis where uncertain
Limb lengths and widths to identify underlying skeletal abnormalities
For treatment
Coordinated multidisciplinary care—ophthalmology, dermatology, neurology, genetics
Cosmetic camouflage is available for visible lesions
Laser therapies may be tried for hyperpigmented lesions similar to those used in the setting of café au lait

Becker's Nevus

The Becker's Nevus (Fig. 11.4) is an organoid nevus that appears in a checkerboard mosaic pattern [20]. A smooth muscle hamartoma is usually accompanied by overlying hyperpigmentation, appearing like a café au lait and hypertrichosis. The constellation of findings can be seen in the infantile smooth muscle hamartoma, or appear around puberty on the trunk or proximal extremities, at which time it is usually termed a Becker's Nevus. The younger the child, the less likely it is that hypertrichosis will be noted [21]. The Becker's Nevus is felt to have estrogen receptors. It may be familial in nature [20]. When it is accompanied by hemimaxillary enlargement, asymmetry of the face, tooth abnormalities, and skin findings, it is termed the HATS association [22]. A rare association with neurofibromatosis type I has been reported [23]. Becker's Nevus Syndrome is the presence of the Becker's Nevus with unilateral breast hypoplasia and skin, muscle, or skeletal abnormalities. Mental retardation may be noted [24].

The Becker's Nevus can be diagnosed clinically in most cases. Confirmatory tests include Wood's lamp to define the extent of pigmentation (especially needed for light-skinned patients or females with minimal, light body hair). Confirmatory biopsy can be performed demonstrating typical histology [21]. Imaging, dental, and orthopedic evaluations can aid in the defining of associated structural abnormalities, if suspected. A solitary report of a melanoma in a Becker's Nevus has appeared in the literature, therefore biopsy of changing lesions or for the appearance of new lumps or bumps is needed [25]. Removal of hair or pigmentation overlying a Becker's nevus has been described, with variable success, using variable lasers, as well as fractional resurfacing laser [26, 27].

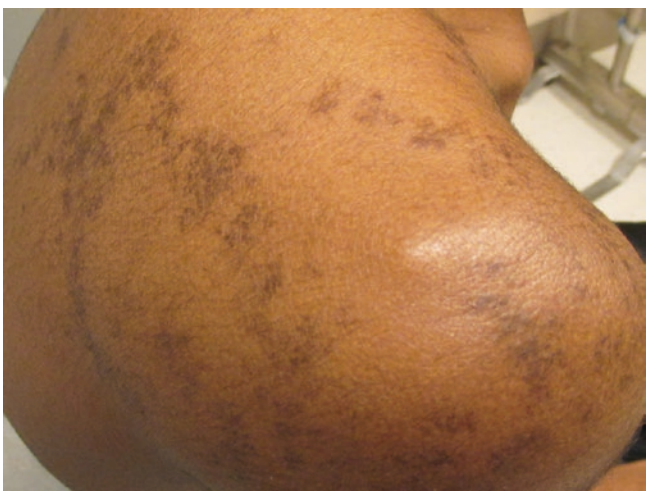

Fig. 11.4 Becker's nevus on the shoulder in an African American male

For diagnosis
Clinical evaluation
Biopsy for confirmation
Chest X-ray, Dental X-rays, and MRI can define underlying defects
For treatment
Biopsy of alterations in pigmentation, lumps, bumps, or nodules
Cosmetic camouflage
Laser therapies have been described including hair removal, pigment removal lasers, and fractional resurfacing

Nevus of Ito and Nevus of Ota

These melanocytic nevi are named based upon their localization in the skin [28]. Presenting in grey-blue sheet of color in the first year of life, they may affect any place in the head and neck region. The Nevus of Ota (Fig. 11.5) usually appears in the first or second trigeminal distribution, with associated ocular component in some cases, while Nevus of Ito appears in the shoulder girdle. In these cases, ongoing ocular assessment is needed to identify associated glaucoma and/or melanoma of the eye. In the skin, palpation for lumps and bumps and ongoing cutaneous evaluation is recommended. Because of the rare association with meningeal melanocytomas which need to be excised, observation for neurologic changes (e.g. headaches) is needed [29, 30]. The lesions are more common in Asians and may cause stigma [28]. A variety of laser techniques for removal are available with variable success [31]. These lesions, in contrast to the Mongolian Spot, do not fade with time.

Congenital Widespread Alterations in Pigmentation

Oculocutaneous Albinism

Clinical Features

Oculocutaneous albinism (OCA) results from gene defects in the melanin synthesis pathway and affects 1:20,000 [32]. The specific defective gene determines if patients will have either decreased melanin synthesis or complete absence of melanin synthesis [32–34]. The adverse effect on melanin is manifested in hair follicles, ocular structures, and the skin. OCA types 1 through 4 have normally structured melanocytes, but the melanocytes are unable to make pigment. Patients with OCA Type I have pink nevi, severe nystagmus, and increased risk of squamous cell carcinomas. OCA Type 1A has

completely absent tyrosinase, and thus begets the most severe clinical manifestations and highest skin cancer risk. In OCA Type 1B, the tyrosinase is present, but decreased, producing clinical variants such as yellow mutant. OCA Type 2 results from a defect in P protein, and results in the brown variant where those afflicted have nystagmus, light brown hair, and pigmented nevi, and may make more pigment as they get older. OCA Type 3 is due to a defect in tyrosine-related protein resulting in the Rufous subtype, where patients have nystagmus, blue or brown iris, light brown to red hair, and light brown-red-bronze skin. OCA Type 4 is due to mutation in membrane-associated transporter protein (MATP), a melanosome membrane transporter (Table 11.3). There are other hypomelanosis disorders that have oculocutaneous manifestations along with systemic manifestations, including Hermansky-Pudlak syndrome, Chediak-Higashi syndrome and Griscelli syndrome.

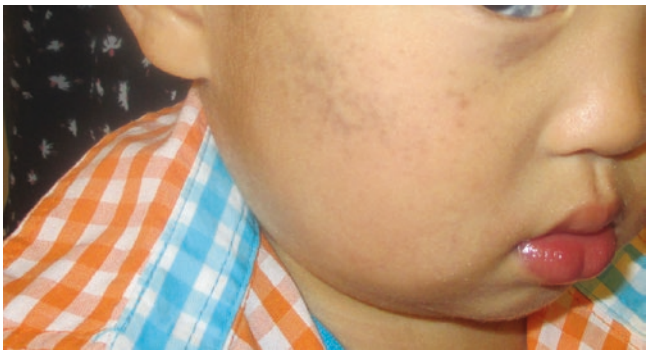

Fig. 11.5 Nevus of Ota in an Asian male infant

Investigations Recommended

For diagnosis
Biopsy to determine presence of melanocytes or not (may be required)
Family history (required)
Genetic testing
Ophthalmologic examination for nystagmus, strabismus, photophobia, poor vision
For on-going management
Dermatology follow up to biopsy any suspicious lesions to rule out skin cancer (Basal cell carcinoma, Squamous cell carcinoma, melanoma)
Ophthalmologic follow-up
Sun avoidance, sunscreen, eye protection, protective clothing

Table 11.3 Types of oculocutaneous albinism (OCA)

Type of OCA	Inheritance	Gene defect and pathogenesis	Distinguishing clinical features
Type 1a (Tyrosine-negative)	AR	TYR, tyrosinase enzyme deficiency; absence of tyrosinase activity or inability tyrosinase to transport to melanosomes	Absence of melanin in skin, hair, and eyes
			White hair may become slightly yellow over time
			Severe nystagmus
			Amelanotic nevi (pink nevi)
			Blue-gray eyes, decreased visual acuity, prominent red reflex throughout life
			Increased risk of squamous cell carcinomas
Type 1b (yellow mutant)	AR	TYR, tyrosinase is present but decreased	Develops some pigment over time
Type 2 (Tyrosinase positive) (brown variant)	AR	P gene, defect in P protein, decreased eumelanin synthesis, normal number of melanocytes	Brown variant is most common form of albinism in those of African descent
			Light brown hair
			Pigmented nevi
			Eye symptoms may improve with age
			May get more pigment with increased age
Type 3 (Rufous)	AR	TYRP-1, Tyrosinase-related protein 1	Nystagmus
			Decreased visual acuity
			Blue-brown iris
			Light brown-red-bronze skin
Type 4		MATP, Mutation in membrane-associated transporter protein, a melanosomes membrane transporter	Similar to OCA type 2

Phenylketonuria

Clinical Features

Phenylketonuria (PKU) results from a deficiency of phenylalanine hydroxylase (PAH) or tetrahydrobiopterin, the phenylalanine hydroxylase co-factor [35, 36]. PKU is inherited via autosomal recessive pattern and affects 1:10,000–15,000 Caucasian newborns. The PAH gene is found on chromosome 12q23.1, but there are over 600 reported mutations. Patients with similar PAH defects may have different phenotypes. Without functioning PAH, the pathway of phenylalanine-to-tyrosine-to-dopamine-to-melanin does not occur. Tyrosine is needed for production of melanin, which is necessary for hair and skin color.

In addition to skin hypopigmentation, mental retardation, dermatitis, photosensitivity, and seizures may occur. Most patients have fair skin, blonde hair, and blue eyes. A musty odor is often noted from the by-products (phenylacetic acid) of the failed metabolic pathway. Patients with high levels of phenylalanine may have atopic dermatitis-like dermatitis and sclerodermoid-like skin changes, which improve with lowered phenylalanine levels.

Screening for PKU is a component of many state-mandated newborn screening programs [35–38]. If recognized early, a phenylalanine-free formula can be instituted, and later a low-phenylalanine diet. The dietary restrictions are instituted to prevent the most severe adverse events and clinical features that result from high phenylalanine levels. Despite these strict diet-control efforts, neurodevelopmental and psychological problems may still emerge.

Investigations Recommended

For diagnosis
Guthrie test (semiquantitative bacterial inhibition assay) in newborn
Tandem mass spectrometry assay in newborn
Confirmation of elevated phenylalanine on newborn screen by quantifying phenylalanine, phenlyalanine to tyrosine ratio (1:1 is normal, over 3:1 is consistent with PKU), and a complete amino acid profile
For ongoing management
Gene mutation analysis may help determine the extent of phenylalanine restriction needed and the likelihood that the patient will respond to supplementation with cofactor (sapropterin or tetrahydrobiopterin)
Serum phenylalanine levels weekly until age 1 year, or more frequently during rapid growth phases; diet changes like introduction of solid foods
Serum phenylalanine levels biweekly—monthly from age 1 to 12 years, then monthly beyond age 12 years, if stable
Monitor essential fatty acids, vitamin levels, and minerals

Silvery Hair Syndromes (Chediak-Higashi Syndrome, Griscelli Syndrome and Elejalde Syndrome)

Clinical Features

Silvery hair is seen in Chediak-Higashi syndrome (CHS), Griscelli syndrome and Elejalde syndrome [39]. The syndromes are rare, but share the unique silvery hair manifestation.

In addition to silvery hair, patients with CHS have mild pigment dilution (hair, skin, eyes) from abnormally aggregated melanosomes, phagocytic immunodeficiency, bleeding, and recurrent infections [39, 40]. Also, progressive sensory or motor defects may occur. Abnormal large lysosomal granules impair the function of phagocytic cells. Natural killer cells are decreased and neutropenia is common. The dysfunctional chemotactic and bactericidal ability of the neutrophils contributes to increased risk of infections.

Patients with Griscelli syndrome have clumps of pigment within their hair shafts. The melanosomes within the melanocytes accumulate and are large and abnormal. This occurs due to abnormal transfer of melanosomes to dendrites. Those with Griscelli syndrome Type I (myosin 5A gene mutation) have albinism, severe neurologic impairment, developmental delay, and mental retardation [41]. Griscelli syndrome Type II (RAB27A mutation) has albinism, immune defects that may be fatal, and hemaphagocytic syndrome, necessitating bone marrow transplant as the only cure. Griscelli Type III (melanophilin MLPH mutation) has purely cutaneous manifestation and lacks neurological manifestations [42].

Like Griscelli syndrome, Elejalde syndrome results from abnormal melanosomes transfer [40]. Clinically, those with Elejalde syndrome have partial albinism and may have severe neurological defects.

Investigations Recommended

For diagnosis
Light microscopy of hair and skin
CHS—regularly spaced large melanosomes in hair shaft
Griscelli—unevenly spaced giant melanosomes (larger than melanosomes in CHS) mainly in medullary zone
Immunologic work-up
Peripheral blood smear
Gene mutation testing
CHS- LYST gene defect (lysosomal trafficking regulator protein)
For on-going management
Ophthalmology
CHS—strabismus, photophobia, nystagmus
Infectious disease

Table 11.4 Therapies

First line	Summary	Level of evidence
Dietary restrictions managed by a metabolic physician expert and nutritionist	Phenylalanine-free amino acid mixtures/ formulas; Low-protein, low-phenylalanine diet	B
Second line		**Level of evidence**
Sapropterin dihyrochloride (synthetic form of cofactor, tetrahydrobiopterin)	Derivative of co-factor for phenylalanine hydroxylase	A

CHS—pyogenic infections of skin, upper respiratory tract, and lungs
Hematology
CHS and Griscelli
Consider stem cell transplant or bone marrow transplant for those with severe immunodeficiency, if appropriate, based upon specific gene defect
CHS
Monitor for neutropenia
Monitor for accelerated lymphohistiocytic phase; hepatosplenomegaly, pancytopenia, jaundice, lymphadenopathy, thrombocytopenia, Epstein-Barr virus
Neurology
CHS—monitor for progressive neurologic defects
Dermatology
Skin cancer screenings
Especially in CHS due to increased ultraviolet sensitivity, risk of actinic keratosis and skin cancer

Piebaldism

Clinical Features

Piebaldism (autosomal dominant) is caused by abnormal migration of melanoblasts from the neuroectoderm to the midline skin during fetal development [43–46]. The differentiation and migration of melanoblasts is defective. This results from a mutation in the c-kit proto-oncogene. Patients with piebaldism have a white forelock and depigmented/hypopigmented macules and patches of the midline forehead, eyebrows, eyelashes, nose, chin, anterior neck, anterior thorax, and anterior abdomen. Both the anterior and posterior aspects of the mid-arm down to the wrist and the mid-thigh down to the mid-calf may also be affected. Within the areas of hypomelanosis, there are often macules and patches of normal to hyperpigmented areas. Sensorineural hearing impairment is rarely involved with piebaldism [47].

Investigations Recommended

For diagnosis
Newborn hearing screen
Referral to otolaryngology, neurology, or gastroenterology only if signs of the rare associations of deafness, cerebellar ataxia, mental retardation, or Hirschsprung disease are present
For ongoing management
Sun protection

Waardenburg Syndrome

Clinical Features

There are four types of Waardenburg syndrome [49–52] Type 1 is autosomal dominant and occurs due to PAX3 mutation. Patients with Type 1 have a white forelock, depigmented skin patches, heterochromia of the iris, dystopia canthorum, synophrys, and broad nasal root. Type 2 is autosomal dominant and occurs due to a mutation in the MITF gene. Patients with Type 2 have similar features as those in Type 1, but deafness is a common feature in Type 2 and dystopia canthorum is absent. Type 3 has autosomal dominant inheritance and is caused by a PAX3 mutation, like Type 1. The features of Type 3 are the same as Type 1, with the addition of upper limb defects like contractures, hypoplasia, and syndactyly. Type 4 has three potential gene defects (SOX 10, endothelin-3, and endothelin receptor) and may be autosomal dominant or autosomal recessive, depending on the gene mutation. The clinical

Table 11.5 Therapies

First line	Summary	Level of evidence
Cosmetic cover-up with make-up for dyspigmentation	For cosmesis of prominent lesions that are clinically notable	B
Second line		**Level of evidence**
Phototherapy (piebaldism)	For those who note pigmentation after sun exposure	C
Autologous cultured melanocytes, ultrathin epidermal sheets and basal layer cell suspension transplants [48]	For stable forms of leukoderma (piebaldism)	C

features of Type 4 are similar to Type 1, but additionally has Hirschsprung disease and deafness.

Investigations Recommended

For diagnosis
Newborn hearing screen
Evaluate for dystopia canthorum: (inner canthal distance)/(outer canthal distance) >0.6
Referral to audiologist, ophthalmology, otolaryngology
Referral to gastroenterology
For on-going management
Sun protection
Ongoing hearing screens and otolaryngology follow-up
Gastroenterology screening and gastrointestinal surgery, as indicated

Acquired Localized Disorders of Pigmentation

Acquired localized forms of hypopigmentation are common in children of color as well as Caucasian children. The leading diagnosis in infancy is post-inflammatory alterations as a result of seborrheic dermatitis. In tweens and teens, the leading diagnosis becomes tinea versicolor. Although segmental vitiligo is localized, the diagnosis is reviewed with the section on generalized dyspigmentation.

Pityriasis Alba

Clinical Features

Pityriasis alba (Fig. 11.6) is most commonly seen in children with atopy [53–55]. Initially a subtle, asymptomatic erythematous patch (easily missed in those with darker skin tones) appears and develops fine scale. The lesion resolves with hypopigmented patches that may persist for months to years.

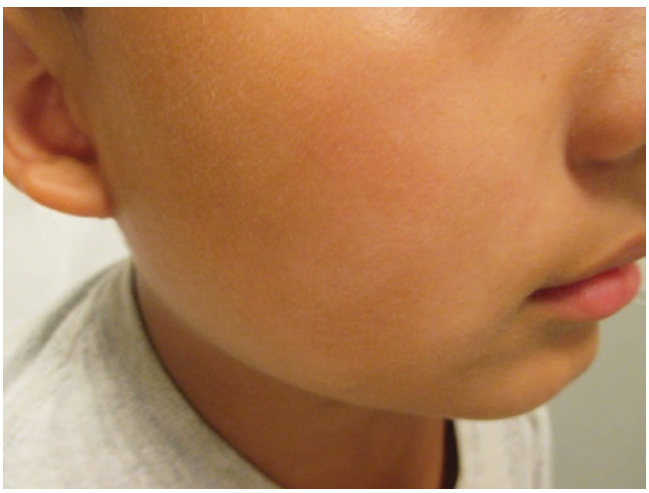

Fig. 11.6 Pityriasis alba of the cheeks in a child of Hispanic descent

Investigations Recommended

For diagnosis
Diagnosis based on clinical appearance.
Wood's lamp may highlight the affected skin areas with hypopigmentation from the surrounding skin
For on-going management
Sunscreen (sun exposure enhances the contrast between normal and affected skin)
Emollients

Table 11.6 Therapies

First line	Level of evidence
Hydrocortisone topical 1 % or 2.5 %	E
Calcitriol topical 0.003 %	A
Tacrolimus 0.1 % ointment	A
Second line	
Excimer laser 308 nm	C

Tinea Versicolor

Clinical Features

Tinea versicolor is a *Malassezia*-induced superficial mycosis that most commonly occurs in adolescents [56–58]. Round to oval hypopigmented or hyperpigmented (depending on skin type) macules, patches, and thin plaques occur on the chest, back, and shoulders. In those with darkly pigmented skin, tinea versicolor may also affect the neck and face. The dyspigmentation may be particularly distressing for those with darker skin tones.

Notably absent from recommended therapies below is oral ketoconazole. Due to hepatotoxicity, the United States Food and Drug Administration (FDA), Canada, and the United Kingdom have removed ketoconazole's approval for superficial fungal infections. In the US, the use of oral ketoconazole is restricted to endemic mycoses where alternate medications are not feasible.

Investigations Recommended

For diagnosis
Usually clinical appearance is so characteristic that no further investigations are required
Use a 15 blade to scrape scale onto a glass side. Add potassium hydroxide and cover slip to the slide to create a wet-mount. Under the microscope, fungal hyphae and spores are visible in a classic spaghetti-and-meatballs pattern
Under a woods lamp, the affected skin lesions may fluoresce yellow-green

Table 11.7 Therapies

First line	Level of evidence
Ketoconazole 2 % topical	A
Ketoconazole foam 1 %	B
Second line	
Clotrimazole, econazole, bifonazole, miconazole, terbenafine, ciclopirox topical	A
Selenium sulfide shampoo	B
Third line	
Oral itraconazole	A

Terre Firme

Dirt, scurf, shmutz, whatever you wish to call it, even seemingly clean children will come in with skin conditions ranging from a dirty neck to thick compounded dirt of the skin. Locations that are common are the neck, behind the ear, and the central chest [59, 60]. Lesions may mimic ichthyosis or acanthosis nigricans. A vigorous scrub with an alcohol pad provides the diagnosis and a loofah sponge can help cleanse these areas in the shower for complete removal.

Post-Inflammatory Pigment Alteration (PIPA)

Inflammatory cutaneous diseases may resolve with hyperpigmentation, hypopigmentation, or a combination of both [61]. Treatment is aimed at controlling the underlying inflammatory cutaneous condition. Sunscreen may help to ameliorate further dyspigmentation.

Acquired Generalized Disorders of Pigmentation

Acanthosis Nigricans

Acanthosis nigricans is a cutaneous, velvety thickening usually associated with the endocrinopathy of the metabolic syndrome and insulin resistance [62, 63]. The condition is more visible in patients of African, Hispanic, and Afrocaribbean descent. The condition will appear with thickened skin over the neck, axillae, sometimes face, elbows, and even rarely in the generalized pattern. When noted in an obese child, clinical screening for excess gum or genital pigmentation (Addisonian), buffalo hump and stria (Cushing's), and screening for insulin resistance (postprandial glucose, hemoglobin A1C and insulin) and metabolic syndrome (cholesterol, triglycerides) are needed, with referral of children with detectable resistance; however, all obese children with acanthosis nigricans are manifesting early insulin resistance and should be referred for nutritional and weight management. When found in a thin child, referral to endocrinology and/or hematology/oncology for work-up will be needed. Association with Cushing's, Addison's, malignancy, and medications has been described.

Investigations Recommended

For diagnosis
Clinical findings of hyperpigmented, velvety, thickened skin in characteristic areas including the neck and axillae are very suggestive of acanthosis nigricans
Patients are most often overweight or obese
Screen for insulin resistance with post-prandial glucose level, hemoglobin A1C, and insulin level
Screen for metabolic syndrome with cholesterol, triglyceride level, blood pressure, glucose level
For thin children, refer to endocrinology and/or hematology/oncology to investigate other underlying causes
For ongoing management
Nutritional and weight management
Exercise

Vitiligo

Vitiligo (Fig. 11.7) is an autoimmune form of pigment loss seen in 0.4 % of the worldwide population, with about half of cases occurring in childhood [64, 65]. Where noted in children, four subtypes have been described—Segmental,

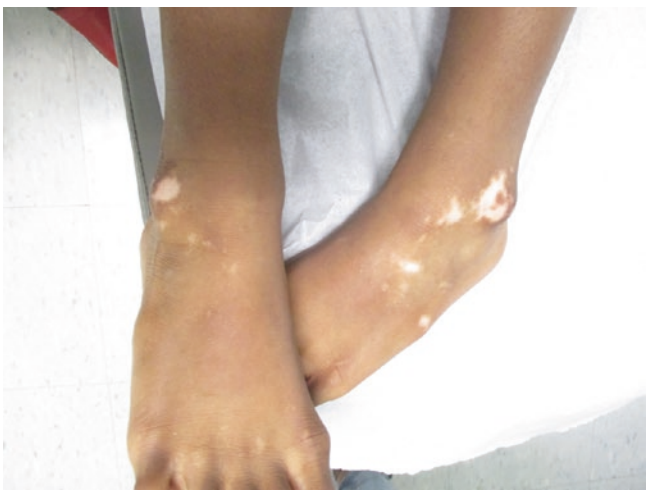

Fig. 11.7 Vitiligo of the ankles in a boy with generalized disease

Non-segmental (or generalized), Mixed, and or Indeterminate types. The disease has been linked via genome-wide association studies to a variety of pigmentary and autoimmune loci [66]. Association with a family history of vitiligo and autoimmunity, as well as a personal history of autoimmunity, exists and has to be monitored for lifetime [65, 67, 68]. These include 26 % of children having clinical or subclinical autoimmune thyroiditis [69]. Other associated illnesses include celiac disease, colitis, rheumatoid arthritis, psoriasis, alopecia areata, and pernicious anemia [64, 67–69] Screening for thyroid auto-antibodies in addition to thyroid function in pediatric vitiligo patients can highlight individuals who require more frequent or closer thyroid monitoring. Complete blood count, metabolic panel, and 25- OH vitamin D levels may aid in monitoring, the latter often being reduced in cases of associated autoimmunity [70].

Segmental vitiligo follows a broad pattern of Blaschko's lines [71]. It appears rapidly across a segment and then remains stable. The loss of pigment often includes the reservoir in hairs in this subtype. Therefore, early intervention works best, including topical tacrolimus, topical corticosteroids, and excimer (308-nm) laser or light sources [72]. Some patients, through a loss of heterozygosity as noted by Happle, will go on to develop generalized vitiligo as well. In the absence of generalized vitiligo, testing for thyroid disease and associated autoimmunity is not needed [71, 73].

Generalized vitiligo or non-segmental vitiligo appears in a common pattern of pigment loss for most patients, periorificial midfacial loss that expands, intertriginous, hands and feet especially periungual, wrists and ankles, and genitalia. The appearance of disease is often associated with poor quality of life, bullying, social anxiety, and anxiety over the potential slow and/or rapid spread of illness with time [74]. Repigmentation can be effected through the introduction of topical corticosteroids (Class II are first line for body), topical calcineurin inhibitors (first line for face), narrowband UVB phototherapy (for generalized disease, carries a risk of skin cancers later in life), and localized resistant cases with excimer laser. Light-skinned children (Fitzpatrick Type I) require no therapy other than sun protection [64, 65, 72].

Investigations Recommended

For diagnosis
Clinical examination with biopsy in unclear cases
Wood's lamp evaluation will highlight areas
Evaluate for irregular pigmented lesions (full-body skin exam)
For on-going management
Screening labs: CBC, CMP, TSH, Anti TPO and anti TG antibodies, 25 OH Vitamin D (repeat annually)
Referral to ophthalmology, ear nose and throat, endocrinology, psychiatry/psychology as needed

Table 11.8 Therapies

First line	Summary	Level of evidence
Cosmetic cover-up with make-up for dyspigmentation	Used to reduce the clinical appearance of lesions	B
Class II corticosteroids for body lesions	Can effect repigmentation with possible side effect of skin thinning	B
Topical calcineurin inhibitors	Can effect repigmentation; bear a black box warning label of potential risk of associated malignancy, lymphoma	B
Second line		
Phototherapy	To stabilize rapidly spreading illness and effect repigmentation (may be associated with late-onset skin cancers later in life)	B
Excimer laser	To repigment localized resistant areas and in recent-onset segmental disease	B
Third line		
Grafting (type is site dependent)	To repigment long-standing stable depigmentation	C

Conclusions

Pigmentary anomalies are common and follow distinct patterns. Good clinical evaluation, on-going care, counseling, and coordinated care with neurology, ophthalmology, genetics, and other subspecialties can aid in diagnosis and identify associated conditions requiring management. Cosmetic camouflage and laser may be used in some cases to reduce the cosmetic burden of visible illness.

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Vascular Disorders and Anomalies

12

Diana H. Lee and Elena B. Hawryluk

Vascular Tumors

Infantile Hemangioma

Clinical Features

Infantile hemangiomas have varying clinical presentations depending on depth, size, and stage of growth cycle. They start in their nascent phase as either a telangiectatic patch, a bruise-like lesion, or an area of pallor, usually at birth or soon thereafter. Most grow noticeably between 2 and 4 weeks of life into red plaques of varying sizes and thicknesses, with the most rapid growth between 5.5 and 7.5 weeks of age. Those that are deeper in the subcutis can appear as more blue or flesh-colored nodules, noted later in infancy. Maximum size is often reached by 9 months, followed by a growth plateau, then an involution phase. Involution occurs over several years, most rapidly between 1 and 4 years of age.

Infantile hemangiomas can present as focal or segmental/regional lesions. Segmental hemangiomas of specific locations may be associated with PHACEs (Posterior fossa, Hemangioma, Arterial lesions, Cardiac abnormalities/aortic coarctation, Eye abnormalities, sternal cleft and supraumbilical raphe) syndrome, or LUMBAR (Lipoma, Urogenital anomalies/Ulceration, Myelopathy, Bony deformities, Anorectal malformations/Arterial anomalies, and Renal anomalies) syndrome.

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Management Strategies

Propranolol has become the preferred first-line therapy for infantile hemangiomas. It is considered appropriate for treatment, especially for ulcerated lesions, ones with impingement on a vital function, and those at risk for permanent disfigurement, preferably during the time of most rapid growth, which is typically during the first 2 months of life [2, 3].

The topical nonselective B-adrenergic receptor inhibitor timolol 0.5 % gel is an effective and safe treatment for superficial infantile hemangiomas [4].

Systemic corticosteroids have historically been used for hemangiomas requiring treatment, but are now second-line for those who do not respond to propranolol or with contraindications to propranolol. Pulsed dye laser (PDL) is used to treat ulceration or reduce redness and telangiectasia. Excisional surgery can be undertaken during or after involution to remove any unsightly remaining soft tissue/fibrofatty residua.

If the infantile hemangioma is segmental on the head/neck or the lower part of the body, further studies should be done to adequately assess for PHACEs or LUMBAR syndrome, respectively.

Investigations Recommended

For diagnosis
PHACE evaluation if segmental on head, neck, upper chest
MRI/MRA head/neck/upper chest
Cardiac examination
ECHO and EKG
Ophthalmologic examination
LUMBAR evaluation if segmental on lower part of the body:
Ultrasound of affected areas of abdomen, pelvis, spine (<3 months of age)
MRI and time-resolved MRA of affected areas (>3 months of age)
For treatment with propranolol
Cardiovascular history and examination
Screening EKG or ECHO (if warranted by history or exam)

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Table 12.1 First line therapies

Propranolol (A) [3] (Fig. 12.1a, b)
Timolol 0.5 % gel (A) [4]

Table 12.2 Second Line Therapies

Systemic corticosteroids (D) [5]
Topical or intralesional steroids (D)
Topical imiquimod (D)
Pulsed dye laser (PDL) (D)
Excisional surgery (D)
Active non-intervention

Kasabach Merritt Phenomenon (KMP)

Clinical Features

Kaposiform hemangioendotheliomas (KHE) and tufted angiomas (TA) are vascular tumors that can be associated with a coagulopathy called Kasabach-Merritt syndrome (KMS). Lesions present as firm, solitary red to violaceous tumors in the skin or soft tissue, often indurated and with ill-defined margins. They can become periodically engorged, purpuric, and tender, which can improve over time. Complete regression is unusual. KMP is an uncommon threatening clinical phenomenon that is comprised of profound thrombocytopenia and hypofibrinogenemia and coagulation activation, as reflected by elevated D-dimer or fibrin degradation products.

Management Strategies

Consensus recommendations exist as outlined in "First Line Therapies" below [6].

Investigations Recommended

For diagnosis
CBC w/platelet count
Coagulation studies (PT, PTT, fibrinogen, D-dimer levels)
MRI w/and w/o contrast
Tissue biopsy

Table 12.3 First line therapies

For enlarging, unresectable KHE with severe thrombocytopenia: IV vincristine once weekly AND oral prednisolone OR IV methylprednisolone
For an enlarging, unresectable KHE without KMP: oral prednisolone
Surgical excision is considered gold standard for cure of KHE, but is often difficult as lesions are often infiltrative

Table 12.4 Second line therapies

Arterial embolization can be an adjunct to surgical resection, and its effects are often temporary (E)
Propranolol (D)
Sirolimus (E)
Interferon alfa-2a and 2b (E)

Multifocal Lymphangioendotheliomatosis with Thrombocytopenia

Clinical Features

This disease entity is comprised of vascular lesions consisting of red-brown macules and plaques, with CD31+ endothelial and LYVE1+ lymphatic differentiation marker of the skin and gastrointestinal (GI) tract. GI bleeding, anemia, thrombocytopenia, and consumptive coagulopathy (low serum fibrinogen, elevated D-dimer) are additional features.

Management Strategies

Effective treatment is challenging, and reports describe use of oral corticosteroids, vincristine, propranolol, amino caproic acid, thalidomide, and interferon alfa-2a, often in some combination [7].

Investigations Recommended

For diagnosis
CBC w/platelet count
Coagulation studies (PT, PTT, fibrinogen, D-dimer levels)
Tissue biopsy

Table 12.5 First line therapies (often in combination)

Corticosteroids (E)
Vincristine (E)
Propranolol (E)
Amino caproic acid (E)
Thalidomide (E)
Interferon alfa-2a (E)

Pyogenic Granuloma

Clinical Features

Pyogenic granuloma, otherwise known as lobular capillary hemangioma, is a benign vascular proliferation found on the skin, commonly papular or pedunculated, often with a history of rapid growth within days or weeks (Fig. 12.2). It can be complicated by bleeding, especially if traumatized.

Management Strategies

Treatment of these lesion is mainly surgical. This includes surgical excision, curettage/shave excision +/– cautery, punch biopsy, as well as ligation. Other treatment options include cryotherapy, laser therapy (CO2, pulsed dye laser, Nd-Yag, 1,064 nm), sclerotherapy, and imiquimod 5 % cream [8].

Investigations Recommended

For diagnosis
Clinical diagnosis or tissue biopsy
For treatment
Tissue biopsy can be therapeutic, though recurrence is possible

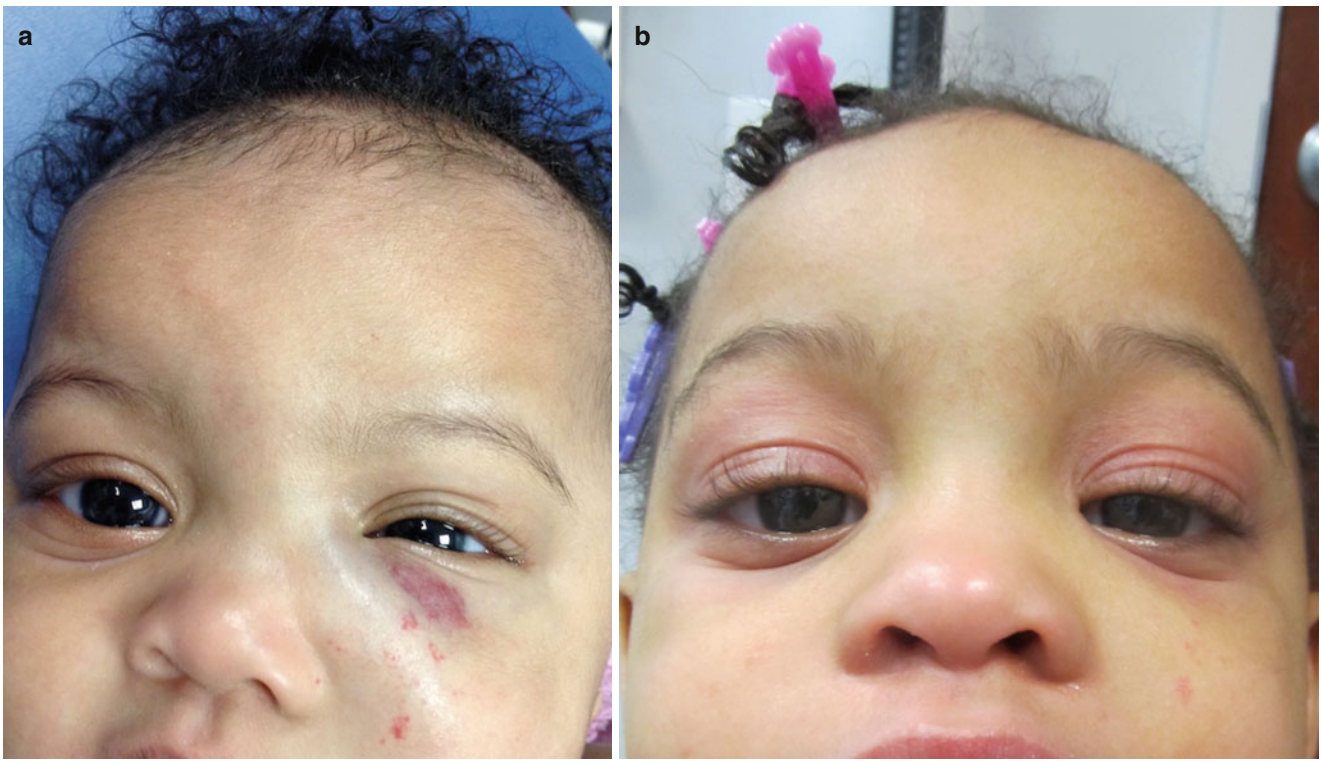

Fig. 12.1 (**a**) Infantile hemangioma, pre-propranolol; (**b**) infantile hemangioma, post-propranolol

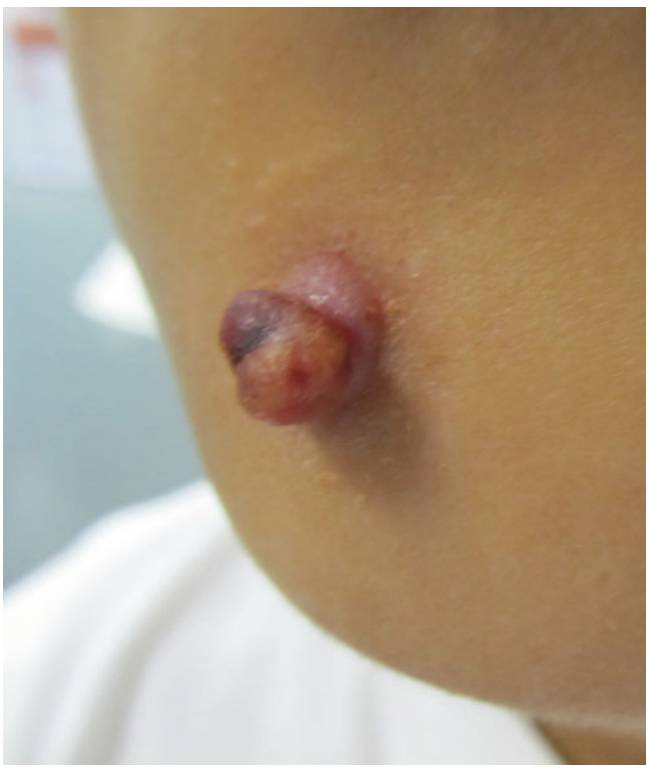

Fig. 12.2 Pyogenic granuloma

Table 12.6 First line therapies

Surgical excision (D)
Curettage/shave excision ± cautery (D)
Punch biopsy (D)
Ligation (D)

Table 12.7 Second line therapies

Cryotherapy (D)
Laser therapy) (D)
Sclerotherapy (D)
Imiquimod 5% cream (D)

Angiofibromas

Clinical Features

Angiofibromas are benign flesh-colored, pink or brown papules that occur more prominently on the face in those with tuberous sclerosis, multiple endocrine neoplasia type 1, and Birt-Hogg-Dube syndrome. Histologically, there is a dermal fibroblastic proliferation in a collagenous stroma, with an increase in thin-walled, dilated blood vessels.

Management Strategies

A variety of destructive modalities have been used to treat angiofibromas, sometimes in combination, such as

dermabrasion, electrosurgery, surgical excision, and laser therapy,—including PDL and CO2 ablative fractional resurfacing. In patients with tuberous sclerosis, both systemic and topical rapamycin have been found to be effective treatments of angiofibromas. Topical rapamycin formulations used range from 0.1 to 1 % in an ointment, gel, cream, or solution base [9].

Investigations Recommended

For diagnosis
Clinical diagnosis or tissue biopsy

Table 12.8 First line therapies

Systemic rapamycin (E) [10]
Topical rapamycin (C) [11]
Electrosurgery (E)
PDL laser (E)
Ablative fractional resurfacing (E)
Dermabrasion (E)

Vascular Malformations

Capillary Malformations

Clinical Features

Capillary malformations (CM) are erythematous patches that may occur anywhere on the skin as a discrete patch, or in an extensive distribution (Fig. 12.3).

Management Strategies

Pulsed dye laser is the preferred laser of choice. The pulsed dye laser (585–595 nm) targets oxyhemoglobin (the targeted chromophore) and destroys capillaries by selective photothermolysis [12], though other wavelengths have been utilized effectively to treat vascular stains and deeper lesions. The pulsed dye laser reduces redness with serial treatments. Parameters including pulse duration, spot size, fluence, and epidermal cooling are adjusted based upon vessel size and depth. Pulsed dye laser can be utilized to treat other vascular lesions such as hemangioma, telangiectasia, and pyogenic granuloma as well.

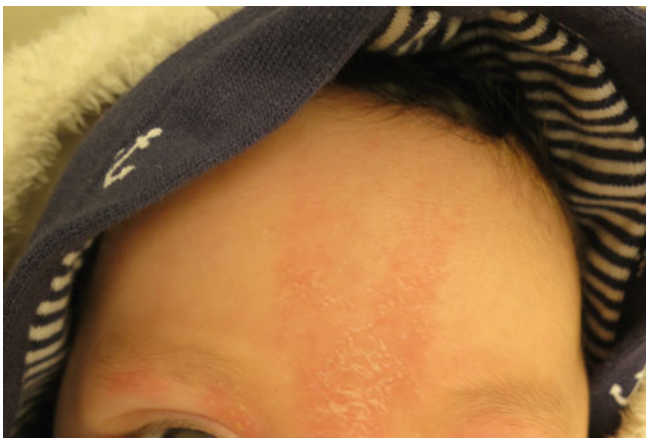

Fig. 12.3 Capillary malformation

Investigations Recommended

- For facial CM with classic distribution, or facial CM/Port Wine Stain with neurologic symptoms: MRI with contrast to evaluate for Sturge-Weber Syndrome, ophthalmology referral
- For CM with asymmetry of lower extremity: orthopedics consultation at age 1 for evaluation and management of overgrowth if present

Table 12.9 First line therapies

Active non-intervention
Pulsed dye laser therapy (B)
Topical rapamycin + pulsed dye laser therapy (A)
Topical imiquimod + pulsed dye laser therapy (B)

Venous Malformations and Lymphatic Malformations

Clinical Features

Venous malformations (VM) can appear as skin-colored to blue, soft, compressible nodules, which can exhibit enlargement in dependent positions (Fig. 12.4). Lymphatic malformations (LM) can appear as small, skin-colored to red hemorrhagic fluid-filled clustered papules, to larger, soft, poorly circumscribed skin-colored nodules or masses.

Management Strategies

VM and LM can be monitored clinically if small and asymptomatic. Larger venous malformations of the limbs should be managed proactively, with regular physical activity and use of compression garments to promote vascular return and prevent edema and its sequelae. Formation of a phlebolith within a VM may be painful, and is treated symptomatically with aspirin and compression. Ultrasound is a useful initial imaging tool, with MRI/A helpful to confirm diagnosis and define extent. Conventional angiography can be used to treat slow-flow vascular malformations

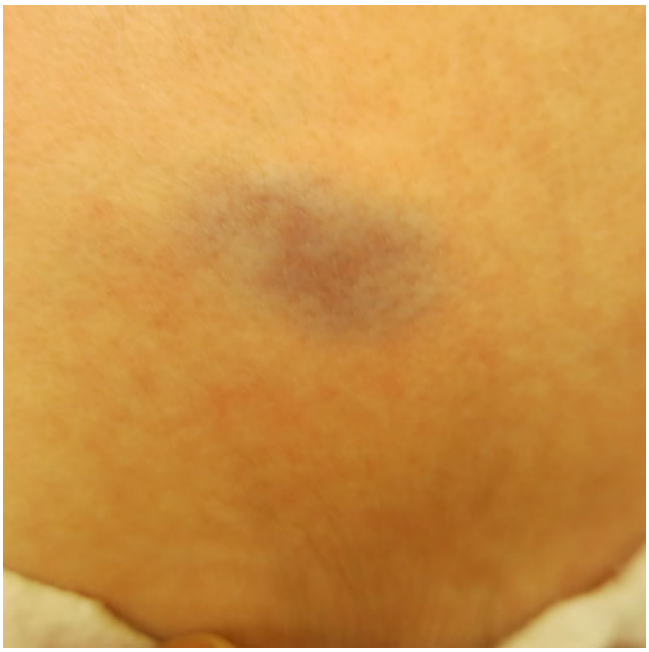

Fig. 12.4 Venous malformation

(VM and macrocystic LM), with sclerotherapy (injection of sclerosant, surfactant, or chemotherapy into abnormal channels), venous embolization (placing sclerosant or occlusive device via catheter), or endovenous laser ablation. Surgery can address small malformations. Medical therapy including sildenafil has been utilized for LM [13], while more severe/complex vascular malformations have been treated with chemotherapy such as vincristine, glucocorticoids, and more recently sirolimus [14].

Investigations Recommended

- Ultrasound or MRI/A for diagnosis and defining extent of involvement, or to assess a changing, enlarging, or symptomatic lesion

Table 12.10 First line therapies (dependent upon size/distribution/symptoms)

Active non-intervention
Physical activity, compression
Surgery
Conventional angiography with sclerotherapy, venous embolization, or endovenous laser ablation
Sildenafil (E)
Vincristine (E)
Glucocorticoids (E)
Sirolimus (E)

Arteriovenous Malformations

Clinical Features

Depending on location, an arteriovenous malformation (AVM) may appear as a pulsatile vascular mass, but may also arise internally, without any surface evidence of disease. These lesions may grow in size over time.

Management Strategies

The management of fast flow malformations depends on their size and location; small and asymptomatic AVMs may be managed expectantly. Larger and symptomatic AVMs, including those that are growing and causing morbidity, may be addressed with chemotherapy, surgical excision, or endovascular therapy using embolic agents, occlusive devices such as coils, or sclerosing agents.

Investigations Recommended

- MRI with contrast to confirm diagnosis
- Imaging of a changing, enlarging, or symptomatic lesion
- Consider further evaluation for syndromes such as hereditary hemorrhagic telangiectasia (HHT) (i.e. brain and lung imaging, genetic testing), if warranted

Table 12.11 First line therapies

Surgery
Chemotherapy (E)
Endovascular therapy with embolic agent, coils, sclerosing agents (E)

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Genodermatoses and Basement Membrane Zone Diseases

13

Vallari Majmudar, Irene Lara-Corrales, and Elena Pope

Epidermolysis Bullosa (EB)

Epidermolysis bullosa is a heterogeneous group of inherited mechanobullous diseases characterized by blistering of the skin, and sometimes the mucous membranes, following minor frictional trauma [1]. The major forms of EB are simplex (EBS), junctional (JEB), dystrophic (DEB) and mixed (Kindler syndrome, which is discussed later). They are categorized according to specific cleavage planes at the dermo-epidermal junction (DEJ) [1].

Most subtypes of **EBS** are dominantly inherited, and may vary from presenting with localized blisters predominantly on acral surfaces (EBS—localized) to generalized blistering (EBS—generalized). Mutations in keratin 5 and 14 cause EBS localized, generalized, Dowling-Meara, and EBS with mottled pigmentation. In the rarer subtypes, EBS with muscular dystrophy and Ogna, the mutation is in the gene encoding plectin, which is a component of the hemidesmosomes [1].

Clinical Features of EBS (Fig. 13.1)

- Blistering occurs more commonly at sites of friction (flexural and extensor surfaces)
- In EBS Dowling-Meara, blisters occur in characteristic clusters (herpetiform), and involvement of mucous membranes including the mouth, larynx, and esophagus is common
- Healing is typically without scarring
- Intra-oral involvement may occur in generalized type of EBS
- Nail dystrophy is rare
- Improvement of the blistering may occur with age

Junctional EB (JEB) is inherited in an autosomal recessive manner. This is a heterogeneous disorder that results from mutations in proteins present at the DEJ (plectin, laminin 332, collagen XVII and α6β4 integrin). These are all components of the anchoring filaments and hemidesmosomes. Subtypes include JEB-Herlitz, JEB non-Herlitz, JEB with pyloric atresia, JEB inversa and laryngo-onycho-cutaneous syndrome (also known as Shabbir syndrome).

Clinical Features of JEB

- Tense bullae on the skin and extensive oral mucous membranes involvement at birth
- Involvement of the buttocks and pinnae, periorificial and subungal involvement is common in Herlitz-JEB
- Nail dystrophy, dental enamel hypoplasia, non-scarring alopecia, and conjunctival involvement are common

JEB-Herlitz is associated with increased risk of sepsis, airway compromise, and death in the first few years after birth. Patients with JEB non-Herlitz have a milder phenotype, but it may sometimes be indistinguishable from JEB-Herlitz, especially in infancy. Patients with JEB non-Herlitz survive into adulthood.

Dystrophic EB (DEB) can be dominantly (DDEB) or recessively (RDEB) inherited. In general, DDEB has a milder phenotype than RDEB. Mutations of genes encoding type VII collagen (COL7A1), present in anchoring fibrils, result in DEB [1].

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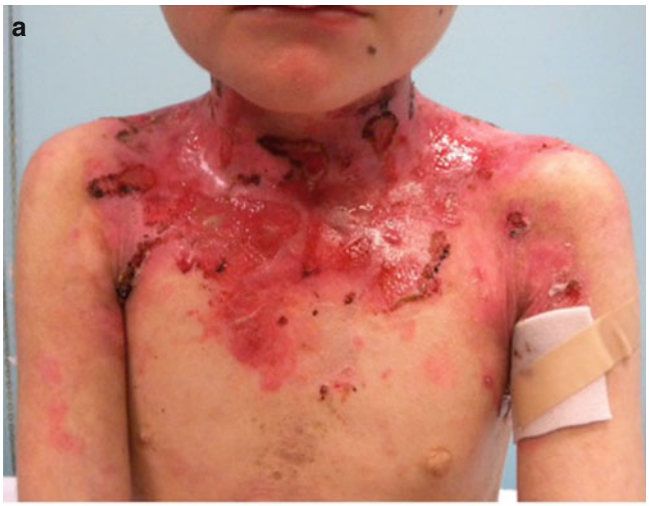

Fig. 13.1 Clinical presentation of patients with Epidermolysis Bullosa. (**a**) Typical blistering leading to chronic wounds in a patient with RDEB. (**b**) Blisters on the foot at the sites of trauma in a patient with EBS

Clinical Features of DEB (See Fig. 13.1)

- Tense blisters/bulla at the sites of trauma, healing with scarring
- Various degrees of mucous membranes involvement, with potential for scarring, depending on the subtype (e.g. esophageal strictures, corneal synechiae, etc.)
- Extensive nail and digit involvement leading, in severe cases, to mitten deformity
- Increased likelihood of squamous cell carcinoma
- Severe cases have complications (e.g. anemia, malnutrition, cardiomyopathy, renal involvement, osteoporosis, etc.)

Specific Strategies

Management strategies involve prompt recognition and diagnosis of EB and its subtype, and supportive care including, but not limited to, blister prevention, wound care, and prevention of complications.

Investigations Recommended

For diagnosis
Skin biopsy for immunofluorescence antigenic mapping
Skin biopsy for transmission electron microscopy (ultrastructural analysis)
Skin biopsy for light microscopy
Genetic testing
Intrauterine skin biopsy (prenatal diagnosis)

Light microscopy is not useful for establishing the subtype of EB, but can help exclude other vesiculobullous diseases.

A biopsy should be taken from an unblistered area of skin, which has been gently rubbed with a pencil eraser for 1 min (this is to create a cleavage in the skin at a microscopic level). A shave biopsy is preferred, as it provides a longer specimen of the DEJ. The specimen is then gently cut in half for ultrastructural and immunohistochemical analysis. Punch biopsies should be avoided, as the rotational action may cause complete separation of the epidermis from the dermis.

Immunofluorescence mapping (IFM), when coupled with the use of specific monoclonal antibodies, can provide considerable insight into the major type of EB and the structural protein most likely mutated. In many centres, this testing can provide fast and reliable subtype diagnosis and can inform on the genetic panel that needs to be requested [2].

Electron microscopy (EM) is the gold standard for determining the cleavage plane, however, it may be cost prohibitive. The main advantage of EM is that it also allows visualization and semi-quantitative assessment of specific structures of the BMZ. Due to very few recommended reference laboratories worldwide, EM is likely to have a decreasing role in the diagnosis of EB in the future, although it is likely to continue to have an important place in research [3]. In EBS the cleavage plane is either at the infra-nuclear portion of the basal keratinocytes or in the suprabasal epidermis. In JEB the cleavage plane occurs within the lamina lucida (hemidesmosomes), and in DEB the cleavage occurs immediately beneath the lamina densa (anchoring fibrils).

Genetic analysis often does not affect management of the patient, but aids in determining inheritance pattern of the condition, and allows prenatal testing. This can be done by a prenatal/uterine skin biopsy in the second trimester. Newer methods include chorionic villus sampling or amniocentesis in affected families, and can be undertaken in the first trimester of pregnancy.

Specific Therapies

By and large, the management therapy in EB is supportive, consisting of:

- **Prevention of new blisters/avoidance of trauma.** It is very important to puncture and drain large bullae in order to prevent extension and supra-infection of lesions. Parents of young babies need to be taught how to handle the baby [4], to use clothing inside out or with no seams, and to place babies on mattresses that diminish chances of friction. Foam pads can be sewn into the lining of clothing, especially over bony prominences, and babies/infants should be gently handled to prevent blistering. In older patients and adults, particularly those with EBS types, keeping soles and feet cool and dry, use of topical antiperspirants (20 % aluminium chloride hexahydrate) for hyperhidrosis of acral areas, and use of well-fitting footwear may be beneficial in preventing blistering. More severe subtypes will benefit from foam dressings that offer some padding/protection of unaffected to freshly wounded or healed skin.
- **Prevention and treatment of infections and promotion of wound healing.** There is no evidence that routine use of topical antibiotics reduces the risk of infection or enhances healing. However, painful or exudative wounds may benefit from local antimicrobials (either as topical antibiotics or dressings with antimicrobials, such as silver or polyhexamethylene biguanide, PHMB). Occasionally, systemic antibiotics are needed. In patients with EBS there is some evidence that oral tetracycline decreases the blistering, particularly in the summer months [5]. Similarly, patients with RDEB may experience enhanced healing while on trimethoprim [6]. Wound healing is further enhanced if the patient has adequate nutrition and a hemoglobin level at least of 100 g/L [7].
- **Education and psychosocial support.** Providing information about the condition and its potential complications is extremely important. Patients and families also need psychological support through specialized practitioners and from non-profit organizations such as the National EB registry (NEBR) or DEBRA (dystrophic Epidermolysis Bullosa Research Association).
- **Multidisciplinary team involvement.** EB is, in severe cases, a multisystem disease. As such, many knowledgeable specialists are required to manage the cutaneous and extracutaneous complications of this rare condition (dermatologists, nurses, plastic surgeons, pediatricians, gastroenterologists, hematologists, ophthalmic surgeons, dentists, dieticians, physiotherapists, etc.).

A two-arm study with 12 patients given oral tetracycline versus placebo found that there was a definite reduction of blisters in those treated with tetracycline. This, however, was not statistically significant. It is recommended that empirical treatment with oral tetracycline can be given in any EBS patient who is sufficiently symptomatic and willing to risk the adverse effects of oral tetracycline [6].

In a proof-of-concept study involving ten patients with RDEB, six out of seven patients had a 50 % reduction in chronic wound surface area while on trimethoprim versus two out of six patients on placebo. While this was not statistically significant, it provided useful information for further prospective studies [7].

Six patients with RDEB were treated with immunomyeloablative chemotherapy and allogenic stem-cell transplantation. All had improved wound healing and a reduction in blister formation at 30–130 days post-transplantation. Increased collagen VII deposition in five patients and a sustained presence of donor cells were found in all six by immunofluorescence [8].

Table 13.1 First line therapies [5]

Modality	Level of evidence
Blister prevention	E
Wound care	E

Table 13.2 Second line therapies

Modality	Dosage	Level of evidence
Tetracycline	1.5 g per day divided BID for 4 months	D
Trimethoprim	4 mg/kg/day divided into BID for 2 months	D
Bone marrow transplantation		D

Epidermolysis Bullosa Acquisita (EBA)

EBA is a chronic subepidermal immunobullous disorder that is rare in children. Three phenotypes have been recognized [9]:

1. Non-inflammatory type that resembles the inherited form of dystrophic EB, with tense bullae on extensor surfaces and at sites of trauma, milia, atrophic scars, pigmentary changes, and nail dystrophy.
2. Inflammatory type with pruritic tense bullae on normal, erythematous or urticarial skin, including sites that are not exposed to trauma.
3. Mucous membrane pemphigoid-like with involvement of conjunctival, oral, nasopharyngeal, and genital mucous membrane, leading to scarring.

The target antigen is type VII collagen. The long-term prognosis in children is good, with remission usually achieved within 1–4 years [10].

Management Strategies

Management strategies include prompt diagnosis and initiation of first line therapies to control the blistering.

Investigations

For diagnosis
Skin biopsy (lesional) for routine light microscopy
Skin biopsy (perilesional) for direct immunofluorescence (DIF)
Serum for indirect immunofluorescence (IIF)
Immunoelectron microscopy

Table 13.3 First line therapies

Modality	Dosage	Level of evidence
Systemic corticosteroids (prednisolone)	1 mg/kg/day	D
Dapsone	1–2 mg/kg/day	D

- Histology of a fresh blister shows a subepidermal bulla and a predominantly neutrophilic infiltrate with eosinophils.
- DIF of perilesional skin shows linear deposits of IgG and C3 along the BMZ and weak staining for IgA and IgM.
- IIF usually shows the circulating antibody on the dermal side of the bulla of salt-split skin.
- Direct immunoelectron microscopy shows IgG deposits under the lamina densa within the region normally occupied by anchoring fibrils [10].

Oral prednisolone is often used in combination with dapsone with very good effect. Complete remission can be achieved within months and children seem to respond much better than adults [11]. Other treatment options are usually not required, but include azathioprine, colchicine, mycophenolate mofetil, gold, and intravenous immunoglobulins (ivIG) [9].

Ectodermal Dysplasia with Skin Fragility (EDSF)

EDSF is a rare autosomal recessive genodermatosis affecting skin, nails, and hair. The international consensus for classification of epidermolysis bullosa (EB) [12] now considers EDSF to be a suprabasal form of EBS. It is due to loss of function mutations in the PKP1 gene that encodes for plakophilin, a protein that is a component of the desmosomal plaque.

It presents with:

- Skin fragility (with flaccid blisters and erosions on minor trauma)
- Hypotrichosis or alopecia
- Focal palmoplantar keratoderma (with painful fissuring)
- Hypohidrosis, nail dystrophy, and cheilitis may also be present [1]

Management Strategies

Management strategies include diagnosis and prevention and management of blisters similarly to EB.

Investigations

For diagnosis
Skin biopsy for immunohistochemical antigenic mapping
Skin biopsy for transmission electron microscopy (ultrastructural analysis)
Skin biopsy for light microscopy
Molecular testing

Histological findings would show hyperkeratosis, acanthosis with widened intercellular spaces and acantholytic keratinocytes. Electron microscopy in EDSF demonstrates poorly developed, small desmosomes as well as a reduction in the number of desmosomes in the epidermis, particularly the lower suprabasal layer. Immunohistochemical analysis would reveal a complete absence of staining for plakophilin 1 [13].

Specific Therapies

Management of skin fragility is similar to that of epidermolysis bullosa, and includes careful handling of patients to prevent skin friction or trauma and managing blisters, as well as prevention and treatment of infections (see above, EB).

Kindler Syndrome

Kindler syndrome is a rare autosomal recessive skin fragility disorder characterized by trauma induced blistering in infancy, followed by photosensitivity and progressive poikiloderma on sun-exposed areas in later childhood [14]. Early diagnosis is difficult, as it may resemble dystrophic EB in childhood [15]. The abnormality is in the protein, kindlin-1 (fermitin family homologue 1) which is thought to be involved in connecting the actin cytoskeleton to the extracellular matrix. Loss of function mutations occur in the identified gene FERMT1 (formerly known as KIND1) located on chromosome 20 [16]. It is now thought to be part of EBS—mixed subtype [12].

Clinical Features

- Blistering is usually acral, but more extensive blistering has also been reported.

- Significant photosensitivity leading to skin atrophy and poikiloderma; this becomes more generalized and may involve non-sun exposed sites too [14].
- Rarer presentations include: nail dystrophy, fusion of the digits, urethral, esophageal or anal stenosis, fusion of labia and chronic inflammation of the oral mucosa (dental caries, periodontitis, angular cheilitis, and desquamative gingivitis).
- Squamous cell carcinoma of the lip and hard palate may also occur [15].

Management Strategies

Management strategies include prompt recognition and diagnosis. Prevention of blistering (similar to EB patients) and sun damage avoidance are very important. Long-term screening and monitoring for squamous cell carcinoma is recommended.

Investigations

Skin biopsy for immunohistochemical antigenic mapping
Skin biopsy for transmission electron microscopy (ultrastructural analysis)
Skin biopsy for light microscopy
Genetic testing

Light microscopy shows features of poikiloderma, which includes hyperkeratosis, epidermal atrophy, vacuolization of the basal layer, capillary dilation, and dermal edema. There would be cleavage at or close to the dermo-epidermal junction, near the basal keratinocyte layer, or beneath it. There may also be disruption of the collagen and elastic fibers in the papillary dermis.

Electron microscopy examination is used to differentiate from EB. Multiple planes of split may be seen within basal keratinocytes and/or in the lamina lucida, as well as reduplication of the lamina densa. The hemidesmosomes and anchoring fibrils and filaments are unaffected.

Immunohistochemical staining with anti-kindlin 1 antibody would show reduced or absent staining in the dermis [15].

Specific Therapies

Therapies in Kindler syndrome are similar to other subtypes of EB (see above). The blistering will improve with age.

In addition to these management strategies, sun protection advice (sun avoidance and use of sunscreen) should be given to delay the onset and severity of the poikiloderma. Regular skin checks should be performed by a dermatologist, due to the risk of developing squamous cell carcinomas [16].

Pemphigus

Pemphigus is a group of autoimmune intraepidermal vesiculobullous diseases that are characterized by the presence of antibodies to desmosomal proteins. It is classified into two main groups:

1. Suprabasal type, which includes pemphigus vulgaris (PV) and pemphigus vegetans
2. Superficial type, which includes pemphigus foliaceus (PF) and pemphigus erythematosus

Pemphigus is rare in children, infrequently seen before puberty. The most common form is PV, followed by PF. Pemphigus vegetans and erythematosus are exceedingly rare in children.

In PV, blisters develop on normal-appearing skin. They are flaccid and rupture easily, leaving painful erosions and crusts (Fig. 13.2). Scarring is unusual. Mucosal involvement, especially oral, is common and may precede skin lesions by

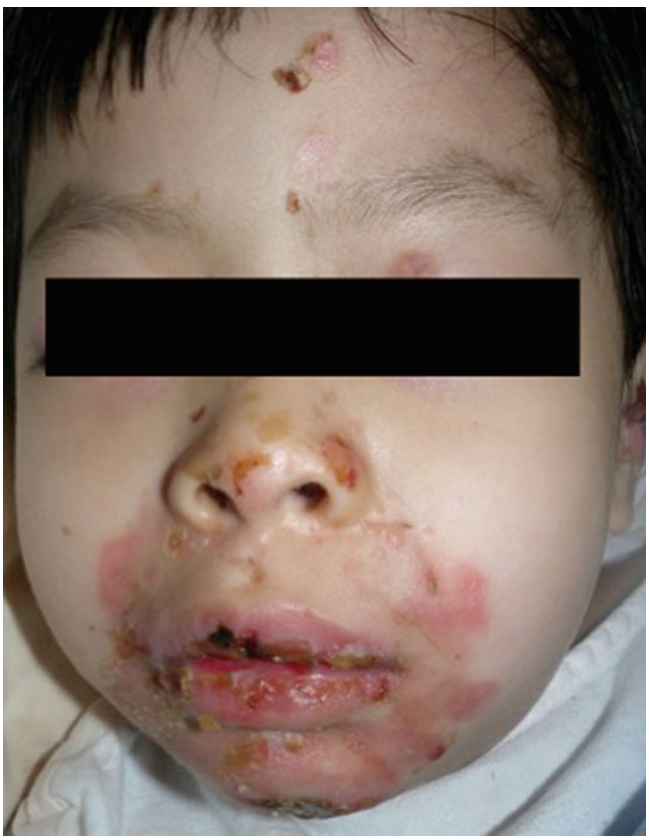

Fig. 13.2 Extensive blistering leading to erosions in pemphigus vulgaris

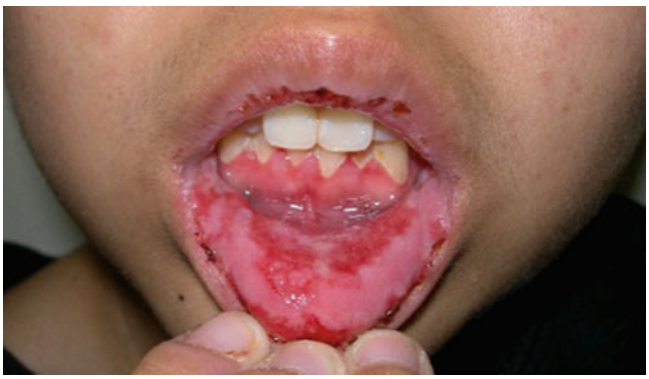

Fig. 13.3 Extensive erosions on the buccal mucosa in a teen with pemphigus vulgaris

several months (Fig. 13.3). Genital and ocular mucosal involvement occurs less frequently [9].

There are two major forms of PF: an endemic form, Fogo selvegam, and a non-endemic form. The endemic form is most commonly seen in South America, especially in children who live in close proximity to rivers where the blackfly, Simulium nigrimanum, (thought to be the vector of this disease) is found. The etiology of the non-endemic form is unknown. The lesions usually present on the scalp, face, and upper trunk as erythematous scaly erosions. Blisters are usually too superficial to allow significant fluid accumulation. Mucosal involvement is minimal to none [14].

Investigations

For diagnosis
Skin biopsy (lesional) for routine microscopy
Skin biopsy (perilesional) for direct immunofluorescence (DIF)
Serum for indirect immunofluorescence (IIF)

Pemphigus Vulgaris [9]

Histology under routine light microscopy shows suprabasal acantholysis with basal keratinocytes remaining attached to the epidermal basement membrane. The dermal infiltrate as well as the blister cavity usually consists of lymphocytes, neutrophils, and eosinophils.

DIF shows deposition of IgG around keratinocytes, giving rise to a "crazy paving" pattern. IIF of the serum usually shows the presence of circulating IgG autoantibody; the titers correlate with clinical severity and can therefore be used to monitor progression. Antibodies are against desmoglein 3 when only mucosal lesions are present, and both desmogleins 1 and 3 in mucocutaneous disease.

Pemphigus Foliaceus/Erythematosus

Histology shows subtle acantholysis and occasionally subcorneal separation. A mild dermal lymphocytic and eosinophilic infiltrate may be found. DIF will usually show a linear deposition of IgG or IgM at the epidermal BMZ. The antigen in PF and erythematosus is desmoglein 1. The prognosis is good with very few fatalities.

Specific Therapies (For PV and PF)

Treatment for PF is similar to that for PV, but due to its less aggressive course, topical corticosteroids are usually sufficient [17].

A review article of all cases of childhood PV identified 47 cases from 20 studies of childhood PV [18]. The authors highlight the beneficial use of topical or intralesional corticosteroids for limited disease in removing debris, promoting healing, and offering symptomatic relief. It has been suggested that oral prednisolone be commenced at 1–1.5 mg/kg/day for a maximum of 3 months and, if the response is adequate, it can be switched to alternate-day therapy and gradually tapered and eventually discontinued. If the patient does not respond to this dosage, then this is an indication for using concomitant therapies (as listed below).

A review article describes 46 cases of childhood PV [19]. The mean age of onset of disease activity was 12 years. Systemic corticosteroids are the recommended mainstay of treatment, even in indolent cases, with an initial dose of 2–3 mg/kg/day with a slow tapering to 0.5–0.8 mg/kg/day in 2 weeks. Adjuvant treatments should be considered for steroid-sparing purposes. Azathioprine was the most commonly used adjuvant in seven cases. The authors recommend that approximately 2 mg/kg/day of azathioprine be used initially, divided into two doses, followed by a maintenance dose of 1 mg/kg once daily.

Another review article analysing 29 reports of PV showed that 26 patients had treatment with oral prednisolone either alone or with adjuvant therapy [20]. In those who had adjuvant therapy, six had azathioprine at 1–4 mg/kg/day, five had methylprednisolone at 1–6 mg/kg/day, four had dapsone at

Table 13.4 First line therapies

Modality	Dosage	Level of evidence
Isolated, persistent lesions		
Topical or intralesional corticosteroids	BID	E
Widespread disease		
Systemic corticosteroids (prednisolone)	1–3 mg/kg/day	D

Table 13.5 Second line therapies

These are used for a steroid-sparing effect, and are often used as an adjuvant to oral corticosteroid therapy.		
Modality	**Dosage**	**Level of evidence**
Azathioprine	2 mg/kg/day divided into 2 doses then 1 mg/kg/day once a day as maintenance	D
Dapsone	50 mg–200 mg/day	E
Cyclophosphamide	50–150 mg/day	E
Gold	15 mg/week	E
Methylprednisolone	1–6 mg/kg/day	E
Rituximab	500 mg twice a day, 15 days apart or 375 mg/m^2 body surface area twice a day, 15 days apart	D

14–200 mg/day, two were treated with cyclophosphamide, two with gold therapy, and one with cyclosporine. Patients who received complete or partial remission were those on oral prednisolone alone or in combination. Three patients responded well to a combination of methylprednisolone and azathioprine, two to rituximab infusions, and three to topical steroids.

A recent publication reports ten patients with pemphigus (seven with PV and three with PF) treated with rituximab [21]. Most had previously received other immunosuppressant agents, including systemic corticosteroids, azathioprine, dexamethasone pulse therapy, methotrexate, and mycophenolate mofetil, but had ongoing disease. All ten patients were treated with either a fixed-dose regimen (rituximab 500 mg BID, 15 days apart) or a body-weight regimen (rituximab 375 mg/m^2 body surface area BID, 15 days apart). Adjuvant oral corticosteroid (0.5–1 mg/kg/day) was also administered. Seven patients had complete remission by a mean of 21 weeks. Relapse/flare occurred in six patients by a mean period of 13 months. Two patients received a second cycle of rituximab infusions, with good clinical response. Infusion reactions were the most common adverse event, but no long-term complications were seen.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is extremely rare in children. It is associated with lymphoproliferative neoplasms, in particular Castleman's disease (angiofollicular lymphoid hyperplasia). Affected children develop severe oral mucositis, conjunctival involvement, and cutaneous and mucosal lichenoid or erosive lesions. Patients often also develop pulmonary destruction leading to bronchiolitis obliterans [22].

Investigations

For diagnosis
Skin biopsy (lesional) for routine microscopy
Skin biopsy (perilesional) for direct immunofluorescence (DIF)
Serum for indirect immunofluorescence (IIF)
Enzyme-linked immunosorbent assay (ELISA), immunoprecipitation and immunoblotting

Histological findings are usually a lichenoid/interface infiltrate, with variable degrees of cell necrosis, intraepithelial acantholysis, or a combination of both.

DIF shows deposition of IgG and C3 in the intercellular spaces, and variable immunostaining at the basement membrane zone. IIF will show circulating IgG autoantibodies. Immunoprecipitation studies should have serum IgG autoantibodies against desmoplakin I, envoplakin, and periplakin. ELISA shows anti-desmoglein 3 or 1 antibodies, and immunoblotting demonstrates antiplectin antibodies [22].

Specific Therapies

Prognosis is poor, with a high mortality rate, especially if there is lung involvement. The clinical and immunopathological findings of 14 paediatric patients with paraneoplastic pemphigus were reviewed [22]. The average age at presentation was 13 years. Severe oral mucositis and lichenoid cutaneous lesions were observed in 14 and 8 patients respectively. Pulmonary destruction leading to bronchiolitis obliterans was seen in 10 patients, association with Castleman's disease in 12 patients, and a fatal outcome in 10 patients. They concluded that pulmonary injury accounts for the high mortality.

There have been some case reports of attempted treatment with high-dose corticosteroids, azathioprine, or rituximab [22–24], but these have been unsuccessful and death has ensued secondary to bronchiolitis obliterans and respiratory failure.

In cases where there is pulmonary involvement, lung transplant may be the only possibility of survival.

Bullous Pemphigoid

Bullous pemphigoid (BP) is a rare disease in children. Two peaks of incidence have been noted—one before the age of 1 and the second at 8 years of age [25].

Specific criteria have been proposed to aid in early recognition of the disease [26]:

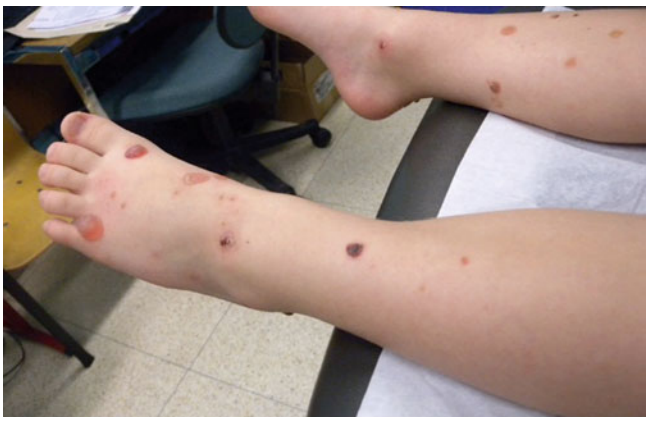

Fig. 13.4 Tense blisters on normal or erythematous skin in a patient with bullous pemphigoid

1. Patients should be aged 18 or younger
2. Clinical appearance of tense blisters on erythematous or normal skin with or without mucous membrane involvement
3. Subepidermal blisters with eosinophils
4. Linear deposits of IgG or C3 at BMZ on DIF or circulating IgG anti-BMZ autoantibodies on IIF

Clinically, patients present with tense, clear or hemorrhagic vesicles or bullae on normal or erythematous skin (Fig. 13.4). Annular or polycyclic urticarial plaques may be seen. Mucous membrane involvement is more common than in adults, and acral involvement is more typical in infants less than 1 year of age. The flexures, face, and genital area are also more commonly involved in infants. Genital involvement is more common in childhood BP than in infantile BP [25].

BP has been reported in psoriasis, after UV radiation, and following vaccination [27]. It has also been noted to occur with certain medications, namely furosemide and non-steroidal anti-inflammatory agents [28].

Investigations

For diagnosis
Skin biopsy (fresh blister) for light microscopy
Skin biopsy (perilesional) for direct immunofluorescence (DIF)/ Immunohistochemistry
Indirect immunofluorescence (IIF) for circulating IgG antibodies to the BMZ

Histology will show subepidermal blistering with an inflammatory infiltrate, mostly composed of eosinophils, with some neutrophils and lymphocytes.

DIF may show a linear deposition of IgG and C3. The IIF on salt-split skin reveals circulating IgG antibody and C3 directed against the epidermal side of the split. Occasionally, dermal binding may be observed despite Western blot revealing an epidermal location for the target antigens.

Immunoblotting reveals the target antigens to be BP 230 and BP 180, which are hemidesmosomal proteins.

Specific Therapies

The prognosis of BP in children is good. In most cases the disease duration is 1 year or less.

A review of the literature, including 79 cases of childhood (including infantile) BP, showed rapid and effective response to systemic steroids. Response was within days to several months, with relapses being rare. The majority of patients were treated with oral prednisolone 1–2 mg/kg/day, but the range was from 0.5 to 4 mg/kg/day [25].

Potent to ultrapotent topical corticosteroids can be used to effectively treat localised blisters [25].

Dapsone and sulphapyridine have been used adjunctively as a steroid-sparing agent in BP [25].

- Oral erythromycin has been used successfully in some patients for BP. It is thought to be its anti-inflammatory mechanism of action, which inhibits chemotaxis of neutrophils or eosinophils. It can be considered as a supplemental or alternative to oral steroids [29].
- Rituximab (chimeric monoclonal antibody which targets the CD20 molecule on the B-cell surface) has been used

Table 13.6 First line therapies

Modality	Dosage	Level of evidence
Oral corticosteroids (prednisolone)	1–2 mg/kg/day	D
Potent to ultrapotent topical corticosteroids	BID	E

Table 13.7 Second line therapies

Modality	Dosage	Level of evidence
Dapsone	2 mg/kg/day	E
Sulphapyridine	1–2 g/day	E
Erythromycin	35 mg/kg/day for 6 weeks	E
Mycophenolate mofetil	20–30 mg/kg/day	E
Cyclosporine	3–4.5 mg/kg/day	E
Omalizumab	100 mg subcutaneously every 2–4 weeks for 7 months	E
Rituximab infusion	375 mg/m^2	E
Methotrexate	10 mg per week	E

successfully in a 5-month-old boy with refractory BP. He failed to respond to oral prednisone, IvIG, dapsone, topical pimecrolimus, cyclosporine and mycophenolate mofetil. He was then treated with 375 mg/m^2 of rituximab via an infusion, and then once more at a lower dose of 187.5 mg/m^2 due to drug-induced fever following the first infusion. Appearance of blisters during the second episode coincided with increasing CD-19 cells [30].

- Omalizumab (recombinant humanized monoclonal antibody that binds to the Ce3 domain of IgE) was administered with successful results in a 5-month-old infant with BP. It was initially administered at 100 mg subcutaneously followed by injections every 2 weeks for 3 months, and then monthly injections for a further 4 months. Complete remission was achieved at day 25. It has been suggested that the mechanism of action is through blocking IgE-eosinophil pathways [31].
- Recently, oral methotrexate of 10 mg/week in combination with oral prednisolone of 1 mg/kg/day induced progressive to total remission of lesions in a 13-year-old boy with BP after 4 weeks of treatment [32].

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is thought to be the most common autoimmune blistering disease in childhood. It is a cutaneous manifestation of celiac disease and, although only 10 % of children have a diagnosis of celiac disease, gluten-sensitive enteropathy with small bowel changes is present in over 90 % of all cases [33].

There is a spectrum of severity ranging from mild pruritic papules on the knees and elbows to widespread excoriations. Intact vesicles are rarely seen, as they have been excoriated secondary to intense pruritus. Sites most commonly affected are extensors surfaces of limbs, buttocks, shoulders, nape of neck, and scalp (Fig. 13.5).

Management Strategies

Management strategies include prompt recognition, referral to a gastroenterologist, and immune-suppressive therapies to control the symptoms and systemic inflammation.

Investigations

For diagnosis
Skin biopsy (lesional) for routine microscopy
Skin biopsy (perilesional) for direct immunofluorescence (DIF)
IgA anti tissue transglutaminase antibodies, anti-endomysial antibodies
Total IgA level
For treatment
Complete blood count (CBC) with differential, liver function tests (LFTs)
Glucose-6-phosphate dehydrogenase levels (G6PD)

- Routine microscopy in DH shows a subepidermal blister with neutrophilic (and occasionally eosinophils) microabscesses within the dermal papillae, often with a mixed inflammatory infiltrate.
- The pathognomonic feature on direct immunofluorescence is the granular deposition of IgA within the dermal papillae, occasionally accompanied by C3. These

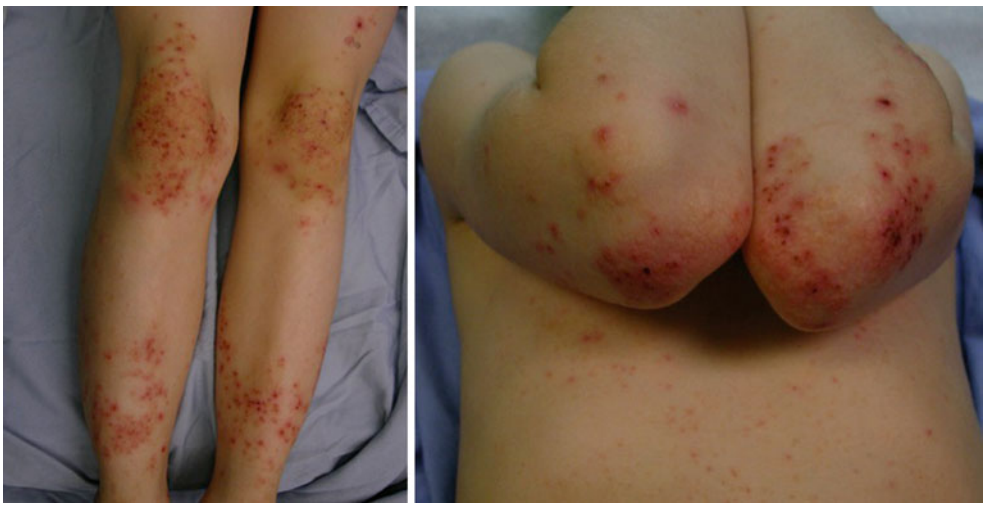

Fig. 13.5 Typical location on the extensor surfaces of a patient with dermatitis herpetiformis: lesions consist of itchy papulo-vesicles that become excoriated

findings are seen in perilesional or uninvolved skin but not in actively blistered areas [34].

- Testing for antiendomysial antibody is a highly specific and moderately sensitive test. IgA anti-tissue transglutaminase (tTG) and anti-epidermal transglutaminase (eTG) antibody testing is performed by enzyme-linked immunosorbent assay (ELISA) and has a specificity of 97.6–100 % and 92–100 % respectively, and sensitivity of 48.8–89.1 % and 60–80.8 % respectively [35].
- Anti-endomysial, anti-tTG, and anti-eTG antibodies are low or undetectable in patients following strict gluten-free diet and, therefore, these may be useful quantitative markers of adherence to this dietary regimen.
- Selective IgA deficiency is about 10–15 times more prevalent in patients with celiac disease compared with the general population, and therefore IgA titres should also be simultaneously performed, as IgA deficiency in a patient can lead to false negative serology. In these patients, IgG antibodies to endomysium and transglutaminases may be useful to monitor disease.
- On direct immunofluorescence, the IgA deposits are not altered by pharmacologic therapy for DH, but do slowly resolve on a gluten-free diet [35].

Specific Therapies

A follow-up study for 3–10 years of 76 children with DH (plus/minus small bowel disease) showed that treatment with a gluten-free diet alone (for a period of 1–6 months) led to a reversal of the intestinal abnormality in 100 % of children, and to the disappearance of cutaneous lesions in 82 % of cases.

Use of dapsone alone was effective in clearing the cutaneous lesions, but not in reversing the intestinal abnormalities [33]. Dapsone is generally well tolerated. Side effects include methemoglobinemia, hemolysis and, rarely, agranulocytosis. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are particularly prone to dapsone-mediated hemolysis and may need to be treated with lower doses and to receive more frequent follow-up. Patients should have regular follow-up with frequent blood counts, in particular CBC with differential weekly for 4 weeks then every 2 weeks for 8 weeks, then every 3–4 months [35].

Dapsone may be tapered by reducing the daily dose or gradually increasing the time interval between doses while clinical remission is maintained. A weekly full blood count and reticulocyte count is recommended for the first month and then monthly for the next 5 months [34].

Three adults with DH responded very well to sulphasalazine after being non-responsive or intolerant to dapsone, and the authors recommend this as an inexpensive, readily available medication [36]. Another article reports two teenage patients who also responded very well to sulphasalazine at 2–4 g/day [37].

There have been reports of success with systemic corticosteroids, cyclosporine, and colchicine, and a combination of heparin, tetracycline, and nicotinomide, but these reports are only in adult patients [38–41].

Table 13.8 First line therapies

Modality	Dosage	Level of evidence
Gluten-free diet		B
Dapsone	1–2 mg/kg/day	B

Table 13.9 Second line therapies

Modality	Dosage	Level of evidence
Sulphasalazine	1–2 g/day	E
(or sulphapyridine)	(250 mg/day)	
Topical corticosteroids (limited disease)	BID	E

Chronic Bullous Disease of Childhood (CBDC)

CBDC is also known as linear IgA disease of children. It is an acquired autoimmune subepidermal blistering disorder characterized by the deposition of a linear band of IgA along the dermal-epidermal junction.

The molecular basis has not been clearly defined, but there is an increased incidence in those with HLA-B8, HLA-DR3, and HLA-DQW2 [42]. It typically occurs in children under the age of 5. There may be a preceding prodromal illness.

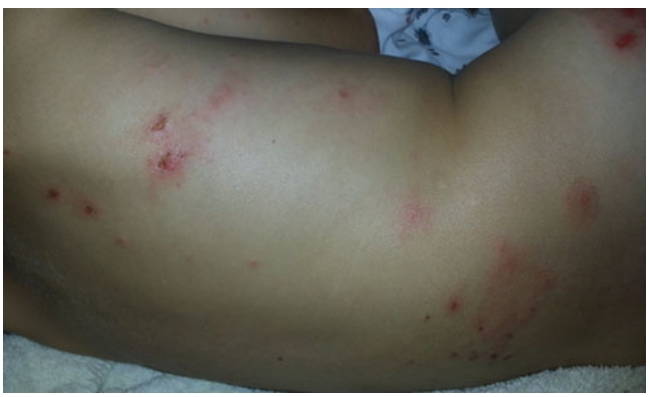

Fig. 13.6 Blistering occurring over urticarial plaques in a patient with chronic bullous disease of childhood

Clinical Features (Fig. 13.6)

- Tense vesicles begin abruptly on normal skin and occasionally on urticarial plaques
- Localized or widespread, with common sites being the face, trunk, extremities, or genital area
- The development of new blisters at the margins of old ones may give an appearance that is described as a "string of pearls," rosettes, or "cluster of jewels" signs; central clearing of peripheral blisters give rise to polycyclic lesions
- Mild pruritis
- The bullae resolve with transient pigmentary changes, but usually no scarring
- Mucous membrane (oral and conjunctiva) may be involved in up to 76 % of cases [43]

Investigations

For diagnosis
Skin biopsy (lesional) for routine microscopy
Skin biopsy (perilesional) for direct immunofluorescence (DIF)
Indirect immunofluorescence (IIF) for circulating IgA antibodies to the BMZ
For treatment
Baseline glucose-6-phosphate-dehydrogenase level (G6PD)
Complete blood count (CBC) with differential, Liver function tests (LFTs)

Histological examination of a fresh lesion is not diagnostic and does not distinguish from other immunobullous disorders. A subepidermal vesicle is seen with neutrophils or eosinophils as the inflammatory infiltrate. DIF will show a linear band of IgA along the dermo-epidermal junction. This may be associated with weaker bands of IgG, IgM, or C3 [44].

Baseline G6PD is recommended especially in those racial groups most at risk. The CBC and LFTs are done for monitoring of hemolysis and changes in liver function, weekly for 1–3 months. Thereafter, the frequency of blood tests can be reduced to monthly. Reticulocyte count can be done if there is suspicion of agranulocytosis.

Specific Therapies

Most cases (65 %) will resolve spontaneously within 5 years of onset [45]. Some may persist, but there is no correlation between the severity of blistering and disease chronicity. Treatment is usually offered to reduce disease severity and to shorten the duration of the illness.

Table 13.10 First line therapies

Modality	Dosage	Level of evidence
Mid- to superpotent topical corticosteroids (mild disease)	BID	D
Dapsone	0.5–1 mg/kg/day	B
	Max 2 mg/kg/day	
Adjunctive oral prednisolone for patients not responding to dapsone	1 mg/kg/day for 1–3 weeks	D
	Reduce to stop over 3–6 weeks	
Flucloxacillin	150–500 mg four times per day	D
Oxacloxacillin	50 mg/kg/day	E
Dicloxacillin	40 mg/kg three times per day	E
Erythromycin	250 mg three times per day	E

Dapsone is effective as a single agent therapy for blister suppression in up to 42 % of patients [45]. Sulphamethoxypyridazine is probably equally effective (see below). It is commenced at the lowest practical dose, (usually 125 mg daily) and increased slowly. Side effects include neutropenia, agranulocytosis, and hepatitis. It has superseded sulphapyridine due to fewer side effects [45]. Prednisone (1–2 mg/kg/day) in doses up to 60 mg/day has been used effectively as an adjunct with dapsone [45]. Topical steroids can be used for limited, mild disease. Once the disease in under control, the drug should be withdrawn over a period of months [45].

An observational case series of seven patients with CBDC treated with flucloxacillin was published [46]. In four cases, there was complete remission within 3–4 months of starting therapy, with no relapses. In the other three cases, flucloxacillin controlled the disease, but with prompt relapse on discontinuation. The group that experienced relapses had been on other treatments, including dapsone and oral corticosteroids, and had delayed commencement of flucloxacillin. The authors recommend early initiation of flucloxacillin, with gradual tapering of the dose over 2.5 months to 6 years, depending on improvement. It is recommended as an alternate first line treatment in those who cannot take dapsone.

Dicloxacillin 40 mg/kg three times per day has also been used with good success in CBDC [47]. There are no recommendations on duration of treatment, as the eruption is found to recur on discontinuation of dicloxacillin.

One paper describes a 5-year-old girl with mixed immunobullous disease who didn't respond to topical steroids [48]. Erythromycin 250 mg three times a day resolved the lesions completely. She required 24 months of continuous treatment. Erythromycin was chosen because it is safe in children and requires no blood monitoring. Anti-

Table 13.11 Second line therapies

Modality	Dosage	Level of evidence
Sulfapyridine	60–150 mg/kg/day	D
Sulfamethoxypyridazine	125 mg/day	D
Colchicine	0.5 mg BID	D

inflammatory properties of erythromycin are thought to be responsible for the improvement. It may take the place of more toxic drugs in children.

In a case series, eight children between 3 and 9 years of age were given colchicine 0.5 mg twice a day for 4–14 months [49]. Five had excellent response on colchicine alone, and a further three required low-dose oral steroid in addition to the colchicine to maintain remission. The authors suggest colchicine as an alternative first-line agent in patients with G6PD deficiency, or when other therapies have failed.

Bullous Systemic Lupus Erythematosus (BSLE)

BSLE is a rare childhood disease. It is an acquired autoimmune blistering disorder that presents in a patient who has been diagnosed with systemic lupus erythematosus (SLE) in accordance with the criteria of the American Rheumatism Association for SLE. It can present as the initial presentation of SLE or occur during the course of the disease. In addition to the diagnostic criteria for SLE, patients with BSLE should fulfill the clinical and investigative criteria listed below.

Criteria for BSLE

- Diagnosis of SLE based on the American Rheumatism Association (need 4 out of 11 criteria)
- An acquired vesiculo-bullous eruption
- Histologic evidence of a subepidermal blister and a predominantly neutrophilic dermal infiltrate
- Direct immunofluorescence microscopy demonstrating IgG (with or without IgA or IgM) deposits at the basement membrane zone
- Evidence of antibodies to type VII collagen
- Evidence of response to dapsone

Sun-exposed sites are preferentially affected, with a pruritic non-scarring eruption consisting of tense blisters on normal or urticated skin. Mucous membrane involvement of the oral, nasal, and genital mucosae may be rarely seen.

The target antigen is usually type VII collagen, but other autoantibodies against BP230, laminin 5 and laminin 6 may also be produced [50].

Investigations

For diagnosis
Skin biopsy (from edge of blister) for routine microscopy
Skin biopsy (perilesional) for direct immunofluorescence (DIF)

Table 13.12 First line therapies

Modality	Dosage	Level of evidence
Dapsone	25–50 mg/day	D
Serum for indirect immunofluorescence (IIF) on salt-split skin		

Table 13.13 Second line therapies

Modality	Dosage	Level of evidence
Intravenous immunoglobulin (IVIG)	2 g/kg given over 5 days	E
Mycophenolate mofetil	500 mg twice a day	E
Hydroxychloroquine	200 mg twice a day	E

For treatment
Baseline glucose-6-phosphate-dehydrogenase level (G6PD)
Complete blood count (CBC) with differential, Liver function tests (LFTs)

- Histology from a fresh blister in BSLE would show a subepidermal blister with the presence of neutrophils in the upper dermis, either in the dermal papillae or under the BMZ.
- DIF would show linear or granular BMZ IgG and complement deposition with weaker staining of IgA and/or IgM.
- IIF on salt-skin substrate would show circulating IgG and IgA autoantibodies on the dermal floor of salt-split skin.
- Ultrastructural examination would show immune deposits on or beneath the lamina densa of the DEJ [9].

Specific Thrapies

The treatment of choice is dapsone, usually 25–50 mg daily. The prognosis of the blistering eruption is good, but the ultimate outcome depends on the degree of systemic involvement of lupus. The response to the lesions is usually dramatic, with improvement within 1–2 days [51].

A case report of a 16-year-old girl with BSLE was initially treated with a combination of dapsone, 100 mg prednisone, and azathioprine. As a complication of immunosuppression, she developed widespread herpetic eruption and therefore prednisone and azathioprine were discontinued. IVIG was commenced at 2 g/kg for 5 days, which

resulted in complete resolution of the bullae. IVIG has been suggested as a safe alternative to conventional therapies [52].

A 13-year-old girl with BSLE was initially commenced on pulsed-dose methylprednisone and 200 mg BID of hydroxychloroquine. This was changed to oral prednisone of 90 mg daily. She responded well to this combination of treatment. Prednisone was being slowly tapered, and she was on 100 mg dapsone twice daily at the time of writing of the case report. The authors comment that bullous SLE is usually unresponsive to oral corticosteroids. Although their patient responded, she required a high dose of the oral prednisolone [53].

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Infectious Diseases: Bacterial Infections

14

Kiran Motaparthi

Staphylococcal and Streptococcal Infections

Clinical Features

Infections Mainly Caused by *Staphylococcus aureus*

Impetigo is a superficial bacterial infection most commonly seen in young children, although any age group may be affected. It may be a primary disease or a secondary infection of an inflammatory dermatosis. Variants include non-bullous impetigo, bullous impetigo, and ecthyma. Non-bullous impetigo is the most common form, and presents with vesicopustules and papules with golden brown crust on the face or extremities. Bullous impetigo is characterized by flaccid blisters that rupture and leave superficial erosions on the trunk (Figs. 14.1 and 14.2). Ecthyma is a deep ulcerative variant that results in punched-out ulcers, most often on the lower extremities (Fig. 14.3). The most common causative pathogen of impetigo is S. aureus, and methicillin-resistant S. aureus (MRSA) accounts for up to 10 % of isolates [1]. Blisters in bullous impetigo result from cleavage of desmoglein 1 by exfoliative toxin A. Beta-hemolytic streptococci are the major causative pathogens of ecthyma, but are involved in only a minority of other variants of impetigo. Postinfectious sequelae, including glomerulonephritis and rheumatic fever, can result from streptococcal impetigo [2].

S. aureus is the most common cause of bacterial folliculitis, which presents with superficial non-scarring pustules on an erythematous base, pierced by a central hair. In contrast, deep staphylococcal folliculitis presents with painful plaques and nodules that heal with scarring; impetigo and furuncles are often associated. A circle of surrounding desquamation is a helpful identifying feature [3]. Both methicillin-sensitive *S. aureus* (MSSA) and MRSA are causative. Folliculitis barbae (sycosis barbae) involves the deep portions of the hair follicles of the beard area (Fig. 14.4) [4]. Staphylococcal folliculitis often involves the scalp, face, and intertriginous areas in children [5].

Abscesses are collections of pus in the skin and soft tissues that present as fluctuant or non-fluctuant nodules with surrounding erythema and edema (Fig. 14.5). Purulent drainage may be seen, and pain and tenderness are common. A furuncle is an abscess of the hair follicle that extends into the dermis and subcutaneous tissue (Fig. 14.6), while a carbuncle is a coalescence of multiple furuncles [6]. Given their close relationship to folliculitis, carbuncles and furuncles are seen on non-glabrous skin, most commonly of the axillae, groin, buttocks, and head and neck. Although abscesses can be polymicrobial, *S. aureus* is the most common cause, accounting for up to 75 % of cases, and both MRSA and MSSA are causative [7].

Similar to bullous impetigo, staphylococcal scalded skin syndrome (SSSS) is caused by cleavage of desmoglein 1 by exfoliative toxins. In contrast, SSSS is due to dissemination of these toxins from a distant nidus of infection, and results in sterile bullae. Flaccid blisters occur most prominently in the intertriginous areas, buttocks, hands, and feet, over a background of diffuse erythema (Fig. 14.7). Mucous membranes are spared. Systemic symptoms, including fever, are common. SSSS occurs almost exclusively in children under 6 years of age, and neonates are particularly susceptible (Fig. 14.8) [8].

In children, the most common sites for cellulitis are the extremities and the head and neck. Periorbital, orbital, and preseptal cellulitis are particularly more common in children than in adults. Erythema, edema, and warmth involving the skin and deep soft tissues is characteristic. Purulence, lymphangitis, lymphadenopathy, purpura, bullae, and necrosis are variable features. Among cases of cellulitis with positive cultures, *S. aureus* is the most common isolate, and MRSA and MSSA are equally causative [9].

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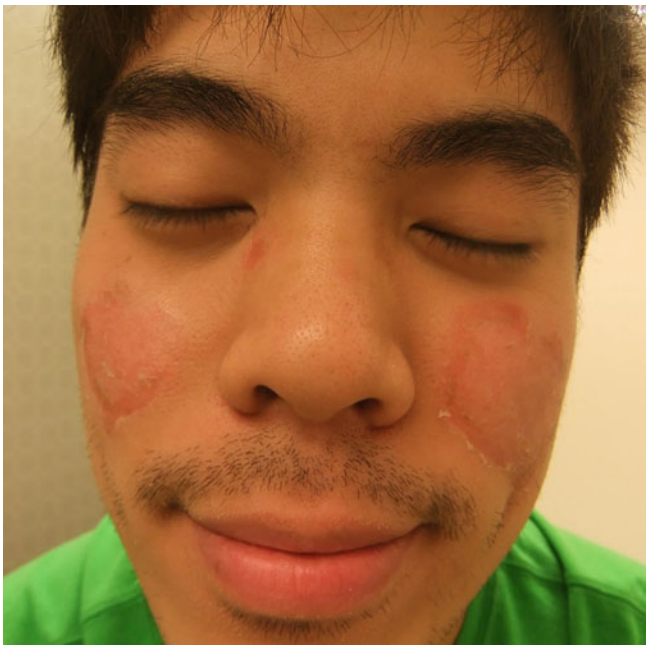


Fig. 14.1 Impetigo. Superficial erosions on the cheeks of an adolescent male

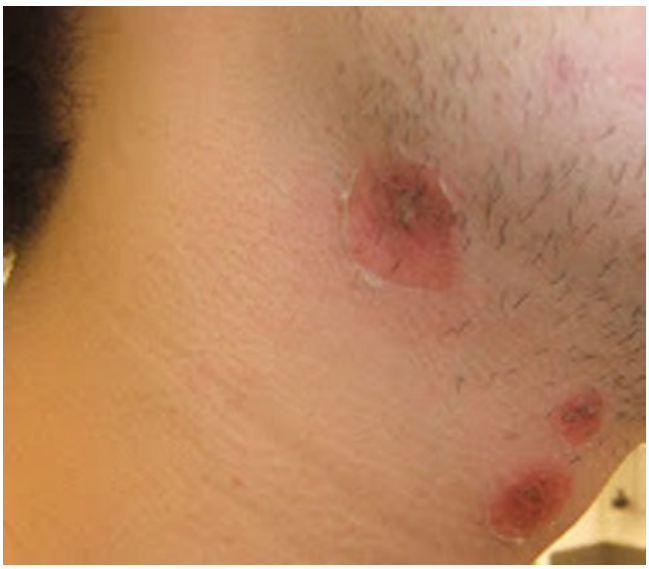


Fig. 14.2 Impetigo. Erosions with superficial desquamation on the neck

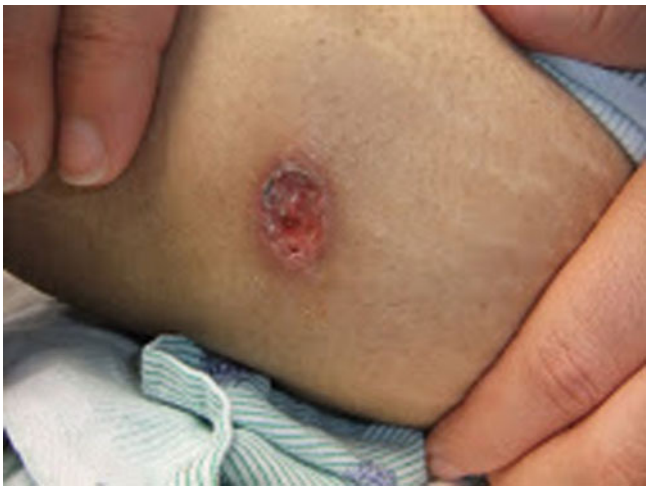


Fig. 14.3 Ecthyma. Punched-out ulcer with purulent exudate on the thigh of a teenage girl

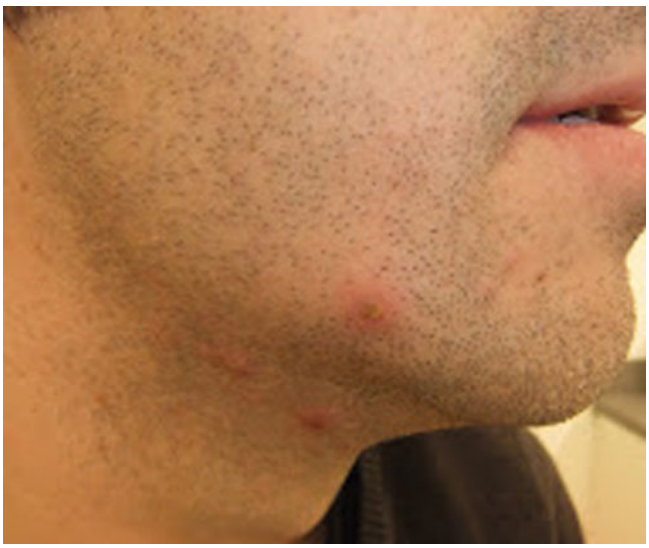


Fig. 14.4 Folliculitis barbae (sycosis barbae). Folliculocentric pustules in the beard area. Culture grew *S. aureus*

Infections Mainly Caused by *Streptococcus pyogenes*

Scarlet fever is an exanthem that occurs in association with pharyngitis due to *Streptococcus pyogenes*, a group A beta-hemolytic *Streptococcus* (GABHS) which elaborates erythrogenic toxins. The median age of affected patients is 4 years old. Erythema begins in the flexural areas and spreads to the rest of the body but spares the circumoral area, palms, and soles. The erythema is composed of pinpoint papules that result in a rough "sandpaper" like texture to the skin which later desquamates. Pastia's lines (linear petechiae of the flexures), strawberry tongue, fever, and lymphadenopathy are present in the majority of patients. Signs and symptoms consistent with streptococcal pharyngitis, including tonsillar edema and the absence of cough and coryza, are typical. Untreated, scarlet fever with pharyngitis may precede the development of acute rheumatic fever [10].

Perineal streptococcal dermatitis (PSD) presents as a well-demarcated erythema that starts at the anus and spreads centrifugally toward the genitals. Eighty percent of patients are between 2 and 7 years of age. Rectal itching, pain, and bleeding are common, but systemic symptoms are absent [11]. GABHS is the causative pathogen in the vast majority

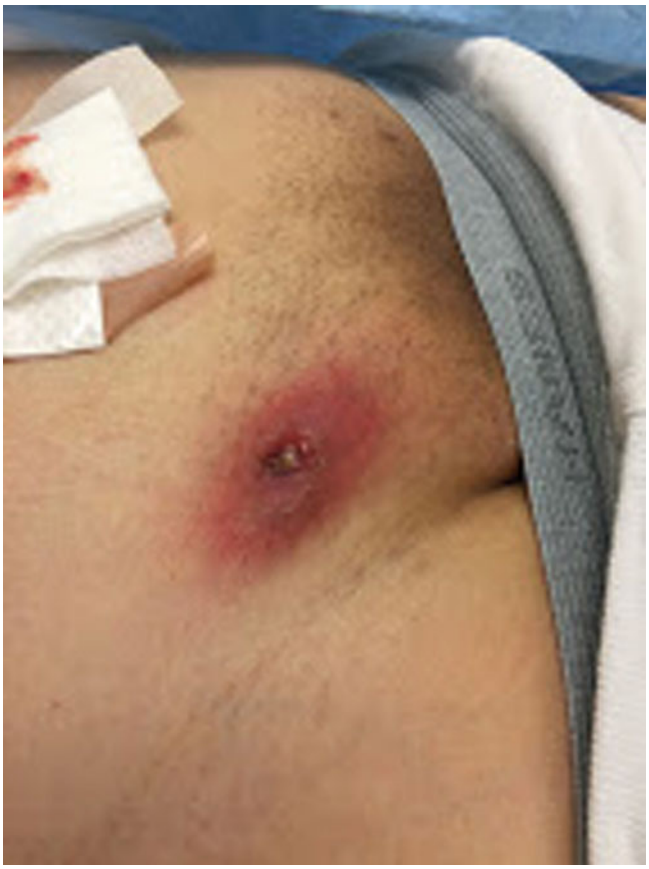


Fig. 14.5 Furuncle. Tender, fluctuant nodule with purulent drainage (Photo courtesy of Sylvia Hsu, MD)

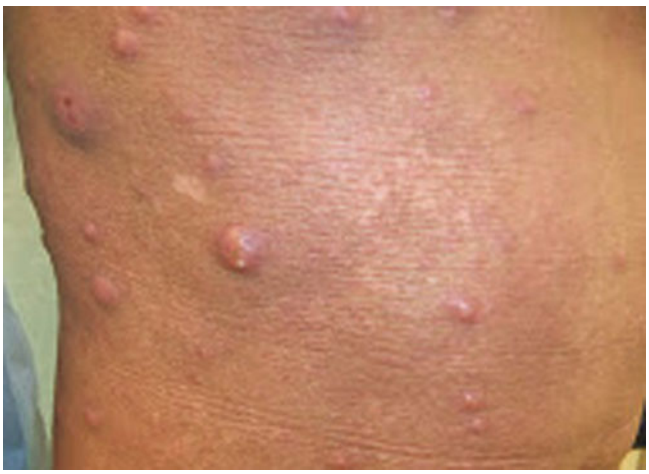


Fig. 14.6 Furunculosis. Multiple abscesses are present in a young adult with severe atopic dermatitis

of cases, although other streptococci and *S. aureus* have been reported to cause a similar clinical picture.

Blistering distal dactylitis (BDD) is an infection localized to the volar fat pad of the distal phalanx that presents with a non-tender, fluid-filled, bulla. Dorsal extension may occur,

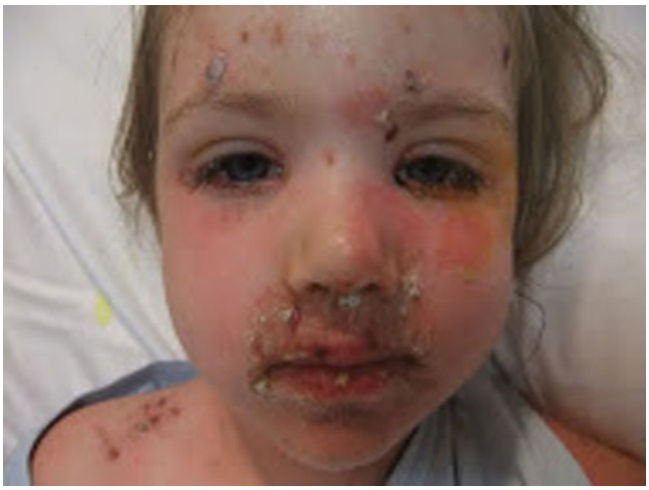


Fig. 14.7 Staphylococcal scalded skin syndrome. Superficial erosions and crusting on a background of diffuse erythema in a 4-year-old girl

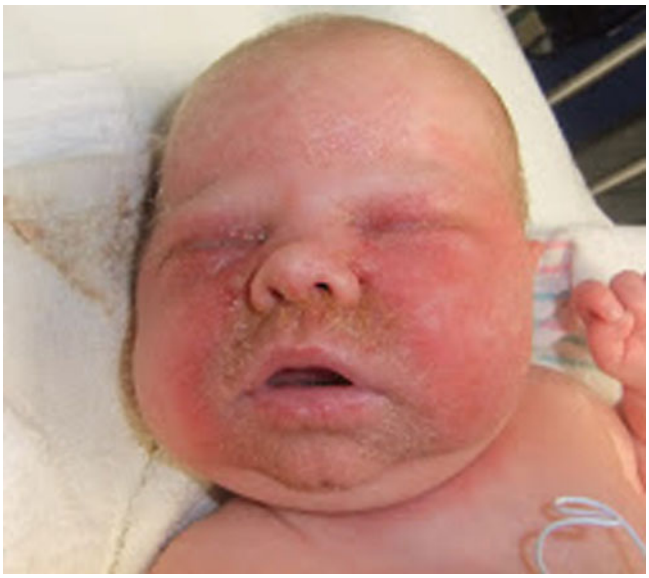


Fig. 14.8 Staphylococcal scalded skin syndrome. A neonate with diffuse erythema, crusting, purulence, and characteristic "sad man" facies

with involvement of the nail folds. GABHS is the most common isolate from cultures, although staphylococci have also been reported in the literature. Children between 2 and 16 years of age are most commonly affected [12].

In contrast to cellulitis, erysipelas involves only the upper dermis and superficial lymphatics. As a result, erysipelas presents with sharply demarcated and elevated erythematous plaques. Systemic symptoms and a very acute presentation are frequent. The most common sites of involvement are the lower extremities. Although both streptococci and staphylococci can cause erysipelas, streptococci are more frequently pathogenic [13].

Toxic shock syndrome (TSS) may be caused by *S. aureus* or *S. pyogenes*, and is characterized by an acute, rapid illness

with fever, hypotension, and multisystem organ involvement. Superantigens underlie the pathogenesis of TSS by binding directly to molecules of MHC class II. Since they are not processed by antigen-presenting cells, superantigens trigger massive T-cell activation and release of cytokines. The major staphylococcal superantigens are TSST-1 and enterotoxins, while the major Streptococcal superantigens are the pyrogenic exotoxins [14].

In streptococcal TSS, fever and localized pain are the most common presenting signs. Children with streptococcal TSS present with bacteremia, osteomyelitis, and cellulitis; unlike in adults, necrotizing fasciitis and myositis are uncommon. Varicella is an important risk factor for the development of invasive GAHBS infections and TSS. Staphylococcal TSS presents with abrupt fever and generalized myalgia, among other constitutional symptoms. In menstrual cases of staphylococcal TSS, tampons serve as a nidus of infection and may result in recurrent disease in patients who fail to develop neutralizing antibodies against bacterial toxins. Non-menstrual cases may begin due to localized skin and soft tissue pyodermas, including postoperative wound infections.

Mucocutaneous findings include diffuse erythroderma that develops within 24–48 h, conjunctival injection and hemorrhages, and beefy red edematous mucous membranes. Desquamation occurs within 7–14 days. Mucocutaneous findings are much more common in staphylococcal TSS than in streptococcal TSS [14].

Necrotizing fasciitis is much less common in children than adults. The average age of the pediatric patient who develops necrotizing fasciitis is 8 years old. Mortality in children overall is less than 10 %, but is much higher in neonates. Risk factors include varicella, immunosuppression, chronic illness, and recent trauma or surgery. Polymicrobial infections are less common in children than in adults, and the most frequently isolated pathogen is GABHS. Erythema, warmth, and pain out of proportion to physical findings are the early signs of necrotizing fasciitis; shock and fever develop within 1–2 days. The subtlety of skin findings may lead to misdiagnosis: superficial findings may be minimal despite rapid underlying necrosis of soft tissue, due to spread of bacteria along fascial planes. In late disease, bullae, necrosis, and crepitus are present [15, 16].

Specific Investigations

For diagnosis
Gram stain
Culture
Skin biopsy
Rapid antigen testing (*S. pyogenes*)
Serology (*S. pyogenes*)
Laboratory evaluation: BUN and creatinine, LFTs, CBC, metabolic panel, creatinine kinase (necrotizing fasciitis and TSS)
Imaging: CT and MRI (necrotizing fasciitis)
For treatment
CBC (for linezolid)

The diagnosis of impetigo can be confirmed by Gram stain and culture of exudate from lesions [6]. Skin biopsy is generally not necessary for diagnosis, but histopathology demonstrates subcorneal pustules with neutrophilic exocytosis overlying dermal edema in non-bullous impetigo. In contrast, bullous impetigo demonstrates fluid-filled blisters and subtle superficial acantholysis. Ecthyma is characterized by ulceration with diffuse infiltrates of neutrophils. Cocci are not always present, but can be highlighted by Gram stain if they are [17].

Differentiation of bacterial folliculitis from sterile folliculitis can be made by culture or Gram stain of pustule contents. Histopathology of acute lesions demonstrates intrafollicular abscess or suppuration, while chronic or longstanding lesions may demonstrate follicle rupture with surrounding foreign body granulomas or scar. Staphylococcal folliculitis often features subcorneal pustules with abscess of the follicular infundibulum in superficial lesions and deeper portion of the follicle and dermis in deep lesions. Gram-positive cocci may sometimes be identified in the follicular lumen [5, 6].

Purulent exudate or drainage from furuncles or carbuncles may be submitted for culture or gram stain if diagnostic confirmation is necessary [6]. Histopathology demonstrates collections of neutrophils extending through the dermis and into the subcutaneous tissue. Ruptured follicles, granulomatous foreign body reaction, and collections of gram-positive cocci may also be seen [17].

When SSSS is suspected, cultures should be obtained from all potential foci of infection, including nasopharynx, blood, and urine [6]. Skin biopsy is sometimes used to distinguish SSSS from Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), although SJS and TEN almost always feature prominent mucosal involvement. Histopathology of frozen or paraffin-embedded specimens demonstrates a pauci-inflammatory blister within the stratum granulosum with acantholysis [18].

In cellulitis and erysipelas, blood cultures are not useful, as they are negative in 95 % of cases [19]. Cultures of needle aspirates and tissue obtained from skin biopsy are also low-yield, positive in less than 40 % of cases [20, 21]. Histopathology of cellulitis is not specific, but demonstrates prominent edema with abundant interstitial neutrophils; necrosis, abscess, and vasculitis may also be seen. Erysipelas demonstrates similar changes, but with more edema and lymphatic dilation, and these changes are more superficial [17].

The diagnosis of scarlet fever is based on the clinical appearance of the exanthem in tandem with microbiologically confirmed streptococcal pharyngitis. Throat culture is

the reference standard for the diagnosis of streptococcal pharyngitis, has a sensitivity of over 90 %, and will also identify less common causes such as group C and G streptococci. Rapid antigen testing permits point-of-contact testing and early institution of therapy; sensitivity is above 70 % and specificity is over 95 % [22]. If rapid antigen testing is obtained first and is negative, throat culture should be submitted. Serologies for antistreptococcal antibodies such as antistreptolysin O, antideoxyribonuclease, and streptokinase are only useful for confirmation of infection in the convalescent period, and are not affected by antibiotic therapy [23].

Children with PSD almost always have concomitant presence of pharyngeal GABHS, although symptomatic pharyngitis is usually absent. Thus, either site may be tested, but testing of both sites is not necessary. Standard bacterial culture and rapid antigen testing are both highly sensitive methods for diagnosis [24].

Culture or gram stain of blister fluid can be used for diagnostic confirmation of BDD and discrimination from herpetic whitlow [12]. Skin biopsy reveals abscess, edema, and overlying epidermal necrosis [17].

In staphylococcal TSS, blood cultures are positive in less than 5 % of children, but cultures from the nidus of infection are usually positive. In streptococcal TSS, cultures from blood and the site of infection are positive in the majority of cases. Laboratory evaluation reveals elevated blood urea nitrogen and creatinine, abnormal liver function tests, hypocalcemia, hypoalbuminemia, anemia, thrombocytopenia, elevated creatinine kinase, and increased immature neutrophils [14]. If skin biopsy is performed, nonspecific but supportive histological features may be demonstrated, including foci of spongiosis with dyskeratotic keratinocytes and exocytosis of neutrophils [17].

Once clinically suspected, definitive diagnosis of necrotizing fasciitis is only made during surgical exploration, based on the findings of "dishwater" discharge, necrosis without bleeding, and a lack of resistance to fascial dissection. Laboratory findings are nonspecific and similar to those seen in TSS. Plain radiographs are not helpful, as they are insensitive for detecting gas in soft tissues, but computed tomography (CT) and magnetic resonance imaging (MRI) are useful in discrimination from nonnecrotizing soft tissue infections. Imaging should not delay surgical or medical therapy, which should be initiated based on clinical impression [16]. Histologic specimens demonstrate diffuse infiltrates of neutrophils with hemorrhage, thrombosis, necrosis, and vasculitis [17].

Impetigo and Ecthyma

For bullous and non-bullous impetigo with limited involvement, topical therapy is sufficient. For impetigo with extensive involvement, numerous lesions, or for ecthyma, oral antibiotics should be given [6].

Table 14.1 First-line therapies for impetigo [25–30]

Cephalexin	50 mg/kg/day in 3 divided doses, three times daily for 10 days	A
Dicloxacillin	25–50 mg/kg/day in 4 divided doses for 10 days	B
Mupirocin 2 % ointment	3 times daily for 5 days	A
Retapamulin 1 % ointment	2 times daily for 5 days	A

Table 14.2 Second-line therapies for impetigo [6, 25, 27, 30, 31]

Oral erythromycin estolate	30–40 mg/kg/day in 3 divided doses for 10 days	A
TMP-SMX	8 mg/kg plus 40 mg/kg/day in 1–2 doses for 3–5 days	B
Oral clindamycin	20 mg/kg/day in 3 divided doses for 7 days	E
Doxycycline	2–4 mg/kg/day in 2 divided doses for 7 days	E
Linezolid	Treatment for 10 days:	A
	<5 years old: 10 mg/kg q8 h	
	5–11 years old: 10 mg/kg q12 h	
	≥12 years old: 600 mg q12 h	

Table 14.3 Third-line therapies for impetigo [25, 26]

Oral penicillin V	40–50 mg/kg/day in 3 divided doses for 10 days	A
Bacitracin ointment 500 units/g	3 times daily for 5 days	A

In a Cochrane systematic review of 57 trials, topical antibiotics were superior to placebo for the treatment of impetigo, but no topical antibiotic was clearly superior. Topical mupirocin was more effective than oral erythromycin, but otherwise topical antibiotics and oral antibiotics did not demonstrate significantly different cure rates. Among oral antibiotics, penicillin was inferior to erythromycin and cloxacillin. A small trial showed oral cephalexin was the most effective therapy, with no associated treatment failures; treatment with oral erythromycin only resulted in one treatment failure out of 25 patients, whereas penicillin V was inferior, with a 24 % treatment failure rate. In an open trial comparing erythromycin and dicloxacillin for impetigo, over 90 % were improved or cured.

In a randomized trial comparing topical mupirocin, topical bacitracin and oral cephalexin, there was no treatment failure with mupirocin or cephalexin, and cephalexin produced the highest cure rate; bacitracin was inferior, with treatment failure occurring in six of nine patients. For impetigo due to MSSA, topical retapamulin was over 85 % effective (compared to 52 % efficacy for placebo.) For impetigo due to MRSA, topical retapamulin was only 64 % effective while linezolid demonstrated a cure rate of over 90 %.

Oral co-trimoxazole (trimethoprim/sulfamethoxazole), clindamycin, doxycycline, and linezolid can be used for the treatment of impetigo due to MRSA. Doxycycline should not be used in children under the age of 8 years due to risk of tooth discoloration. For non-bullous impetigo, treatment was successful in 85 % of children who received intramuscular benzathine penicillin and in 85 % of children who received either 3- or 5-day courses of co-trimoxazole; however, 90 % of cultures were positive for *S. pyogenes* with our without *S.aureus*.

As mentioned in the discussion of first-line therapies, a large Cochrane review showed that, among oral antibiotics, penicillin was inferior to erythromycin and cloxacillin. A randomized trial showed topical bacitracin was inferior to topical mupirocin and oral cephalexin, with treatment failure occurring in six of nine patients. Thus both should be reserved as third-line therapies and used only if the first- and second-line therapies are not options.

Staphylococcal Folliculitis Including Folliculitis Barbae (Sycosis)

Topical antibiotic therapy is sufficient first-line treatment for most cases of bacterial folliculitis. In a large prospective study of patients with pyoderma including bacterial folliculitis, mupirocin ointment was effective in almost all patients, and resulted in cure in almost 75 % of patients. Topical clindamycin has a long history of successful use for bacterial folliculitis, and most isolates from bacterial folliculitis due to *S. aureus* are sensitive to clindamycin. Topical retapamulin has demonstrated efficacy in high-quality studies for the treatment of pyoderma, including impetigo and secondarily-infected dermatitis due to MSSA and MRSA. Thus, the use of retapamulin in bacterial folliculitis is reasonable as well.

For patients with extensive skin involvement, folliculitis refractory to topicals, or folliculitis barbae (sycosis), oral antibiotics should be administered for 7–10 days. For most patients, cephalosporins or antistaphylococcal penicillins are sufficient, but for patients with risk factors or cultures positive for MRSA, clindamycin, TMP-SMX, or a tetracycline class antibiotic (in patients older than 8 years) should be used. These recommendations are based upon evidence from randomized controlled trials and prospective open studies of children and adults with skin and soft tissue infections, largely due to *S. aureus*.

Adjunctive treatments to eliminate carriage of *S. aureus*, to reduce the risk of recurrence, are reasonable for children with a history of pyoderma including bacterial folliculitis, impetigo, and furunculosis. However, a systematic review of multiple topical and oral antibiotics did not find sufficient evidence for the use of these agents to eradicate nasal or extranasal carriage of MRSA. Nonetheless, in an open study of children and adults with a history of community-acquired pyoderma and nasal or extranasal MRSA or MSSA colonization, mupirocin with or without bleach baths or chlorhexidine was effective in eradicating colonization over a 4-month period. The best regimen, mupirocin with bleach baths, was over 70 % effective. However, recurrent infections still occurred in 36 % of these patients, despite eradication of *S. aureus* colonization at 4 months.

Table 14.4 First-line therapies for staphylococcal folliculitis [6, 29, 30, 32–35]

Medication	Dosing (duration of treatment: 5–10 days)	Evidence level
Mupirocin 2 % ointment	Apply 3 times daily	B
Clindamycin 1 % (solution/lotion)	Apply 2 times daily	D
Retapamulin 1 % ointment	Twice daily	A

Table 14.5 Second-line therapies for staphylococcal folliculitis [6, 36–40]

Medication	Dosing (duration of treatment: 7–10 days)	Evidence level
Cephalexin	25–50 mg/kg/day po in 3–4 divided doses	A
Dicloxacillin	25–50 mg/kg/day po in 4 divided doses	A
TMP-SMX	8–12 mg/kg/day po in two divided doses based on TMP	A
Clindamycin	40 mg/kg/day po divided in 3–4 doses	A
Doxycycline	25–50 mg/kg/day po in 4 divided doses	B

Table 14.6 Third-line (adjunctive) therapies for staphylococcal folliculitis [41, 42]

Medication	Dosing	Evidence level
Mupirocin 2 % ointment	Apply to nares 2–3 times per day for 5 days per month	B
Chlorhexidine 4 % rinse	Daily body washes for 5 days	B
Dilute bleach baths	Daily baths for 5 days	B

Furuncles and Carbuncles

In pediatric patients presenting to the emergency department with furuncles, the use of TMP-SMX following standard incision and drainage did not improve resolution of the acute infection or reduce the risk of long-term recurrence. However, the risk of short-term recurrence (within 30 days) was lower in the group that received post-drainage antibiotics. Additionally, clinical non-response in patients with furuncles due to MSSA or MRSA was associated with lack of receipt of incision and drainage, rather than directed antimicrobial therapy. Therefore, for children with a single furuncle or carbuncle less than 2 cm in size, incision and drainage alone, without antibiotic treatment, is sufficient.

Table 14.7 First-line therapies for furuncles [6, 43–45]

Medication	Dosing	Evidence level
Incision and drainage		A

Table 14.8 Second-line therapies for furuncles [6, 36–40, 46–48]

Medication	Dosing (duration of treatment: 5–7 days)	Evidence level
TMP-SMX	8–12 mg/kg/day po in two divided doses based on TMP	A
Clindamycin	40 mg/kg/day po divided in 3–4 doses	A
Tetracycline class antibiotic:	Doxycycline:	B
Doxycycline, minocycline	4 mg/kg/day po divided in two doses	
	Maximum single dose: 100 mg	
Linezolid	30 mg/kg/day po divided in three doses	B
Cephalexin	25–50 mg/kg/day po in 3–4 divided doses	A
Dicloxacillin	25–50 mg/kg/day po in 4 divided doses	A

For children with multiple lesions, or a single abscess greater than 2 cm in size, cellulitis, immunosuppression, systemic signs or symptoms, indwelling device, or without clinical response to incision and drainage alone, oral antibiotics should be administered. In children and adults with abscesses greater than 2 cm in diameter, due to MRSA and MSSA, the cure rates were higher in patients who received TMP-SMX along with incision and drainage compared to surgery alone (80 % versus 74 %, respectively). In contrast, in a study of patients with abscesses due to MRSA, in 88 % of cases cephalexin offered no additional benefit to incision and drainage alone. Therefore, when empiric antibiotic therapy is given for furuncles and carbuncles, coverage for MRSA should be selected in patients with risk factors for MRSA or from areas with high prevalence of MRSA: clindamycin, tmp-smx, tetracycline class antibiotics, or linezolid are acceptable. Otherwise, coverage of MSSA is acceptable: an antistaphylococcal penicillin or cephalosporin. Duration of therapy is 5–7 days. For patients who fail to respond to incision and drainage and oral antibiotics, or with extensive involvement or systemic toxicity, parenteral therapy with one of the first-line agents, or vancomycin, should be used.

The evidence for the use of these antibiotics is supported by randomized controlled trials and prospective open studies with children and adults.

In an open study of patients with three or more episodes of furunculosis due to MSSA, suppressive azithromycin was 80 % effective in preventing recurrence.

Another prospective study demonstrated 87 % efficacy in preventing recurrence in patients with a history of four or more prior episodes, following combination therapy with clindamycin, mupirocin, and chlorhexidine.

Table 14.9 Third-line therapies (for recurrent furunculosis) [49–51]

Medication	Dosing	Evidence level
Azithromycin	10 mg/kg po weekly for 12 weeks with maximum dose 500 mg	B*
Oral clindamycin, topical mupirocin and chlorhexidine	Clindamycin:	B*
	20–40 mg/kg/day po in 3–4 divided doses for 21 days	
	Mupirocin:	
	Nasal application for 5 days	
	Chlorhexidine:	
	Skin disinfection daily for 21 days	
Rifampin	10 mg/kg/day po for 10 days with maximum daily dose 600 mg	B*

In patients with recurrent furunculosis with nasal swab cultures positive for *S. aureus*, a course of rifampin, added to standard antibiotic therapy with TMP-SMX at the time of an episode, resulted in elimination of the carrier state and prevention of recurrence in over 70 % of cases. Clindamycin and rifampin provide coverage of MRSA.

Staphylococcal Scalded Skin Syndrome (SSSS)

In a recent American study of antibiotic susceptibilities of *S. aureus* cultured from children with SSSS, 86 % of isolates were sensitive to oxacillin (14 % of isolates were MRSA), and 52 % of isolates were susceptible to clindamycin. Based on this information, empiric therapy of SSSS should include a penicillinase-resistant penicillin in combination with clindamycin until culture results are available to tailor therapy. Although clindamycin inhibits toxin production by *S. aureus*, it should not be used as monotherapy [52].

Based on a retrospective review of 39 neonates with SSSS, there were no significant differences in response to therapy between the beta-lactamase-resistant semisynthetic penicillins, cephalosporins, or combination therapy with both. Thus, these are first-line agents.

Vancomycin should be reserved for patients who fail to respond to standard, first-line therapy, or when susceptibility testing identifies MRSA. Macrolides including erythromycin can also be used effectively for the treatment of SSSS.

Retrospective data suggest that systemically unwell children may benefit from the use of FFP or IVIG to neutralize exotoxin antibodies. However, patients treated with IVIG for SSSS have longer hospital stays than patients receiving standard therapy.

Table 14.10 First-line therapies for SSSS [8]

Medication	Dosing	Evidence level
Penicillinase-resistant penicillin:	Nafcillin:	D
Nafcillin, oxacillin, dicloxacillin	Neonates: 25 mg/kg/dose IV every 6–12 h	
	Infants and children: 100 to −200 mg/kg/day IV in divided doses every 6 h with	
	Maximum daily dose 12 g	
Clindamycin	Neonates:	D
	5 mg/kg/dose IV every 6–12 h	
	Infants and children:	
	20–40 mg/kg/day IV divided every 6–8 h	
	Maximum single dose 600 mg	
Cephalosporins:	Ceftriaxone:	D
Ceftriaxone, cefpodoxime, cefdinir	50 mg/kg IV once daily	
	Maximum daily dose 1 g	

Table 14.11 Second-line therapies for SSSS [53–55]

Medication	Dosing	Evidence level
Vancomycin	40–60 mg/kg/day IV divided every 6–8 h	E
	Maximum daily dose: 2–4 g	
Macrolides:	Erythromycin:	E
Erythromycin, clarithromycin	Neonates:	
	10 mg/kg/dose IV every 8–12 h	
	Infants and children:	
	15–20 mg/kg/day IV divided every 6 h	
	Maximum daily dose: 4 g	

Table 14.12 Third-line therapies for SSSS [8, 56, 57]

Medication	Dosing	Evidence level
Fresh frozen plasma (FFP)	10 mL/kg	D
Intravenous immunoglobulin (IVIG)	0.4 g/kg/day IV for 5 days	D

Scarlet Fever

Scarlet fever, like acute rheumatic fever, toxic shock syndrome, acute glomerulonephritis, and pediatric autoimmune neuropsychiatric disorder associated with GAS (PANDAS), is a nonsuppurative complication of GAS tonsillopharyngitis. The treatment of scarlet fever is the same as that for streptococcal pharyngitis. Antibiotic treatment is most helpful in altering the disease course if started within the first 48 h of illness. Antibiotic treatment also reduces the risk of acute rheumatic fever [58].

Table 14.13 First-line therapies for scarlet fever [59–64]

Medication	Dosing	Evidence level
Penicillin	Penicillin V:	A
	250–500 mg po 2–3 times daily for 10 days	A
	Penicillin G benzathine 900,000 U mixed with penicillin G procaine 300,000 U IM single dose (patients <27 kg)	A
	Penicillin G benzathine	
	1.2 million U (patients>27 kg)	
Amoxicillin	50 mg/kg/day po in 2–3 divided doses for 10 days	A
	Maximum daily dose: 1 g	
Cephalexin	25–50 mg/kg/day po in 2 divided doses for 10 days	A
	Maximum daily dose: 1 g	

Table 14.14 Second-line therapies for scarlet fever [65–68]

Medication	Dosing	Evidence level
Azithromycin	12/mg/kg/dose po on day 1 followed by 6 mg/kg/dose po on days 2–5	A
	Maximum single dose: 250/500 mg	
Clarithromycin	7.5 mg/kg/dose po twice daily for 10 days	A
	Maximum dose 250 mg	
Clindamycin	7 mg/kg/dose po 3 times daily for 10 days	A
	Maximum dose 300 mg	

Penicillin is the preferred first-line treatment for streptococcal pharyngitis. Intramuscular penicillin is the only drug with data demonstrating prevention of rheumatic fever, but a 10-day course of oral penicillin is considered equivalent for this purpose. Meta-analysis has demonstrated that the risk of bacteriologic and clinical failure is reduced by treatment with cephalosporins such as cephalexin compared to penicillin. Thus, cephalexin and other first-generation cephalosporins are first-line treatments. However, second- and third-line cephalosporins are associated with emerging resistance.

Based on a multiple randomized controlled trials, there are no significant differences in the efficacy of macrolides compared to penicillin in children with GAS pharyngitis. However, resistance rates can be as high as 20%, and the incidence of adverse events in children is higher with macrolides than with penicillin. In patients allergic to penicillin and cephalexin, another acceptable and effective alternative agent is clindamycin.

Perineal Streptococcal Dermatitis

In a large retrospective review of children up to 12.5 years of age, treatment with amoxicillin was associated with a recurrence rate of 12.4 %. The recurrence rate of PSD following treatment with penicillin or amoxicillin was 38 %, while the recurrence rate following treatment with a beta-lactamase resistant antibiotic was lower at 28 %. In 13 of 14 patients treated with cefuroxime, clinical improvement was rapid and GABHS was not isolated from the perianal skin. In comparison, GABHS was found in 8 of 15 patients following treatment with penicillin.

Blistering Distal Dactylitis

While the typical age in children is between 2 and 16 years old, cephalexin was successful in patients down to infancy.

In reports, dicloxacillin was used successfully for staphylococcal disease.

Erysipelas

For the treatment of streptococcal and staphylococcal skin and soft tissue infections, ampicillin and ceftriaxone were both over 90 % effective in terms of clinical and bacteriologic response rates.

In children with infections due mainly to *S. aureus* and *S. pyogenes*, outpatient treatment with once-daily ceftriaxone is highly effective and associated with equivalent outcomes of intravenous administration during hospitalization. If the diagnosis of nonpurulent cellulitis, rather than erysipelas, is still under consideration, then cefazolin is preferred over ceftriaxone for coverage of MSSA.

Table 14.15 First-line therapies for PSD [11, 69, 70]

Cefuroxime	20 mg/kg/day, divided in 2 doses for 7 days	B
Amoxicillin	50 mg/kg/day po in 1 to −2 doses for 10 days with maximum daily dose 1,000 mg	D
Azithromycin	12 mg/kg/day po for 5 days with maximum daily dose 500 mg	E

Table 14.16 Second-line therapies for PSD [69, 70]

Penicillin V	50,000–100,000 U/kg/day, divided in 3 doses, for 10 days	B

Table 14.17 Third-line therapies for PSD [71, 72]

Erythromycin 3 % cream	Apply 3 times daily for 15 days	E
Mupirocin 2 % ointment	Apply twice daily for 10 days	E

Early studies demonstrated roughly equivalent efficacy for macrolides compared to cephalosporins and antistaphylococcal penicillins in the treatment of uncomplicated skin and soft tissue infections. However, given the emerging resistance of erythromycin-resistant group A Streptococcus in children, this agent is not a preferred therapy for erysipelas.

Cellulitis

For children with non-purulent cellulitis, empiric treatment should include coverage for beta-hemolytic streptococci and MSSA. Children with purulent cellulitis, including primary or secondary non-drainable abscess, should receive empiric coverage for MRSA. These recommendations apply to non-facial cellulitis in infants, children, and adolescents [6, 37].

For nonpurulent cellulitis, empiric therapy can be selected from one of the following: a cephalosporin, clindamycin, or an antistaphylococcal penicillin such as dicloxacillin. Symptomatic improvement should occur within 48 h and cutaneous signs should improve within 72 h. If not, MRSA should be suspected and clindamycin, or amoxicillin with TMP-SMX, or amoxicillin with doxycycline or minocycline should be given. These regimens can also be initiated in patients with risk factors for MRSA infections.

In a randomized controlled trial, TMP-SMX in combination with cephalexin was not superior to cephalexin alone for nonpurulent cellulitis in children and adults, with cure rates above 80 % for both regimens. A variety of cephalosporins

Table 14.18 First-line therapies for BDD [12, 73]

Cephalexin	25–50 mg/kg/day po in divided doses for 14 days	E
Oral penicillin V	25–75 mg/kg/day po in 3–4 divided doses for 10 days with maximum daily dose 2,000 mg	E
Penicillin G benzathine	<27 kg: 600,000 units IM × 1 ≥27 kg: 1.2 million units IM × 1	E

Table 14.19 Second-line therapies for BDD [74]

Dicloxacillin	50–75 mg/kg/day po in 4 divided doses for 10 days	E
Erythromycin	30–50 mg/kg/day po divided q 6–12 h (max 4 g/day)	E

Table 14.20 First-line therapies for erysipelas [75]

Medication	Dosing (duration of treatment: 5–10 days)	Evidence level
Penicillin	25–50 mg/kg/day po in 3–4 divided doses	A
Amoxicillin	25–50 mg/kg/day po in 3 divided doses	A

Table 14.21 Second-line therapies for erysipelas [76, 77]

Medication	Dosing (duration of treatment: 5–10 days)	Evidence level
Ceftriaxone	50–75 mg/kg/day IV or IM in 1–2 doses	A
Cefazolin	100 mg/kg/day IV in 1–2 doses	A

Table 14.22 Third-line therapies for erysipelas [39, 78, 79]

Medication	Dosing (Duration of treatment: 5–10 days)	Evidence level
Macrolides:	Erythromycin:	A
Erythromycin, azithromycin	35–50 mg/kg/day po in 2–4 divided doses	

Table 14.23 First-line therapies for cellulitis [6, 36–38, 80–83]

Medication	Dosing (duration of treatment: 5 days)	Evidence level
Cephalosporins:	Cephalexin:	A
Cephalexin, cefadroxil, cefuroxime, cefaclor	25–50 mg/kg/day po in 3–4 divided doses	
Clindamycin	20–30 mg/kg/day po in 4 divided doses	A
Dicloxacillin	25–50 mg/kg/day po in 4 divided doses	A
TMP-SMX	8–12 mg/kg/day po in two divided doses based on TMP component	A
Tetracycline class:	Doxycycline:	B
Doxycycline, minocycline	4 mg/kg/day po divided in two doses	
	Maximum single dose 100 mg	
Amoxicillin-clavulanate	25 mg/kg/day of the amoxicillin component in 2 divided doses po	A

other than cephalexin have been tested in high-quality studies and demonstrated similar efficacy for uncomplicated cellulitis in children and adults. Amoxicillin-clavulanate was as effective as cefaclor in an early study, but its current use is preferred for coverage of *S. pyogenes* rather than *S. aureus*. Thus when used for cellulitis, an antistaphylococcal agent should be added.

For patients with purulent cellulitis, empiric therapy with clindamycin, TMP-SMX, or—in children older than 8 years of age—minocycline or doxycycline. Once the culture results of the abscess, culture, or exudate are available, therapy should be tailored. In adults and children with purulent and non-purulent cellulitis, cure rates were similar for clindamycin in comparison to TMP-SMX. Cases of purulent cellulitis included MRSA infections. In a separate open study of adults with purulent MRSA skin and soft tissue infections, the majority of isolates were sensitive to tetracycline class antibiotics, clindamycin, and TMP-SMX.

Table 14.24 Second-line therapies for cellulitis [39, 40]

Medication	Dosing (duration of treatment: 5 days)	Evidence level
Linezolid	30 mg/kg/day po divided in three doses	B

For patients who respond to empiric therapy, a total of 5 days of antibiotic treatment is sufficient. However, for patients with slow response, therapy may be extended to 14 days. For patients with systemic toxicity, progression of signs or symptoms, or immunosuppression, parenteral therapy with the first-line antibiotics, their equivalents, or vancomycin, should be used in place of oral treatment.

In retrospective and open prospective studies, linezolid was as effective as vancomycin for the treatment of complicated cellulitis, or cellulitis in patients requiring hospitalization. This drug provides coverage of MSSA, MRSA, and beta-hemolytic streptococci, but is reserved as an alternative agent for patients intolerant of or refractory to first-line therapies.

Streptococcal Toxic Shock Syndrome (TSS)

First-line therapy for streptococcal TSS is a beta-lactam agent and clindamycin. Clindamycin can be combined with either a carbapenem or a penicillin with beta-lactamase inhibitor. Although S.pyogenes is highly susceptible to penicillin, monotherapy is associated with high mortality rates. In a retrospective studies, use of clindamycin, including as part of combination therapy with a beta-lactam, was associated with improved outcomes and decreased mortality in children with severe invasive GAS infections.

Once the diagnosis of streptococcal TSS has been established, treatment should be switched to a combination of clindamycin and penicillin G to complete at least 14 days of therapy. GAS isolates with inducible resistance to macrolides or lincosamides are uncommon in the United States, but penicillin is used as part of dual therapy for coverage of potential clindamycin resistance.

Clindamycin may be combined with one of the alternative agents for therapy, vancomycin and daptomycin. These drugs are useful in patients with allergy to penicillins and/or carbapenems.

IVIG has been used based on the idea that passively transferred antibodies can neutralize streptococcal toxins. However, retrospective data show that children with streptococcal TSS do not have improved outcomes following adjunctive treatment with IVIG. Hyperbaric oxygen has also been used in small numbers of patients with streptococcal TSS.

Table 14.25 First-line therapies for streptococcal TSS [84–88]

Medication	Dosing (duration of treatment: at least 14 days)	Evidence level
Treatment should consist of a beta-lactam agent AND clindamycin		
Clindamycin	30–40 mg/kg/day IV divided every 6–8 h	D
Carbapenems:	Meropenem:	E
Meropenem, imipenem	10–20 mg/kg/dose IV every 8 h	
Beta-lactam with beta-lactamase inhibitor:	Piperacillin-tazobactam: 100 mg piperacillin/kg/dose IV every 8 h with maximum daily dose 16 g	D
Piperacillin-tazobactam		
Ticarcillin-clavulanate		
Penicillin G	200,000–300,000 units/kg/day IV divided every 4 h with maximum daily dose 24 M units	D

Table 14.26 Second-line therapies for streptococcal TSS [89]

Medication (in combination with Clindamycin)	Dosing	Evidence level
Vancomycin	45–60 mg/kg/day IV divided every 6–8 h with maximum daily dose 4,000 mg	E*
Daptomycin	4–10 mg/kg/day IV	E*

Table 14.27 Third-line therapies for streptococcal TSS [90, 91]

Medication	Dosing	Evidence level
Intravenous immunoglobulin (IVIG)	Single dose or once daily on 3 consecutive days	D
Hyperbaric oxygen		D*

Staphylococcal Toxic Shock Syndrome (TSS)

Based on retrospective data, all patients with suspected staphylococcal TSS should receive empiric therapy with clindamycin and vancomycin. Once culture and sensitivity results are available, treatment can be narrowed and tailored. For patients with staphylococcal TSS due to MSSA, clindamycin should be combined with an antistaphylococcal penicillin. For patients with staphylococcal TSS due to MRSA, clindamycin should be combined with vancomycin or linezolid. Treatment should be continued for a total of 7–14 days of antimicrobial therapy.

The use of clindamycin is important given that vancomycin and antistaphylococcal penicillins do not suppress toxin synthesis by *S. aureus*.

Table 14.28 First-line therapies for staphylococcal TSS [92–94]

Medication	Dosing	Evidence level
Vancomycin	40 mg/kg/day IV in 4 divided doses	D
Clindamycin	25–40 mg/kg/day IV in 3 divided doses	D

Table 14.29 Second-line therapies for staphylococcal TSS [93–95]

Medication	Dosing	Evidence level
Antistaphylococcal penicillin:	Nafcillin:	D
Oxacillin, nafcillin	100–150 mg/kg/day IV in 4 divided doses	
Linezolid	10 mg/kg/dose IV every 12 h	E*

Table 14.30 Third-line therapies for staphylococcal TSS [96, 97]

Medication	Dosing	Evidence level
IVIG	200 mg/kg/day for 5 days	E*

As stated above, the use of clindamycin is important, given that vancomycin and antistaphylococcal penicillins do not suppress toxin synthesis by *S. aureus*. Anecdotal evidence supports the use of linezolid, based on successful clinical response as well as suppression of toxin synthesis.

Unlike in streptococcal TSS, little evidence currently supports the use of IVIG in staphylococcal TSS. Superantigens produced by *S. aureus* may be less susceptible to inhibition by IVIG than those produced by *S. pyogenes*.

Necrotizing Fasciitis

As in adults, early (within the first 24 h of diagnosis) surgical debridement is critical in the treatment of necrotizing fasciitis and improving survival. In addition, empiric antibiotic therapy should consist of three antimicrobials: clindamycin, a carbapenem or beta-lactam with beta-lactamase inhibitor, and an antibiotic with activity against MRSA [6]. Treatment should be tailored once culture and susceptibility results are available, if possible. In the setting of GAS infection, treatment can be narrowed to the combination of penicillin and clindamycin [97].

For treatment of necrotizing fasciitis, earlier studies reported the need for aggressive surgical debridement, such as fascial excision. However, more recent studies have advocated conservative surgical management, which is described as separation of gangrenous skin from surrounding healthy tissue, wound washing, frequent application of dressings with antibiotic ointment, and healing by granulation. Compared to aggressive management, conservative debridement is associated with shorter hospital stays, improved cosmesis and function with

Table 14.31 First-line therapies for necrotizing fasciitis [6, 99–101]

Medication	Dosing	Evidence level
Surgical debridement	N/A	D

Table 14.32 Second-line therapies for necrotizing fasciitis [6, 86, 98, 102]

Medication	Dosing	Evidence level
Carbapenem:	Meropenem:	D
Meropenem, imipenem, or ertapenem	20 mg/kg/dose IV every 8 h	
Beta-lactam with beta-lactamase inhibitor:	Piperacillin-tazobactam:	D
Piperacillin-tazobactam,	100 mg piperacillin/kg/dose IV every 8 h with maximum daily dose 16 g	
Ampicillin-sulbactam		
Clindamycin	40 mg/kg/day IV divided every 8 h	D
Active agent against MRSA:	Vancomycin:	D
Vancomycin, daptomycin, or linezolid	15 mg/kg/dose IV every 6–8 h	
Penicillin G	300,000 units/kg/day IV divided every 6 h	D

minimal scarring or restricted movement, and shorter duration to healing.

Prompt antibiotic treatment, along with aggressive supportive treatment (fluid resuscitation and electrolyte replacement) should also be initiated at the time of presumptive diagnosis. Empiric therapy should be broad and provide coverage of gram-positive (especially GAS), gram-negative, and anaerobic organisms.

Based on retrospective data, children with invasive soft tissue infection due to *S. pyogenes* were more likely to have a favorable outcome if clindamycin was used in combination with a beta-lactam antibiotic; the use of a beta-lactam alone was associated with a 68 % failure rate. Clindamycin should be included in all treatment regimens.

In a randomized, controlled trial of adults with streptococcal toxic shock syndrome with or without necrotizing fasciitis, a greater than threefold reduction in mortality was associated with IVIG treatment. Hyperbaric oxygen may be useful as an adjunctive treatment for necrotizing fasciitis. Several retrospective studies have demonstrated a survival benefit with decreased need for aggressive debridements.

The incidence of invasive GAS infections is dramatically increased in household contacts of patients with severe infections such as streptococcal toxic shock or necrotizing fasciitis. Routine screening and chemoprevention for contacts of index patients are not recommended. However, for immunocompromised patients who are household contacts of patients with necrotizing fasciitis due to GAS, prophylaxis should be considered.

Table 14.33 Third-line therapies for necrotizing fasciitis [87, 103–108]

Medication	Dosing	Evidence level
Intravenous immune globulin (IVIG)	1 g/kg IV on day 1; 0.5 g/kg IV on days 2 and 3	A*
Hyperbaric oxygen	2–3 daily 90-min sessions at 3 atm	D*
Postexposure prophylaxis:	25–75 mg/kg/day po in divided doses every 6–8 h	E
Penicillin VK		

Pseudomonas Infections

Clinical Features

Pseudomonas aeruginosa is a gram-negative aerobic bacillus that can cause mild infections in immunocompetent hosts or severe hospital-acquired infections, especially in immunocompromised hosts.

Folliculitis and hot foot syndrome are benign, self-limited infections that occur following exposure to contaminated water. Pseudomonas folliculitis is characterized by tender or pruritic follicular papules, nodules, or pustules, often associated with low-grade fever and malaise (Figs. 14.9 and 14.10). Hot foot syndrome is common in children, and results in tender nodules on the soles. Both folliculitis and hot foot syndrome resolve without antibiotic therapy [109, 110].

Ecthyma gangrenosum occurs in the setting of *P. aeruginosa* bacteremia and sepsis in immunocompromised patients, including those with neutropenia. It results from bacterial invasion of the media and adventitia of vessels with secondary ischemic necrosis. Single or multiple lesions begin as painless red macules, which then evolve into pustules, vesicles, and eventually ulcers with gangrene. Rapid progression is typical [111].

Noma neonatorum is a very rare gangrenous form of noma involving the mucocutaneous junctions of the oral, nasal, and anal area. It presents during the first few weeks of life in premature and low-birthweight neonates, and causes mutilating and disfiguring destruction of soft tissues, skin, and bone. In low-birthweight neonates, it is usually quickly fatal. *P. aeruginosa* is causative of the skin lesions and also results in septicemia [112].

Specific Investigations

For diagnosis
Culture
Histopathology with gram stain
For treatment
Renal function should be monitored during therapy with aminoglycosides and colistimethate

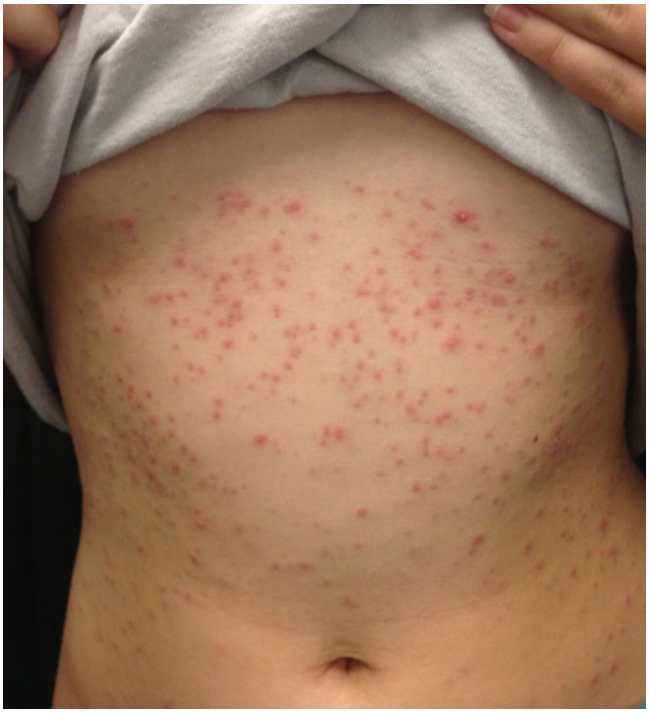


Fig. 14.9 Hot tub folliculitis. Papulopustules on the trunk in a child following exposure to pool water. Culture grew *P. aeruginosa* (Photo courtesy of Adam Rees, MD)

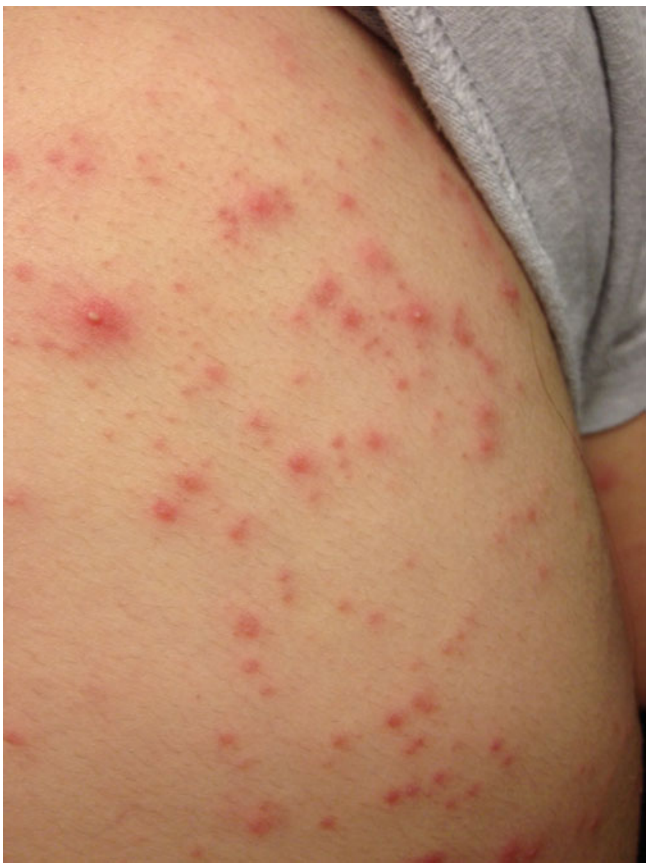


Fig. 14.10 Close-up of hot tub folliculitis shown in Fig. 14.9

Diagnosis of pseudomonas folliculitis or hot foot syndrome is clinical, but histopathology with gram stain or culture can be used to confirm cases, if necessary [110].

If ecthyma gangrenosum is suspected clinically, blood cultures should be obtained and prompt antibiotic therapy initiated. As bacteremia is not present in all patients, negative blood cultures do not exclude this diagnosis. Exudates from skin lesions should also be obtained for culture. Importantly, given the nonspecific clinical findings and the variety of organisms that may cause gangrenous ulcers in immunocompromised patients, skin biopsy for histopathology and bacterial, fungal, and mycobacterial tissue culture should be obtained. Biopsy of skin lesions shows hemorrhagic necrosis, gram-negative bacilli, and vasculitis [113].

In noma neonatorum, blood cultures, and cultures with susceptibility, testing from skin lesions should be obtained. Histopathology and tissue culture should also be considered [114].

Ecthyma Gangrenosum

When the clinical diagnosis of ecthyma gangrenosum is made, empiric combination antimicrobial treatment should be initiated and should include antipseudomonal agents. Retrospective and prospective data have suggested that multiagent empiric therapy, compared to empiric monotherapy, is associated with lower rate of mortality in patients with *Pseudomonas* bacteremia.

However, once results of culture identify *Pseudomonas*, antipseudomonal monotherapy should be selected based on susceptibility testing. Most studies examining directed combination therapy compared to monotherapy have not demonstrated survival benefit. Nonetheless, monotherapy with an aminoglycoside agent is not recommended, as retrospective data has revealed higher rates of treatment failure and mortality in *P. aeruginosa* bacteremia. Of note, a retrospective study found that combination therapy was linked to superior outcomes in children with *Pseudomonas* septicemia.

Only a few retrospective studies are available to support specific therapies for *Pseudomonas* in children, but the same antibiotics effective in adults are recommended in children. However, the use of fluoroquinolones should be carefully considered before electing this therapy in patients under 18 years of age, given the risk of adverse events involving joints and surrounding tissues. There is no current evidence that limited courses of treatment with fluoroquinolones cause sustained injury of this type in children, and these agents may be highly useful in children with serious infections due to susceptible isolates.

Retrospective studies support the use of colistin in severe, refractory cases due to multidrug-resistant *P. aeruginosa*, but treatment with this agent is limited by nephrotoxicity and

Table 14.34 First-line therapies for ecthyma gangrenosum [115–123]

Medication	Dosing	Evidence level
Penicillins:	Piperacillin-tazobactam:	D
Piperacillin-tazobactam	100 mg piperacillin/kg/dose IV every 8 h with maximum daily dose 16 g	
Ticarcillin		
Cephalosporins	Ceftazidime:	D
Ceftazidime	30–50 mg/kg/dose IV every 8 h with maximum daily dose 6 g	
Cefipime		
Monobactams	Aztreonam:	D
	30 mg/kg/dose IV every 8 h with maximum daily dose 8 g	
Carbapenems:	Meropenem:	D
Imipenem	30–60 mg/kg/day IV in 3 divided doses	
Meropenem	Maximum daily dose: 3 g	
Aminoglycosides:	Amikacin:	D
Gentamycin	15–22.5 mg/kg/day IV divided every 8 h	
Amikacin		
Fluoroquinolones:	Ciprofloxacin:	D
Ciprofloxacin	20–30 mg/kg/day IV divided every 12 h with maximum daily dose 800 mg	
Levofloxacin		

Table 14.35 Second-line therapies for ecthyma gangrenosum [124–126]

Medication	Dosing	Evidence level
Colistimethate (Colistin)	2.5–5 mg/kg/day IV in 1–2 doses	D

Table 14.36 Third-line therapies for ecthyma gangrenosum [127]

Medication	Dosing	Evidence level
Surgery		D

ototoxicity. Alternatively, combination regimens, such as cefepime with amikacin, may be used.

In pediatric oncology patients, most with neutropenia, radical debridement was important in the adjunctive treatment of progressive lesions to prevent mortality. However, this is not warranted for infections with limited involvement.

Noma Neonatorum

Given the rarity of noma neonatorum, treatment is only based on anecdotal evidence. In a patient with multidrug-resistant *P. aeruginosa*, colistin (colistimethate) was used successfully with complete healing. Therapy should be tailored based on in vitro susceptibility results, once available.

Table 14.37 First-line therapies for noma neonatorum [114]

Medication	Dosing	Evidence level
Colistimethate	2.5–5 mg/kg/day IV in 1–2 doses	E

Table 14.38 Second-line therapies for noma neonatorum [112]

Medication	Dosing	Evidence level
Amikacin	15–22.5 mg/kg/day IV divided every 8 h	E
Clindamycin	20–40 mg/kg/day IV divided every 6–8 h	E
	Maximum single dose 600 mg	
Fluoroquinolones:	Ciprofloxacin:	E
Ofloxacin, ciprofloxacin	20–30 mg/kg/day IV divided every 12 h with maximum daily dose 800 mg	

Noma

Clinical Features

Noma is a polymicrobial infection associated mainly with anaerobic bacteria. Causative organisms include *Fusobacterium* species, *Prevotella intermedia*, alpha-hemolytic streptococci, *Pseudomonas*, *Actinomyces*, *Peptostreptococci*, and spirochetes. The incidence of noma is highest in sub-Saharan Africa and among infants and young children. Risk factors include poverty, malnutrition, poor sanitation and oral hygiene, proximity to livestock, nomadic lifestyle, and high prevalence of other infectious diseases such as malaria and tuberculosis [128]. Noma begins as an ulcerative gingivitis and then spreads rapidly causing destructive gangrene of the skin, muscle, and bone of the mouth and face. In the acute phase, fetid breath, facial swelling, and mouth soreness are characteristic. Bluish-black discolored patches follow gingivitis, with rapid progression to perforation and then gangrene. Mortality rates are high without prompt treatment [129].

Specific Investigations

For diagnosis
Culture
Histopathology
For treatment
No specific investigations

Histopathology demonstrates ulceration with necrosis and surrounding epidermal hyperplasia. Numerous neutrophils may be present. Gram-positive cocci of various morphologies and gram-negative cocci bacilli may be seen. Cultures

Table 14.39 First-line therapies for noma [130–133]

Medication	Dosing	Evidence level
Penicillin	Penicillin VK:	D
	25–50 mg/kg/day in 3 divided doses	
	Penicillin G procaine:	
	25,000–50,000 units/kg/day in divided doses 1–2 times/day	
Metronidazole	30 mg/kg/day in 3–4 divided doses	D
Amoxicillin	80–100 mg/kg/day po divided every 8 h with maximum single dose 500 mg	D
Streptomycin	20–30 mg/kg/day IV divided every 12 h with maximum daily dose 2 g	D

Table 14.40 Second-line therapies for noma [130, 131, 134–137]

Medication	Dosing	Evidence level
Surgery		D
Wound care	Antiseptic dressings	D
	Chlorhexidine digluconate 0.12 % solution	
Nutritional supplementation	Protein-enriched formula	D
	Fluid and electrolyte replacement	

are polymicrobial, but *Fusobacterium necrophorum* has been observed most frequently [129].

High-quality evidence regarding the optimal treatment of noma is lacking, and treatment recommendations are based on typical in vitro susceptibilities of causative organisms, as well as retrospective studies. Penicillin, either oral or parenteral, has been used successfully in combination with metronidazole or streptomycin. Amoxicillin may be substituted for penicillin in combination therapy with metronidazole. Metronidazole can also be used as monotherapy.

Surgery is often required as an adjunctive treatment to antibiotics in noma. During the acute infection, surgical debridement is employed to limit spread of the infection and to promote healing. Following resolution of the acute infection and necrosis, reconstructive surgery improves function and cosmesis.

Wound care is also important during the acute phase of infection, to prevent further spread and secondary infection. Antiseptic dressings and chlorhexidine oral rinses are recommended. Nutritional supplementation has improved outcomes during acute infection. Protein-enriched formulas, via oral or parenteral feeding, in addition to fluid and electrolyte replacement, are administered.

Neisseria Infections

Clinical Features

Gonococcemia, or disseminated gonococcal infection, is caused by bacteremic spread of the of the sexually-transmitted, gram-negative facultatively intracellular diplococcus *Neisseria gonorrhoeae*, resulting in a triad of tenosynovitis, cutaneous lesions, and polyarthralgias. Painless lesions which are few in number present as hemorrhagic macules, papules, vesicles, or pustules, and are transient (Figs. 14.11 and 14.12) . Fever, malaise, and multiple

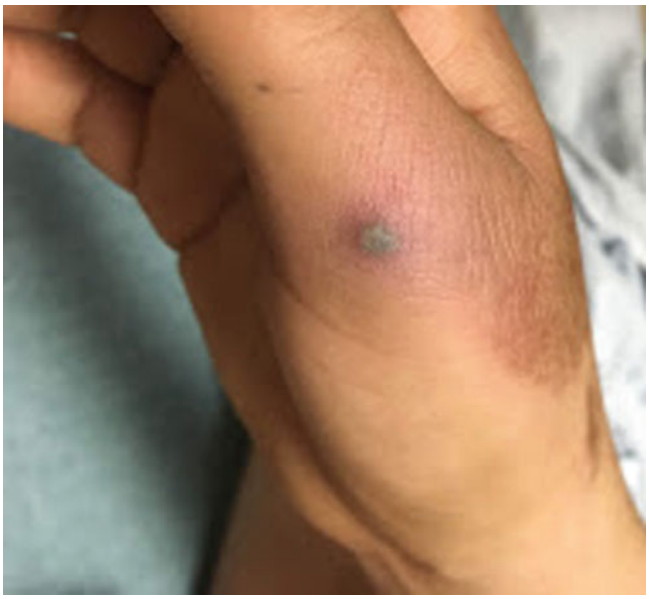


Fig. 14.11 Gonococcemia (disseminated gonococcal infection). Hemorrhagic vesicopustule on an acral surface in an adolescent patient (Photo courtesy of Yousuf Qureshi, MD)

inflamed tendons of the wrist, fingers, ankle, and toes are common features. Purulent asymmetric oligoarthritis of the knees, wrists, and ankles without skin lesions may also occur [138].

Neisseria meningitidis is the leading cause of bacterial meningitis in children and young adults in the United States, with a mortality rate of 13 %. Meningitis may occur with or without meningococcemia, and vice versa [139]. The typical initial presentation of meningitis due to *N. meningitidis* consists of the sudden onset of fever, nausea, vomiting, headache, and myalgias in an otherwise healthy patient. Rash and meningismus are also often present. However, clinical expression is highly variable and often incomplete. The first clinical symptoms are worrisome signs of early sepsis: leg pain, cold hands and feet, and pallor or mottling; 72 % of children demonstrate one of these features in the first 8 h after onset. Rash is present in up to 70 % of cases, is usually petechial, and often involves the trunk, lower extremities, and mucous membranes. Ecchymoses, painful purpura, and geographic areas of hemorrhagic necrosis may develop:

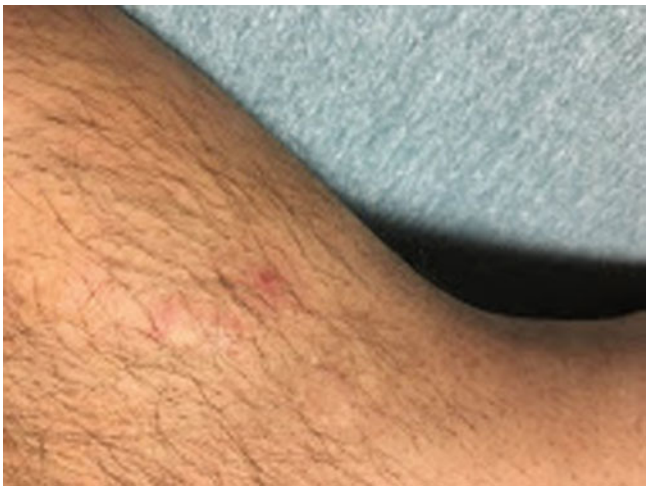


Fig. 14.12 Gonococcemia (disseminated gonococcal infection). Cutaneous lesions are often sparse and subtle (Photo courtesy of Yousuf Qureshi, MD)

these findings are indicative of purpura fulminans and disseminated intravascular coagulation (DIC) [140].

Chronic meningococcemia and chronic gonococcemia produce indistinguishable clinical findings, and cannot be differentiated except by the isolation of the causative organism [141].

Specific Investigations

For diagnosis
Gram stain
Culture (Thayer-Martin media)
Nucleic acid amplification testing (NAAT)
Histopathology
For treatment
If chloramphenicol is used, CBC should be monitored, given the risk of bone marrow suppression

N. gonorrhoeae are recovered from less than 50 % of purulent synovial effusions due to disseminated gonococcal infections (DGI), positive blood cultures occur in less than one-third of patients, and skin lesions are always sterile. At least two sets of blood cultures should be obtained in suspected cases. In addition, synovial, skin, urethral or cervical, rectal, and pharyngeal specimens should be submitted for nucleic acid amplification testing (NAAT), the preferred method of diagnosis. If NAAT is not available, then cultures from these sites should be submitted. Cultures should be performed on Thayer-Martin media. If urethritis is present, gram stain of the urethral exudate should be examined for the gram negative intracellular diplococci, and diagnosis can be made based on this finding despite negative cultures. If skin biopsy is performed, vasculitis with thrombosis and pustules may be seen, but bacteria are rarely identified. All patients should undergo testing for other sexually transmitted infections, such as HIV, *Chlamydia trachomatis*, and syphilis serology, since coexistent infection with other sexually transmitted pathogens is common [142].

In meningococcemia, the frequency of positive blood cultures is 50–60 %, while the frequency of positive cerebrospinal fluid (CSF) cultures is 80–90 %, even in patients without meningeal signs [143]. Gram stain of CSF is valuable and may provide rapid confirmation of diagnosis. Latex agglutination, loop-mediated isothermal amplification (LAMP), rapid polysaccharide dipstick test, and PCR can also be performed on CSF [144–147]. Skin biopsy, when combined with culture and gram stain, demonstrates a sensitivity of 56 % in isolating *N. gonorrhoeae*. Routine histopathology demonstrates vasculitis, thrombotic vasculopathy, and necrosis [148]. Although the gold standard for diagnosis remains culture, antibiotic therapy should not be delayed by any diagnostic measure when meningococcemia is suspected.

Disseminated Gonococcal Infection

Ceftriaxone or cefotaxime, intravenous or intramuscular, are the preferred first-line initial treatments for disseminated gonococcal infection. Oral azithromycin or doxycycline (in patients older than 8 years) should also be administered alongside the parenteral cephalosporin for dual coverage and to treat potential *C. trachomatis* coinfection. Dual coverage is recommended because of the increasing resistance of *N. gonorrhoeae* to cephalosporins.

Antibiotic therapy should be administered for 7 days, provided that clinical signs and symptoms of infection have resolved. In patients with purulent arthritis, parenteral therapy for up to 14 days in combination with joint drainage is recommended.

In patients who lack septic arthritis, respond promptly to first-line parenteral therapy, and for whom susceptibility testing demonstrates sensitivity to a second-line agent, the 7-day course of antibiotic therapy can be completed with cefixime, amoxicillin, or doxycycline (in patients over 8 years of age). Ciprofloxacin is also considered an appropriate agent for step-down therapy, but the use of fluoroquinolones is generally not recommended in patients under 18 years of age. If susceptibility testing is not available, step-down therapy with oral antibiotics is not recommended, and the course of therapy should be completed with parenteral ceftriaxone or cefotaxime.

Infected partners of patients should be treated with single-dose intramuscular ceftriaxone, single-dose oral azithromycin, or a 7-day course of oral doxycycline.

Table 14.41 First-line therapies for disseminated gonococcal infection [149, 150]

Medication	Dosing	Evidence level
Ceftriaxone	50 mg/kg IM or IV daily	B
	Maximum daily dose 1 g	
	Duration of therapy: 7–14 days	
Cefotaxime	50–180 mg/kg IV every 8 h	B
	Maximum single dose 1 g	
	Duration of therapy: 7–14 days	
Azithromycin	20 mg/kg po as a single dose	D
	Maximum dose: 1 g	
Doxycycline	2–4 mg/kg/day divided every 12 h	D
	Duration of therapy: 7 days	
	Maximum single dose: 100 mg	

Table 14.42 Second-line therapies for disseminated gonococcal infection [149, 151]

Medication	Dosing	Evidence level
Cefixime	8 mg/kg/day divided every 12 h	D
	Maximum single dose 400 mg	
Amoxicillin	25–50 mg/kg/day in divided doses every 8 h	D
	Maximum single dose 500 mg	
Doxycycline	2–4 mg/kg/day divided every 12 h	D
	Duration of therapy: 7 days	
	Maximum single dose: 100 mg	

Meningococcemia

Treatment should be initiated within 30 min of presumptive diagnosis, and should be started immediately after blood cultures are obtained; treatment should not await lumbar puncture. Data from a prospective open trial studying children and adults (more than 80 % of patients were under 18 years of age) with epidemic disease, and retrospective data from pediatric studies, support the use of monotherapy with ceftriaxone. In the prospective study, the treatment failure rate was 9 % and the mortality rate was 6 %. Cefotaxime is equivalent to ceftriaxone, and these are the treatments of choice prior to available susceptibility testing. Seven days of parenteral therapy is effective and adequate.

Penicillin may be used for effective therapy if susceptibility testing indicates that the causative isolate of *N. meningitidis* is sensitive. However, penicillin resistance has been present for decades, and since therapy must be initiated before susceptibility testing, this is not a first-line treatment. For patients who are allergic to cephalosporins or penicillin, chloramphenicol has been shown to be as effective as ceftriaxone, with the same treatment failure and mortality rate for epidemic disease. However, given the more favorable side effect profile of beta-lactam antibiotics, as well as the possibility for high-level resistance in causative isolates, chloramphenicol is a second-line therapy.

Table 14.43 First-line therapies for meningococcemia [152–156]

Medication	Dosing (duration of treatment: 7 days)	Evidence level
Ceftriaxone	100 mg/kg/day divided every 12–24 h	B
	Maximum daily dose: 4 g	
Cefotaxime	225–300 mg/kg/day divided every 8 h	B
	Maximum single dose: 2 g	

Table 14.44 Second-line therapies for meningococcemia [153, 155, 157, 158]

Medication	Dosing (duration of treatment: 7 days)	Evidence level
Penicillin G	300,000 units/kg/day	D
	Maximum daily dose: 24 million units	
Chloramphenicol	100 mg/kg/day IV	B
	Maximum daily dose: 4 g	

Table 14.45 Third-line therapies for meningococcemia [159–161]

Medication	Dosing	Evidence level
Protein C concentrate	200–600 IU/kg/day	B
	For 7 days	

Protein C activation is impaired in meningococcal infection and patients with purpura fulminans in particular have reduced levels of activated protein C (APC). A randomized controlled trial demonstrated that treatment with protein C concentrate led to dose-related increases in plasma APC levels and resolution of indicators of coagulation imbalances such as d-dimer levels in children with purpura fulminans due to meningococcemia. Mortality and amputation rates were not affected by treatment. However, an open study in a similar group of patients demonstrated improved survival and a decreased number of amputations.

Corynebacterial Infections

Clinical Features

Erythrasma is a chronic superficial infection caused by *Corynebacterium minutissimum*, a gram-positive, non-spore forming bacillus. It is rare in children. In adolescents and young adults, it is more common and involves the interdigital toe webs, axillae, and groin. Thin brown patches or plaques with or without maceration and scale are typical (Figs. 14.13 and 14.14). Occasional genital or perianal involvement may occur. Infection is usually asymptomatic but may be pruritic [162].

Pitted keratolysis presents as crateriform pits on the pressure-bearing aspects of the soles (Fig. 14.15) and is caused by *Cornyebacterium* species, *Kytococcus sedentarius*, or *Dermatophilus congolensis*. It is associated with

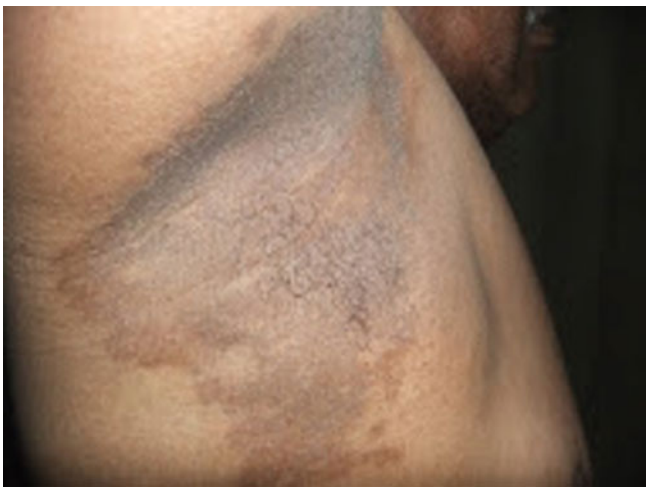


Fig. 14.13 Erythrasma. Thin brown plaques in the axillae

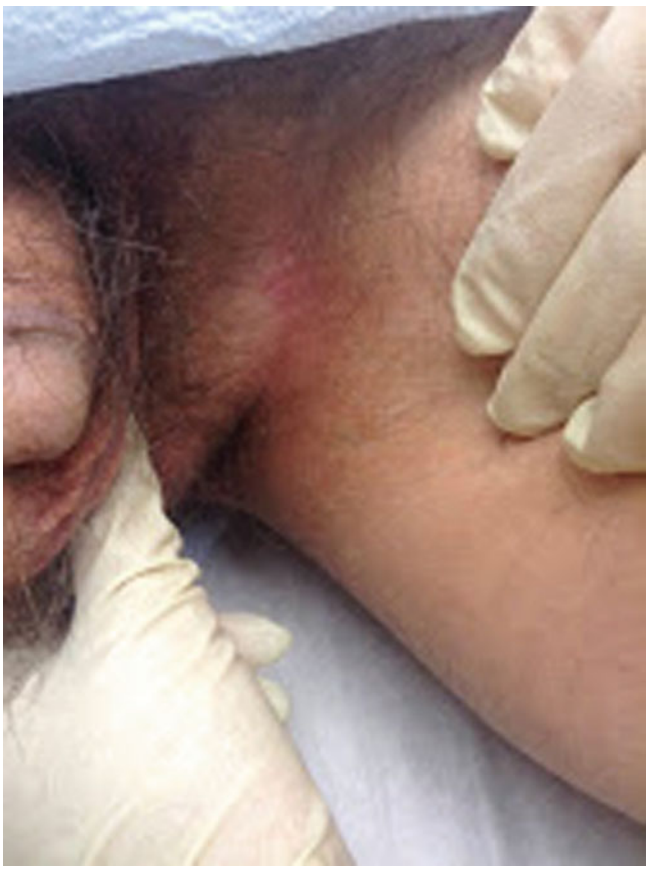


Fig. 14.14 Erythrasma. Erythematous patches in the groin with a non-specific clinical appearance (Photo courtesy of Sylvia Hsu, MD)

malador, hyperhidrosis, pruritus, and sometimes burning sensation or tenderness [163].

Trichomycosis presents as asymptomatic soft tan concretions of the axillary or pubic hair, and is associated with malodor and hyperhidrosis [164]. Thus, it may be seen in postpubertal adolescents. *Cornyebacterium* species including

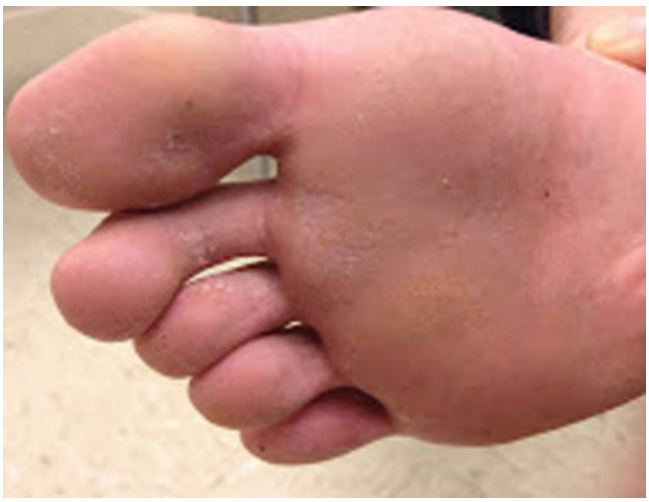


Fig. 14.15 Pitted keratolysis. Crateriform pits on the plantar surface (Photo courtesy of Sylvia Hsu, MD)

C. tenuis are causative. It may be associated with concomitant pitted keratolysis and erythrasma [165].

Specific Investigations

For diagnosis
Gram stain
Wood's lamp
Histopathology
Culture
For treatment
No specific investigations required

A gram stain of skin scraping will identify gram-positive rods and filaments in erythrasma. Examination with wood's lamp in a dark room demonstrates coral-red fluorescence due to porphyrin production by *C. minutissimum* (Fig. 14.16). The causative bacteria can also be seen as small light blue colonies in the stratum corneum on histopathology; PAS, gram, or Giemsa stains can be used to highlight the organisms, but skin biopsy is usually performed to exclude inflammatory dermatoses [166]. Culture is rarely indicated, but can be performed.

Pitted keratolysis is generally a clinical diagnosis. Wood's lamp is less sensitive for detection than in cases of erythrasma, but may be helpful if positive. If skin biopsy is performed, bacterial colonies can be identified in the stratum corneum [163]. Culture is possible, but rarely performed or necessary.

In trichomycosis, KOH or gram stain of the concretions demonstrates that they are composed of bacilli. Wood's lamp is very useful and demonstrates fluorescence in most cases [165]. Bacterial culture is not necessary, but can be performed.

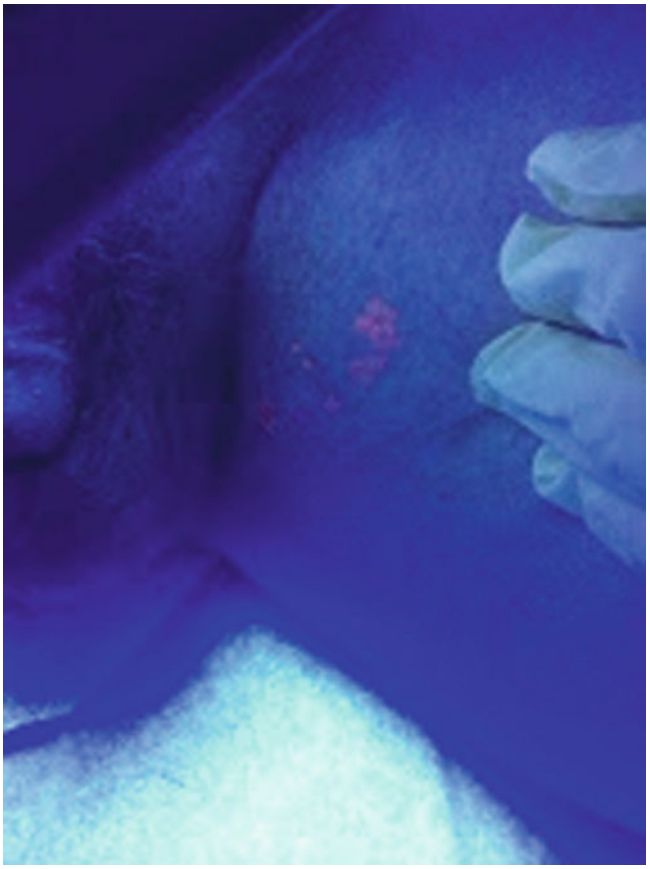


Fig. 14.16 Erythrasma. Characteristic coral red fluorescence during illumination with Wood's lamp (Photo courtesy of Sylvia Hsu, MD)

Table 14.46 First-line therapies for erythrasma [167–170]

Medication	Dosing	Evidence level
Topical clindamycin 1 %	Twice daily for 2–3 weeks	D
Topical erythromycin 2 %	Twice daily for 2–3 weeks	D
Topical imadazole antifungals:	Twice daily for 6 weeks (on average)	A*
Oxiconazole, miconazole, econazole		

Table 14.47 Second-line therapies for erythrasma [171–173]

Medication	Dosing	Evidence level
Oral erythromycin	50 mg/kg/day po divided every 6–8 h for 14 days with maximum daily dose 2 g	A*
Oral clarithromycin	1 g po single dose	A*

Table 14.48 Third-line therapies for erythrasma [174, 175]

Medication	Dosing	Evidence level
Photodynamic therapy	One or two irradiations:	C*
	80 J/cm^2 by red light (broad band, peak at 635 nm)	
Tetracycline	25–50 mg/kg/day po in divided doses every 6 h for 14 days with maximum daily dose 3 g	D*

Erythrasma

Although there are no randomized trials studying the topical clindamycin and topical erythromycin for the treatment of erythrasma, they are considered first-line therapies given their long history of clinical efficacy, safety, availability, and low cost. Several randomized studies have examined the clinical utility of topical imidazole antifungals, finding that over 90 % of patients were cured. However, these studies also examined superficial fungal infections as well as co-infections. Additionally, the duration of successful treatment occurred within a wide range: between 7 and 60 days (approximately 40 on average in a study by Grigoriu et al.).

Oral antimicrobial therapy should be reserved for patients with extensive or refractory disease, given the potential for antibiotic resistance following failed oral therapy. In an early randomized trial, cure or improvement was obtained in 77 % of patients treated with oral erythromycin, compared to 87 % of patients treated with topical fusidic acid. A more recent double-blind study also found topical fusidic acid to have the highest cure rate (97 %) for erythrasma; single-dose clarithromycin and a 2-week course of erythromycin demonstrated cure rates of 67 % and 53 %, respectively. Based on this data, fusidic acid is the most effective evidenced-based treatment for erythrasma, but unfortunately is not available in the United States.

C. minutissimum produces natural porphyrins, accounting for the observed fluorescence under Wood's light, a quality which can be exploited by photodynamic therapy. In a small trial, one or two red light irradiations resulted in complete response in only 3 of 13 patients. Tetracycline has also been used for erythrasma, but should be considered a third-line therapy, given its side effect profile and reduced efficacy compared to oral erythromycin. Tetracycline should be avoided in children younger than 8 years of age.

Pitted Keratolysis

Table 14.49 First-line therapies for pitted keratolysis [176]

Medication	Dosing	Evidence level
Topical erythromycin 2 %	Twice daily for 10 days	C

In 97 adults and children (youngest age 8 years) with pitted keratolysis, hyperhidrosis was an associated finding in nearly all patients. Topical erythromycin resulted in complete clearance of cutaneous findings and hyperhidrosis in all patients, with only a 6 % recurrence rate. Although hyperhidrosis is generally

considered to be a predisposing factor for this infection, the authors postulated that hyperhidrosis may be secondary to eccrine gland dysfunction resulting from *Kytococcus* infection.

Table 14.50 Second-line therapies for pitted keratolysis [177–179]

Medication	Dosing	Evidence level
Mupirocin 2 % ointment	Twice daily for 2 weeks	E*
Clindamycin 1 %-benzoyl peroxide 5 %	Twice daily for 3–4 weeks	E*

Mupirocin 2 % ointment has been effective for pitted keratolysis in case reports. In a small series, resolution of clinical signs and symptoms of pitted keratolysis resolved following treatment with clindamycin 1 %-benzoyl peroxide 5 % gel for 3–4 weeks.

Table 14.51 Third-line therapies for pitted keratolysis [180]

Medication	Dosing	Evidence level
Botulinum toxin injection	50 U total for each plantar surface, with 2 U per each of 25 sites marked (each site 2 cm apart)	E*

In two patients with disease refractory to antibiotics, botulinum toxin injection resulted in elimination of hyperhidrosis and pitted keratolysis within 14–30 days following treatment.

Trichomycosis

Table 14.52 First-line therapies for trichomycosis [165, 181]

Medication	Dosing	Evidence level
Shaving of affected area	For 2–3 weeks	D*

In general the most effective and rapid treatment of trichomycosis is to shave or removed the affected hair. Of note, however, recurrence is common if shaving is only performed once and without an adjunct treatment such as benozyl peroxide or sulfur-containing soap. Topical antibiotics such as clindamycin and erythromycin are also curative. Overall, these treatments have demonstrated over 90 % cure rates in a retrospective review.

Table 14.53 Second-line therapies for trichomycosis [165, 181]

Medication	Dosing	Evidence level
Topical clindamycin 1 %		D*
Topical erythromycin 2 %		D*

Erysipeloid

Clinical Features

Erysipelothrix rhusiopathiae is a non–spore forming, gram-positive bacillus capable of causing self-limited soft tissue infection or serious systemic infection. Infection in humans is usually due to occupational exposure to domestic or marine animals. Erysipeloid is a localized cutaneous infection that follows minor trauma, and results in a subacute cellulitis appearing as a violaceous lesion with central clearing and a raised border (Sect. 14.17). Stiffness, pain, and local lymphangitis may be seen. If diffuse cutaneous disease, progression occurs from erysipeloid to widespread sites, sometimes with urticarial or bullous lesions. Systemic infection is rare, and associated with skin findings of erysipeloid or diffuse cutaneous disease, in addition to bacteremia and visceral involvement such as endocarditis [182].

Specific Investigations

For diagnosis
Gram stain
Culture
For treatment
No specific investigations required

The best way to diagnose erysipeloid is based on clinical findings. Gram stain or culture of tissue or aspirates obtained from cutaneous lesions are often negative. Blood cultures should be obtained in suspected cases of diffuse cutaneous or systemic disease. *E. rhusiopathiae* grows within 2–3 days. Of note however, misidentification as *Lactobacillus* or *Enterococcus* species may occur [183].

Erysipeloid is typically an occupational infection seen in individuals exposed to livestock or involved in fishing. It is rare in children; [184] thus there are no controlled or comparative studies in pediatric patients, and treatment is based on in vitro data and clinical experience.

Table 14.54 First-line therapy for localized erysipeloid [182, 185–188]

Medication	Dosing	Evidence level
Oral penicillin V	25–75 mg/kg/po divided every 6–8 h for 7 days, with maximum daily dose 2 g	D*

Penicillin and imipenem are the most active agents in vitro against *E. rhusiopathiae*. Other agents with activity include cephalosporins, fluoroquinolones, erythromycin, clindamycin, and linezolid. Although in vitro data supports the use of fluoroquinolones in localized cutaneous as well as diffuse cutaneous and systemic infections, this class of antibiotics should not be used in children under 18 years of age.

Localized cutaneous disease typically resolves within 3 weeks without treatment, but antimicrobial therapy is recommended to hasten resolution, alleviate symptoms, and reduce the risk of relapse.

Table 14.55 Second-line therapies for localized erysipeloid [185–188]

Medication	Dosing	Evidence level
Cephalexin	25–50 mg/kg/day po in 3–4 divided doses for 7 days	D*
Clindamycin	20 mg/kg/day in 3 divided doses for 7 days	D*
Erythromycin	30–50 mg/kg/day po divided every 6–12 h for 7 days with maximum daily dose 4 g	D*

Table 14.56 Third-line therapies for diffuse cutaneous erysipeloid (duration of treatment: 7 days) or with systemic involvement (duration of treatment: 4 weeks) [189]

Medication	Dosing	Evidence level
Penicillin G	200,000–300,000 units/kg/day IV in divided doses every 6 h with maximum daily dose 8 M units	D*
Ceftriaxone	100 mg/kg/day IV divided every 12–24 h	D*
Imipenem	60–100 mg/kg/day IV divided every 6 h with maximum daily dose 4 g	D*
Daptomycin	4–10 mg/kg/day IV	D*

For diffuse cutaneous disease or systemic infection (bacteremia, with or without bacteremia), parenteral antibiotics are recommended. Data for efficacy of these agents in more severe disease is based on clinical reports and series.

Anthrax

Clinical Features

Bacillus anthracis causes cutaneous, inhalation, and gastrointestinal tract anthrax. Naturally occurring cases are sporadic and zoonotic, due to contact with or inhalation or consumption of spores from infected animals or animal products. Bioterrorism-related disease may result in outbreaks. Cutaneous disease begins as a small painless papule, which becomes a vesicle and then erodes, leaving a necrotic ulcer with eschar. Edema and lymphadenopathy are common. Systemic symptoms are common; mortality is rare with treatment, but may be as high as 20 % without treatment. In contrast, inhalation and gastrointestinal infections carry mortality rates of up to 92 % and 60 %, respectively. Meningitis may occur as complication following any of the three forms of infection, and is fatal in over 90 % of patients [190, 191].

Specific Investigations

For diagnosis
Gram stain
Culture
PCR
Histopathology with immunohistochemistry
Enzyme-linked immunosorbent assay (ELISA)
For treatment
No specific investigations

Given the urgency of the clinical scenario, the presence of a painless eschar with extensive edema in conjunction with gram-positive rods and neutrophils on gram stain should prompt presumptive diagnosis and rapid empiric therapy. Two swabs should be used to obtain material from cutaneous lesions, with one swab submitted for gram stain and culture and the other for PCR. Additionally, a skin biopsy involving the lesion and adjacent skin should be evaluated by histopathology and immunohistochemistry. A second skin biopsy should be obtained for gram stain, culture, and PCR in patients with less than 1 day of antibiotic therapy. A confirmed case requires two non-culture methods for detection of *B. anthracis*, which may include anti-protective antigen (PA) immunoglobulin (IgG) detected by an enzyme-linked immunosorbent assay (ELISA). The CDC provides detailed guidelines for collection of diagnostic laboratory specimens for the diagnosis of cutaneous, inhalation, and gastrointestinal anthrax [192].

Management Strategy

B. anthracis is highly susceptible to penicillin, fluoroquinolones, tetracyclines, erythromycin, and streptomycin [193, 194]. However, beta-lactam use can induce resistance during treatment [195]. Of note, *B. anthracis* is not susceptible to cephalosporins.

The following therapies are appropriate for children with cutaneous anthrax without systemic involvement, extensive edema, or lesions involving the head and neck. For bioterrorism-associated cases, the total duration of treatment is 60 days, to provide prophylaxis against late-occurring inhalational anthrax due to inhaled spores. For infections acquired naturally (from animals or hides), the duration of therapy is 7–10 days. Treatment recommendations are based on historical experience and in vitro susceptibilities.

For children with systemic anthrax with or without meningitis, or for children with cutaneous anthrax with systemic involvement, extensive edema, or lesions involving the head or neck, prompt hospitalization and combination parenteral antibiotic therapy is required. As a child is started on therapy, cutaneous anthrax can also evolve into systemic disease, requiring more aggressive therapy [196].

Table 14.57 First-line therapies for cutaneous anthrax [123, 196, 197]

Medication	Dosing	Evidence level
Ciprofloxacin	30 mg/kg/day po divided every 12 h	D
	Maximum dose: 500 mg	
Doxycycline	Less than 45 kg:	D
	4.4 mg/kg/day po divided every 12 h	
	Greater than 45 kg:	
	100 mg po every 12 h	
	Maximum dose: 100 mg	
Clindamycin	30 mg/kg/day po divided every 8 h	D
	Maximum dose: 600 mg	
Levofloxacin	Less than 50 kg:	D
	16 mg/kg/day po divided every 12 h	
	Greater than 50 kg:	
	500 mg po daily	
	Maximum dose: 250 mg	

Prior to culture and susceptibility testing, ciprofloxacin is the treatment of choice. Acceptable alternative empiric agents include clindamycin, doxycycline, and levofloxacin. If in vitro susceptibility testing identifies an isolate sensitive to penicillin, therapy should be modified from a first-line agent to oral penicillin or amoxicillin. Although doxycycline is typically avoided in children under the age of 8 years for most indications, the risk of dental staining is very low following short courses of doxycycline. Given that prompt treatment is critical, doxycycline is a first-line agent for children with anthrax. Similarly, fluoroquinolones are acceptable in children with anthrax, despite the fact that their use is typically avoided in patients under 18 years of age. There is no current evidence that limited courses of treatment with fluoroquinolones cause sustained injuries to the joints or surrounding tissues in children.

Table 14.58 Second-line therapies for cutaneous anthrax [196]

Medication	Dosing	Evidence level
Penicillin VK	50–75 mg/kg/day po divided every 8 h	D
Amoxicillin	75 mg/kg/day po divided every 8 h	D
	Maximum dose: 1 g	

Adjunct therapies for cutaneous anthrax [198–203]

Medication	Dosing	Evidence level
Raxibacumab	Single dose:	E
	>50 kg: 40 mg/kg IV	
	15–50 kg: 60 mg/kg IV	
	<15 kg: 80 mg/kg IV	
Anthrax immune globulin (AIG)		D
Corticosteroids	Dexamethasone 0.6 mg/kg/day	D
Amoxicillin for post-exposure prophylaxis	45 mg/kg/day po in 3 divided doses for 60 days	E

Two antitoxins are available for adjunctive therapy of anthrax: AIG (a polyclonal human immunoglobulin) and raxibacumab (a humanized monoclonal antibody). Raxibacumab is FDA-approved for the treatment and prevention of anthrax in children. AIG is not currently FDA-approved. However, AIG has retrospective supportive evidence in humans, while raxibacumab does not. Nonetheless, the AAP and CDC recommend adjunctive therapy with an antitoxin in all potential (including bioterrorism-related exposure such as inhalation of spores) or confirmed cases of systemic anthrax in children.

Glucocorticoids may be a useful adjunctive therapy for children with cutaneous anthrax involving the head and neck with significant edema. Observational studies in adults and children support the use of steroids in this scenario.

Pharmacokinetic studies and historical data have suggested that amoxicillin may be an effective agent for post-exposure prophylaxis in children at risk for inhalation anthrax due to exposure to spores.

Bartonella: Cat Scratch Disease

Clinical Features

Cat scratch disease (CSD) is a self-limited regional lymphadenopathy caused by *Bartonella henselae*, a gram-negative bacterium. Cats are the natural reservoir for *B. henselae*, and transmission occurs following cat scratch or bite, or a flea bite. Infection in children is very common, and presents in 90% of cases as a localized cutaneous lesion at the site of inoculation. This primary lesion may be erythematous, papular, pustular, or vesicular. Proximal to this inoculation lesion, tender regional lymphadenopathy (most commonly of the axillary, epitrochlear, cervical, supraclavicular, and submandibular lymph nodes) develops. The cutaneous lesion usually resolves in 1–3 weeks, while the the lymphadenopathy resolves without treatment in 1–4 months [204].

In otherwise healthy individuals, CSD is generally a localized and self-limited infection [205]. However, in some patients, including those with immunocompromise, rare dissemination to the liver, spleen, eye, or central nervous system can occur, and results in life-threatening complications. In children, visceral organ involvement, including hepatosplenic or bony disease, is one of the more common manifestations after lymphadenopathy alone [206].

Specific Investigations

For diagnosis
Serology
Culture
Histopathology
PCR

For treatment
No specific investigations required

In general, the diagnosis is based upon the history of cat or flea exposure, in conjunction with appropriate clinical findings. Serology, culture, histopathology, and/or PCR are supportive methods, and one of these laboratory methods should be used to confirm the diagnosis [207, 208]. The indirect fluorescence assay (IFA) can be used to detect IgG antibodies against *B. henselae*, but sensitivity and specificity are not optimal [209]. In general, IgG titers <1:64 are considered negative, while those between 1:64 and 1:256 indicate possible infection, and those >1:256 are strongly suggestive of active infection [210]. Even under optimal conditions, cultures from blood or tissue are usually negative; B. henselae is fastidious and slow-growing. Skin biopsy of the inoculation lesion demonstrates a zonal pattern: central necrosis surrounded by granulomas with lymphocytes in the outermost layer. Lymph node biopsy may show similar findings, stellate granulomas, or abscesses. Warthin-starry stain is highly nonspecific, but very sensitive, and highlights bacilli in chains, clumps, or filaments within areas of necrosis in skin or lymph nodes. PCR has high specificity and a sensitivity ranging from 43 % to 76 %, and can be performed on blood or tissue [211].

Most patients with CSD have a self-limited course characterized by regional lymphadenopathy, and treatment is not required for mild or moderate lymphadenitis. Treatment is recommended for patients with severe lymphadenitis, or to hasten resolution in patients with mild or moderate disease [212]. However, in up to 14 % of patients, visceral disease due to dissemination may occur, resulting in hepatosplenic disease, neuroretinitis, encephalitis, or endocarditis [204]. The treatment of visceral disease is beyond the scope of this text.

In a randomized, double-blind, placebo-controlled trial of immunocompetent adults and children, a 5-day course of azithromycin resulted in an 80 % decrease of initial lymph node volume by ultrasonography in 50 % of patients. Another study of three children with CSD demonstrated 50 % reduction in lymph node size within 5 days, and complete resolution of lymphadenopathy within 2 weeks, following treatment with oral azithromycin for 5–10 days.

Table 14.59 First-line therapies for CSD [213, 214]

Medication	Dosing	Evidence level
Azithromycin	10 mg/kg on day 1, then 5 mg/kg for 4 days	A

Table 14.60 Second-line therapies for CSD [215]

Medication	Dosing	Evidence level
Rifampin	10 mg/kg twice daily, with maximum daily dose 600 mg, for 7–10 days	D
Trimethoprim-sulfamethoxazole	Trimethoprim 8 mg/kg/day and sulfamethoxazole 40 mg/kg/day, in two divided doses for 7–10 days	D

A retrospective review of 18 different antimicrobials taken for at least 3–5 days found that 14 antibiotics were of little value in the reduction of CSD symptoms or lymphadenopathy. Among the useful oral antibiotics, rifampin, ciprofloxacin, and trimethoprim-sulfamethoxazole were 87 %, 84 %, and 58 % effective, respectively.

Fungus-Like Bacteria: Actinomycosis and Nocardiosis

Clinical Features

Actinomyces species are non-spore forming, gram-positive, facultative anaerobic bacteria that cause cervicofacial, central nervous system, thoracoabdominal and pelvic actinomycosis. Cervicofacial disease is the most common presentation, and is characterized by chronic, progressive non-tender masses that evolve into abscesses with fistulae and sinus tracts which drain exudate with sulfur granules. Occasionally it may present as an acute suppurative infection with pain. The mandible is the most common site of infection; the cheek, chin, and upper jaw may also be involved. Bony involvement is rare. *Actinomyces* species are a part of the normal oral flora; infection occurs following tissue injury. Predisposing factors include dental infections including caries, extractions, immunosuppression, and malnutrition [216].

Nocardia species are gram-positive aerobic bacteria that cause chronic infections of the central nervous system, lungs, eyes, bone, or skin. Cutaneous disease is present in less than 10 % of patients affected. Two-thirds of affected patients are infected in the context of immunosuppression, including organ or stem cell transplantation, diabetes, corticosteroid therapy, and HIV. Primary cutaneous disease occurs following direct inoculation from organisms in the environment following trauma. Ulcers, pyoderma, nodules, abscesses, cellulitis, and lymphocutaneous lesions with sporotrichoid spread are seen [217]. Given that primary and secondary cutaneous disease cannot be distinguished clinically, disseminated disease should be assumed until excluded.

Actinomycetoma is a variant of mycetoma caused by *Nocardia* or *Actinomyces* species (in contrast to eumycetoma, which is a true fungal infection). Actinomycetoma

presents with enlarging nodules at the site of inoculation, associated with sinus tract formation and draining sinuses with granules. Deep extension to muscle or bone may occur [218].

Specific Investigations

For diagnosis
Gram stain
Culture
Histopathology
Immunohistochemistry
PCR
For treatment
CBC
LFTs
Kidney function tests (BUN, creatinine)
G6PD level

Needle aspiration or tissue from patients with suspected actinomycosis can be cultured, but must be incubated for a minimum of 14 days. By histopathology, sulfur granules are easily missed by routine tissue staining; thus several biopsies are recommended for higher diagnostic yield. Sulfur granules are composed of tangles of filamentous bacteria [219]. While the thin filaments of actinomycosis and nocardiosis can be distinguished from the thick hyphae of eumycetoma, filaments of *Nocardia* and *Actinomyces* are very difficult to distinguish histologically [220]. Thus, culture is the most important method for diagnosis. Monoclonal antibody staining and PCR are newer, highly specific methods for identification of *Actinomyces* [221].

Granules in nocardiosis and actinomycosis can be crushed and evaluated by gram stain to demonstrate filamentous bacteria. *Nocardia* is partially-acid fast, a helpful feature that allows rapid identification before culture results are available. Isolation of *Nocardia* can be difficult, sometimes requiring specialized media for cultures; growth occurs within 1–3 weeks [222]. Histopathology demonstrates suppurative or caseating granulomas or abscesses with necrosis; organisms occasionally may be visualized [223]. PCR is accurate and rapid, but unfortunately is not widely available [224].

Laboratory monitoring may be necessary for patients with nocardiosis. CBC and LFTs should be monitored in patients on dapsone, and G6PD levels should be obtained prior to initiation of therapy. Hematologic abnormalities including thrombocytopenia may occur during linezolid therapy, so monitoring of CBC is recommended. In patients treated with amikacin, renal function should be monitored.

Actinomycosis

Table 14.61 First-line therapies for actinomycosis [219, 225, 226]

Medication	Dosing	Evidence level
Oral penicillin V	For 2–6 months	D
Amoxicillin	For 2–6 months	D

Oral amoxicillin has been found to be equally effective compared to penicillin; however, in small case series, long-term penicillin therapy has been reported as the medical treatment of choice. For cervicofacial actinomycosis, high-dose penicillin has been described as the preferred treatment.

Table 14.62 Second-line therapies for actinomycosis [227, 228]

Medication	Dosing	Evidence level
Erythromycin	For 2–6 months	D
Clindamycin	For 2–6 months	D
Tetracyclines	For 2–6 months	D

In vitro studies and clinical series have shown tetracyclines, erythromycin, and clindamycin to be effective alternative treatments which may be used in patients allergic to penicillin. Tetracyclines should be avoided in children under 8 years of age.

Table 14.63 Third-line therapies for actinomycosis [229]

Medication	Dosing	Evidence level
Surgery	Excision of recalcitrant lesions or drainage of abscesses, in conjunction with antimicrobial therapy	D

When surgery is used for recalcitrant lesions, including sinus tracts and abscesses, antibiotic therapy should be used in conjunction. A combined approach can be successful for severe or refractory disease.

Nocardiosis

Due to variable resistance of Nocardia species to antibiotics, two or three antibiotics are empirically used for severe infections. However, for cutaneous infection in immunocompetent patients, monotherapy is sufficient as follows.

Table 14.64 First-line therapies for nocardiosis [230, 231]

Medication	Dosing	Evidence level
Trimethoprim-sulfamethoxazole	For 3–6 months for isolated cutaneous infection	D
Trimethoprim-sulfamethoxazole and dapsone	For 6–12 months for non-severe mycetoma	D

In a 2010 retrospective study of 765 clinical isolates of *Nocardia* species, 61 % were resistant to sulfamethoxazole,

while 42 % were resistant to trimethoprim-sulfamethoxazole. However, in a repeat study 2 years later among 552 clinical isolates, only 2 % were found to have resistant MICs for trimethoprim-sulfamethoxazole and/or sulfamethoxazole. Thus, trimethoprim-sulfamethoxazole is the treatment of choice for Nocardiosis, but susceptibility testing must be performed when tailoring therapy for individual patients.

Table 14.65 Second-line therapies for nocardiosis [232–234]

Medication	Dosing	Evidence level
Minocycline	For 3–6 months for isolated cutaneous infection	D
Amoxicillin-clavulanate	For 3–6 months for isolated cutaneous infection	D
Linezolid	For 3–6 months for isolated cutaneous infection	D

Among alternatives to sulfonamides, minocycline, amoxicillin-clavulanate, linezolid, imipenem, and amikacin were found to be effective in vitro against *Nocardia* species, based on MICs. In a separate in vitro study, linezolid and amikacin were the only two antimicrobials to which all isolates were susceptible. However, long-term linezolid therapy is associated with hematologic toxicity, which requires monitoring.

Table 14.66 Third-line therapies for nocardiosis [235, 236]

Medication	Dosing	Evidence level
Intravenous imipenem with or without amikacin	3-week course; repeated at 6-month intervals for severe mycetoma	D
Surgery	For severe mycetoma	D

In a small series of patients with limited disease of shorter duration (less than 2 years), treatment with sulfonamides for an average of 15 months was successful. In contrast, in patients with more extensive disease including bony involvement, duration of 10 years, and refractory to sulfonamide treatment, a 3-week course of parenteral imipenem with or without amikacin was successful after two courses of treatment.

Surgery is typically not required for the treatment of nocardial mycetoma, which can be treated successfully with antibiotics alone. However, surgery can be used in conjunction with antimicrobials for refractory or severe disease.

Treponemal Infections

Clinical Features

Congenital syphilis refers to transplacental transmission of *Treponema pallidum*, which can occur at any time during pregnancy, but occurs with increasing frequency as gestation advances. In women with untreated primary or secondary syphilis, there is 60–90 % chance of fetal transmission. In latent syphilis, the rate is 10–40 %. Infection may result in intrauterine demise, stillbirth, prematurity, or a wide variety of clinical findings. Only severe infections are clinically apparent at birth [237].

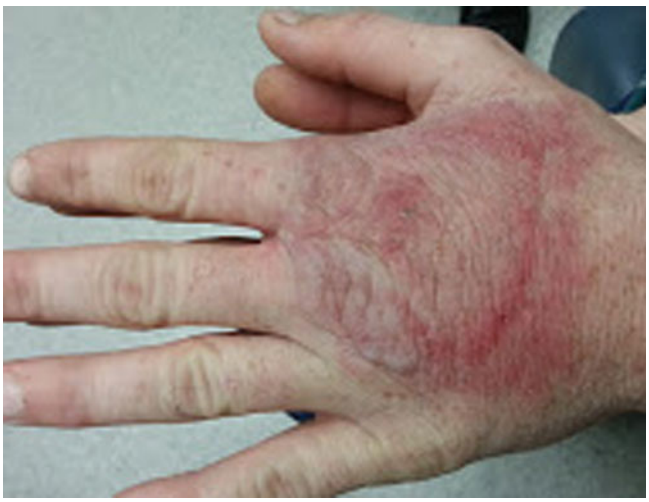


Fig. 14.17 Erysipeloid. Violaceous plaque with central clearing and targetoid, expanding border on the dorsal hand (Photo courtesy of Sylvia Hsu, MD)

Early congenital syphilis has its onset before 2 years of age, most often within 6–12 weeks after birth. Only 10–40 % of neonates with congenital syphilis demonstrate signs and symptoms at birth, including a morbilliform rash that desquamates and then becomes dusky or copper in color. Bullous or ulcerative lesions may also be seen. Mucous patches, fissures, and condyloma lata are uncommon. Systemic findings include fever and lymphadenopathy, hepatosplenomegaly, rhinitis, cardiopulmonary disease, neuro-ophthalmologic manifestations, renal failure, and radiographic abnormalities of long bones [238].

Late congenital syphilis has its onset after 2 years of age and develops in 40 % of infants born to mothers with untreated or inadequately treated syphilis. Cutaneous findings include perioral fissures or scars and gummas of the skin or mucous membranes. Interstitial keratitis, hypoplastic teeth, and sensorineural hearing loss form the Hutchinson triad, which is specific for late disease. A variety of other neurological, skeletal, and ophthalmological complications may result [239] (Fig. 14.17).

The presentation of acquired syphilis in children and adolescents is the same as that in adults. Almost all preadolescent children with acquired syphilis were infected during sexual contact with adults; thus infection in this age group represents abuse and must be reported and investigated. Transmission occurs via direct contact with an infectious lesion during sexual activity [240].

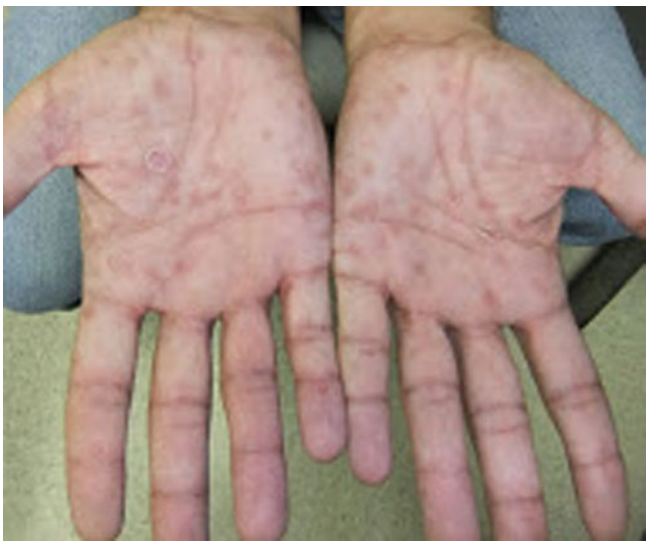
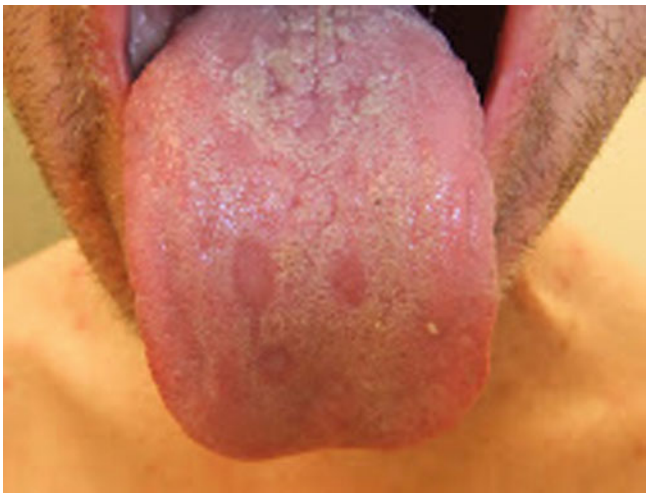


Fig. 14.18 Secondary syphilis. Red to copper-brown papules with desquamation on the palms of a male patient with HIV



Fi. 14.19 Secondary syphilis. Mucous patches

Early syphilis includes primary, secondary, and early latent disease. Latent disease is defined as asymptomatic infection with a normal physical examination in association with a positive serology; early latent disease refers to infection within 1 year. In primary syphilis, a papule at the inoculation site ulcerates to form a painless chancre which has a raised indurated margin and may be associated with lymphadenopathy. Secondary syphilis occurs in 25% of untreated patients, and is characterized by a diffuse papular or macular eruption involving the palms and soles and demonstrating a copper or red-brown color (Fig. 14.18). Scale, pustules, and nodules may be seen, but vesicles and blisters are absent. Large white-gray lesions in moist areas are known as condyloma lata. Mucous patches may also be present (Fig. 14.19). Associated findings include systemic symptoms, lymphadenopathy, alopecia, hepatitis, and renal disease. Tertiary or late syphilis is rare and refers to late latent disease, cardiovascular syphilis, neurosyphilis, and gummatous syphilis. Gummas may occur in the skin, bones, or visceral organs; in the skin they appear as heaped-up granulomatous nodules or plaques or ulcerative lesions [241].

The endemic nonvenereal treponematoses include yaws (*Treponema pallidum* subsp *pertenue*), bejel (*T. pallidum* subsp*endemicum*), and pinta (*Treponema carateum*). Yaws and bejel affect skin and bones and mainly occur in children, while pinta only affects skin and affects adolescents and adults. All are transmitted by direct skin-to-skin contact [242].

In yaws, the primary lesion ("mother yaw") is most commonly found on the legs or ankles, and starts as a papule that ulcerates and then heals within several months. Secondary lesions may be papular, eroded, or discoid, and often accompany lymphadenopathy, keratoderma, and periostitis. Tertiary yaws consists of destructive gummas of the skin, bones, and soft tissues. The primary lesions of bejel are located within the oropharyngeal mucosa. Secondary manifestations include shallow ulcers of the lips and oropharynx (mucous patches), angular stomatitis, and skin lesions in moist intertriginous areas. Late disease presents with destructive granulomatous lesions. In pinta, the primary lesion is a large expanding plaque, usually on the lower extremities. Secondary lesions are pruritic and red, gray, or blue-black. Years later, postinflammatory hypopigmentation results [243].

In the United States, *Borrelia burgdorferi* is the sole cause of lyme disease, which is transmitted by the bite of infected *Ixodes ricinus* ticks. Early localized disease is characterized by single or multiple lesions of erythema migrans (EM) in almost 90% of affected children [244]. EM begins as a red macule at the site of the tick bite, and then expands to form a large annular erythematous patch or plaque at least 5 cm in diameter. Central clearing may be present, but uniform erythema is more common. Pruritus, burning sensation, vesiculation, or central necrosis are occasional features [245]. If early disease is not treated, the spirochete disseminates, producing multiple EM lesions in conjunction with cranial nerve palsies, meningitis, and carditis. Late disease occurs months to years later, and the most common manifestation is arthritis [244].

Specific Investigations

For diagnosis
Serology: Nontreponemal (VDRL, RPR) and treponemal (FTA-ABS, MHA-TP) tests, and antibodies to *B. burgdorferi*
Darkfield microscopy and direct fluorescent antibody (DFA) testing
Histopathology with immunohistochemistry
PCR
Culture (only for *B. burgdorferi*)
For treatment
Serology: Nontreponemal tests at 6 and 12 months after treatment

Maternal nontreponemal tests (RPR or VDRL) must be performed prior to evaluating infants for congenital syphilis. In infants, serum RPR or VDRL, darkfield microscopic exam or direct fluorescent antibody (DFA) staining, and, if less than 1 month of age, pathologic examination of the placenta or umbilical cord with antitreponemal antibody staining should be performed. It is important to remember that positive assays for treponemal and nontreponemal IgG antibodies in babies may reflect passively transferred maternal antibodies; for this reason, detection of IgM against T. pallidum (19 s FTA-ABS IgM or Western blot) is more specific. In older infants and children, CSF analysis, CBC, and radiographic or neurological imaging, and ophthalmologic exam may be helpful adjunctive evaluations. The CDC and American Academy of Pediatrics provide algorithmic guidelines for the evaluation of congenital syphilis [149, 246].

Nontreponemal tests (VDRL and RPR) are highly sensitive and quantitative but nonspecific, with false positives in pregnancy, drug use, and other infections. They are useful as an initial screening test, decrease in titers following treatment, and increase in titer with reinfection. Treponemal tests (FTA-ABS, MHA-TP, TP-PA, and TP-EIA) are specific, qualitative, useful for confirming infection, and do not distinguish between active and treated syphilis. Direct methods are not widely available, but are highly sensitive and specific, particularly in primary disease: darkfield microscopy and direct fluorescent antibody testing (DFA-TP) are examples [247]. False negative nontreponemal tests occur in up to 30 % of patients with primary syphilis, and in the context of prozone reactions during secondary syphilis (when antibody titers are very high). Treponemal assays become positive earlier than nontreponemal tests. *T. pallidum* cannot be cultured [248].

Rapid point-of-care serologic testing uses blood from finger sticks, demonstrates high sensitivity and specificity, and is expensive. It is based on specific treponemal assays [249]. PCR of swab testing from mucosal sites is also over 90 % sensitive and specific [250]. Histopathology of primary syphilis demonstrates an ulcer with mixed infiltrates, while that of secondary syphilis often shows a lichenoid or psoriasiform pattern with plasma cells. Tertiary syphilis is characterized by diffuse granulomatous inflammation. Immunohistochemistry for T. pallidum is positive in all cases of secondary syphilis [17].

Nontreponemal antibody titers should be obtained at baseline prior to treatment, and then 6 and 12 months after treatment [251]. A fourfold decrease in titer is considered a treatment response and should be seen 6 months after treatment, while a fourfold increase indicates treatment failure [252].

Histopathology of yaws and bejel resembles that of syphilis, and treponemes can be visualized similarly [253]. In pinta, loss of melanin, epidermal atrophy, and an absence of treponemes and inflammation is characteristic [254]. It should be noted that the causative organisms of the endemic treponematoses cannot be distinguished morphologically or serologically from *T. pallidum*. The serological tests used to diagnose endemic treponematoses are the same as those used to diagnose syphilis. RPR and VDRL become positive within 2–4 weeks after appearance of the primary lesions [255]. Specific treponemal tests may also be used. Rapid point-of-care treponemal tests have become available for testing on whole blood without refrigeration, and are the best method for diagnosis outside of the laboratory [256].

In early Lyme disease (erythema migrans), the diagnosis should be made on clinical grounds alone. Serology should not be performed in early Lyme disease, as it is most often negative. In patients with early disseminated or late disease, serologic tests are usually positive for both IgM and IgG antibodies to *B. burgdorferi*. According to CDC criteria for diagnosis, the presence of erythema migrans or one late manifestation of disease in conjunction with positive serology or isolation of *B. burgdorferi* is sufficient. Serology should only be performed in patients with symptoms of early disseminated or late Lyme disease, exposure to ticks, and history of residence or travel to endemic areas. ELISA is utilized first, and may be false-positive due to other spirochete and bacterial infections, autoimmune disease, or Epstein Barr virus infection. A positive ELISA should be confirmed by Western blot, which is more specific. Both tests evaluate IgG and IgM against *B. burgdorferi*. Of note, antibody levels remain elevated after adequate therapy [257]. PCR of CSF, synovial fluid, and skin biopsies (of erythema migrans) offers sensitivity of 100 %, 80 %, and up to 62 %, respectively [258, 259]. Cultures can be performed on skin biopsy specimens, blood, or CSF; The positivity of blood cultures increases from 46 % to 71 % when PCR is performed following incubation [260].

Table 14.67 First-line therapies: congenital syphilis [149, 246, 261]

Medication	Dosing	Evidence level
Aqueous crystalline penicillin G	Neonates <7 days of age:	B
	50,000 U/kg/dose IV every 12 h for 10–14 days	
	Neonates >7 days of age:	
	50,000 U/kg/dose IV every 8 h for 10–14 days	
	Infants 1 month of age or older:	
	50,000 U/kg/dose IV every 6 h for 10–14 days	

The CDC and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases provide guidelines for the evaluation and management of congenital syphilis. Penicillin is the only drug with documented efficacy for treatment of congenital syphilis. For neonates or infants with proven or probable congenital syphilis (whether symptomatic or asymptomatic), the treatment is aqueous penicillin G. Desensitization should be performed if penicillin allergy develops.

Table 14.68 Second-line therapies: congenital syphilis [261–264]

Medication	Dosing	Evidence level
Benzathine penicillin G	50,000 U/kg IM single dose	B

For asymptomatic children born to mothers treated adequately and successfully with penicillin more than 1 month before delivery, a single dose of benzathine penicillin G may be an option if clinical follow-up to exclude later development of syphilis can be guaranteed. In two randomized trials studying treatment outcomes in infants with asymptomatic congenital syphilis, there were no treatment failures with either a 10-day course of procaine penicillin G or a single IM dose of benzathine penicillin G. RPR became nonreactive in nearly all children following treatment. In spite of this data, rare treatment failures have occurred in infants with asymptomatic congenital syphilis. Thus, this treatment regimen is restricted to asymptomatic infants who are born to mothers with adequate and successful treatment with penicillin (more than 1 month before delivery), who have undergone complete evaluation, and for whom clinical follow-up can be guaranteed.

Syphilis

Recommendations for the treatment of syphilis are largely based on historical cumulative experience and in vitro susceptibilities. Prospective or retrospective data is available, but is based on treatment in adults. Resistance to penicillin in *T. pallidum* has not been reported [265]. Patients treated for syphilis should be screened and treated for other sexually transmitted diseases, including HIV [237].

Table 14.69 First-line therapies for syphilis [149, 246]

Medication	Dosing	Evidence level
Benzathine penicillin G	Early syphilis:	B
	50,000 U/kg IM once	
	Late syphilis:	
	50,000 U/kg IM weekly for 3 weeks	
	Maximum single dose: 2.4 million U	
Penicillin G	Neurosyphilis:	B
	Penicillin G procaine 50,000 U/kg/day IM and probenecid 40 mg/kg/day in 4 divided doses for 10–14 days	
	Penicillin G: 200,000–300,000 U/kg/day IV in divided doses every 4–6 h for 10–14 days	
	Maximum daily dose: 24 million U	

Table 14.70 Second-line therapies for syphilis [266–277]

Medication	Dosing	Evidence level
Doxycycline	Early and late syphilis:	D*
	4 mg/kg/day in two divided doses	
	Maximum single dose: 100 mg	
Ceftriaxone	Early and late syphilis, neurosyphilis: 1–2 g IM/IV daily × 10–14 days	B*

In penicillin-allergic patients, doxycycline and ceftriaxone can be used in early and late syphilis. Numerous retrospective studies of HIV-positive and HIV-negative adults with early syphilis demonstrated equivalent efficacy for doxycycline compared to benzathine penicillin G. Ceftriaxone has demonstrated efficacy equivalent to that of penicillin for the treatment of early syphilis, late syphilis, and neurosyphilis in HIV-negative and HIV-positive patients. Treatment is support by several prospective and retrospective studies.

Table 14.71 Third-line therapies for syphilis [278–281]

Medication	Dosing	Evidence level
Azithromycin	Early syphilis:	B*
	40 mg/kg po single dose	
	Maximum dose: 2 g	

In open trials involving HIV-positive and negative adults, single-dose azithromycin was equivalent to benzathine penicillin G for early syphilis. However, this is a third-line agent for syphilis because of reported treatment failures, as well as increasing in vitro resistance of *T. pallidum* to macrolides. Thus, doxycycline is preferred as a second-line agent in penicillin-allergic patients.

Yaws, Pinta, and Bejel

Table 14.72 First-line therapies for endemic treponematoses [281–285]

Medication	Dosing	Evidence level
Benzathine penicillin G	600,000 U IM single dose	D
Azithromycin	30 mg/kg po single dose, maximum 2 g	B

A single dose of a long-acting penicillin (such as IM benzathine penicillin G) is the preferred antibiotic for treatment and eradication, based on history of clinical use. Azithromycin may also be used as an alternative treatment for bejel and pinta. In a large open trial, yaws in children was treated successfully with either a single oral dose of azithromycin or a single IM dose of benzathine penicillin. Both treatments demonstrated cure rates over

90 %. However, there is evidence that macrolides can select for resistance in *T. pallidum*, mediated through a single-step mutation of the 23S rRNA gene. In contrast, penicillin resistance is unlikely, as it would require multiple mutations.

Table 14.73 Second-line therapies for endemic treponematoses [286, 287]

Medication	Dosing	Evidence level
Erythromycin	8–10 mg/kg po 4 times daily for 15 days	D*
Doxycycline	Twice daily for 15 days	D*

Erythromycin and doxycycline are acceptable second-line treatments for endemic treponematoses.

Lyme Disease

Table 14.74 First-line therapies: erythema migrans [288–290]

Medication	Dosing	Evidence level
Doxycycline (for children 8 years of age or older)	2 mg/kg po twice daily, maximum 100 mg per dose, for 10–21 days	A
Amoxicillin	50 mg/kg/day divided into three doses, maximum 500 mg per dose, for 14–21 days	B
Cefuroxime	30 mg/kg/day divided into two doses, maximum 500 mg per dose, for 14–21 days	B

Overall, doxycycline, amoxicillin, and cefuroxime have demonstrated equivalent efficacy for the treatment of early Lyme disease (erythema migrans) and are the first-line therapies. In an open trial, oral cefuroxime and penicillin V, both given for 14 days, were equally effective for the treatment of erythema migrans in children under 15, with no recorded treatment failures. Another open trial compared amoxicillin to cefuroxime treatment for 20 days for early Lyme disease in children 12 years of age or younger, and showed complete resolution in 67 %, 92 %, and 87 % of the amoxicillin, low-dose (20 mg/kg/day), and high-dose (30 mg/kg/day) cefuroxime groups, respectively; resolution of constitutional symptoms occurred in 100 %, 69 %, and 87 %, respectively. At follow-up, there was no evidence of late disease in patients from any treatment group. Finally, a double-blind, randomized study found that, among immunocompetent adults and children older than 12 years of age, cefuroxime and doxycycline either improved or cured erythema migrans in 93 % and 88 % of patients, respectively. Development of late sequelae of Lyme disease was very rare in either treatment group (Table 14.75).

Table 14.75 First-line therapies: acrodermatitis chronica atrophicans [291]

Medication	Dosing	Evidence level
Doxycycline (for children 8 years of age or older)	2 mg/kg po twice daily, maximum 100 mg per dose, for 21 days	D*
Amoxicillin	50 mg/kg/day divided into three doses, maximum 500 mg per dose, for 21 days	D*
Cefuroxime	30 mg/kg/day divided into two doses, maximum 500 mg per dose, for 21 days	D*

No randomized trials have addressed the efficacy of treatment of acrodermatitis chronica atrophicans, but the same first-line treatments for early Lyme disease (doxycycline, amoxicillin, cefuroxime) are used, for a duration of 21 days. Improvement in skin lesions and related symptoms have been reported with antibiotic therapy (Table 14.76).

Table 14.76 Second-line therapies: erythema migrans [292–295]

Medication	Dosing	Evidence level
Azithromycin	10 mg/kg/day for 7–10 days	B
Erythromycin	12.5 mg/kg po four times daily for 14–21 days	B
Clarithromycin	7.5 mg/kg twice daily for 14–21 days	B

In two open trials, azithromycin was shown to have comparable efficacy and adverse effects of treatment compared to amoxicillin and penicillin V in children with early Lyme disease, in terms of duration of erythema migrans and appearance of minor or major manifestations of borreliosis. One year after treatment, all patients in both trials were asymptomatic. Another macrolide, clarithromycin, also demonstrated efficacy and safety comparable to that of amoxicillin in children 15 years of age or younger with erythema migrans.

Mycobacterial Infections

Clinical Features

Non-tuberculous mycobacteria (NTM) are acid-fast bacteria with wide distribution: soil, water, and animals. Rapidly growing species grow within 7 days and include *Mycobacterium fortuitum*, *M. abscessus*, and *M. chelonae*. Slowly growing species require several weeks to grow and include *M. avium* complex (MAC), *M. marinum*, and *M. kansasii*. In children, NTM cause lymphadenopathy, skin

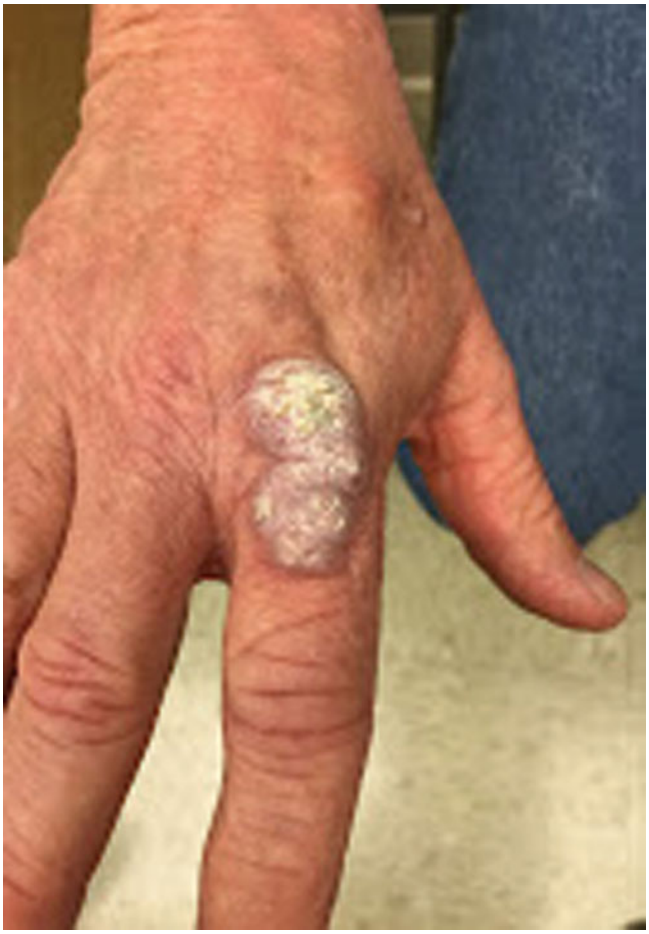


Fig. 14.20 *Mycobacterium marinum* infection. Verrucous nodule on the dorsal hand (Photo courtesy of Sylvia Hsu, MD)

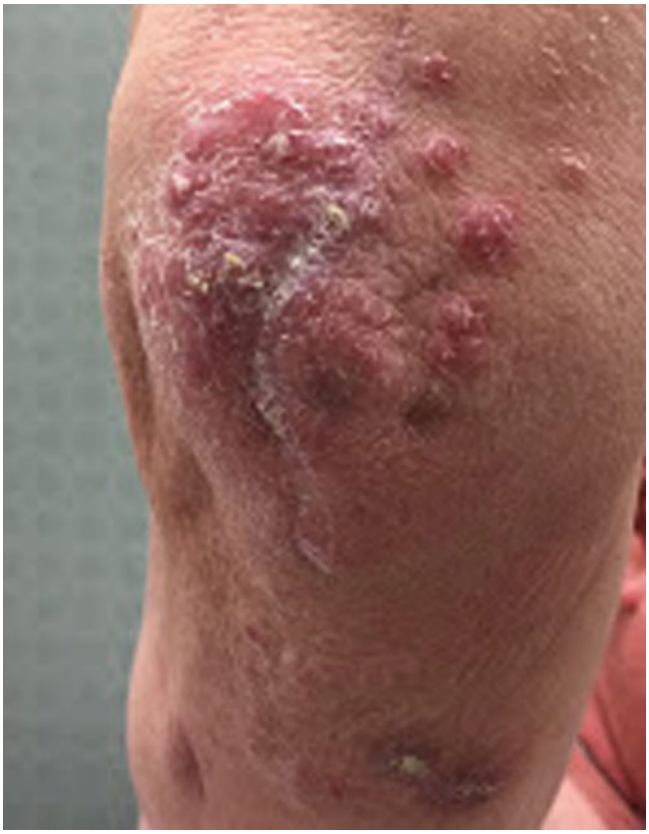


Fig. 14.21 *Mycobacterium marinum* infection. Sporotrichoid papules on nodules on the arm (Photo courtesy of Sylvia Hsu, MD)

and soft tissue infections (SSTI), and pulmonary and disseminated disease. Skin abrasions and penetrating injuries are the usual portal of entry for SSTI in otherwise healthy children. Clinical findings are polymorphous and include ulcers, plaques, folliculitis, and nodules; most lesions occur without pain or systemic symptoms. Rapidly growing NTM may produce cellulitis, furuncles, or draining abscesses. *M. marinum* may produce solitary papules or ulcers, or a nodular lymphangitis with sporotrichoid spread (Figs. 14.20 and 14.21). SSTI may be complicated by myositis, osteomyelitis, or tenosynovitis [296, 297].

Cutaneous tuberculosis (TB) occurs in only 1–2 % of all cases of infections caused by *M. Tuberculosis* complex. When present, cutaneous manifestations depend on the host's immune status, prior sensitization, and portal of entry [298]. Exogenous inoculation occurs via minor trauma in nonsensitized or sensitized patients, and results in primary inoculation TB and tuberculosis verrucosa cutis (TVC), respectively. Primary inoculation TB occurs as a nodule or ulcer associated with regional lymphadenoapthy. TVC is most common on acral sites such as the hand, and presents as a verrucous plaque with or without central clearing [299]. Contiguous spread from adjacent infections in sensitized patients results in scrofuloderma, tuberculosis cutis orificialis (TBCO), and lupus vulgaris. Scrofuloderma presents with firm, painless, nodules in the neck axillae and groin, overlying sites of primary infection. Ulcers and sinus tracts with watery and purulent exudate develop. TBCO occurs at mucocutaneous junctions such as perioral or anogenital skin; autoinoculation results in painful and friable ulcerative nodules. Lupus vulgaris is a reactivation disease and classically presents with a red-brown plaque with central clearing on the head or neck (Fig. 14.22) [300]. Hematogenous spread results in metastatic tuberculous abscesses, acute miliary TB, and lupus vulgaris. Metastatic tuberculous abscesses present with single or multiple, non-tender, fluctuant, subcutaneous nodules on the extremities. Cutaneous lesions of acute miliary TB result in red or purpuric papules with vesicles that later become umbilicated and crusted [298].

Tuberculids are cutaneous hypersensitivity reactions to underlying TB. Papulonecrotic tuberculid presents with erythematous papules that subsequently become pustular or necrotic, recur, and heal with scars. Lichen scrofulosorum presents with folliculocentric, asymptomatic, grouped, yellow-red or brown papules. Erythema induratum describes

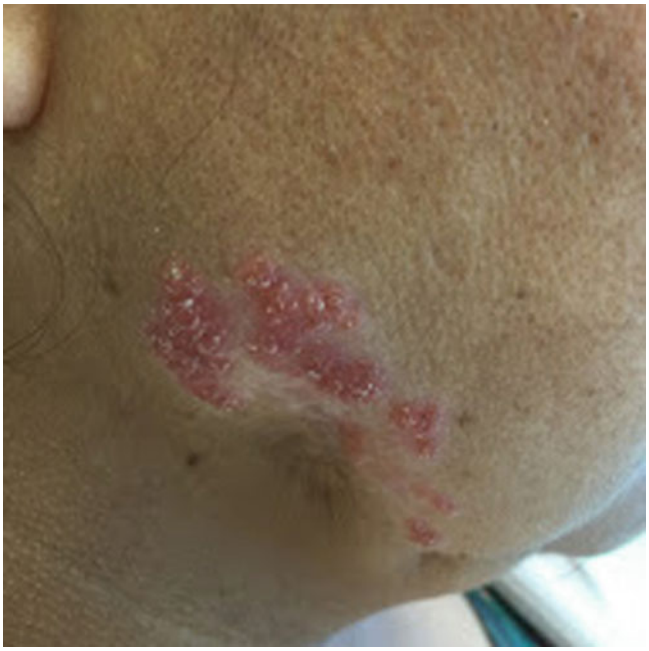


Fig. 14.22 Lupus vulgaris. Pink coalescent plaques with scarring on the cheek of a female patient with a positive quantiferon gold test and chest radiograph consistent with pulmonary tuberculosis. Lupus vulgaris results from contiguous or hematogenous spread of infection in sensitized hosts (Photo courtesy of Sylvia Hsu, MD)

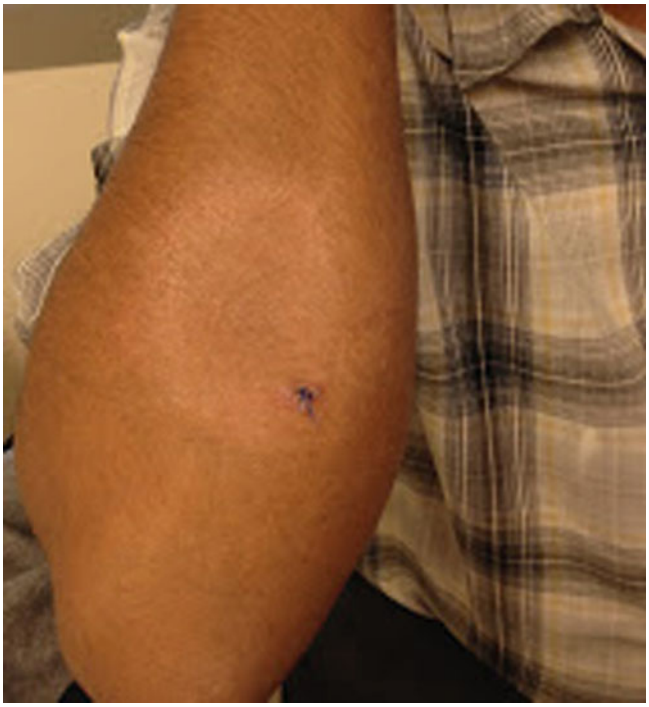


Fig. 14.23 Tuberculoid leprosy (Hansen's disease). Hypopigmented anesthetic patch on the arm (Photo courtesy of Sylvia Hsu, MD)

tender, red subcutaneous nodules on the most commonly located on the posterior aspects of the lower legs; draining ulcers may develop [299].

Hansen's disease (Leprosy) is caused by *Mycobacterium leprae* and involves the skin and nerves. It is poorly contagious, highly responsive to treatment, and may cause chronic sequelae due to neuropathy. In the United States, most of the few hundred cases each year are in immigrants, although some are due to contact with armadillos. Transmission likely occurs via the respiratory route or direct close contact [301]. Cell-mediated host immune response is strongest in tuberculoid disease and weakest in lepromatous disease. Tuberculoid leprosy presents with multiple hypopigmented or erythematous anesthetic patches or plaques (Fig. 14.23). Tender, enlarged peripheral nerves may be present. In contrast, lepromatous leprosy presents with generalized infiltrative papules and nodules, and may result in leonine facies or septal perforation. Indeterminate disease presents with a single macule with reduced sensation; it may regress spontaneously or evolve into an established subtype. Borderline disease presents with macules, plaques, or nodules. The WHO classifies paucibacillary (PB) disease as five or fewer lesions, while multibacillary disease (MB) corresponds to six or more lesions. Type 1 reactions (reversal) occur in borderline disease and often present with erythema, induration or ulceration of preexisting lesions, edema, and neuritis. Type 2 reactions (erythema nodosum leprosum, ENL) occur in lepromatous disease and present with numerous painful dermal and subcutaneous nodules [302].

Specific Investigations

For diagnosis
Culture
High-pressure liquid chromatography (HPLC) and polymerase chain reaction (PCR)
Tuberculin skin test (TST) and interferon-gamma release assay (IGRA)
Histopathology with special stains for acid-fast bacilli (AFB)
For treatment
CBC
LFTs
Kidney function tests (BUN, creatinine)
G6PD level prior to initiating dapsone

Definitive diagnosis of SSTI due to NTM is made by culture of tissue, exudate, or aspirate from skin or soft tissue lesions. Tuberculin skin test (TST) supports the diagnosis of NTM but a positive test is nonspecific (also positive in tuberculosis) and a negative test does not exclude infection by NTI [303]. Rapid methods for identification of NTM species from culture include high-pressure liquid chromatography (HPLC) [304] and polymerase chain reaction (PCR) [305]. Although these methods are relatively specific, they do not

provide the important susceptibility testing. Histopathology is variable: granulomas, abscesses, and necrosis may be seen, but organisms are identified in only a small minority of cases. Additionally, organisms are only seen as acid-fast bacilli, and so NTM cannot be distinguished from M. tuberculosis based on this method [306].

Mycobacterial culture is the gold standard for diagnosis of cutaneous TB and allows for susceptibility testing. Stained smear, utilizing exudate from lesions, is more rapid but less specific, as it identifies AFB [307]. Histopathology of cutaneous TB often demonstrates tuberculoid granulomas with central caseating necrosis and peripheral lymphocytes. However, this pattern is nonspecific, and AFB identification with special stains, while supportive, is also not specific to TB [308]. TST demonstrates a specificity of 63 % and a sensitivity between 33 % and 96 % for cutaneous TB. It is positive in TVC, scrofuloderma, lupus vulgaris, and tuberculids. TST is negative in primary inoculation TB, TBCO, metastatic tuberculous abscesses, and acute miliary TB [300]. Interferon-gamma release assays (IGRA) demonstrate a sensitivity of 92 % and specificity of 76 % in cutaneous TB; false-positive tests may occur with *M. marinum* and *M. kansasii* infections [309]. IGRAs may be used in place of TST [310]. PCR is a specific and more rapid method of identification for TB compared to culture, but is most useful in multibacillary disease as an adjunct to culture. Tuberculids may demonstrate positivity for *M. Tuberculosis* DNA, but bacilli are not isolated from these lesions [311].

Definitive diagnosis of leprosy is made in the context of one pertinent symptom or cutaneous finding and confirmatory histopathology demonstrating acid-fast bacilli. In lepromatous leprosy, a diffuse infiltrate of foamy macrophages (Virchow cells) are parasitized by abundant organisms. In tuberculoid disease, organisms are rare or absent, but linear granulomas are seen extending along nerves. Indeterminate lesions demonstrate nonspecific perineural infiltrates with rare organisms. ENL features leukocytoclastic vasculitis and dense neutrophilic infiltrates with numerous acid-fast bacilli. However, in many cases, diagnosis is largely clinical, with or without supportive laboratory tools. The National Hansen's Disease Programs (NHDP) Clinical Center offers histopathologic and molecular assays for the detection of *M. leprae* in tissues, free of cost [312]. PCR is performed by the NHDP, is useful when histopathology and clinical exam is inconclusive, and is applied to skin biopsies. It is over 90 % sensitive and 100 % specific in lepromatous leprosy, but only 34 % sensitive and 80 % specific in tuberculoid disease [313]. Mycobacterial culture can be performed to exclude infection due to other NTM or *M. tuberculosis*, but cannot isolate *M. leprae*. Slit skin smears, which collect dermal fluid for Ziehl–Neelsen staining, are highly insensitive in pediatric leprosy (15–20 %). Combined with PCR, ISH, and immunocytochemistry however, skin smears have a sensitivity of over 70 %, 80 %, and 65 %, respectively, for the diagnosis of pediatric leprosy [314, 315].

Nontuberculous Mycobacterial Infections (Table 14.77)

Table 14.77 First-line empiric therapies for SSTI due to NTM [297]

Medication	Dosing	Evidence level
Macrolide antibiotic	Azithromycin:	D
	5–12 mg/kg po daily	D
	Maximum daily dose 600 mg	
	Clarithromycin:	
	15–30 mg/kg/day po divided in 2 doses	
	Maximum daily dose 1 g	
Doxycycline	2–4 mg/kg/day po divided in 2 doses	D
	Maximum single dose: 100 mg	
Trimethoprim-sulfamethoxazole (TMP-SMX)	8–12 mg/kg/day (based on TMP) po divided in 2 doses	D
	Maximum daily dose (TMP): 320 mg	
Ciprofloxacin	20 mg/kg/day po divided in 2 doses	D
	Maximum daily dose: 1.5 g	

No randomized, controlled trials have evaluated the efficacy of treatments for NTM infections in children. Therefore, the treatment recommendations are based on case series, in vitro susceptibility data, and historical clinical experience.

Prior to speciation and susceptibility testing, empiric therapy should be initiated with a macrolide in addition to a fluoroquinolone, TMP-SMX, or doxycycline. Fluoroquinolones should be used with caution in patients under 18 years of age, and doxycycline should be reserved for patients older than 8 years (Table 14.78).

Table 14.78 First-line directed therapies for SSTI due to NTM [6, 297, 316–320]

Medication	Dosing	Evidence level
Amikacin	15–20 mg/kg IV once daily	D
	Maximum daily dose: 1.5 g	
Tobramycin	7 mg/kg IV once daily	D
	Maximum daily dose: 300 mg	
Meropenem	30–60 mg/kg/day IV in 3 divided doses	D
	Maximum daily dose: 3 g	
Cefoxitin	160 mg/kg/day IV in 4 divided doses	D
	Maximum daily dose: 12 g	
Rifampin	10–20 mg/kg/day po once daily	D
	Maximum daily dose: 600 mg	
Ethambutol	15 mg/kg/day po once daily	D
	Maximum daily dose: 2.5 g	

Once in vitro susceptibility testing is available, directed combination therapy with two drugs should be selected. Antimicrobial agents from the lists of first-line empiric or directed therapies are acceptable. Duration of treatment is for a minimum of 6–12 weeks, and therapy should be continued for 1–2 months after clinical signs and symptoms have resolved.

M. fortuitum is susceptible to macrolides such as azithromycin; carbapenems including meropenem, fluoroquinolones, and TMP-SMX. *M. abscessus* is sensitive to treatment with macrolides, cefoxitin, carbapenems, and amikacin. *M. chelonae* can be treated with macrolides, tobramycin, and meropenem. *M. marinum* is susceptible to macrolides, rifampin, ethambutol, and TMP-SMX.

For severe infections due to rapidly growing mycobacteria (*M. abscessus*, *M. chelonae*, *M. fortuitum*), parenteral therapy should be selected. For patients with ulcers, deep or bony infections, or infections due to indwelling devices, two or three antimicrobials should be selected, based on susceptibility testing or according to the suspected species.

Table 14.79 Second-line (adjunctive) therapy for SSTI due to NTM [320, 321]

Medication	Dosing	Evidence level
Surgery	N/A	D

Treatment of NTM cutaneous and soft tissue infections in children often requires a combination of medical and surgical therapies. Incision and drainage of abscesses, removal of foreign bodies serving as niduses of infection, or surgical debridement are recommended.

Table 14.80 Third-line therapy for SSTI due to NTM [322, 323]

Medication	Dosing	Evidence level
Observation		D

If spontaneous resolution of infection due to NTM occurs, it may take up to 1 year. Therefore, antibiotic therapy, with or without surgical intervention, are preferred treatments.

Cutaneous Tuberculosis

Underlying systemic disease is more common in children with cutaneous TB compared to adults [324]. The treatment of cutaneous TB is the same as that for systemic TB, and multidrug therapy with a short course four-agent regimen for 2 months, followed by a two-drug regimen for the next 4 months, is preferred. Direct observed therapy (DOT) is recommended. The initial phase of treatment is bactericidal, while the longer phase of treatment eradicates remaining bacteria [300, 307].

Therapy for Drug-Susceptible Tuberculosis [325, 326]

Medication	Dosing	Evidence level
Isoniazid (INH)	10–15 mg/kg daily dose 20–30 mg/kg/dose if twice weekly Maximum dose 300 mg daily and 900 mg twice weekly	D
Rifampin (RIF)	10–20 mg/kg daily dose 10–20 mg/kg/dose if twice weekly Maximum dose 600 mg	D
Pyrazinamide (PZA)	30–40 mg/kg daily dose 50 mg/kg/dose if twice weekly Maximum dose 2 g	D
Ethambutol (EMB)	20 mg/kg daily dose 50 mg/kg/dose if twice weekly Maximum dose 2.5 g Duration of therapy: 6 months INH, RIF, PZA, and EMB for 2 months INH and RIF for 4 months	D

First-line pediatric treatment for TB is similar to that of adults, and is outlined in guidelines endorsed by the CDC and the WHO. The treatment regimens below apply to newly diagnosed cases of TB in children without prior history of treatment, multidrug-resistant TB (MDR-TB), or osteoarticular or meningeal disease. For these more-complicated scenarios, review of detailed and specific WHO and CDC guidelines, in addition to expert consultation, is advised. Pyridoxine supplementation should be considered for exclusively breastfed infants, malnourished children, and for children infected with HIV.

Therapy for Drug-Resistant Tuberculosis [325, 327–330]

Medication	Dosing	Evidence level
Levofloxacin (other fluoroquinolones: moxifloxacin, oflaxacin)	Age ≥5 years: 7.5–10 mg/kg orally Age <5 years: 15–20 mg/kg orally in two divided doses Maximum daily dose 750 mg	D
Amikacin (other injectable aminoglycosides: streptomycin, kanamycin)	15–22.5 mg/kg IM or IV Maximum daily dose 1 g	D
Ethionamide	15–20 mg/kg/day po in 2 divided doses Maximum daily dose 1 g	D
Cycloserine	10–20 mg/kg/day po in 2 divided doses Maximum daily dose 1 g	D
Para-aminosalicylic acid	150 mg/kg po in 2–3 divided doses Maximum daily dose 12 g	D

For children with MDR-TB, treatment should be individualized, guided by the drug susceptibility data, and should include at least four drugs, with the selection of drugs based on the extent and site of disease, as well as response to treatment.

In a retrospective study of 149 children with MDR-TB, treatment with at least four drugs—including an injectable agent in 66% of patients—for a median duration of 13 months, resulted in cure or probable cure in over 90% of patients. Treatment of MDR-TB in children should include one fluoroquinolone and one injectable agent. These should be used in concert with the first-line TB drugs above and, if needed, ethionamide, cycloserine, and/or aminosalicylic acid, to complete a regimen of at least four active drugs based on susceptibility data. Although fluoroquinolones are generally contraindicated in children less than 18 years of age, their use is justified in MDR-TB.

It should be noted that paradoxical deterioration in immunocompetent children during TB treatment is not uncommon, and in several retrospective studies, occurred in 10–14% of patients anywhere from 10 to 180 days after initiation of therapy. Systemic features include enlarging lymphadenopathy, worsening of pulmonary disease, or new lesions.

Leprosy

Table 14.81 First-line therapies for leprosy [331–340]

Medication	Dosing	Evidence level
Dapsone	1 mg/kg po once daily	D
	Maximum daily dose: 100 mg	
Rifampin	10–20 mg/kg po once daily	D
	Maximum daily dose: 600 mg	
Clofazimine	1 mg/kg po once daily	D
	Maximum daily dose: 50 mg	

For tuberculoid or paucibacillary leprosy (tuberculoid or borderline tuberculoid disease), treatment with dapsone and rifampin should be administered for 12 months. For lepromatous or multibacillary leprosy (lepromatous, borderline lepromatous, or borderline disease), treatment should include dapsone, rifampin, and clofazimine for 24 months. The National Hansen's Disease Program (NHDP) in the United States advocates a longer duration of therapy than the WHO, and also advocates daily rather than monthly treatment with rifampin. Treatment with daily rifampin was notable for absence of relapse.

WHO recommendations for shortened courses of therapy and monthly rifampin were based in part on cost and availability of effective medications in endemic areas. However, shorter treatment regimens and monthly rifampin were associated with significant rates of relapse, up to 25% within 12 years after treatment. Thus, the NDHP recommendations are preferred as first-line therapy for treatment of leprosy in the United States.

Controlled trials regarding multidrug regimens for the treatment of leprosy in children are lacking. However, the efficacy of the first-line agents has been demonstrated clinically and confirmed by in vitro studies. While higher-quality evidence is available for these therapies in adults with leprosy, several retrospective studies in children support the same treatments.

Table 14.82 Second-line therapies for leprosy [335, 341, 342]

Medication	Dosing	Evidence level
Minocycline	100 mg daily (adult dosing)	B*
Clarithromycin	500 mg daily (adult dosing)	B*

Minocycline was an effective alternative monotherapy for refractory disease in a small open trial, but this agent should be used as part of multidrug regimen. Clarithromycin is the only macrolide effective against *M. leprae*. Prospective data demonstrated that clarithromycin or minocycline, alone or in combination, were rapidly effective in terms of clinical improvement and elimination of viable *M. leprae* bacteria in patients with lepromatous leprosy. Minocycline is reserved for use in patients older than 8 years of age.

Fluoroquinolones, including ofloxacin and levofloxacin, are highly active against M. leprae, and are widely used as second-line therapies, but they are not recommended in children by the NDHP.

Therapies for Immunologic Reactions in Leprosy [343–351]

Medication	Dosing	Evidence level
Prednisone (for type 1 reactions)	1 mg/kg/day po	A*
Cyclosporine (for type 1 reactions)	5 mg/kg/day po in 2–3 divided doses	B*
Thalidomide (for ENL)	100–300 mg po at bedtime for 2 weeks then taper in 50 mg decrements every 2–4 weeks	A*
Clofazimine (for ENL)	2 mg/kg po every other day	E/A*
Pentoxifylline (for ENL)	20 mg/kg/day po	A*

A high-dose (60 mg/day), 20-week regimen of prednisone was more effective in preventing relapse than lower-dose regimens in adults with type-1 reactions. For patients with severe type 1 reactions refractory to prednisone, cyclosporine has been effective. Prednisone is also useful for ENL, but thalidomide induces faster cutaneous and systemic clinical responses, and results in fewer relapses with longer periods of remission.

Thalidomide is over 90 % effective for the treatment of ENL, with demonstrated response within 48 h, based on randomized, controlled trials. Slow tapering from an effective dose is more important the dose used in reducing the risk of relapse. In chronic cases of ENL, clofazimine was superior to prednisone in controlling symptoms of ENL and in preventing recurrence. A systematic review found that treatment with clofazimine was associated with fewer recurrences than thalidomide. However, clofazimine is not preferred for the treatment of acute ENL. Compared to thalidomide, pentoxifylline was effective in over 60 % of patients with ENL. This agent is more widely available and easier to obtain than thalidomide, given the latter drug's teratogenicity.

Rickettsial Diseases with Cutaneous Manifestations

Clinical Features

Rocky Mountain spotted fever (RMSF) is a potentially lethal, but curable, acute infection caused by *Rickettsia rickettsii*, a gram-negative obligate intracellular bacterium that causes vascular endothelial injury. It is the most common rickettsial infection in the United States. It is common in children, with a high incidence in patients under 10 years of age. The major vector within the United States is Dermacentor variabilis (American dog tick); infection occurs within 2 weeks following tick bite. Prodromal symptoms include fever and headache; rash develops by the fifth day of illness in 90 % of patients, and is characterized as morbilliform or petechial. The eruption begins on acral sites and spreads centrally; palms and soles are involved. Encephalitis, abdominal pain, bleeding, pedal edema, cardiac arrhythmias, pulmonary distress, and shock may occur. Thrombocytopenia is common, while white blood cell counts are normal [352].

Human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA, previously human granulocytic ehrlichiosis) are tick-borne illnesses with similar findings that are caused by *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum*, respectively. The principal vector of HME is the Lone Star tick (*Amblyomma americanum*), while the vector for HGA in the United States is *Ixodes scapularis*. In children, the major disease manifestations are macular, maculopapular, or petechial rash in two-thirds of patients; fever; myalgia; headache; and lymphadenopathy. Leukopenia, due to lymphopenia or neutropenia, and thrombocytopenia occur in 50–90 % of patients [353].

Murine (endemic typhus) is a rare rickettsial disease caused by *Rickettsia typhi*. It is transmitted by the rat flea, *Xenopsylla cheopis*, the cat flea, *Ctenocephalides felis*, and the mouse flea, *Leptopsyllia segnis*. Endemic typhus is typically mild, and characterized by the clinical triad of fever, headache, and rash in less than half of children. The rash is morbilliform and spreads peripherally, sparing the palms and soles. Gastrointestinal symptoms are very common in children; patients with severe disease may develop cardiopulmonary or renal disease. Thrombocytopenia is common [354].

Rickettsia akari causes rickettsialpox and is transmitted from the house mouse (*Mus musculus*) by the mite *Liponyssoides sanguineus*. The clinical triad of manifestations are initial skin lesion at bite site, abrupt fever and constitutional symptoms, and a papulovesicular rash. The initial lesion is a tiny papule which vesiculates and then forms an eschar in 90 % of patients. Fever, malaise, and headache develop 1 week after the initial lesion, and are followed by a generalized morbilliform eruption which becomes papulovesicular and may involve palms, soles, face, and mucosae. Leukopenia is common [355].

Specific Investigations

For diagnosis
CBC
Histopathology with direct immunofluorescence or immunohistochemistry
Serology
PCR
For treatment
CBC monitoring for patients receiving chloramphenicol

Given the risk of mortality with delayed treatment, presumptive diagnosis of RMSF should be clinical, and empiric treatment should be administered, keeping in mind that some patients do not develop rash and that laboratory confirmation cannot be made in the early phase of disease. *R. rickettsii* cannot be grown in cell-free culture media. Histopathology with direct immunofluorescence (DIF) or immunoperoxidase offers a sensitivity of 70–90 % and a specificity near 100 %; additionally, DIF results are available within a few hours. However, histopathology is not useful in patients who have received treatment for 48 h or more [356]. Serology via indirect fluorescent antibody (IFA) is 95 % sensitive, but is only useful for retrospective diagnosis and should not influence clinical decisions; IgM and IgG antibodies appear 7–10 days after the onset of illness, and false-negative results occur in the early phase of illness and during treatment [357].

Serology (IFA) is the preferred diagnostic test for HME and HGA, and demonstrates 94–100 % sensitivity. However, similar to serology in RMSF, this is more retrospective in utility and should not dictate clinical decisions in early illness. Intracytoplasmic inclusions (morulae) in neutrophils are specific, but only present in a minority of patients. PCR offers up to 70 % sensitivity for HME and up to 87 % sensitivity for HGA. Culture is extremely difficult [358].

HME and RMSF are often indistinguishable clinically. CBC may be useful, given that leukopenia is common in HME and absent in RMSF; in contrast, thrombocytopenia is common in both diseases [352].

The mainstay of diagnosis for murine typhus is serology (IFA), but this is retrospective. While sensitive, cross reaction with other *Rickettsia* species may occur. No reliable diagnostic test is available for the early phase of illness [359].

In rickettsialpox, the most commonly used diagnostic test is retrospective serology (IFA). Histopathology with DIF can be used but cannot distinguish *R. akari* from *R. ricketsii*. Epidermal and dermal necrosis and neutrophil-heavy infiltrates are seen on skin biopsy. PCR can specifically identify *R. akari* in tissue [355].

If chloramphenicol is used, CBC should be obtained at baseline and then every 2 days during therapy given the risk of hematologic abnormalities.

Table 14.83 First-line therapy for rickettsial diseases [197, 358, 360, 361]

Medication	Dosing	Evidence level
Doxycycline	Under 45 kg: 2.2 mg/kg twice daily for 7–14 days 45 kg or over: 100 mg twice daily for 7–14 days	D

Doxycycline is the treatment of choice for all rickettsial diseases, based on in vitro susceptibility data, animal studies, and historical clinical experience.

Although doxycycline is typically avoided in children under the age of 8 years for most indications, it is the drug of choice for all rickettsial diseases, regardless of age. The risk of dental staining is very low following short courses of doxycycline. Among 58 children who received two 14-day courses of doxycycline for RMSF before 8 years of age, no cases of drug-induced discoloration occurred based on dental examination after eruption of permanent teeth. Additionally, there was no difference in tooth shade or enamel hypoplasia when compared to children with no history of doxycycline use prior to the age of 8 years.

Table 14.84 Second-line therapy for rickettsial diseases [358, 360, 362–364]

Medication	Dosing	Evidence level
Chloramphenicol	50 mg/kg/day in 4 divided doses	D

In animal studies in which RMSF was induced, chloramphenicol demonstrated clinical efficacy comparable to that of tetracycline class antibiotics. Chloramphenicol is the only known alternative therapy for RMSF. However, although it can be used in patients with RMSF and history of severe adverse drug reactions to doxycycline, chloramphenicol is associated with a comparatively higher risk mortality when used for treatment. Thus, doxycycline is strongly preferred, and should be administered whenever possible.

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Infectious Diseases: Leishmaniasis

15

Kiran Motaparthi

Clinical Features

Leishmania (genus) is a hemoflagellate protozoan parasite that causes visceral, cutaneous (CL), and mucocutaneous leishmaniasis (MCL). CL is the most common form of the disease, and 90% of cases occur in Asia, Africa, South America, and the Middle East [1]. Old World (Eastern hemisphere) CL is caused by the species *L. tropica, L. major, L. aethiopica, L. infantum, and L. donovani.* New World (Western hemisphere) CL is caused by the *L. mexicana* species complex (*L. mexicana, L. amazonensis, and L. venezuelensis*) or the *L. Viannia braziliensis* species complex (*L. subgenus Viannia braziliensis*, *L. subgenus Viannia guyanensis, L. subgenus Viannia panamensis,* and *L. subgenus Viannia peruviana*). Lesions of CL occur within months of infection and are described as papules, nodules, and plaques, often with crusting and ulceration (Figs. 15.1, 15.2, and 15.3); lymphadenopathy and sporotrichoid spread are variable features. Atrophy and scarring are common following healing [2].

MCL (*espundia*) results from dissemination of parasites from the skin to oropharyngeal or nasal mucosa in untreated or incompletely treated cases of New World CL. Responsible species include *L. amazonensis* and the *L. Viannia braziliensis* species complex. MCL typically occurs within several years of the onset of CL. Ulcerative plaques result in stuffiness, bleeding, and septal perforation [2].

Old World infections are transmitted by the sandfly *Phlebotomus* while the vector for New World infections is the sandfly *Lutzomyia* [1].

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Management Strategy

Overall, two-thirds of CL can be cured without systemic therapy [3]. For Old World CL, systemic treatment is recommended for patients with multiple (>4) or large (>5 cm) lesions, involvement of potentially disfiguring sites (face, hands, feet, joints), or a history of immunosuppression. In the absence of these criteria, local therapy may be utilized for Old World CL. Systemic treatment options for Old World CL include pentavalent antimonials (Sb^v) and oral azoles. Local therapies for Old World CL include paromomycin ointment, intralesional antimonials, thermotherapy, and cryotherapy.

Systemic treatment is warranted for New World CL in patients with multiple or large (>3 cm) lesions, involvement of potentially disfiguring sites, a history of immunosuppression, low probability of follow-up, severe lesions or concomitant mucosal disease. If none of these criteria are present, local therapy (thermotherapy, paromomycin ointment, intralesional antimonials) may be used. MCL requires systemic therapy. Systemic treatments for New World CL and MCL include Sb^v, miltefosine, pentamidine, azoles, amphotericin B deoxycholate, and liposomal amphotericin B [4].

Specific Investigations

For diagnosis
Histopathology
Culture
Polymerase chain reaction (PCR)
Tissue impression smear (touch preparation)
Dermal scraping (thin smear)
For treatment
Electrocardiogram (ECG)
Laboratory: liver function test (LFT), renal function (blood urea nitrogen and creatinine), metabolic panel (blood glucose, potassium), amylase and lipase
Blood pressure

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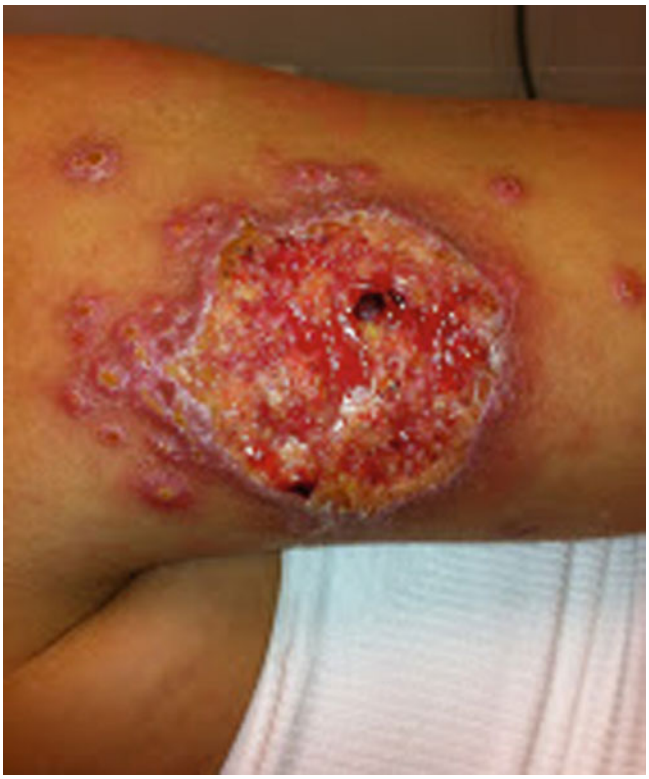

Fig. 15.1 New World Leishmaniasis. Ulcerated plaque with satellite lesions on the arm of a young female. PCR identified *L. panamensis*

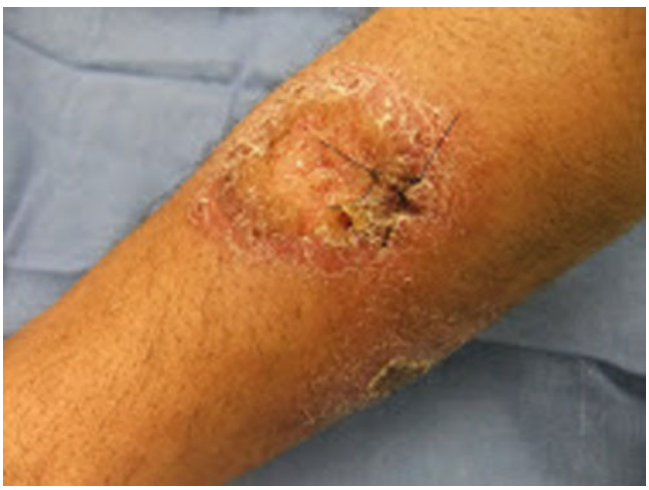

Fig. 15.2 New World Leishmaniasis. Crusted, eroded plaques on the arm due to *L. panamensis*

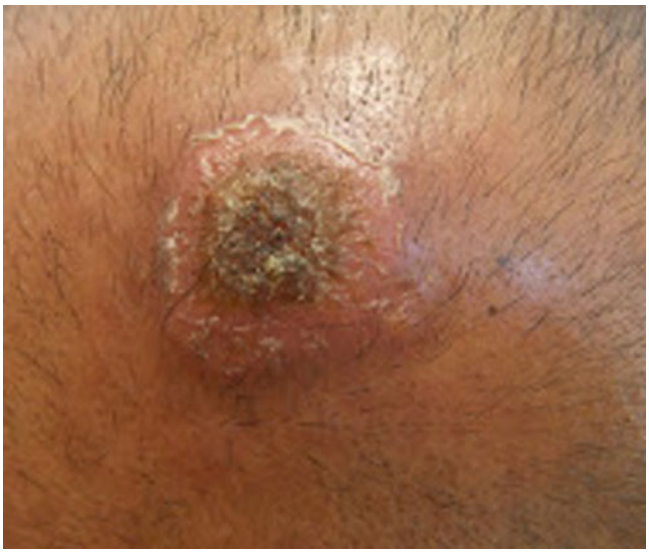

Fig. 15.3 New World Leishmaniasis. Furuncular nodule due to *L. panamensis*

Table 15.1 First-line therapies for old world CL

Medication	Dosing	Species	Evidence level
Sb^v	20 mg/kg/day × 14 days (systemic)	*L. major*	A [6]
	5 injections of 2–5 mL every 5–7 days (intralesional)		A [7]
Miltefosine	2.5 mg/kg/day × 28 days	*L. major*	A [6]
15 % paromomycin with or without 0.5 % gentamicin ointment	BID × 20 days	*L. major*	A [8]
CO_2 slush	1 min to lesion, repeat monthly		B [9]
Cryotherapy	Weekly treatment for 1–4 weeks	*L. major*	B [10]

Table 15.2 Second-line therapies for old world CL

Medication	Dosing	Species	Evidence level
Itraconazole	4 mg/kg/day × 6 weeks		A [11, 12]
	200 mg/day × 8 weeks		
Thermotherapy (radiofrequency waves)	50 °C × 30 s	*L. tropica*	A [7]

For optimal diagnosis, three punch biopsies should be obtained. The first sample should be submitted in formalin for histopathology, the second rolled on a glass slide then fixed with methanol and stained for Giemsa for touch preparation, and the third submitted in Roswell Park Memorial Institute (RPMI) media for culture and PCR analysis. Histopathology is up to 70 % sensitive in the detection of intracellular amastigotes. Cultures are positive within 4 weeks in over 80 % of cases in which organisms are identified on histology, and in almost 30 % of cases negative on histology. Fine-needle aspirates and dermal scrapings may

Table 15.3 Third-line therapies for old world CL

Medication	Dosing	Species	Evidence level
Observation			E [3]

Table 15.4 First-line therapies for new world CL and MCL

Medication	Dosing	Species	Evidence level
Sb^v	20 mg/kg/day × 20 days for CL; × 30 days for MCL	*L. v braziliensis* *L. v guyanensis* MCL	A [13]
Liposomal amphotericin B	3 mg/kg/day × 7 days then 3 mg/kg twice weekly × 3 weeks	*L. v braziliensis*	B [14]
Miltefosine	2.5 mg/kg/day × 28–42 days	*L. braziliensis* *L. v panamensis* *L. mexicana*	A [15]

Table 15.5 Second-line therapies for new world CL

Medication	Dosing	Species	Evidence level
Ketoconazole	600–800 mg/day × 28 days	*L. v panamensis* *L. mexicana*	A [16, 17]
15 % paromomycin/12 % methylbenzethonium chloride	To lesion daily × 20 days	New World CL	B [18]

Table 15.6 Third-line therapies for new world CL

Medication	Dosing	Species	Evidence level
Pentamadine	4 mg/kg every 3 days × 3 doses	*L. v guyanensis*	A [19]
	2 mg/kg every 2 days × 7 doses	*L. braziliensis*	B [20]
Allopurinol	100 mg qid × 28 days	*L. panamensis* *L. braziliensis*	A [13]

be used for cultures in lieu of punch biopsy. PCR offers a detection rate up to 97 % and, unlike culture and histology, provides speciation which is important for treatment [3]. The United States Centers for Disease Control and Prevention (CDC) provides RPMI media and evaluation of biopsy specimens for histology, culture, touch preparations, and PCR free of charge. Details regarding collection and submission of specimens can be accessed online at: http://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_-diagnosis_guide_leishmaniasis_nov.2015.pdf [4].

The major toxicities of systemic pentavalent antimonials (Sb^v, sodium stibogluconate, and meglumin antimoniate) are cardiac arrhythmias, hepatitis, pancreatitis; minor effects include arthralgias and myalgias. The adverse effects of amphotericin B include infusion reactions, renal failure, hypokalemia, and myocarditis. Miltefosine is associated with renal and hepatic toxicity as well as gastrointestinal side effects and teratogenicity. Paromomycin is an aminoglycoside associated with hepatic transaminitis and rare ototoxicity. Pentamadine may cause hypotension, hyperglycemia or hypoglycemia, and gastrointestinal side effects. Azole antifungals can be hepatotoxic. Thus, ECG, LFT, blood urea nitrogen and creatinine, blood glucose, potassium, and amylase and lipase should be evaluated prior to and during systemic treatment for CL and MCL [5].

In one study, both intramuscular stibogluconate and oral miltefosine showed greater than 80 % cure rates for CL caused by *L. major*. Another study, however, showed only 45 % efficacy for intramuscular stibogluconate (20 mg/kg for 21 days), whereas intralesional stibogluconate (five injections of 2–5 mL every 5–7 days) was 75 % effective, and thermotherapy (radiofrequency waves applied once at 50 °C for 30 s), a second-line therapy, was 70 % effective for Old World CL. A randomized, placebo-controlled trial of paromomycin ointment (with or without gentamicin ointment) demonstrated over 80 % efficacy in the treatment of Old World CL due to *L. major*. A study performed in Yemen reported CO_2 slush applied once or twice was over 90 % effective for the treatment of Old World CL. Finally, cryotherapy was shown to be cost-effective and cured 84 % of lesions with minimal scarring and side effects following weekly treatments for 1–4 weeks.

The efficacy of oral itraconazole is significantly lower than that of the above first-line therapies. While in one smaller trial [11], 70 % efficacy for itraconazole was demonstrated, less than 60 % efficacy was demonstrated in a larger study [12], and this result was not statistically significant compared to placebo.

Old World CL is usually self-limiting, but given the potential for scarring and atrophy, disfigurement is a potential complication of observation (self-healing) [3].

In a randomized, controlled trial, intramuscular Sb^v resulted in a 93 % cure rate in patients with New World CL caused by *L. panamensis* and *L. braziliensis*. Monotherapy with allopurinol only achieved a 33 % cure rate. A prospective study of IV sodium stibogluconate versus IV liposomal amphotericin B showed higher cure rates (85 % versus 70 %) with liposomal amphotericin B. This treatment was also significantly less toxic and more cost-effective. A placebo-controlled trial of oral agent miltefosine showed 90 % efficacy against *L. v panamensis* and 60 % efficacy against *L. mexicana*.

In one randomized study, ketoconazole produced a 76 % cure rate in patients with New World CL due to *L. panamensis*, compared to a 68 % cure rate with Sb^v. A separate randomized trial demonstrated the importance of speciation

prior to treatment, showing Sb^v being 96 % effective against *L. braziliensis*, but only 57 % effective for disease due to *L. mexicana*. In contrast, ketoconazole was 89 % effective against *L. mexicana* but only 30 % effective against *L. braziliensis*. A study in Ecuador reported topical treatment with a combination ointment of 15 % paromomycin and 12 % methylbenzethonium chloride resulted in 72 % healing at the 50-day mark, and 90 % healing at the 100-day mark.

A randomized, controlled trial demonstrated roughly equivalent efficacy for pentamidine and Sb^v (meglumine), 58.1 % and 55.5 % respectively, in the treatment of New World CL due to *L. v guyanensis*. A separate non-blinded comparison between Sb^v and pentamadine for the treatment of New World CL caused by *L v braziliensis* demonstrated a 78 % cure rate for Sb^v and a 35 % cure rate for pentamadine.

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Infectious Diseases: Superficial Fungal Infections

16

Kiran Motaparthi

Dermatophytosis

Clinical Features

Dermatophytosis (tinea), caused by three genera of filamentous fungi, *Trichophyton, Microsporum,* and *Epidermophyton*, is the most common superficial fungal infection in children. Dermatophytoses are classified based on their anatomic locations. Depending on the species, infection can be anthropophilic (contact with infected humans), zoophilic (contact with infected animals), or geophilic (contact with soil).

Tinea corporis refers to dermatophytosis of the trunk or extremities except the palms and soles; pruritic plaques with central clearing, peripheral scale and, occasionally, pustules are characteristic features (Fig. 16.1). Majocchi's granuloma is a variant of tinea corporis, with predominant involvement of hair follicles that clinically produces folliculocentric pustules or papules (Fig. 16.2) [1, 2].

Tinea pedis is common in adolescents but is very rare in prepubertal children, and most commonly presents as interdigital scaling, erythema, maceration, or erosion. Erythema and scaling of the plantar surfaces, sometimes with vesicles and pustules (inflammatory or bullous tinea pedis) are also seen. Tinea cruris is associated with tinea pedis, and presents with pruritic thin patches or plaques with well-demarcated borders that involve the groin but typically spare the scrotum.

Tinea manuum (dermatophytosis of the palms), like onychomycosis, is rare in children, and usually presents as unilateral scaling erythema.

Tinea faciei involves the face, with similar clinical characteristics to that of tinea corporis (Figs. 16.3 and 16.4). Tinea barbae is a variant that involves the beard or facial hair of adolescent males.

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Tinea capitis is very common in the pediatric population and may be seen in up to 8 % of inner-city school-age children. The typical presentation is circumscribed patches of alopecia with scaling, erythema, and broken hairs ("black dot" of endothrix infection). Pustules may be present. Cervical or occipital lymphadenopathy is a helpful clue to the diagnosis. Kerion is a variant characterized by markedly inflamed plaque or nodule with exuberant pustules and crust (Figs. 16.5 and 16.6).

Onychomycosis may be due to dermatophyte, yeast such as *Candida*, or non-dermatophytic molds. Although rare in children, the most common cause of onychomycosis in children is dermatophytosis. Distal lateral and proximal subungual disease are characterized by yellow to white discoloration and subungual debris (Fig. 16.7). Superficial white onychomycosis is an infection of the nail plate alone.

Specific Investigations

For diagnosis
Potassium hydroxide (KOH) scraping
Fungal culture
Wood's lamp (tinea capitis)
Dermoscopy (tinea capitis)
Histopathology
For treatment (with systemic antifungals)
Complete blood count (CBC)
Liver function tests (LFTs)

For dermatophytosis of the skin and hair, KOH preparation may be obtained by scraping active scale with a glass slide, and demonstrates a high sensitivity for diagnosis. Of note, KOH is insensitive in Majocchi's granuloma due to the potential absence of hyphal elements in the stratum corneum. Fungal cultures allow confirmation of fungal infection within a few days and eventual speciation, but are less sensitive than KOH and take several weeks to grow on Sabouraud dextrose

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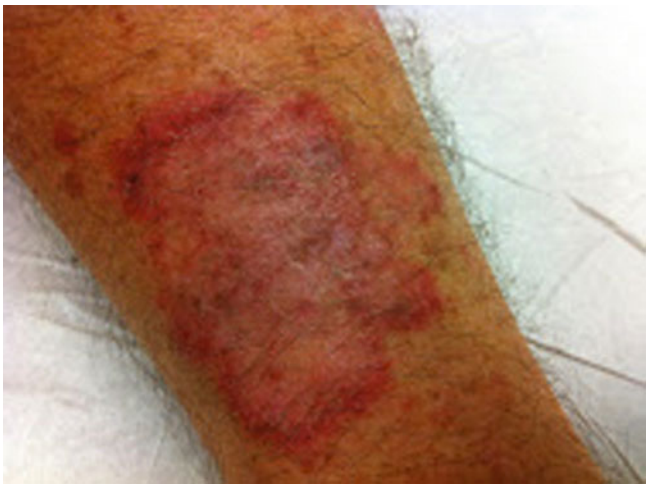

Fig. 16.1 Tinea corporis. Erythematous plaque with elevated border

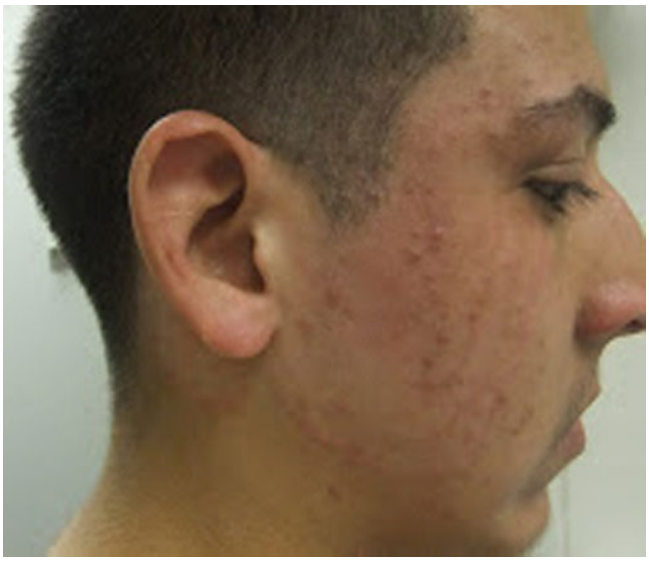

Fig. 16.2 Majocchi's granuloma. Folliculocentric papules and pustules within a thin plaque with an expanding, elevated border on the cheek of an adolescent male

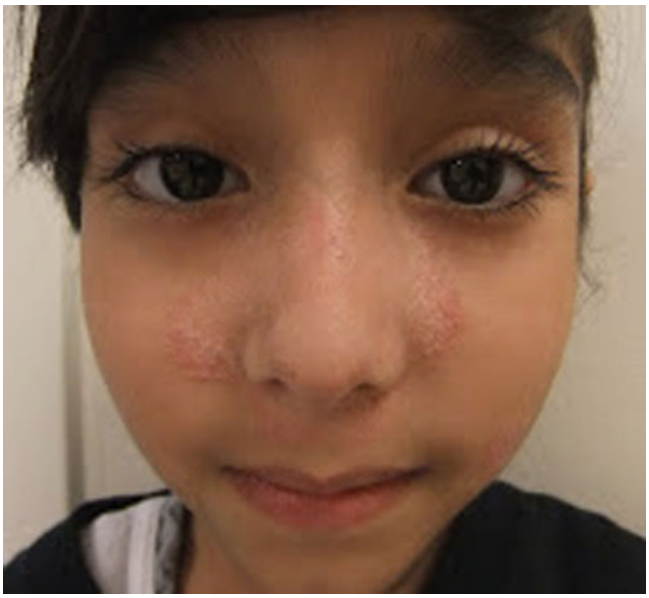

Fig. 16.3 Tinea faciei. Scaling thin plaque with elevated border on the mid-face of a young girl

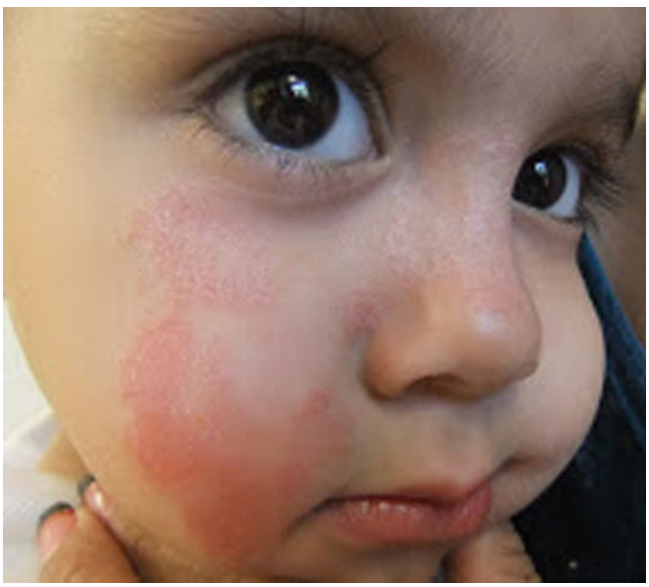

Fig. 16.4 Tinea faciei. Unilateral thin erythematous plaque with central clearing in an infant

agar, Mycosel agar, or dermatophyte test medium. They are obtained by scraping of scale or hair with a disposable toothbrush, cytobrush, or sterile swab. Based on studies of patients with onychomycosis, KOH demonstrates a sensitivity of 76–94 % and specificity of over 70 % while culture demonstrates a sensitivity of 53–59 % and specificity of over 80 %. Histopathologic examination (nail clipping with PAS) is the gold standard for diagnosis of onychomycosis, with a sensitivity of 80–98 % and a specificity over 70 %. Skin biopsy (for histopathology, with or without PAS) is rarely necessary, but may be helpful in cases of Majocchi's granuloma, or in cases simulating inflammatory dermatoses [3–5].

For tinea capitis, Wood's lamp examination is helpful in cases of *Microsporum* infection, which demonstrates bright green fluorescence in a dark room. Given that fungal cultures take several weeks for speciation, empiric systemic antifungal therapy is recommended in clinically suspected cases of tinea capitis in children, and that terbinafine is superior for *Trichophyton* species while griseofulvin is superior for *Microsporum* species, the Wood's lamp is a very useful adjunctive diagnostic method that allows selection of empiric therapy in tinea capitis. Dermoscopy of hair and scalp (trichoscopy) may be a useful adjunctive measure. Findings include broken hairs, dystrophic hairs, corkscrew hairs, comma hairs, black dots, horizontal white bands in hair shafts and translucent, easily deformable hairs [6–8].

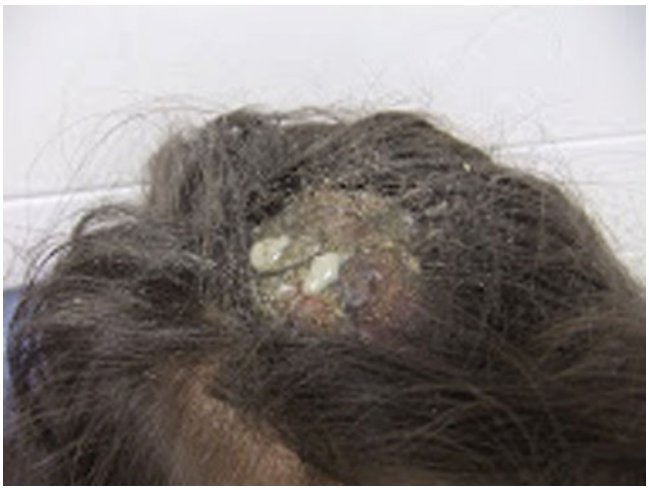

Fig. 16.5 Kerion. Large nodule with crusting and purulent drainage on the scalp of a young girl

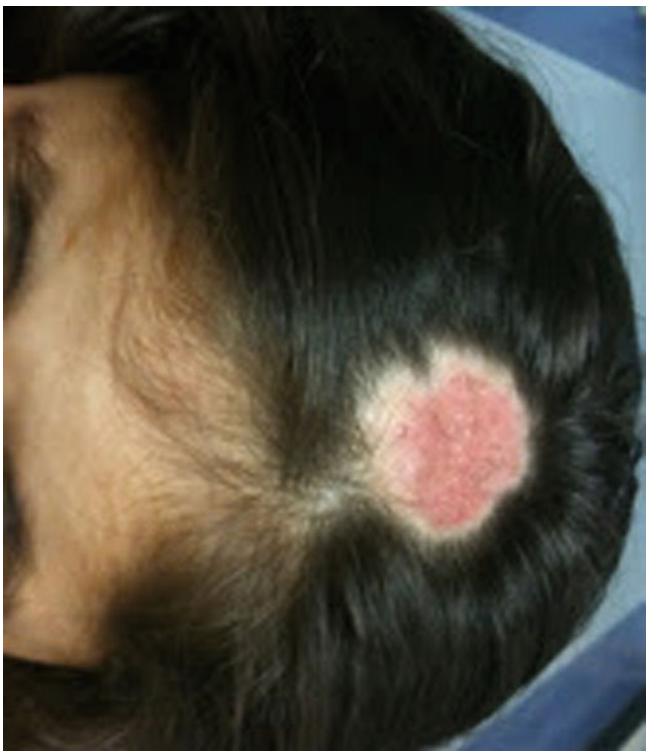

Fig. 16.6 Kerion. Resolution of nodule and purulence following 1 month of oral terbinafine. Regrowth of hair was observed at follow-up

In otherwise healthy children, baseline laboratory evaluation is not required prior to treatment with systemic antifungals for dermatophytosis. In children with pre-existing liver dysfunction or hematologic abnormalities, however, LFTs or CBC should be evaluated, respectively. Additionally, these tests should be performed in otherwise healthy children with lengthy courses of treatment: greater than 8 weeks of griseofulvin, 6 weeks of terbinafine, or 4 weeks of azole therapy [9].

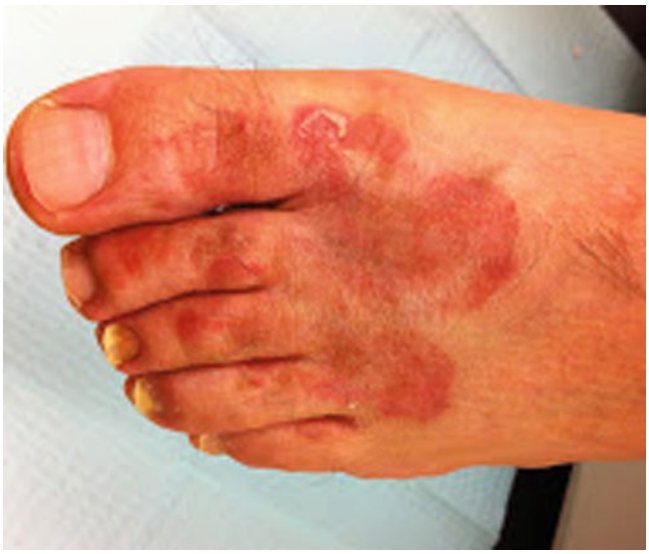

Fig. 16.7 Onychomycosis and tinea corporis. Yellow, dystrophic toenails and thin erythematous plaque on the dorsal foot

Tinea Capitis and Barbae

Management Strategy

Treatment requires oral antifungal therapy; topical antifungals are unable to adequately penetrate follicles and should be avoided. Terbinafine and griseofulvin are the only FDA-approved medications for the treatment of tinea capitis.

Terbinafine and griseofulvin have both shown efficacy in the treatment of tinea capitis, with terbinafine showing greater efficacy for *Trichophyton* species and griseofulvin for *Microsporum* species. In one study using both agents for 6 weeks, complete cure and mycologic cure were higher for terbinafine than for griseofulvin (45.1 % vs 39.2 % and 61.5 % vs 55.5 %, respectively); however, in two meta-analyses, no significant difference in efficacy was identified. Both meta-analyses, however, did show terbinafine was more effective in the treatment of *Trichophyton* species while griseofulvin was more effective for *Microsporum* species. Additionally, terbinafine was administered for a shorter mean duration (4 weeks) than griseofulvin (8 weeks).

In one randomized-controlled trial, fluconazole for 3 weeks (6 mg/kg/day), fluconazole for 6 weeks (6 mg/kg/day), and griseofulvin for 6 weeks (11 mg/kg/day microsize formulation) all produced similar and low mycologic (44.5 %, 49.6 %, and 52.2 %, respectively) and clinical cure rates. In another randomized trial, fluconazole for 4 weeks was 78 % effective, while griseofulvin for 6 weeks was 76 % effective in curing tinea capitis. In a study comparing multiple oral antifungal agents in the treatment of *T. tonsurans or T. violaceum*, efficacy percentages were 92 % for griseofulvin (6 weeks), 94 % for terbinafine, 86 % for itraconazole

and 84 % for fluconazole (each taken for 2 weeks). Six weeks of itraconazole 100 mg daily and ultramicrosize griseofulvin 500 mg daily produced 88 % cure rates in a patient cohort in which 90 % of the tinea capitis infections were due to *M. canis*.

Both selenium sulfide and ciclopirox shampoo, when used in combination with griseofulvin, demonstrated over 90 % mycologic cure rate. While one study of three children with kerion [19] demonstrated a benefit to oral steroid use, a larger retrospective study [20] found no benefit to oral or intralesional steroids.

Table 16.1 First-line therapies for tinea capitis and barbae [10–12]

Medication	Dosing	Evidence level
Terbinafine	Granules: treatment duration for 6 weeks	A
	<25 kg: 125 mg/day	
	25–35 kg: 187.5 mg/day	
	>35 kg: 250 mg/day	
	Tablets: treatment duration for 6 weeks	A
	10–20 kg: 62.5 mg/day	
	20–40 kg: 125 mg/day	
	>40 kg: 250 mg/day	
Griseofulvin	Microsize (tablets or suspension)	A
	20–25 mg/kg/day for 6–12 weeks with maximum daily dose 1,000 mg	
	Ultramicrosize (tablets only)	A
	10–15 mg/kg/day for 6–12 weeks with maximum daily dose 750 mg	

Table 16.2 Second-line therapies for tinea capitis and barbae [13–18]

Medication	Dosing	Evidence level
Fluconazole	6 mg/kg/day × 3–6 weeks with maximum daily dose 400 mg	A
	6 mg/kg/week × 6–12 weeks (pulse regimen)	B
Itraconazole	3–5 mg/kg/day × 4–6 weeks with maximum daily dose 400 mg	A
	3–5 mg/kg/day × 1 week each month for 2–3 months (pulse regimen)	B

Table 16.3 Adjunctive therapies for tinea capitis and barbae [19–21]

Medication	Dosing	Evidence level
Antifungal shampoo:	Affected patients and close or household contacts: twice weekly for 8 weeks	A
Selenium sulfide 1 %		
Ciclopirox 1 %		
Ketoconazole 2 %		B
Systemic glucocorticoids (kerion)	Prednisone 0.5–1 mg/kg/day for 1 week	E

Tinea Corporis, Faciei, and Cruris

In a large, pooled, meta-analysis, naftifine and terbinafine were the most effective agents in achieving mycologic and clinical cures, although efficacy was similar between azoles and allylamines. For tinea cruris, follow-

Table 16.4 First-line therapies for tinea corporis, faciei, and cruris [22–26]

Medication	Dosing	Evidence level
Topical allylamines:	Once to twice daily for 2–4 weeks	A
Terbinafine 1 % cream		
Naftifine 1 % cream or gel		
Topical benzylamine:	Once daily for 2 weeks	B
Butenafine 1 % cream		
Oral terbinafine	Treatment duration: 1–2 weeks	A*
	Granules:	
	<25 kg: 125 mg/day	
	25–35 kg: 187.5 mg/day	
	>35 kg: 250 mg/day	
	Tablets:	
	10–20 kg: 62.5 mg/day	
	20–40 kg: 125 mg/day	
	>40 kg: 250 mg/day	
Itraconazole	Treatment duration: 1 week	A
	3–5 mg/kg/day with maximum daily dose 200 mg	

Table 16.5 Second-line therapies for tinea corporis, faciei, and cruris [22, 25–27]

Medication	Dosing	Evidence level
Topical azoles:	Duration: 2–4 weeks	A
Clotrimazole 1 % cream	Twice daily	
Econazole 1 % cream	Once daily	
Ketoconazole 2 % cream	Once daily	
Oxiconazole 1 % cream	Once or twice daily	
Sertaconazole 2 % cream	Twice daily	
Ciclopirox 0.77 % cream	Twice daily	A
Tolnaftate 1 % cream	Twice daily	A
Fluconazole	Duration: 2–4 weeks	A*
	6 mg/kg once weekly	
Griseofulvin	Duration: 2–4 weeks	A
	Microsize formulation 10–20 mg/kg/day	
	Ultramicrosize formulation 5–15 mg/kg/day	

ing 2 weeks of topical treatment, butenafine was over 79 % effective for clinical cure while terbinafine was 62 % effective. Mycologic cure rates were superior for butenafine compared to terbinafine (94 % and 62 %, respectively) as well. Additionally, treatment response was more rapid with butenafine. In a study of systemic treatment of tinea corporis, terbinafine was superior to griseofulvin (87 versus 73 % effective). Another study of tinea corporis comparing itraconazole to griseofulvin showed a 91 % response rate to itraconazole versus 64 % response rate to griseofulvin. Itraconazole was also significantly more useful in obtaining mycologic cure (87 % versus 57 %).

Tinea Pedis and Manuum

Allylamines and butenafine were the most effective topical agents for curing tinea pedis. However, allylamines were only slightly more effective than azoles. Ciclopirox, tolnaftate, and undecanoates were less effective than azoles and allylamines.

A systematic review demonstrated allylamines to be slightly more effective than azoles in curing tinea pedis, and azoles were more effective than tolnaftate.

Itraconazole and oral terbinafine were equally effective in curing tinea pedis. Terbinafine was significantly more effective than griseofulvin, while no significant difference was found between fluconazole and itraconazole.

Table 16.6 First-line therapies for tinea pedis and manuum [28–30]

Medication	Dosing	Evidence level
Topical allylamines:	Once to twice daily × 4 weeks	A
Terbinafine 1 % cream		
Naftifine 1 % cream or gel		
Topical benzylamine:	Twice daily for 4 weeks	A
Butenafine 1 % cream		
Oral terbinafine	Treatment duration: 2 weeks	A
	Granules:	
	<25 kg: 125 mg/day	
	25–35 kg: 187.5 mg/day	
	>35 kg: 250 mg/day	
	Tablets:	
	10–20 kg: 62.5 mg/day	
	20–40 kg: 125 mg/day	
	>40 kg: 250 mg/day	
Itraconazole	Treatment duration: 1 week	A
	3–5 mg/kg/day with maximum daily dose 200 mg	

Table 16.7 Second-line therapies for tinea pedis and manuum [28–30]

Medication	Dosing	Evidence level
Topical azoles:	Duration: 4 weeks	A
Clotrimazole 1 % cream	Twice daily	
Econazole 1 % cream	Once daily	
Ketoconazole 2 % cream	Once daily	
Oxiconazole 1 % cream	Once or twice daily	
Sertaconazole 2 % cream	Twice daily	
Ciclopirox 0.77 % cream	Twice daily	A
Tolnaftate 1 % cream	Twice daily	A
Fluconazole	Duration: 2–6 weeks	A
	6 mg/kg once weekly	
Griseofulvin	Duration: 4–8 weeks	A
	Microsize formulation	
	10–20 mg/kg/day	
	Ultramicrosize formulation	
	5–15 mg/kg/day	

Dermatophytic Onychomycosis (Tinea Unguium)

Management Strategy

While onychomycosis is common in adults, it is less common in children under the age of 18 years. Thus, the evidence available from high-quality trials involves adult patients. Nonetheless, mycologic cure rate percentages (in descending order of superiority), based on standard dosing regimens for adults, are 76 % for terbinafine, 63 % for itraconazole pulse therapy, 60 % for griseofulvin, 59 % for itraconazole continuous therapy, and 48 % for fluconazole [31].

A prospective review of onychomycosis in children demonstrated the rarity of this condition under 18 years of age. Within a small sample size of 17 patients, oral agents were superior to topical agents. Among the oral agents, terbinafine was superior to itraconazole, which was superior to fluconazole. Of note, the evidence level for the use of these systemic agents in adults with onychomycosis is A.

In a study of children under 18 years older using ciclopirox 8 % nail lacquer solution, 77 % achieved mycologic cure and 71 % had clinical response. In adults, efinaconazole 10 % solution demonstrated a mycologic cure rate up to 55.2 % and complete cure up to 17.8 % following 48 weeks of daily treatment in multicenter, randomized, double-blind studies.

In an open trial of an over-the-counter mentholated ointment, Vicks Vaporub (eucalyptus oil, camphor, menthol, thymol, and oils of turpentine, nutmeg and cedar

Table 16.8 First-line therapies for dermatophytic onychomycosis [31, 32]

Medication	Dosing	Evidence level
Terbinafine	Toenails: 12 weeks	C/A*
	Fingernails: 6 weeks	
	10–20 kg: 62.5 mg/day	
	20–40 kg: 125 mg/day	
	>40 kg: 250 mg/day	
Itraconazole	Toenails: 12–16 weeks	C/A*
	Fingernails: 18–26 weeks	
	<20 kg: 5 mg/kg/day	
	20–40 kg: 100 mg daily	
	40–50 kg: 200 mg daily	
	More than 50 kg: 200 mg twice daily	
Fluconazole	Toenails: 18–26 weeks	C/A*
	Fingernails: 12–16 weeks	
	3–6 mg/kg per weekly dose	

Table 16.9 Second-line therapies for dermatophytic onychomycosis [33, 34]

Medication	Dosing	Evidence level
Ciclopirox nail lacquer solution 8 %	Daily for 32 weeks	A
Efinaconazole 10 % solution	Daily for 48 weeks	A*

Table 16.10 Third-line therapies for dermatophytic onychomycosis [35, 36]

Medication	Dosing	Evidence level
Mentholated ointment (Vicks VapoRub)	Daily for 48 weeks	C*
Laser therapy		B*

leaf), 27.8 % of patients had a clinical and mycologic cure following 48 weeks of daily application. The Nd:Yag 1,064-nm laser, delivered over four or eight weekly treatments, was up to 68 % effective in terms of clinical response. Both studies were performed in adult patients only.

Tinea Versicolor

Clinical Features

Tinea versicolor or pityriasis versicolor is caused by organisms of *Malassezia* genus, which are normally commensal, but become pathologic when the yeast form transforms into mycelia under conditions of heat, sweating, oily skin, or immunosuppression. Small patches and plaques with scale and hyperpigmentation or hypopigmentation, most commonly on the trunk and shoulders, are common (Fig. 16.8). Occasionally, involvement of intertriginous areas and, in younger children, the head and neck, may be seen (Fig. 16.9). Post-inflammatory pigmentary alteration may become chronic.

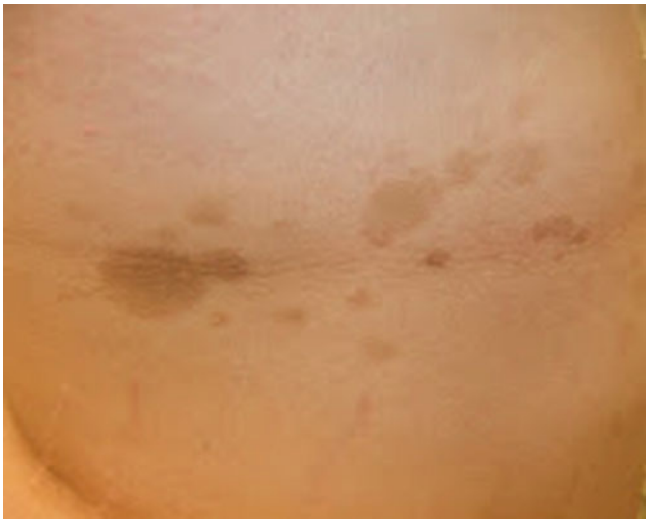

Fig. 16.8 Tinea versicolor. Hyperpigmented patches on the trunk

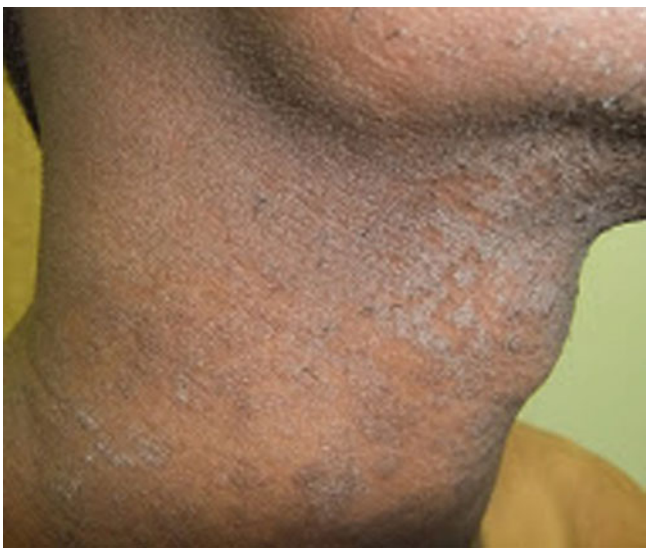

Fig. 16.9 Tinea versicolor. Extensive case with thin hyperpigmented plaques with fine scale on the neck of a young adult male

Specific Investigations [1, 2]

For diagnosis
KOH
Fungal culture
Histopathology
For treatment (with systemic antifungals)
CBC
LFTs

KOH preparation shows short fungal hyphae and groups of spores ("spaghetti and meatballs"). Fungal culture is nonspecific for diagnosis and is not recommended, since *Malassezia*

is normal skin flora. Skin biopsy for histopathology with or without PAS is usually not necessary, but is very accurate in confirming the diagnosis, showing abundant organisms in the stratum corneum, associated with no or little inflammation.

Given the very short duration of treatment courses with systemic antifungals, laboratory evaluation is not necessary. In patients with pre-existing hepatic hematologic abnormalities or in patients who require multiple courses treatment for refractory disease, CBC and LFTs should be evaluated.

Management Strategy

In general, topical therapy is the treatment of choice for tinea versicolor. However, a systematic review of controlled trials found most studies to lack the power to detect statistically meaningful differences, although most topical agents are effective compared to placebo. Systemic therapy is highly effective, but is typically reserved for adults with refractory or recurrent disease, and evidence from trials evaluating systemic treatment in children is not yet available. Nonetheless, the most effective regimens based on systematic review of studies in adults are itraconazole (200 mg/day × 5–7 days), fluconazole (300 mg/week × 2 weeks), and pramiconazole (200 mg/day × 2 days) [37, 38].

In studies including both adult and older pediatric patients, ketoconazole cream resulted in 98 % clinical response and 84 % mycologic cure rate compared to placebo. Ketoconazole shampoo was also effective, with clinical response comparable between a single application of ketoconazole shampoo and a 3-day regimen (73 % versus 69 % effective). Topical terbinafine 1 % cream demonstrated mycological clearance in 81 % of patients and clinical response in 72 % of patients with TV. Seventy-seven percent of patients treated with ciclopirox cream, compared with 45 % of patients treated with clotrimazole, had clinical and mycologic cures.

In a randomized, double-blind study, selenium sulfide 2.5 % lotion was superior to placebo; in clinical practice, selenium sulfide 2.5 % shampoo is more often prescribed. Another double-blind study showed zinc pyrithione shampoo was superior to its shampoo base, with all treated patients demonstrating clinical response.

Table 16.11 First-line therapies for tinea versicolor [39–42]

Medication	Dosing	Evidence level
Ketoconazole 2 % cream	Once daily × 11–22 days	A
Ketoconazole 2 % shampoo	Single use or daily × 3 days	A
Terbinafine 1 % cream	Twice daily × 1 week	A
Ciclopirox olamine 1 % cream	Twice daily × 14 days	A

Table 16.12 Second-line therapies for tinea versicolor [43, 44]

Medication	Dosing	Evidence level
Selenium sulfide 2.5 % lotion	Once daily × 7 days	A*
Selenium sulfide 2.5 % shampoo	Once daily × 7 days	E
Zinc pyrithione 1 % shampoo	Once daily × 14 days	A*

Table 16.13 Third-line therapies for tinea versicolor [45–47]

Medication	Dosing	Evidence level
Whitfield ointment (3 % salicylic acid and 6 % benzoic acid)	Twice daily for 4 weeks	A*
Sulfur-salicylic acid shampoo	Once daily × 1 week	A
Propylene glycol 50 % in water	Twice daily × 2 weeks	B*
Selenium sulfide 1 % shampoo (non-prescription)	Once daily × 7 days	E

While these are not typically used for the treatment of TV, older studies have shown good efficacy. In one double-blind trial, Whitfield ointment was equally effective compared to clotrimazole 1 % cream, producing 80 % mycologic cure rate. Treatment of tinea versicolor with sulfur-salicylic shampoo led to mycologic cure in 86 % of patients. A smaller study of 20 patients using propylene glycol 50 % in water BID reported that all patients demonstrated clinical response, with only 10 % having slight burning sensation after application.

Tinea Nigra

Clinical Features

Tinea nigra is a rare asymptomatic infection of the palms or soles, caused by the dematiaceous fungus *Hortaea werneckii*. It presents as pigmented macules or patches, generally unilateral in distribution, and is more common in tropical regions [48].

Specific Investigations

For diagnosis
KOH
Dermoscopy
Histopathology
For treatment
No specific laboratory investigations required

Table 16.14 First-line therapies for tinea nigra [50]

Medication	Dosing	Evidence level
Ciclopirox olamine gel 0.77 %	Three times daily × 3 days	E*

Table 16.15 Second-line therapies for tinea nigra [51, 52]

Medication	Dosing	Evidence level
Isoconazole cream	Twice daily × 20–30 days	E*
Terbinafine 1 % cream	Daily × 15 days	E*
Ketoconazole 2 % cream	Twice daily × 15 days	D
Whitfield's ointment (3 % salicylic acid and 6 % benzoic acid)	Twice daily × 18 days	D

Table 16.16 Third-line therapies

Medication	Dosing	Evidence level
No treatment (observation)		D

Clinical exam and KOH are sufficient for diagnosis in most cases, but the most common clinical concern is acral nevus or melanoma. Dermoscopy has been shown to be a useful non-invasive tool to aid in discrimination from melanocytic lesions and, in one series, was shown to suggest the diagnosis in over 50 % of cases. Dermoscopic findings include superficial fine, light brown strands which form a reticular patch with uniform brown color; unlike melanocytic lesions, furrows and ridges are not followed [49]. Skin biopsy is usually performed to rule out a melanocytic neoplasm, and is definitively diagnostic, demonstrating numerous pigmented hyphae in the stratum corneum.

Management Strategy

Treatment of this superficial mycosis is largely based on case reports, with evidence-based studies and trials with statistical power lacking.

Piedra

Clinical Features

Piedra is an asymptomatic superficial fungal infection limited the the hair shaft. Black piedra is caused by the dematiaceous fungus *Piedraia hortae*, is characterized by hard black nodules or concretions of scalp hair, and is most commonly seen in tropical locations. In contrast, white piedra is caused by *Trichosporon* species, results in soft white concretions of scalp as well as pubic, axillary, and facial hair, and is most common in temperate climates.

Some *Trichosporon* species such as *T. asahii* are associated with invasive infections in immunocompromised patients; cutaneous manifestations are seen in one-third of patients, and include purpuric nodules, disseminated papules, and bullae. The most common clinical setting for invasive infection is neutropenia; other conditions, including AIDS, burns, indwelling catheters, corticosteroid therapy, and heart valve surgery, are predisposing factors. Invasive infection is usually fatal [53–55].

Specific Investigations

For diagnosis
KOH
Fungal culture
For treatment
No specific investigations are required

Infected hairs are treated with KOH and then examined under the microscope [53]. In white piedra, darkly staining and loosely packed concretions are formed by septate hyphae, blastoconidia, and arthroconidia. In black piedra, pigmented brown-black nodules are observed. These are composed of tightly packed septate, thick-walled hyphae, asci, and ascospores.

Fungal culture is typically not required in superficial infections, but is important in invasive infections due to *Trichosporon* species [56]. *P. hortae* will grow on Sabouraud dextrose agar, as well as media containing cycloheximide (Mycosel agar and dermatophyte test medium). However, *Trichosporon* species are inhibited by cycloheximide and should therefore be cultured on Sabouraud dextrose agar at 28–30 °C.

White Piedra

Task force guidelines published in 1996 by the American Academy of Dermatology state the treatment of choice for both white and black piedra is to remove all infected hair by shaving or clipping. However, this is often not an acceptable treatment option for patients, and thus treatments with oral and topical antifungal agents have been studied. In a retrospective series of eight children, all demonstrated clearance of scalp infection using a combination of oral antifungals and ketoconazole 2 % shampoo, without shaving. In an open trial of oral itraconazole 100 mg/day, 11 out of 12 female patients demonstrated clinical and mycologic clearance of scalp infection after 8 weeks of treatment with oral itraconazole. No shaving was required.

The American Academy of Dermatology guidelines also report on topical treatments in addition to hair removal

Table 16.17 First-line therapies for white piedra [57–59]

Medication	Dosing	Evidence level
Removal of hair by shaving or clipping		D*
Itraconazole and ketoconazole 2% shampoo	Itraconazole: 100 mg/day × 1 month Ketoconazole: daily × 2 months	D
Itraconazole	100 mg/day × 4–8 weeks (until culture negativity achieved)	C*

Table 16.18 Second-line therapies for white piedra [53, 57, 60]

Medication	Dosing	Evidence level
Ketoconazole 2% shampoo or cream preceded by clipping or shaving affected area	Once daily for several months until clinical clearance	D
Miconazole 2% cream, isoconazole cream, or econazole nitrate 1% cream preceded by clipping or shaving affected area	Once daily for several months until clinical clearance	D

(considered treatment of choice, as above). In patients allergic to azoles, alternative topical antifungals include ciclopirox olamine cream, selenium sulfide 2% foam, 6% precipitated sulfur in white petrolatum, amphotericin B lotion, and Castellani's paint. Eradicaton is often difficult with clipping or shaving hair, and follow-up cultures may remain positive despite clinical clearance.

Black Piedra

Table 16.19 First-line therapies for black piedra [57]

Medication	Dosing	Evidence level
Removal of hair by shaving or clipping		D*

Table 16.20 Second-line therapies for black piedra [53, 60, 61]

Medication	Dosing	Evidence level
Oral terbinafine	250 mg/day × 6 weeks	E
Topical antifungals preceded by shaving or clipping	Once daily for several months until clinical clearance	E

Candidiasis

Clinical Features

Candidiasis presents in children with a wide spectrum of findings, ranging from localized mucosal infection to widespread dissemination [62–64]. *Candida* species are part of the normal flora, but become pathologic when they overgrow in the context of imbalance of other microbes, immunosuppression, or hematogenous spread in patients with prosthetic heart valves or central nervous system shunts.

Oropharyngeal candidiasis (thrush) is common in young infants, but may also be seen in older children following treatment with antibiotics or steroids, or in the context of immunosuppression such as HIV/AIDS or chemotherapy. White pseudomembranous plaques on the soft palate and tongue are most common. Less commonly, acute atrophic glossitis may result in a painful, erythematous, and smooth tongue. Infection may be asymptomatic or associated with dysphagia. Angular cheilitis (perleche) results in painful fissuring in the corners of the mouth, usually due to excess moisture or licking.

Candida diaper dermatitis is also very common in infants, and presents as confluent erythema with papules, pustules, and satellite lesions of the crural region. Persistent or refractory diaper dermatitis may indicate an underlying immunodeficiency, immunocompromised state, or chronic mucocutaneous candidiasis (CMCC).

Candida intertrigo occurs in flexural areas prone to moisture accumulation, and with closely opposed surfaces such as the neck, axillae, and intergluteal folds. Similar to diaper dermatitis, erythematous and macerated plaques with satellite lesions, pustules, and erosions are common.

Vulvovaginitis may occur in infants or adolescents [64]. In infants, diapers, antibiotics, and immunocompromise are all risk factors. In adolescents, contraceptive devices, oral contraceptives, and pregnancy are predisposing. Clinical features include erythema, swelling, and thick white or thin watery discharge. Associated symptoms include pain, itching, and dysuria. Similarly, balanitis may be seen in infants or adolescents and presents as white or erythematous patches, sometimes with erosions, on the penis.

Neonates, immunosuppressed children, and children hospitalized in intensive care units (ICUs) are at risk for candidemia and systemic candidiasis [65]. In neonates, risk factors include extremely low or very low birth weight (less than 1000 g or less than 1500 g respectively), prematurity, administration of broad-spectrum antibiotics, or invasive procedures. Vertical transmission results from maternal vaginitis, heavy vaginal colonization, or breastfeeding. Horizontal transmission results from spread from health care workers and often involves contaminated surfaces. Predisposing factors for candidemia in immunosuppression include hematologic malignancy, neutropenia, chemotherapy, and antibiotics. Patients in ICUs are at particular risk in the context of burns, trauma, indwelling catheters, antibiotics, hemodialysis, and mechanical ventilation.

Signs and symptoms of sepsis in addition to organ failure may be seen. Cutaneous manifestations include clusters of

painless pustules on an erythematous base, with or without necrosis, macular eruptions, skin abscesses, and purpuric nodules due to septic emboli [66].

Congenital candidiasis presents with generalized small macules or papules on an erythematous base, with evolution into pustules or vesicles [67]. Involvement of the palms, soles, and umbilical cord is common. In otherwise healthy infants, the skin lesions resolve within a week and can be treated with topical agents. However, preterm neonates are at risk for systemic infection and should be empirically treated for candidemia until systemic infection is ruled out.

CMCC is a heterogeneous group of disorders characterized by genetic immune defects leading to chronic, persistent, and refractory non-invasive *Candida* infections of the skin, mucous membranes, and nails. Autoimmune endocrinopathies are often associated. Associated mutations include AIRE (autoimmune regulator) [68], STAT1 [69], IL17RA (interleukin 17 receptor alpha) [70], Lyp [71], Dectin-1 [72], and TLR3 (toll like receptor 3).

Mutations in AIRE are associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED), which features hypoparathyroidism, adrenal failure, type 1 diabetes, vitiligo, and alopecia areata among potential autoimmune associations. The onset of CMCC typically occurs in childhood, although this is often variable [68].

Specific Investigations

For diagnosis
KOH
Fungal culture
Histopathology
Genetic testing (for CMCC)
For treatment
CBC
LFTs
Other laboratory: renal function (blood urea nitrogen and creatinine) and metabolic panel (blood glucose, potassium), EKG

The different *Candida* species generally are capable of producing all of the clinical syndromes, although infection with *C. albicans* is the most common.

For uncomplicated skin and mucosal infections, KOH can be performed to confirm the presence of budding yeast with or without hyphae. Culture in this scenario is not required, but should be performed in refractory or resistant mucocutaneous infection to identify potential azole-resistant species. *C. glabrata* and *C. krusei* are less susceptible to azole antifungal agents, and *C. lusitaniae* may be resistant to amphotericin B.

Skin biopsy is not required for uncomplicated mucocutaneous infections, but is accurate, and typically demonstrates numerous organisms in the stratum corneum and sometimes epithelium. Punch biopsy may also be useful in invasive or disseminated infections, often demonstrating abscesses, yeasts, and hyphae, and can be used to obtain tissue for culture [63].

Candida in a blood culture should not be considered a contaminant and should always prompt a search for the source of the fungemia. In some patients, candidemia is a manifestation of disseminated candidiasis, while in others it reflects colonization of an indwelling intravenous catheter. Because the sensitivity of a single blood culture is low in detecting disseminated candidiasis, multiple or repeat blood cultures should be performed. If an indwelling catheter is present, cultures should be obtained through the catheter and a peripheral vessel to distinguish between disseminated infection and catheter-related candidiasis. Of note, *Candida* species typically require 1–4 days for growth on culture [73].

Antibody and antigen assays are not sensitive enough for clinical use. Beta-D-glucan assay has demonstrated high sensitivity, and PCR is highly specific and as sensitive as blood cultures, but experience with these tests in children is limited [74, 75].

Genetic analysis for disease-causing mutations can be used to confirm suspected cases of CMCC, but not all genetic mutations are known. Diagnosis relies on the constellation of clinical findings present. Serum *Candida* antibodies are not of value in the diagnosis of CMCC, nor are skin or serum IgE tests for *Candida*.

Prior to short-term systemic azole therapy in otherwise healthy children, laboratory evaluation is not required. In patients undergoing multiple courses of treatment, or with pre-existing hepatic dysfunction or hematologic abnormalities, LFTs and CBC are recommended. The adverse effects of amphotericin B include infusion reactions, renal failure, hypokalemia, and myocarditis. Thus for patients undergoing treatment with amphotericin, renal function (blood urea nitrogen and creatinine), metabolic panels (blood glucose, potassium), and EKG should be monitored.

Oropharyngeal Candidiasis

Nystatin has long been considered the first treatment for oropharyngeal candidiasis, with suspension showing an 80 % cure rate. Studies of other topical agents (suspensions, lozenges, gels) have often shown similar to improved efficacy. In one study, miconazole gel was significantly superior to nystatin suspension in demonstrating clinical cure (99 % versus 54 %) in immunocompetent infants. Miconazole was also superior in eradicating yeast. In another study, fluconazole

oral suspension demonstrated a 100 % cure rate, compared to only 32 % cure with nystatin suspension. Nonetheless, given the typically limited nature of oropharyngeal candidiasis in immunocompetent infants, nystatin and clotrimazole are preferred as first-line agents. Of note, nystatin and clotrimazole lozenges should not be used in children younger than 4 years old, as they are a choking hazard.

In immunocompromised infants and children, fluconazole demonstrated 91 % clinical cure and 76 % mycologic cure, compared to only 51 % clinical cure and 11 % mycologic cure for treatment with nystatin. Fluconazole was also superior to nystatin in achieving clinical and mycologic cure in children with HIV and oropharyngeal candidiasis. Clotrimazole lozenges demonstrated a similar cure rate to that of fluconazole suspension, but fluconazole was superior in mycologic cure rates. Although gentian violet was superior to nystatin in achieving clinical cure, it is preferred as a third-line therapy, given the risk for staining lips and clothing as well as potential for irritation and ulceration.

Table 16.21 First-line therapies for oropharyngeal candidiasis [76–78]

Medication	Dosing	Evidence level
Nystatin suspension	Infants:	A
	<30 days old: 50,000 units to each cheek four times daily × 7–14 days	
	>30 days old: 100,000 units to each cheek four times daily × 7–14 days	
	Children >4 years old:	A
	600,000 units four times daily for 7–14 days	
	One to two lozenges (each 200,000 units) four times daily for 7–14 days	
Clotrimazole	Children >4 years old:	A
	Lozenge (10 mg) five to six times daily for 7–14 days	
Miconazole gel (25 mg)	Four times daily for 14 days	A

Table 16.22 Second-line therapies for oropharyngeal candidiasis [79, 80]

Medication	Dosing	Evidence level
Fluconazole	6 mg/kg on day 1, followed by 3 mg/kg daily for 14 days, maximum daily dose 200 mg	A

Table 16.23 Third-line therapies for oropharyngeal candidiasis [80]

Medication	Dosing	Evidence level
Gentian violet 0.5 or 1 % solution	Once or twice daily application for 3 days	A

Candidal Intertrigo and Diaper Dermatitis

In a randomized trial of over 90 infants with diaper dermatitis complicated by *Candida* infection, clotrimazole was curative in 68 % of patients, while nystatin produced cure in 47 % of patients. However, microbiologic cure rate was 100 % for both agents. In an open study, sertaconazole cream produced clinical and mycological cure in over 88 % of infants with candidal diaper dermatitis.

Miconazole demonstrated a clinical cure rate of 38 % compared to 11 % for vehicle, although microbiologic cure was higher. Ciclopirox, in an open study, produced a clinical cure in 50 % of infants with diaper dermatitis due to *Candida*.

In refractory or severe disease, oral azole antifungal therapy may be used. Ketoconazole is effective but should not be used, given the risk of hepatotoxicity.

Candidal Vulvovaginitis

In a systematic review, no significant differences in mycological or clinical cure rates were found between topical (intravaginal) and systemic (oral) azole antifungal short-term therapy. In open studies and randomized trials, single-dose

Table 16.24 First-line therapies for candidal intertrigo and diaper dermatitis [81, 82]

Medication	Dosing	Evidence level
Clotrimazole 1 %	Twice daily for 14 days	A
Sertaconazole 2 %	Twice daily for 14 days	B
Nystatin 100,000 IU	Twice daily for 14 days	A

Table 16.25 Second-line therapies for candidal intertrigo and diaper dermatitis [83, 84]

Medication	Dosing	Evidence level
Miconazole 0.25 % in zinc oxide/petrolatum	Twice daily for 7 days	A
Ciclopirox 077 %	Twice daily for 7 days	B

Table 16.26 Third-line therapies for candidal intertrigo and diaper dermatitis [85]

Medication	Dosing (duration of treatment: 2–6 weeks or until resolution)	Evidence level
Fluconazole	6 mg/kg once then 3 mg/kg/day	E
Itraconazole	5–10 mg/kg/day divided in two doses	E

Table 16.27 First-line therapies for candidal vulvovaginitis [86]

Medication	Dosing	Evidence level
Fluconazole	150 mg PO once	A

Table 16.28 Second-line therapies for candidal vulvovaginitis [86–91]

Medication	Dosing	Evidence level
Clotrimazole	Intravaginal tablet 200 mg daily for 7 days	A
	Intravaginal tablet 500 mg or 10 % cream single dose	B
Terconazole	0.4–0.8 % cream daily for 7 days	A
	80 mg intravaginal tablet daily for 3 days	A
Miconazole	2% cream daily for 7 days	A
	Intravaginal tablets also available	

Table 16.29 Third-line therapies for candidal vulvovaginitis [92–95]

Medication	Dosing	Evidence level
Fluconazole	Severe disease:	A
	150 mg PO every 3 days, for a total of 3 doses	
	Recurrent disease:	A
	150 mg PO every 3 days, for a total of 3 doses, followed by:	
	150 mg PO every week, for 6 months	

oral fluconazole and a 1-week course of intravaginal clotrimazole have demonstrated comparable efficacy in terms of clinical (83–97 %) and mycological cure rates (70–80 %). Randomized-controlled trials have also found short courses of terconazole and miconazole, in the form of intravaginal tablets or topical creams, to be as effective in producing clinical and mycologic cures in comparison to single-dose oral fluconazole. Nonetheless, fluconazole is the preferred first-line therapy, given the convenient dosing, low cost, and ease of administration.

In the context of severe vulvovaginitis, *Candida* species other than *C. Albicans* such as *C. glabrata*, immunosuppression, or a history of recurrent disease (four or more episodes per year), more aggressive therapies are warranted. In patients who cannot take fluconazole, induction therapy for 10–14 days with a topical azole followed by weekly clotrimazole 200 mg intravaginal tablet for 6 months, is an alternative for recurrent disease. Single-dose fluconazole was 85 % effective, while a two-dose regimen was 94 % effective in patients with severe, but not recurrent, vulvovaginitis. For patients with recurrent vulvovaginitis, weekly treatment with single-dose fluconazole was over 90 % effective at prevention after 6 months of treatment, and resistance in clinical isolates was not induced. These results, and data from similar studies, were further validated in a systematic review.

Table 16.30 First-line therapies for neonatal and systemic candidiasis [92, 97, 98]

Medication	Dosing	Evidence level
Amphotericin B deoxycholate	0.5 mg/kg initial dose followed by 1 mg/kg/day IV	B
	Duration: 14 days after sterilization or until cumulative dose of 25–30 mg/kg	

Table 16.31 Second-line therapies for neonatal and systemic candidiasis [99–103]

Medication	Dosing (duration: 14 days after sterilization)	Evidence level
Fluconazole	25 mg/kg loading dose followed by 12 mg/kg/day IV	B
Lipid-based amphotericin B	3–5 mg/kg/day IV	D

Table 16.32 Third-line therapies for neonatal and systemic candidiasis [104–107]

Medication	Dosing (duration: 14 days after sterilization)	Evidence level
Echinocandins:		
Caspofungin	70 mg/m^2 loading dose followed by 50 mg/m^2/day IV, with maximum daily dose 70 mg	D
Micafungin	2–4 mg/kg/day IV	C
Flucytosine (enteral only)	50–150 mg/kg/day total, divided in 4 doses	D

Neonatal and Systemic Candidiasis

Management Strategies

Importantly, medical hardware suspecting of acting as a nidus for infection should be removed immediately following detection of candidemia. In a retrospective study of neonates with candidemia, failure to remove an indwelling central venous catheter was associated with a nearly 40 % increase in mortality [96].

Amphotericin B is the most commonly used agent based on experience with its use, the *in vitro* susceptibility of most *Candida* species, and its tolerability in neonates with systemic or disseminated candidiasis.

In two open studies, there was no statistically significant difference in case fatality following treatment with fluconazole compared to amphotericin B for invasive candidiasis in infants. However, some species such as *C. krusei*, *C. glabrata*, and *C. parapsilosis*, are often fluco-

Table 16.33 First-line therapies for chronic mucocutaneous candidiasis [108, 109]

Medication	Dosing (duration varies depending on infection)	Evidence level
Fluconazole	6 mg/kg po initial dose (maximum 200 mg) followed by 3 mg/kg/day po (maximum daily dose 100 mg)	D

Table 16.34 Second-line therapies for chronic mucocutaneous candidiasis [110]

Medication	Dosing (duration variable depending on infection)	Evidence level
Itraconazole	2.5 mg/kg/day po twice daily, with maximum daily dose 200 mg	D
Voriconazole	9 mg/kg po twice daily with maximum daily dose 350 mg	D
Posaconazole	800 mg/day po in 2–4 divided doses	D

nazole-resistant. For this reason, fluconazole should not be used as first-line or empiric monotherapy. Instead, amphotericin B should be used until culture and susceptibility results are available. Lipid-based formulations of amphotericin B are considered to be less nephrotoxic, but retrospective data demonstrate higher mortality for infants with systemic candidiasis treated with lipid-based amphotericin B than those treated with conventional amphotericin B deoxycholate.

Based on retrospective reviews, caspofungin is an effective alternative therapy for neonates with persistent candidemia or refractory invasive candidiasis. In a systematic review of trials involving 30 premature and non-premature infants with invasive candidiasis, the rate of treatment success was 73 % with micafungin.

Flucytosine is not useful as monotherapy due to rapid induction of resistance, but is useful in combination with amphotericin B for treatment of CNS candidiasis. However, levels must be monitored closely due to the risk of bone marrow suppression.

Chronic Mucocutaneous Candidiasis

Fluconazole is the preferred first-line treatment, given that the most common isolate in CMCC is *C. Albicans*. However, fluconazole resistance may occur, particularly in the context of chronic suppressive therapy.

If resistance to fluconazole develops, then itraconazole, voriconazole, or posaconazole may be used for treatment of cutaneous infections.

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Infectious Diseases: Deep Fungal Infections

17

Kiran Motaparthi

Subcutaneous Mycoses: Sporotrichosis, Chromoblastomycosis, Mycetoma, Rhinosporidiosis

Clinical Features

Sporotrichosis is chronic infection caused by the dimorphic fungus *Sporothrix schenkii*, which is transmitted by direct inoculation of soil through skin. The most common form of sporotrichosis is lymphocutaneous, characterized by the development of an erythematous papule or nodule at the site of inoculation. Subsequently, additional lesions, with or without ulceration, occur proximally along lymphatic channels. The most common site of involvement is the upper extremity (Fig. 17.1). Fixed cutaneous lesions, in the form of verrucous or ulcerative plaques, may occur on the face or extremities. In immunocompromised states, visceral spread, such as pulmonary disease, may occur [1].

Chromomycosis is caused by inoculation of a dematiaceous fungus from the soil into skin. Typical lesions of chromomycosis in children or adolescents are erythematous nodules or verrucous plaques, most often located on the upper extremity. This is of notable contrast to disease presentation in adults, which usually occurs on the lower extremity. In one study of chromomycosis in South American children, *Cladophialophora carrionii* was the most common cause, while most studies in adults have show *Fonsecaea pedrosoi* to be the most common cause [2, 3].

Eumycetoma is a chronic mycotic infection of the skin and soft tissue. Infection follows inoculation injury from a contaminated thorn or splinter. At least 30 species of molds are implicated; *Pseudallescheria boydii* is the most common causative species in the United States, while *Madurella mycetomatis* is the most common cause worldwide. Infection most often involves the feet or lower extremities, and is characterized by large verrucous nodules with abscesses, sinus tracts, and macroscopic grains (Fig. 17.2). Eumycetomas are usually confined to subcutaneous tissues, but can involve fascia, bone, and regional lymph nodes via contiguous dissemination. Fibrosis, deformity, and lymphedema eventually result if untreated [4].

Rhinosporidiosis is a non-contagious chronic granulomatous infection caused by *Rhinosporidium seeberi*, and is characterized by polyps which are sessile or pedunculated, and mainly affect the nasal mucosa and, less commonly, the conjunctival or ocular mucosa. Cutaneous lesions may occur due to spread from adjacent mucosa, direct inoculation, or hematogenous spread. Infection in adolescents and young adults is common [5, 6].

Specific Investigations

For diagnosis
Fungal culture
KOH
Histopathology
For treatment
CBC, LFTs, lipid panel, metabolic panel (potassium, blood glucose), kidney function tests (BUN and creatinine), EKG
Thyroid function tests (TFTs)

Fungal culture is the most sensitive method for the diagnosis of sporotrichosis. Aspirate from a nodule or tissue from a punch biopsy should be inoculated onto Sabourad dextrose agar; growth occurs within 5 days at room temperature. Histopathology may be supportive, but is rarely diagnostic, given the difficulty of finding the sparse organisms, which are 3 μm or smaller in diameter. Nonspecific findings, including suppurative granulomas and asteroid bodies, are often present [7]. An enzyme immunoassay for serologic testing of *S. schenkii* has demonstrated up to 90 % sensitivity and 80 % specificity, but is not available widely [8].

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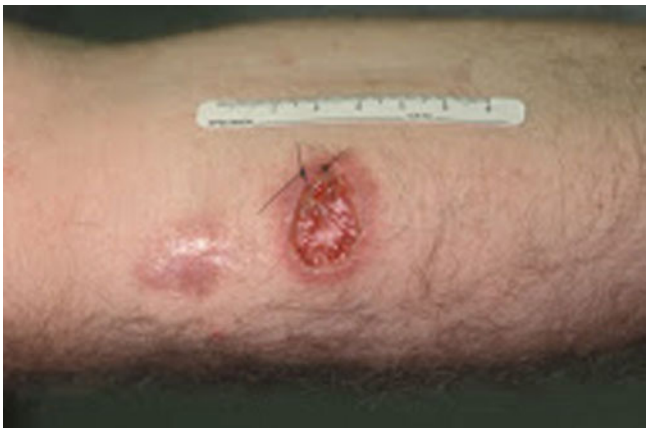

Fig. 17.1 Lymphocutaneous sporotrichosis. Erythematous nodule and ulceration present along the lymphatics of the upper extremity (Photo courtesy of Sylvia Hsu, MD)

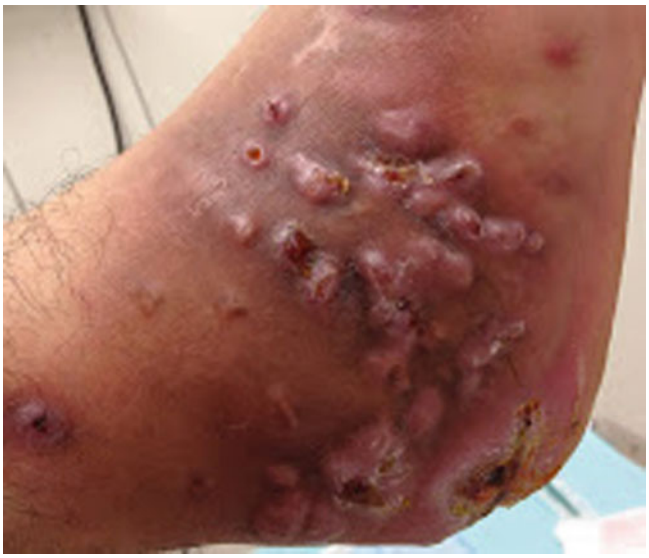

Fig. 17.2 Eumycetoma. Multiple coalescent verrucous nodules with sinus tract formation on the foot, resulting in deformity (Photo courtesy of Sylvia Hsu, MD)

In chromomycosis, KOH is highly sensitive in identifying the characteristic sclerotic or medlar bodies. Fungal culture on Sabourad or Mycosel agar is sensitive and specific. Histopathology often demonstrates granulomatous inflammation, pseudocarcinomatous hyperplasia, and pigmented yeast forms with single septations [9].

Eumycetoma can be diagnosed by the clinical findings in combination with black macroscopic grains, which are only found with fungal infections; yellow or white grains indicate fungal or bacterial infection. KOH demonstrates broad, septate, and branching hyphae. Culture should be performed but requires 6–8 weeks for growth. Histopathology is also helpful and demonstrates hyaline or pigmented hyphae in microscopic grains. Radiography, including X-ray, computed tomography, and magnetic resonance imaging should be considered in extensive cases, to exclude bony and soft tissue involvement [10].

In rhinosporidiosis, KOH or histopathology are diagnostic, demonstrating large sporangia 200 μm in diameter and filled with smaller endospores. Culture is not helpful, as *R. seeberi* is intractable to isolation or growth in microbiologic culture media [11].

Given the lengthy duration of systemic azole therapy required for theses diseases, baseline and periodic evaluation of CBC and LFTs is recommended. In the case of itraconazole, periodic evaluation of serum lipids is recommended, given the risk of hypertriglyceridemia. SSKI therapy requires monitoring of thyroid function tests, including TSH and FT4. Kidney function tests as well as potassium levels should be monitored during amphotericin B treatment; EKG is also recommended, given the risk of arrhythmia.

Table 17.1 First-line therapy for sporotrichosis [12–14]

Medication	Dosing	Evidence level
Itraconazole	6–10 mg/kg/day up to maximum daily dose 400 mg daily × 3–6 months (2–4 weeks after clinical clearance)	B

Clinical cure was obtained in almost 95 % of patients with cutaneous sporotrichosis, including children, treated with oral itraconazole. In another study, clinical response rate to itraconazole was over 80 %.

Table 17.2 Second-line therapy for sporotrichosis [15, 16]

Medication	Dosing	Evidence level
Saturated solution of potassium iodide (SSKI)	One drop in juice or milk three times daily, increased weekly to a maximum of one drop per kg or 40–50 drops three times daily	B

In a randomized non-blinded study, clinical cure rates were high and similar (above 89 %) for pediatric patients treated with either daily dosing or four times daily dosing of SSKI.

Table 17.3 Third-line therapies for sporotrichosis [17]

Medication	Dosing	Evidence level
Amphotericin B deoxycholate followed by itraconazole	Amphotericin B: 0.7 mg/kg/day until improved Itraconazole: 6–10 mg/kg/day up to maximum daily dose 400 mg × 12 months	E*

Initial treatment with intravenous amphotericin B followed by long-term therapy with itraconazole is reserved for disseminated sporotrichosis and based on case reports.

Table 17.4 First-line therapies for chromomycosis [2, 9]

Medication	Dosing	Evidence level
Itraconazole	100 mg/day for 1 month	E*
5-Fluorouracil (5-FU) 1 % cream	Once daily for 3 weeks to 3 months	D*

Complete clinical and mycologic remission was achieved in 85 % of the patients treated with itraconazole or 5-FU cream. Similar results were obtained for electrodesiccation or fulguration, but given the more invasive nature and potential for scarring, this is considered an alternative to itraconazole or 5-FU. Ajoene gel (isolated from alcoholic extracts of garlic) also demonstrated a high rate of efficacy, but may be difficult to obtain.

Table 17.5 Second-line therapies for chromomycosis [2, 9]

Medication	Dosing	Evidence level
Electrodesiccation or fulguration		E*
Cryosurgery		D*

Low cure rates (31 %) were observed in a study of 51 cases, but cryosurgery and itraconazole produced the best results overall, sometimes in combination.

Table 17.6 Third-line therapies for chromomycosis [2, 9]

Medication	Dosing	Evidence level
Ajoene 0.5 % gel		D*

Table 17.7 First-line therapies for eumycetoma [18, 19]

Medication	Dosing	Evidence level
Itraconazole	× 12 months	E*
Voriconazole		E
Posaconazole		E*

In one study, itraconazole was moderately efficacious, associated with improvement in 42 % of cases, although none showed mycologic or clinical remission. Voriconazole is the treatment of choice for eumycetoma caused by *P. boydii*. Posaconazole can be used as an equally effective alternative to itraconazole and voriconazole.

Table 17.8 Second-line therapies for eumycetoma [20–24]

Medication	Dosing	Evidence level
Surgery	Preceded by at least 6 months of antifungal therapy	E*
Ketoconazole	× 6 months	C

Radical surgical procedures should be avoided, but combined medical therapy and conservative excision have produced good results. Relapse rates after surgery alone are high (over 50 %), so antifungals should be administered for at least 6 months prior to surgery, and then in the post-surgical period to reduce recurrence. In a small study of oral ketoconazole, 5 of 13 patients were completely cured, and 4 improved following at least 6 months of treatment. Despite its historical role as the preferred agent for this disease, toxicity limits its use, and it is now only considered an alternative agent.

Table 17.9 First-line therapies for rhinosporidiosis [25]

Medication	Dosing	Evidence level
Surgery		E*

Local surgical excision is the treatment of choice, but has been associated with 10 % recurrence rate. Concurrent medical treatment with dapsone has been used to decrease this risk.

Table 17.10 Second-line therapies for rhinosporidiosis [26, 27]

Medication	Dosing	Evidence level
Dapsone		E*

Case reports have described long courses of dapsone being used as monotherapy or in combination with surgery. It has also been used in combination with surgery or other antimicrobials such as cycloserine and ketoconazole for disseminated disease.

Systemic Mycoses: Blastomycosis, Coccidioidomycosis, Paracoccidioidomycosis, Histoplasmosis

Clinical Features

Blastomycosis is caused by inhalation of the conidia of the dimorphic fungus *Blastomyces dermatitidis*. The lungs are the most common site of disease, and infection may be asymptomatic or severe. Cutaneous disease results from hematogenous spread from the lungs, and occurs in up to one-fifth of patients. Verrucous lesions with irregular borders and microabscesses, ulcerative plaques with elevated borders, subcutaneous nodules, and cold abscesses may be seen [28].

Coccidioidomycosis is caused by the dimorphic fungi, *Coccidioides immitis*, or *Coccidioides posadasii*, which are endemic to arid regions. Patients of African or Filipino ancestry or those with a history of immunosuppression are at increased risk of infection. Cutaneous lesions are either due to disseminated disease via hematogenous spread from a pulmonary nidus or, less commonly, primary infection.

Organism-specific manifestations include nodules, pustular lesions, verrucous plaques, abscesses, and fistulae. Reactive cutaneous manifestations include erythema nodosum, erythema multiforme, an acute exanthem, Sweet's syndrome, and interstitial granulomatous dermatitis [29, 30].

Paracoccidioidomycosis is a systemic mycotic disease caused by the dimorphic fungus *Paracoccidioides brasiliensis*. It is endemic in Central and South America, where it is widely present as a soil saprophyte. Exposure is often occupational, and the main portal of entry is inhalation. Acute or subacute disease is most often seen in children and adolescents: features include lymphadenopathy, hepatosplenomegaly, fever, and bone marrow dysfunction, but skin and pulmonary involvement are uncommon. In contrast, the chronic form of the disease involves the lungs, mucosa, skin, lymph nodes, and adrenal glands. Mucosal and skin findings simulate those of leishmaniasis. Painful ulcers with ragged borders and petechiae are seen most often in the mouth or larynx. Ulcerative or verrucous nodules or plaques are seen in the skin [31, 32].

Histoplasma capsulatum is a dimorphic intracellular fungus found worldwide. Cutaneous lesions are present in up to 15 % of patients with disseminated histoplasmosis (Figs. 17.3 and 17.4). A variety of manifestations are seen, including nodules, plaques, ulcers, pustules, abscesses, erythroderma, cellulitis and panniculitis, and purpura [33].

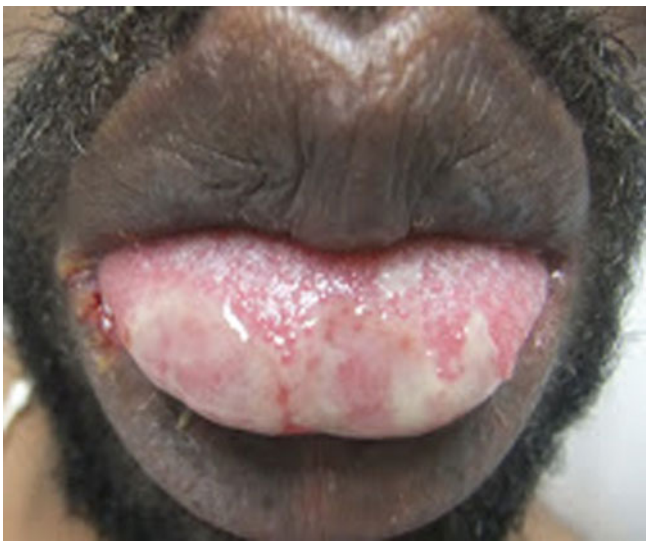

Fig. 17.3 Disseminated histoplasmosis. Erosive plaques of the oral mucosa in a patient with AIDS

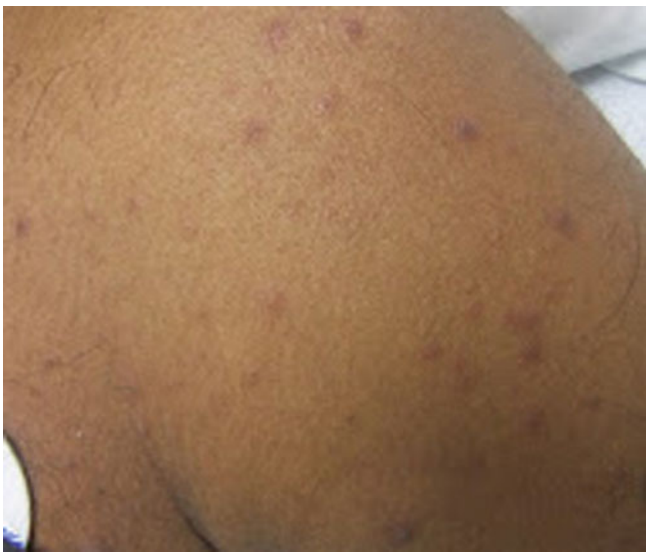

Fig. 17.4 Disseminated histoplasmosis. Violaceous papules distributed over the trunk and extremities in a patient with AIDS

Specific Investigations

For diagnosis
KOH
Fungal culture
Histopathology
Antigen detection (EIA)
Serology (EIA, immunodiffusion, complement fixation)
Skin testing (Coccidioidomycosis)
Imaging (Computed tomography or x-ray, for paracoccidioidomycosis)
For treatment
Repeat serology to monitor treatment response (paracoccidioidomycosis)
CBC, LFTs, lipid panel, metabolic panel (potassium, blood glucose), kidney function tests (BUN and creatinine), EKG

For blastomycosis, KOH preparation has a diagnostic yield of less than 50 %, despite multiple specimens. Histopathology demonstrates suppurative granulomas, but yeast forms may be difficult to visualize. When identified, they are 8–15 μm in diameter, with refractile walls and single broad-based buds. Definitive diagnosis requires fungal culture, and *B. dermatitidis* grows within 1–4 weeks [34]. Antigen detection assays for blastomycosis demonstrate overall sensitivity of 90 %, but specificity is less than 80 % due to cross-reactive antigens in histoplasmosis, paracoccidioidomycosis, and penicilliosis. Sensitivity is higher in urine than in serum. Given the lower specificity, culture is still the gold standard [35].

Cutaneous coccidioidomycosis should be diagnosed either by direct visualization of the organism or by culture. *Coccidioides* spp will grow on routine media, but may take more than 1 week to isolate. Spherules of *Coccidioides* are large, up to 70 μm in diameter, and can be detected with KOH prep or in histologic sections. Despite their size, organisms are often sparse, so multiple level sections should be examined by the dermatopathologist [36]. Overall, serologic tests for the detection of IgG and IgM antibodies against

Coccidioides are highly specific, but sensitivity is variable in early infection, as antibody production may not occur for weeks to months after illness onset. Immunodiffusion testing is the most specific serology available, while enzyme-linked immunoassay (EIA) has a sensitivity of 100 %. Thus, EIA should be used a screening test and immunodiffusion should be used for confirmation [37–39]. Complement fixation and tube precipitin-type assays are less accurate than these two newer methods. EIA for antigenuria is over 70 % sensitive, but also detects *Histoplasma* antigen. Skin testing for coccidioidomycosis is not recommended to diagnose current illness. Skin tests are positive for life, even in healthy patients with adequate prior treatment. In contrast, skin tests can be negative in infected patients with anergy. Thus, it is more useful as a prognostic test [40].

Paracoccidioidomycosis is diagnosed via direct microscopic visualization and/or by culturing *P. brasiliensis* from clinical specimens. KOH prep is positive in over 90 % of cases. Skin biopsy may be obtained in chronic disease, and demonstrates suppurative granulomas in most cases; *P. brasiliensis* is seen as a round or oval yeast 4–40 μm, with two or more narrow-necked budding cells (resembling a "pilot's wheel" or "Mickey mouse head"). Quantitative immunodiffusion is the most useful serologic test for diagnosis and for monitoring response to therapy, given its high sensitivity and specificity—up to 97 and 100 %, respectively. Cultures are positive in up to 80 % of cases, but can take up to 30 days to grow. In addition to imaging of affected areas (computed tomography or X-ray) to evaluate lymphadenopathy and pulmonary lesions, all patients with suspected paracoccidioidomycosis should have specimens submitted for direct microscopy, culture, and serology [41].

In a study of HIV-infected patients with disseminated histoplasmosis, skin biopsy with special stains for fungi (gomori methenamine silver or PAS) allowed direct visualization of *Histoplasma* in over 86 % of cases. The most common histologic pattern is a diffuse infiltrate of macrophages parasitized by yeast 2–3 μm in size. However, organisms may also be extracellular [42, 43]. EIA antigen testing in disseminated histoplasmosis demonstrates a sensitivity ranging from 75 % to 100 %, with increased sensitivity in serum compared to urine, and in immunocompromised patients. However, false-positive tests can occur in patients with blastomycosis or coccidioidomycosis [44]. PCR is positive in over 70 % of culture-positive tissue samples [45]. Immunodiffusion and complement fixation methods detect anti-*Histoplasma* antibodies in 70 % of immunocompromised and 90 % of immunocompetent patients with disseminated infection, but are often negative in patients on tumor necrosis-alpha inhibitor therapy [46]. Blood cultures are positive in 65 % of patients with disseminated histoplasmosis; tissue cultures from skin biopsy specimens can also be submitted.

Blastomycosis

Table 17.11 First-line therapies for blastomycosis [28, 47–52]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D/C*
Amphotericin B deoxycholate	0.7 mg/kg/day IV	D/B*
Itraconazole	2–5 mg/kg/dose po twice daily for 6 months, with maximum single dose 200 mg	B*

For patients with severe disseminated infection, amphotericin B should be used. Pooled retrospective data show that amphotericin B is up to 91 % effective for blastomycosis. Although liposomal amphotericin B does not have as much supportive data, it should be used when available, and is particularly preferred in cases with CNS involvement. Itraconazole may be used in patients with mild to moderate disease not involving the CNS. In an open study, 90 % of patients with blastomycosis demonstrated clinical response to treatment with 6 months of itraconazole, making this a first-line therapy for blastomycosis. Although ketoconazole has strong supportive trial data for its curative success in blastomycosis, its use can be associated with severe hepatotoxicity as well as infection relapse. Therefore it is not recommended for the treatment of any endemic mycosis, including blastomycosis.

Table 17.12 Second-line therapies for blastomycosis [53–56]

Medication	Dosing	Evidence level
Fluconazole	For 6 months	B*
Voriconazole	9 mg/kg/dose every 12 h IV with maximum daily dose 350 mg	D*
Posaconazole	12 mg/kg/day in 3 divided doses	D*

Fluconazole was 65 % effective at doses under or equal to 400 mg/day, but was successful in 87 % of patients treated with doses above 400 mg/day for 6 months in open studies. Voriconazole has been successful in small series for the treatment of refractory blastomycosis with CNS involvement. Posaconazole has also been used.

Coccidioidomycosis

Table 17.13 First-line therapies for coccidioidomycosis [57]

Medication	Dosing	Evidence level
Itraconazole	For 12 months	C/A*
Fluconazole	For 12 months	C/A*

A randomized, controlled trial demonstrated 72 % response rate for itraconazole and 57 % response rate for fluconazole after 12 months of treatment. While the majority of patients included were adults, there were a few cases in children as young as 6 years old.

Table 17.14 Second-line therapies for coccidioidomycosis [58, 59]

Medication	Dosing	Evidence level
Posaconazole	For 12 months	C*
Voriconazole	For 6 months	C*

Case series support the use of posaconazole, which has shown up to 73 % efficacy in refractory infections. Voriconazole demonstrated similar results for the treatment of resistant disease, albeit following a shorter treatment course.

Table 17.15 Third-line therapies for coccidioidomycosis [60]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D
Amphotericin B deoxycholate	0.7 mg/kg/day IV	D

Amphotericin B treatment is reserved for patients with rapidly worsening or CNS disease. Otherwise, treatment with oral azoles is preferred. Of note, in children with primary cutaneous disease and solitary lesions in whom disseminated disease has been excluded, observation or conservation excision, if feasible, can be considered.

Paracoccidioidomycosis

Table 17.16 First-line therapies for paracoccidioidomycosis [61–63]

Medication	Dosing	Evidence level
Itraconazole	5 mg/kg po once daily for 6–12 months	A

Oral antifungal therapy can be used in most (mild to moderate) cases of paracoccidioidomycosis. Among children and adults with paracoccidioidomycosis treated with itraconazole for an average of 6 months, 91 % of patients showed either marked improvement or resolution. In a small randomized trial, itraconazole, ketoconazole, and sulfadiazine were roughly equivalent in efficacy following treatment for at least 24 months. For patients with severe infection, including hypotension, respiratory failure, or severe malnutrition, therapy should be started with amphotericin B and then transitioned to oral therapy once improved.

Table 17.17 Second-line therapies for paracoccidioidomycosis [64, 65]

Medication	Dosing	Evidence level
Voriconazole	9 mg/kg/dose every 12 h IV with maximum daily dose 350 mg	B*
Trimethoprim/sulfamethoxazole (TMP-SMX)	10 mg/kg/day based on the TMP component, for at least 24 months	B*

Measured in terms of complete or partial treatment response, itraconazole was over 94 % effective compared to voriconazole, which was over 88 % effective. Voriconazole also has excellent in vitro activity against *P. brasiliensis*, but better data is available to support the use of itraconazole as a first-line therapy. In a separate open study, TMP-SMX was as effective as itraconazole, but treatment duration was four times as long with TMP-SMX.

Table 17.18 Third-line therapies for paracoccidioidomycosis [66]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D*
Amphotericin B deoxycholate	0.7 mg/kg/day IV Duration: 20–40 days or until clinical improvement then transition to oral therapy	D*

Therapy with amphotericin B is reserved for severe or refractory disease, and retrospective reviews have supported the use of this agent in this context.

Histoplasmosis

Table 17.19 First-line therapies for histoplasmosis [67–70]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3 mg/kg/day IV	A
Amphotericin B deoxycholate	1.0 mg/kg/day IV For 2 weeks or greater duration until clinical improvement, then step down to itraconazole	A
Itraconazole	2–5 mg/kg/dose po tid for 3 days then bid for 12 months, with maximum single dose 200 mg	B

In adult patients with AIDS and moderate-severe disseminated histoplasmosis, liposomal amphotericin B demonstrated better clinical success (88 %) than conventional amphotericin deoxycholate (64 %), in addition to improved survival and reduced nephrotoxicity; however, in children,

amphotericin B deoxycholate is usually well tolerated, and the lipid preparations are not preferred. If liposomal formulations are not available, then amphotericin B deoxycholate should be used for induction.

Itraconazole demonstrated 85 % clinical response in adult patients with AIDS and histoplasmosis. However, patients with moderate to severe disease responded poorly. Additionally, clearance of fungemia is slower with itraconazole than with amphotericin B. Therefore, itraconazole is reserved as induction therapy for patients with mild disease without fungemia, and for maintenance therapy after successful induction. Maintenance therapy should continue for 1 year, to reduce the risk of relapse.

Table 17.20 Second-line therapies for histoplasmosis [71–75]

Medication	Dosing	Evidence level
Fluconazole	3–6 mg/kg/day po or IV for maintenance therapy	B
Posaconazole	12 mg/kg/day in 3 divided doses	D*
Voriconazole	9 mg/kg/dose every 12 h IV with maximum daily dose 350 mg	D/C*

Itraconazole is superior to fluconazole in terms of clearance of fungemia as well as clinical response. Additionally, fluconazole is not as active as itraconazole against *H. capsulatum* in vitro. Although 74 % of patients responded to induction therapy with fluconazole in a large open study, almost half of patients demonstrated a relapse of their disease at 1 year while on maintenance therapy. Thus, fluconazole is reserved as a second-line therapy when amphotericin B and itraconazole cannot be tolerated. In a small case series, posaconazole has been effective for severe refractory infection as salvage therapy. Posaconazole demonstrates high *in vitro* activity against *H. capsulatum*. Voriconazole has also been used successfully as salvage therapy in disseminated histoplasmosis, but has inferior *in vitro* activity compared to itraconazole, and like posaconazole, has not been evaluated in a high-quality study.

Opportunistic Mycoses: Aspergillosis, Cryptococcosis, Fusariosis, Mucormycosis

Clinical Features

Aspergillus species are ubiquitous, and inhalation occurs often without sequelae in healthy hosts. In the setting of immunosuppression, most often during treatment for hematologic malignancies, or stem cell or solid organ transplantation, *A. fumigatus*, *A. flavus*, and *A. terreus* invade pulmonary or cutaneous tissue and may disseminate widely in the presence of angioinvasion. Neutropenia, high-dose corticosteroids, burns, and the neonatal period are also risk factors. Cutaneous aspergillosis may be primary, resulting from inoculation from trauma, or secondary, resulting from contiguous or hematogenous spread. Primary cutaneous aspergillosis may present as acute paronychia, necrotic plaques or nodules at the site of catheter insertion, or an erythematous edematous plaque. Secondary cutaneous aspergillosis may present with inflammatory or necrotic nodules, periorbital cellulitis, or ulcers [76, 77].

Cryptococcus neoformans and *Cryptococcus gattii* are encapsulated yeasts found worldwide in soil and bird guano that cause infections predominantly in patients with immunosuppression: HIV/AIDS, corticosteroids, organ transplantation, sarcoidosis, and malignancy. Following inhalation, meningoencephalitis, pulmonary infection, or disseminated disease may occur. Cutaneous lesions are seen in up to 15 % of patients with disseminated cryptococcosis. Plaques, purpura, ulcers, abscesses, cellulitis, and molluscum contagiosum-like lesions in patients with HIV may be seen [78]. Primary cutaneous disease is also possible following inoculation by minor trauma and, unlike secondary cutaneous lesions, may occur in immunocompetent hosts and is associated with favorable prognosis [79, 80].

Fusarium species are hyaline fungi present worldwide in soil, plant parts, and water. Superficial infections such as keratitis, onychomycosis, and intertrigo occur in immunocompetent hosts, while invasive infections occur only in patients with immunosuppression including neutropenia, hematologic malignancy, stem cell transplantation, and corticosteroid therapy. Sinusitis, pneumonia, fungemia, and dissemination can occur. Invasive infections occur via inhalation, direct inoculation, or spread from a superficial infection [81]. In this context, cutaneous lesions may be localized, as in cellulitis, or disseminated, with multiple necrotic painful lesions resembling those of ecthyma gangrenosum. Lesions at different stages of evolution, lymphangitic spread, target lesions, and blisters may be seen. Primary cutaneous disease in otherwise healthy hosts occurs at sites of burns or trauma, and presents with cellulitis, ulcers, verrucous nodules, and abscesses [82].

Rhizopus, *Mucor*, and *Rhizomucor* are genera of ubiquitous fungi that belong to the order Mucorales and cause most mucormycosis infections. Almost all infections occur in the context of immunosuppression, including poorly-controlled diabetes with ketoacidosis. Other risk factors include corticosteroid treatment, stem cell transplantation, hematologic malignancy, iron overload or deferoxamine treatment, HIV/AIDS, and burns. Inhalation of spores in susceptible individuals can lead to rhino-orbital-cerebral and pulmonary

infections, the most common forms of the disease [83]. In contrast, cutaneous disease is always due to direct inoculation, and may occur following minor iatrogenic trauma such as intravenous line placement. Rarely, primary cutaneous disease may occur in immunocompetent individuals. Cutaneous disease usually presents with single cellulitis-like or ecthyma-like lesion. As with other forms of mucormycosis, rapidly progressive tissue necrosis often ensues due to infarction resulting from angioinvasion. Dissemination from cutaneous lesions can also occur [84].

Specific Investigations

For diagnosis
Culture
Histopathology with GMS, PAS, mucicarmine, alcian blue, or India ink
EIA for galactomannan or beta-D-glucan polysaccharides
Cryptococcal antigen testing (EIA, latex agglutination, lateral flow assays)
PCR
Imaging (computed tomography)
For treatment
CBC, LFTs, lipid panel, metabolic panel (potassium, blood glucose), kidney function tests (BUN and creatinine), EKG
Flucytosine levels (for induction treatment in cryptococcosis)

Definitive diagnosis of aspergillosis requires culture in combination with the histopathologic demonstration of tissue invasion by hyphae. Organisms are observed in biopsy specimens as narrow (3–6 μm wide), septate, and hyaline hyphae, with branching at an acute angle (45°). GMS or PAS may be useful to recognize hyphae, which can be seen invading blood vessels of the dermis or subcutis. It is important to note that histopathology alone is very nonspecific, since other hyaline molds such as *Scedosporium* and *Fusarium* have the same appearance, although Mucorales can be distinguished morphologically. The polysaccharide galactomannan can be detected in serum by EIA, which has demonstrated up to 71 % sensitivity and 93 % specificity in cases of aspergillosis [85]. False-positive results may occur in patients with infections due to *Fusarium*, *Penicillium*, *or Histoplasma* species, or in patients who have received intravenous piperacillin-tazobactam. The beta-D-glucan assay is less specific (positive in candidiasis), but more sensitive than EIA for galactomannan; both tests are useful detecting invasive aspergillosis prior to the onset of clinical findings in susceptible patients [86]. PCR demonstrates sensitivity up to 84 %; when two PCR tests are positive, the specificity is 95 % [87]. Given that the lungs are the most common site in invasive aspergillosis, CT imaging is an important component of evaluation.

Cutaneous cryptococcosis is best diagnosed by visualization of encapsulated yeast forms (5–7 μm in diameter) and isolation in culture. Mucicarmine and alcian blue highlight the capsule, while Fontana-Masson highlights the cell wall. In contrast, india ink demonstrates the yeast as halos against a black background [87]. Depending on the host response, histopathology may demonstrate suppurative granulomas with fewer organisms, or abundant organisms with minimal inflammation (gelatinous). Various methods are available for the evaluation of disseminated or systemic infection: serum cryptococcal antigen, culture, imaging, and PCR. The sensitivity of serum cryptococcal antigen testing is over 94 % for CNS disease and 90 % for lung disease; the sensitivity of CSF testing is over 87–100 % with a specificity of 100 %. Of note, cryptococcal antigen testing cannot distinguish between *C. neoformans* and *C. gattii* and is not useful for monitoring response to treatment. Standard assays utilize EIA or latex agglutination, while lateral flow assays offer rapid screening and are also highly sensitive [88]. Blood, sputum, CSF, and tissue from skin biopsies can be cultured on standard media. Cerebral and lung CT should be performed if disease in those locations is suspected. PCR is sensitive and can distinguish between *C. neoformans* and *C. gattii*, but is reserved for use in cases where direct visualization and culture are negative [89].

Histopathology and culture are the best methods for diagnosis of cutaneous fusariosis. In tissue, *Fusarium* species appear similar to *Aspergillus* and *Scedosporium*: septate hyaline hyphae branching at acute angles (45°). Thus, the finding of an angioinvasive hyalohyphomycosis by histopathology is nonspecific, and definitive diagnosis requires culture. Cutaneous lesions are present in over 80 % of patients with disseminated disease, are the only source of diagnostic material over half of cases, and often precede fungemia. Thus skin biopsies should always be performed, and submitted for histology and culture, when this diagnosis is entertained. Fusarium grows rapidly on media that lack cycloheximide; blood cultures are positive in 40 % of patients with invasive disease [90]. Beta-D-glucan is released by *Fusarium* but also by *Candida*. Galactomannan antigen assay has a sensitivity of 83 % but a specificity of 67 %, since it is also positive in aspergillosis [91].

Given that attempted cultures of Mucorales often yield no growth, the need for rapid diagnosis, and the importance of empiric therapy, histopathologic identification may provide the only direct evidence of mucormycosis. Presumptive diagnosis is made based on the presence of broad (up to 15 μm in diamater) aseptate hyphae with irregular branching patterns. While speciation should not be attempted by the dermatopathologist, distinction from *Aspergillus* is helpful, if possible, as Mucorales are not sensitive to voriconazole, the treatment of choice for aspergillosis [92]. PCR may also be helpful when cultures are negative, and can be applied with high sensitivity to histologic specimens [93].

Aspergillosis

Table 17.21 First-line therapies for aspergillosis [94–97]

Medication	Dosing	Evidence level
Voriconazole	Loading dose: 6 mg/kg twice daily IV for 1 day	A
	Maintenance: 4 mg/kg daily IV or 9 mg/kg po twice daily for several months	

In a large open trial of patients with invasive aspergillosis, voriconazole treatment resulted in survival rate over 70 %, while amphotericin B deoxycholate achieved a survival rate of less than 60 %. Voriconazole is also the preferred treatment given the lower risk of severe adverse effects.

Table 17.22 Second-line therapies for aspergillosis [96–99]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg IV daily	B
Amphotericin B deoxycholate	1 mg/kg IV daily	B
Posaconazole	4 mg/kg po three times daily for several months	A
		B*
Isavuconazole (Isavuconazonium sulfate 372 mg = Isavuconazole 200 mg)	Loading dose: 200 mg TID × 2 days, then 200 mg daily	A*
	Maintenance: for several months	(No dosing guidelines for pediatric patients yet)

In patients who are intolerant of, or refractory to, therapy with voriconazole or amphotericin B, posaconazole is an alternative treatment; in one open trial, posaconazole was successful in 42 % of patients treated. Isavuconazole was non-inferior to voriconazole in a randomized, controlled trial of patients with invasive aspergillosis; however, this study also evaluated patients with infections due to filamentous molds other than *Aspergillus*.

Table 17.23 Third-line therapies for aspergillosis [100–106]

Medication	Dosing	Evidence level
Itraconazole	5–10 mg/kg/day in two divided doses daily for several months	B*
Echinocandins (concurrently with voriconazole):		
Caspofungin	70 mg/m2 on day 1 then 50–70 mg/m2 daily IV with maximum single dose 70 mg	B*
Anidulafungin	200 mg IV on day 1 then 100 mg IV daily (adolescents)	B*
Micafungin	1.5–3 mg/kg daily IV	B*

Itraconazole has demonstrated efficacy comparable to that of amphotericin B, but has inferior activity *in vitro* against *Aspergillus*. Caspofungin is approved for the treatment of aspergillosis, and has equivalent activity to that of the other echinocandins micafungin and anidulafungin. In patients intolerant of or refractory to standard treatment, overall clinical response to caspofungin was 45 %.

Echinocandins should not be used as monotherapy for aspergillosis, but can be used in combination with other treatments, including voriconazole. Several trials have produced data supportive of therapy combining voriconazole with echinocandins over monotherapy with voriconazole or amphotericin B alone. Similarly, the combination of liposomal amphotericin B and echinocandins has also demonstrated superiority to polyene therapy alone. However, retrospective data and *in vitro* studies do not support the use of amphotericin B in combination with azoles. In fact, azole therapy may be antagonistic toward the mechanism of action of amphotericin B.

Cryptococcosis

Management Strategies

Therapy regarding treatment of pediatric cryptococcosis is based on data from studies in adults. Given that most children with cutaneous cryptococcosis have underlying disseminated disease, the following treatment recommendations are best-suited for children with disseminated disease, but without a history of HIV or organ transplantation [107–109].

Table 17.24 First-line therapies for cryptococcosis [110–117]

Medication	Dosing	Evidence level
Liposomal amphotericin B	5 mg/kg/day IV	A*
OR		
Amphotericin B deoxycholate AND Flucytosine	1 mg/kg day IV	A*
	100 mg/kg/day po in 4 divided doses	
	Duration of induction: 2 weeks then transition to consolidation therapy	A*
Fluconazole	Consolidation: 10–12 mg/kg/day po for 8 weeks	A*
	Maintenance: 6 mg/kg/day po for 6–12 months	

Several high-quality studies of HIV-infected patients with cryptococcosis have demonstrated that higher dose amphotericin B in conjunction with flucytosine provides improved clinical response, sterilization of cerebrospinal fluid, and survival benefit compared to induction monotherapy with

lower dose amphotericin B and without flucytosine. Given the risk of myelosuppression with flucytosine induction, flucytosine peak levels should be maintained between 30 and 80 mcg/mL, and CBC should monitored regularly.

Consolidation and maintenance therapy should follow induction in order to reduce the risk of relapse. Comparative studies have shown that risk of relapse of cryptococcosis is 15–20 times greater without consolidation therapy. Fluconazole is preferred over itraconazole, due to it superior ability to sterilize the cerebrospinal fluid. Itraconazole is used for consolidation and maintenance when fluconazole cannot be tolerated.

Table 17.25 Second-line therapies for cryptococcosis [111, 114, 118, 119]

Medication	Dosing	Evidence level
Itraconazole	Consolidation: 2.5–5 mg/kg po 3 times daily for 3 days (maximum daily dose 600 mg) followed by 2.5–5 mg/kg po 1–2 times daily (maximum daily dose 400 mg) for at least 8 weeks	A*
	Maintenance: 5 mg/kg po daily for 6–12 months	
Voriconazole	Consolidation: 9 mg/kg po twice daily for 10–12 weeks with maximum dose 350 mg	B*
Posaconazole	Consolidation: 4 mg/kg po 3 times daily	B*

For patients with persistent or relapsed infection that is not susceptible to fluconazole, voriconazole or posaconazole may be used for salvage consolidation therapy. Several open trials have supported the use of these alternative agents in this context.

Fusariosis

This section focuses on invasive infection associated with cutaneous lesions, rather than primary superficial infections such as onychomycosis.

Table 17.26 First-line therapies for fusariosis [49, 111, 114, 118, 119, 120–123]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D/C*
	Duration: several weeks or until clinical improvement with immune reconstitution (resolution of neutropenia)	
Voriconazole	Loading dose: 6 mg/kg twice daily IV for 1 day	D/C*
	Maintenance: 4 mg/kg IV daily	
	Step-down therapy:	
	9 mg/kg po twice daily for several months, with maximum single dose 350 mg	

Retrospective data supports the use of liposomal amphotericin B for fusariosis, and this is the first-line preferred therapy for invasive or disseminated infection, demonstrating improvement or cure in 46%. Conventional amphotericin B deoxycholate should not be used for fusariosis, as it is associated with a higher case-fatality rate.

Voriconazole treatment was associated with up to 52% clinical response rate in retrospective studies. Voriconazole may be used as monotherapy, as step-down therapy following induction treatment, or as combination treatment with amphotericin B. Strictly speaking, retrospective data do not demonstrate a clear benefit for combination therapy, but survival of patients with invasive fusariosis has improved in recent years with an increased use of voriconazole and combination therapy.

Table 17.27 Second-line therapies for fusariosis [124, 125]

Medication	Dosing	Evidence level
Posaconazole	Step-down therapy:	C
	4 mg/kg po three times daily for several months	
Isavuconazole	Step-down therapy:	D*
	Po daily for several months	

In open studies, posaconazole salvage treatment was associated with a successful outcome in 48% of patients with fusariosis refractory to standard treatment. In small series and reports, isavuconazole has produced partial or complete response in patients with invasive fusariosis.

Mucormycosis

Primary cutaneous disease is associated with a favorable prognosis, and rarely disseminates. Prognosis is very poor in pulmonary or disseminated disease [92].

Table 17.28 First-line therapies for mucormycosis [126–130]

Medication	Dosing	Evidence level
Liposomal amphotericin B	5 mg/kg/day IV	D
Amphotericin B deoxycholate	1 mg/kg/day IV	D
	Duration of treatment: several weeks, or until favorable clinical response then transition to oral antifungal	
Posaconazole	Loading dose: IV twice daily for the first day	D/C*
	Maintenance: IV daily for several months	
Isavuconazole	Loading dose: po three times daily for the first 2 days	D
	Maintenance: po daily for several months	

The initial treatment of choice for mucormycosis is liposomal amphotericin B, based on retrospective data, historical experience, and in vitro data. The liposomal formulation of the drug is preferred if available. It is important to note that treatment should be initiated when this diagnosis is suspected, and not delayed until identification by culture or microscopy is available, given a twofold increase in mortality with delayed treatment. Additionally, when microscopy reveals an angioinvasive hyphal infection, amphotericin B should be selected for treatment until culture results are available, given that *Aspergillus* is sensitive to voriconazole while Mucorales are not. Surgical debridement should also be undertaken at the time of presumptive diagnosis.

Posaconazole and isavuconazole both have *in vitro* activity against Mucorales, and data supportive for their use as step-down therapy after induction or for salvage therapy in patients with disease refractory to treatment with amphotericin B. In a retrospective study of patients requiring salvage therapy, clinical response occurred in 60% of patients treated with posaconazole. Given issues with bioavailability of the oral solution formulation of posaconazole, only the IV formulation or extended-release oral tablets should be used. Isavuconazole demonstrated efficacy in a single-arm open study.

Table 17.29 Second-line therapies for mucormycosis [131–134]

Medication	Dosing	Evidence level
Caspofungin	(Not specified)	D/C*
Deferasirox	20 mg/kg/day for 14 days	C*

In a small retrospective study, patients with mucormycosis who received combination therapy with caspofungin and amphotericin B had better outcomes than those who received monotherapy alone. However, echinocandins do not have *in vitro* activity against Mucorales, and this data suggests utility as an adjunct treatment only.

Given that the iron chelator deferoxamine is a risk factor for mucormycosis, deferasirox has been used as adjunctive therapy to amphotericin B, but with mixed results. In a small open study, survival rate was high, but in a randomized, controlled trial, survival was poorer than with placebo.

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Viral Diseases and Exanthems of the Skin

18

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Herpes Simplex

Herpes simplex virus (HSV) includes HSV-1 and HSV-2 and is part of the larger herpesvirus family. HSV-1 is commonly associated with oral and labial lesions and HSV-2 with genital lesions, although this is not exclusive, and they are clinically indistinguishable. Infection is classified as primary or recurrent. Following primary infection, the virus establishes latency in the regional ganglia and can reactivate.

Herpetic Gingivostomatitis

Clinical Features

Gingivostomatitis is the most common manifestation of primary HSV during childhood. It is almost always caused by HSV-1. Symptoms generally begin with a prodrome of fever, malaise, irritability, and anorexia. The enanthem starts with gingival swelling and clusters of vesicles on an erythematous base on the palate, tongue, and gingivae. These lesions subsequently evolve into painful, shallow gray erosions and ulcerations. The lips and perioral skin can also be affected. The diagnosis is generally determined clinically, but can be confirmed by laboratory investigations. Viral culture, direct fluorescent antibody (DFA), and polymerase chain reaction (PCR) have varying sensitivities and specificities. PCR is currently regarded as both a rapid, sensitive, and specific method, and is increasingly used when available.

Healing time ranges from 1 to 3 weeks, depending upon the severity of the ulcerations. Other features include drooling, foul breath, and cervical and submandibular lymphadenopathy. Dehydration from refusal to drink, lip adhesions, and secondary bacteremia are potential complications.

Management Strategies

Pain control with acetaminophen and/or ibuprofen can help improve oral intake and irritability. Dehydration may result, and children should be appropriately hospitalized for intravenous hydration. Topical therapies such as a petroleum jelly to the lips prevent adhesions. Other topical treatments such as "magic mouthwash" (diphenhydramine, magnesia-alumina, Kaolin pectin, and/or viscous lidocaine) or topical anesthetics are not routinely recommended, given the lack of evidence of benefit in clinical trials, potential for harm (toxicity from systemic absorption, allergic reaction, suppression of the gag reflex) and difficult application (inability to "swish and spit," pain with manipulation of lesions) [1, 2]. Topical antivirals in immunocompetent children are also not recommended.

Oral acyclovir is recommended for immunocompetent children who are seen within 72–96 h of disease onset if they have significant discomfort and decreased oral intake (Table 18.1). Treatment has been found to decrease the duration of symptoms and may shorten the period of viral shedding [3, 4]. Please refer to the "Herpes Labialis" section for recommendations on recurrent and prophylactic management. Side effects of acyclovir include headache, nausea, vomiting, diarrhea, and renal failure, which are more likely if the child is dehydrated. There are no pediatric dosing guidelines for valacyclovir or famciclovir in individuals <18 years with gingivostomatitis.

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Table 18.1 Oral and intravenous antiviral dosing guidelines for herpes simplex virus in the immunocompetent host

Antiviral	Population	Route	Age/weight	Dosing
Acyclovir[a,b]	Eczema herpeticum	PO	All ages	15 mg/kg/day (400 mg maximum) in 3–5 divided doses for 10–14 days or until all mucocutaneous lesions are healed
Acyclovir[a,b]	Eczema herpeticum	IV	<12 years	30 mg/kg/day in 3 divided doses for 10–14 days or until all mucocutaneous lesions are healed
Acyclovir[a,b]	Eczema herpeticum	IV	≥12 years	15 mg/kg/day in 3 divided doses for 10–14 days or until all mucocutaneous lesions are healed
Acyclovir[a,b]	Mucocutaneous; first episode	PO	All ages	40–80 mg/kg/day in 3–4 divided doses for 5–10 days (maximum pediatric dose 1,000 mg/day)
Acyclovir[a,b]	Mucocutaneous; first episode	PO	≥12 years	1,000–1,200 mg/day in 3–5 divided doses for 7–10 days
Acyclovir[a,b]	Mucocutaneous; first episode	IV	All ages	15 mg/kg/day in 3 divided doses for 5–7 days
Acyclovir[a,b]	Mucocutaneous; recurrent	PO	≥12 years	1,000 mg/day in 5 divided doses for 5 days, or 1,600 mg/day in 2 divided doses for 5 days, or 2,400 mg/day in 3 divided doses for 2 days
Acyclovir[a,b]	Mucocutaneous chronic suppressive	PO	All ages	30 mg/kg/day in 3 divided doses for up to 12 months; maximum daily dose 1,000 mg/day; re-evaluate after 6–12 months
Acyclovir[a,b]	Mucocutaneous chronic suppressive	PO	≥12 years	800 mg/day in 2 divided doses for up to 1 year
Famciclovir[a,b]	Recurrent herpes labialis	PO	Adult	1,500 mg as a single dose
Famciclovir[a,b]	Genital herpes; first episode	PO	Adult	750 mg/day in 3 divided doses for 7–10 days
Famciclovir[a,b]	Genital herpes; recurrent	PO	Adult	2,000 mg/day in 2 divided doses for 1 day
Famciclovir[a,b]	Genital herpes; chronic suppression	PO	Adult	500 mg/day in 2 divided doses for up to 1 year, then reassess for recurrence
Valacyclovir[a,b]	Recurrent herpes labialis	PO	>12 years	4,000 mg/day in 2 divided doses for 1 day
Valacyclovir[a,b]	Genital herpes; first episode	PO	Adult	2,000 mg/day in 2 divided doses for 10 days
Valacyclovir[a,b]	Genital herpes; recurrent	PO	Adult	1,000 mg/day in 2 divided doses for 3 days
Valacyclovir[a,b]	Genital herpes; chronic suppression	PO	Adult	500 mg daily for <10 outbreaks/year or 1,000 mg daily for ≥10 outbreaks/year, then reassess for recurrence

Dosing guidelines derived from: [207, 208]

[a]Dosing should be decreased in patients with impaired renal function

[b]Refer to *AAP Red Book* and *Harriet Lane* as referenced above for further details regarding administration and side effects

Immunocompromised children should also be treated with oral or intravenous acyclovir depending upon the severity of the case (Table 18.2) [5, 6]. Topical acyclovir may accelerate healing of lesions in immunocompromised children (Table 18.3). Acyclovir resistance can occur and foscarnet is a potential treatment [7].

Table 18.2 Antiviral dosing guidelines for herpes simplex virus in the immunocompromised host

Antiviral	Population	Route	Age	Dosing
Acyclovir[a,b]	Mucocutaneous initial infection	PO	≥2 years	1,000 mg/day in 3–5 divided doses for 7–14 days; maximum dose for child 80 mg/kg/day
Acyclovir[a,b]	Mucocutaneous initial infection	IV	All ages	30 mg/kg per day in 3 divided doses for 7–14 days
Acyclovir[a,b]	Mucocutaneous chronic suppresion	PO	≥2 years	600–1,000 mg/day in 3–5 divided doses during period of risk
Acyclovir[a,b]	Mucocutaneous chronic suppresion	IV	All ages	15 mg/kg in 3 divided doses during period of risk
Famciclovir[a,b]	Herpes labialis; recurrent in setting of HIV infection	PO	Adult	1,000 mg/day in 2 divided doses for 7 days
Famciclovir[a,b]	Genital herpes; recurrent in setting of HIV infection	PO	Adult	1,000 mg/day in 2 divided doses for 7 days
Famciclovir[a,b]	Genital herpes; Chronic suppression in setting of HIV infection	PO	Adult	1,000 mg/day in 2 divided doses during period of risk
Foscarnet[a,b]	Infection resistant to acyclovir	IV	Adult	80–120 mg/kg per day in 2–3 divided doses until infection resolves
Valacyclovir[a,b]	Genital herpes; recurrent in setting of HIV infection	PO	Adult	2,000 mg/day in 2 divided doses until all mucocutaneous lesions are healed
Valacyclovir[a,b]	Genital herpes; chronic suppression in setting of HIV infection	PO	Adult	1,000 mg/day in 2 divided doses during period of risk

Dosing guidelines derived from: [207, 208]
[a]Dosing should be decreased in patients with impaired renal function
[b]Refer to *AAP Red Book* and *Harriet Lane* as referenced above for further details regarding administration and side effects

Table 18.3 Topical antiviral dosing guidelines for herpes simplex virus

Antiviral	Population	Route	Age	Dosing
Acyclovir	Recurrent herpes labialis	5% topical cream	≥12 years	Apply 5 times daily
Acyclovir	Initial genital herpes; localized HSV	5% ointment	Adult	Apply 6 times daily
Docosanol	Recurrent herpes labialis	10% cream	≥12 years	Apply 5 times daily
Ganciclovir	Ocular herpes	0.15% gel	≥2 years	Apply 1 drop 5 times daily until epithelial healing occurs, then 3 times daily for 1 week
Penciclovir	Recurrent herpes labialis	1% cream	≥12 years	Apply every 2 h while awake
Trifluridine	Ocular herpes	1% solution	≥6 years	Instill 1 drop every 2 h for a total of 8–9 doses daily for 1–2 weeks

Approved indications and regimens compiled from studies listed above and Lexicomp

Specific Investigations Recommended

For diagnosis
Viral culture
Polymerase chain reaction (PCR)
Direct fluorescent antibody (DFA)
Tzanck smear
Serologic testing

Table 18.4 First line therapies

Supportive care	A [1, 2]
Oral acyclovir	A [3, 4]

Table 18.5 Second line therapies

Intravenous acyclovir	A [5,6]

Table 18.6 Third line therapies

Foscarnet	E [7]

Herpes Labialis

Clinical Features

Herpes labialis generally refers to HSV infection on the lips and is the most common form of recurrent herpes infection. Primary infection may be subclinical or appear as gingivostomatitis (refer to above section "Herpetic Gingivostomatisis"). Symptoms typically begin with a prodrome of tingling, burning, or itching. Around 1–2 days later, a localized cluster of small vesicles on an erythematous base appear. As the vesicles rupture, they form painful erosions, which crust over in about 8 days. Other areas of the face may be involved (Fig. 18.1). Immunosuppressed children can develop severe, chronic disease, which may become resistant to antivirals. The diagnosis is generally determined clinically, but can be confirmed by laboratory investigations. The sensitivity of these tests is generally regarded as lower with recurrent episodes since viral shedding is intermittent and declines rapidly as lesions heal.

Management Strategies

Herpes labialis may self-resolve and require no intervention. Symptomatic treatment includes oral analgesics, petroleum jelly, and topical antibiotics to decrease risk of bacterial superinfection. As with herpes gingivostomatitis, other topical treatments such as "magic mouthwash" or topical anesthetics are not routinely recommended in children. Zilactin, a nonprescription topical medication containing lidocaine and hydroxypropyl cellulose, can protect lesions from trauma and irritants, but studies regarding its efficacy and safety in young children are lacking. Topical benzocaine may cause methemoglobinemia and should not be used in children younger than 2 years.

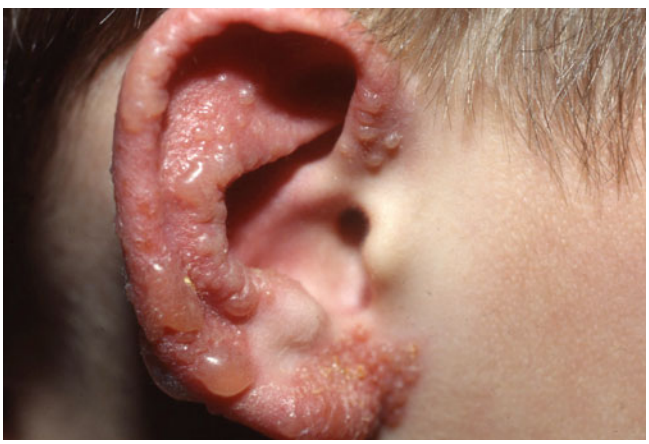

Fig. 18.1 Clustered vesicles of HSV-1 on the ear

For recurrent herpes labialis, episodic therapy with antivirals may be beneficial if initiated at first sign of symptoms. Topical antivirals, such as acyclovir, penciclovir, and docosanol can modestly decrease the time to lesion healing, although are not approved in children <12 years (Table 18.3) [8–10]. Oral acyclovir may provide greater benefit than topical antivirals if treatment is initiated during the prodromal stage; benefits include decreased duration of symptoms and time to healing (Table 18.1) [11, 12]. For those ≥18 years with recurrent disease, valacyclovir or famiciclovir can be considered [13, 14]. There are no clinical trials directly comparing antiviral medications. For immunocompromised children, oral acyclovir can be considered; however, those with spreading or persistent infection should be treated with intravenous acyclovir (Table 18.2) [15–17].

Although there are no studies for prophylactic therapy in children, antivirals should be considered for frequent recurrences, immunosupression, and serious systemic complications such as erythema multiforme and eczema herpeticum (Table 18.1 and 18.2) [18, 19]. To reduce frequency and severity, antiviral treatment should be continuous for several weeks to months. After approximately 6 months to 1 year of treatment, acyclovir should be discontinued and the recurrence rate re-evaluated. UV protection may also help reduce viral reactivation [20].

Specific Investigations Recommended

For diagnosis
Viral culture
Polymerase chain reaction
Direct fluorescent antibody
Tzanck smear

Table 18.7 First line therapies

Supportive care	A [2]
Oral acyclovir	A [11, 12]
Topical acyclovir	A* [9]
Topical penciclovir	A* [10]
Topical docosanol	A* [8]

Table 18.8 Second line therapies

Valacyclovir	A [14]
Famciclovir	A* [13]

Table 18.9 Third line therapies

Intravenous acyclovir	A [16,17]
Foscarnet	E [15]

Table 18.10 Prophylactic treatment

Sunscreen	A* [20]
Oral acyclovir	A* [19]
Valacyclovir	A* [18]

Genital Herpes

Clinical Features

Genital herpes is a widespread sexually transmitted disease primarily caused by HSV-2, but HSV-1 is increasing in prevalence, especially amongst young adults. Primary genital herpes demonstrates painful vesicles on an erythematous base 2–20 days after exposure. Distribution includes the vulva, labia, vagina, perineum, penile shaft, glans penis, urethra, and less often the scrotum; extragenital involvement may also be seen. Painful erosions or ulcers occur following rupture of vesicles and can be associated with burning, pruritus, vaginal or urethral discharge, and regional lymphadenopathy. Influenza-like systemic symptoms are also common and include fever, malaise, myalgias, and headache. Symptoms generally improve over 5–7 days, and cutaneous lesions heal over 2–4 weeks. Aseptic meningitis and sacral radiculomyelitis are potential complications.

The diagnosis is generally determined clinically, but can be confirmed by laboratory investigations. Viral culture, direct fluorescent antibody (DFA) and Polymerase chain reaction (PCR) have varying sensitivities and specificities. PCR is currently regarded as both a rapid, sensitive, and specific method and is increasingly used when available. The diagnosis of genital HSV in a child should prompt question of sexual abuse.

Recurrent genital herpes can be trigged by menstruation, febrile illness, or stress. Outbreaks are typically preceded by a prodrome of pain, itching, and paresthesia. Compared to primary genital herpes, recurrent lesions are less severe, with fewer vesicles. Shedding of the virus can occur even without active lesions (subclinical shedding) and increases with frequency of symptomatic recurrences.

Management Strategies

The treatment of genital herpes includes supportive care and antivirals to promote rapid healing, decrease recurrences, decrease viral shedding, and minimize complications [21, 22]. There is no curative therapy.

For primary genital infections, supportive care includes analgesics and Sitz baths. Systemic antiviral therapy should be initiated promptly, even before laboratory confirmation. Antiviral dosing for immunocompetent patients is provided in Table 18.1. Oral acyclovir initiated within 6 days of onset of disease shortens the duration of illness and viral shedding by 3–5 days [23]. Acyclovir is the only antiviral approved for genital herpes in children, but famciclovir and valacyclovir are well studied in adults; they do not seem to be more effective than acyclovir, but allow for less frequent dosing [24, 25]. Topical acyclovir should not be used, as it is less effective than oral acyclovir.

Antivirals can also be used for recurrent episodes (Table 18.1) and have been shown to decrease duration of lesions and viral shedding and increase proportion of aborted episodes [26–29]. The prescription should instruct patients to initiate treatment immediately when symptoms begin.

Prophylactic therapy has not been studied in children, but in adults, daily oral antiviral suppressive therapy is effective in decreasing the frequency of symptomatic recurrences and improving quality of life [30–32]. Thus, children with frequent recurrences may benefit from continuous oral acyclovir, and a reasonable starting dose in provided in Table 18.1. After approximately 6 months to 1 year of treatment, acyclovir should be discontinued and the recurrence rate re-evaluated.

Immunocompromised patients have more frequent recurrences, develop more severe lesions, and require longer treatment periods (Table 18.2). Intravenous acyclovir should be administered for severe or disseminated cases. Long-term suppressive therapy has been used, although may lead to selection of resistant strains of the virus. In acyclovir-resistant cases, intravenous foscarnet may be required [33].

Evaluation for other sexually transmitted diseases should be considered, and potential sexual abuse cases must be referred to the appropriate investigative agencies. The recurrent nature of the disease can have significant psychological effects on patients; education about the risk of transmitting genital herpes and safe sex practices should be provided [34].

Specific Investigations Recommended

For diagnosis
Viral culture
Polymerase chain reaction
Direct fluorescent antibody
Tzanck smear
Serologic testing
Skin biopsy of atypical lesion

Table 18.11 First line therapies

Oral acyclovir	A* [23, 27, 29]

Table 18.12 Second line therapies

Valacyclovir	A* [24, 28]
Famciclovir	A* [25, 26]

Table 18.13 Third line therapies

Intravenous acyclovir	E [21, 22]
Foscarnet	E [33]

Table 18.14 Prophylactic treatment

Condoms	A* [34]
Oral acyclovir	A* [31, 32]
Valacyclovir	A* [30, 31]

Ocular Herpes Infection

Clinical Features

Ocular herpes infection can result in numerous complications including blepharitis, conjunctivitis, keratitis, uveitis, and acute retinal necrosis. HSV keratitis typically appears as an infection of the superficial layer of the cornea (epithelial keratitis) while deeper involvement of the cornea (stromal keratitis), uvea, and retina are associated with a greater risk of visual loss.

HSV keratitis has an acute onset with pain, photophobia, blurred vision, and watery discharge. Physical exam is notable for conjunctival injection, decreased corneal sensation, and characteristic dendritic lesions of the cornea. The eyelid may also be involved, leading to blepharitis (Figs. 18.2 and 18.3). Infections may be unilateral or bilateral, and bacterial superinfection is not uncommon. The diagnosis is generally determined clinically, but can be confirmed by laboratory investigations. Ocular samples should be taken from scrapings of epithelial lesions.

Children typically have more severe cases then adults, with higher levels of inflammation, risk of amblyobia, and estimated recurrence rates of 50 %. Recurrent HSV keratitis continues to be a leading cause of corneal blindness in the United States.

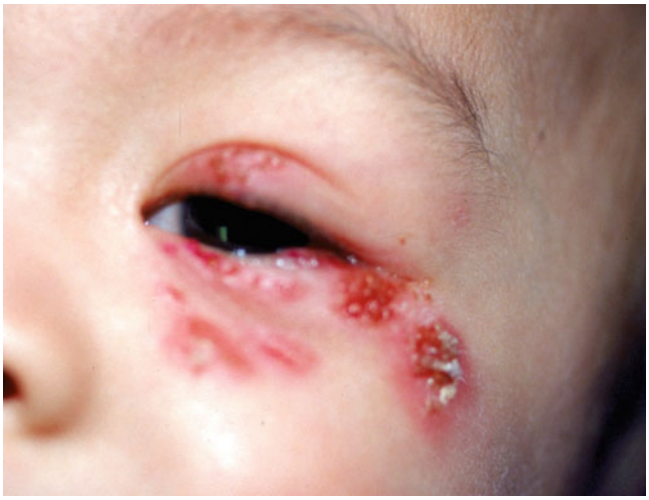

Fig. 18.2 Grouped erosions in a periocular distribution in a patient with recurrent herpes keratitis

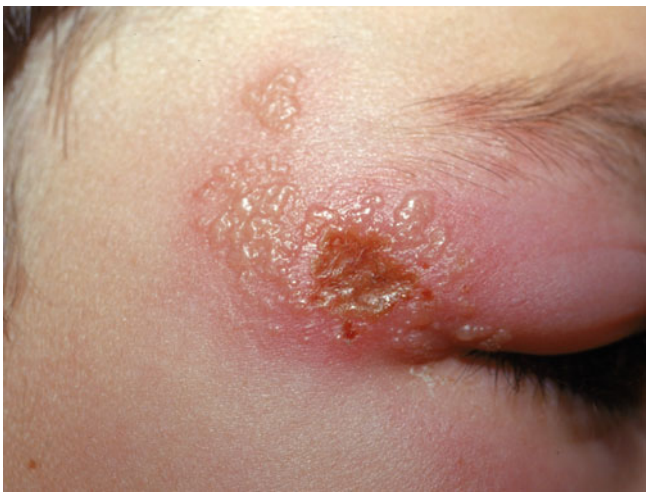

Fig. 18.3 Clustered vesicles with central erosion and dramatic eyelid edema from HSV

Management Strategies

Management depends upon whether the infection is primary or recurrent and the location of the infection within the eye [35]. From a dermatologist's perspective, the most important action is to promptly consult an ophthalmologist, especially if there is facial involvement in a child with disseminated mucocutaneous herpes.

For primary infection involving the superficial layer of the cornea (epithelial keratitis), topical antiviral therapy was previously the standard of care, but randomized trials in adults have also shown oral antivirals to be equally effective [36, 37]. Oral antivirals may be superior, given difficulty of topical antiviral application with small children. Topical ganciclovir 0.15 % gel and trifluridine 1 % drops are potential antiviral treatments (Table 18.3). Oral acyclovir has been reported to be effective in children with ocular herpes, although the study did not evaluate if oral acyclovir should be used in lieu of topical antiviral medications [36]. Topical glucocorticoids should be avoided as they can exacerbate epithelial lesions.

For deeper involvement of the cornea (stromal keratitis), a combination of topical corticosteroids and antivirals is currently the standard of care [38]. The addition of oral acyclovir to these two treatments has not been shown to provide additional benefit. Topical cyclosporine may be considered for those non-responsive to topical prednisolone, although this has only been studied in adults [39].

The most important management issue in HSV ocular infection is prevention of recurrences, as these can lead to corneal scarring and blindness. Suppressive acyclovir has been successful and well tolerated in children and should be considered, given the high rate of recurrence.

Specific Investigations Recommended

For diagnosis
Viral culture
Polymerase chain reaction
Direct fluorescent antibody
Enzyme-linked virus inducible system (ELVIS)

Table 18.15 First line therapies

Epithelial Keratitis	
Topical ganciclovir	A* [37]
Topical trifluridine	A* [37]
Oral acyclovir	A* [36, 37]
Stromal Keratitis	
Topical corticosteroids	A* [38]
Topical trifluridine	D [38]
Oral acyclovir	D [35]

Table 18.16 Second line therapies

Topical cyclosporine	E* [39]

Eczema Herpeticum

Clinical Features

Eczema herpeticum or Kaposi's varicelliform eruption is a severe, disseminated HSV infection in patients with atopic dermatitis or other chronic skin conditions such as pemphigus, Darier disease, or burns. Patients typically have abrupt onset of fever, malaise, lymphadenopathy, and widespread monomorphic vesicles and erosions. Often "punched-out" erosions with hemorrhagic crust are more evident than intact vesicles (Fig. 18.4). Lesions are most prominent in areas of chronic skin disease, but also favor the head, neck, and trunk.

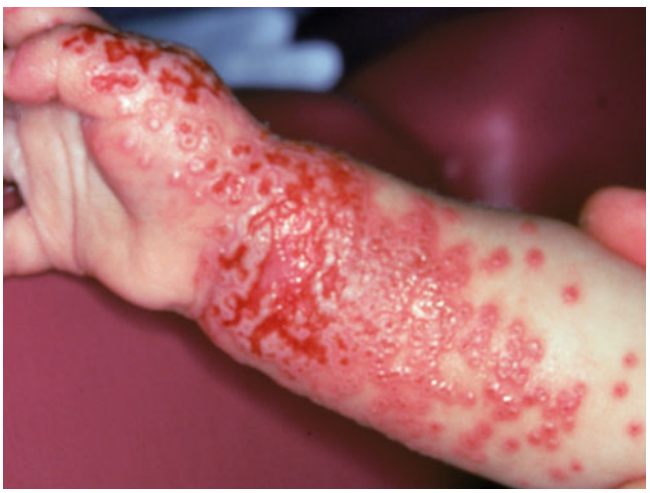

Fig. 18.4 Punched out erosions in the setting of atopic dermatitis representing eczema herpeticum

If eczema herpeticum is suspected, treatment should be initiated while awaiting diagnostic results such as viral culture, DFA, and PCR. Complications include ocular involvement, secondary bacterial super infections (*Staphylococcus aureus* and/or group A streptococci), fluid loss, and viremia.

Management Strategies

The mainstay of treatment is systemic antiviral therapy (Table 18.1) [40, 41]. For most pediatric patients, hospital admission and intravenous acyclovir is the standard of care [42]. There are limited studies available evaluating acyclovir therapy, but one large multicenter retrospective cohort study showed that delayed acyclovir initiation was associated with increased hospital length of stay [43].

Other treatment considerations include intravenous hydration with attention to electrolyte balance, pain control, and antibiotic therapy for secondary bacterial infection [44]. Empiric antibiotic therapy has not been associated with shorter hospital length of stay, but it is critical to recognize systemic bacterial illness early [44]. Topical therapy includes bland emollients and topical corticosteroids as needed [45]. Facial involvement necessitates an ophthalmologic evaluation to monitor for ocular involvement.

Specific Investigations Recommended

For diagnosis
Viral culture
Polymerase chain reaction
Direct fluorescent antibody
Tzanck smear
Skin biopsy of atypical lesion
Serologic testing

Table 18.17 First line therapies

Intravenous acyclovir	D [40, 42, 43]
Oral acyclovir	D [40, 41]
Topical corticosteroids	D [45]

Table 18.18 Second line therapies

Oral antibiotics	D [44]
Intravenous antibiotics	D [44]

Herpetic Whitlow

Clinical Features

Herpetic whitlow is a deep, painful, vesicular or bullous eruption with surrounding erythema involving the pulp of the distal fingertip(s) (Fig. 18.5). It can be a complication of

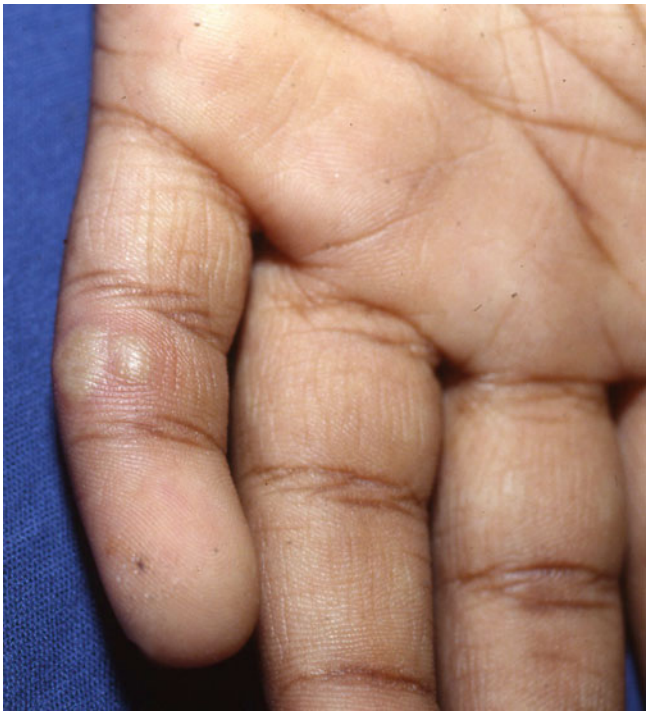

Fig. 18.5 Tense grouped vesicles in a patient with herpetic whitlow

primary oral or genital herpes. The prodrome includes a tingling and burning sensation of the finger(s) and influenza-like symptoms including fever and localized lymphadenopathy. Blister fluid is initially clear, but then appears purulent, mimicking a bacterial infection. Diagnostic studies such as viral culture, PCR, DFA, and Tzanck should be considered to confirm diagnosis. If untreated, symptoms generally spontaneously resolve in 1–3 weeks, but can recur.

Management Strategies

Treatment is typically supportive including anti-inflammatory agents, immobilization, and dry dressings to prevent transmission [46].

Oral antiviral therapy has been accepted as an effective means of reducing the duration of symptoms in primary infection and recurrent episodes (Table 18.1) [47]. Intravenous acyclovir is recommended for immunocompromised patients or those with severe infections (Table 18.2). Topical acyclovir is not believed to be helpful, and surgical intervention should be avoided. Prophylactic oral acyclovir may be effective in suppressing recurrent infections.

Specific Investigations Recommended

For diagnosis
Viral culture
Polymerase chain reaction
Direct fluorescent antibody
Tzanck smear
Skin biopsy of atypical lesion

Table 18.19 First line therapies

Supportive care	D [46]
Oral acyclovir	D [47]

Herpes Gladiatorum

Clinical Features

Herpes gladiatorum is the term used when herpes simplex virus is transmitted during contact sports such as wrestling and rugby. It is characterized by widespread grouped vesicles on an erythematous base, and typically occurs on the head, neck, and upper extremities. Because lesions may become abraded during competition, they may have an atypical appearance. Systemic symptoms include fever, malaise, headache, and regional lymphadenopathy. Diagnosis may be made clinically, but when possible, laboratory confirmation should be performed. There is a general consensus in the literature that herpes gladiatorum is misdiagnosed, and diagnostic tests are underutilized.

Management Strategies

Herpes gladiatorum can be treated with oral antivirals. Depending upon the age of the patient and immunosupression status, antivirals include acyclovir, valacyclovir, and famiciclovir (Tables 18.1 and 18.2). No clinical studies have been performed on patients with primary herpes gladiatorum. Return-to-play criteria has been published by the National Collegiate Athletic Association and National Federation of State High School Associations Sports Medicine Advisory Committee and is summarized in Table 18.20 [48–50].

Recurrent infections should also be treated with antivirals (Tables 15.1 and 15.2). In a double-blind, placebo-controlled prospective study of 20 wrestlers and coaches with confirmed recurrent HSV, a 7-day regimen of valacyclovir 500 mg twice daily reduced the length of time until clinical clearance [51].

Table 18.20 Guidelines for return to competition for wrestlers with herpes gladiatorum

	National Collegiate Athletic Association	National Federation of State High School Associations
Primary infection	(1) Skin lesions must be surmounted by a firm adherent crust at competition time and have no evidence of secondary bacterial infection	(1) All lesions must be scabbed over with no oozing or discharge and no new lesions should have occurred in the preceding 48 h
	(2) Wrestlers must have developed no new blisters for 72 h before the examination	(2) Wrestlers should be treated and not allowed to compete for a minimum of 10 days. If general body signs and symptoms like fever and swollen lymph nodes are present, that minimum period of treatment should be extended to 14 days
	(3) Wrestlers must be free of signs and symptoms like fever, malaise, and swollen lymph nodes	
	(4) Wrestlers must have been on appropriate dosage of systemic antiviral therapy for at least 120 h before and at the time of the competition	
Recurrent infection	(1) Skin lesions must be surmounted by a firm adherent crust at competition time, and have no evidence of secondary bacterial infection	(1) All lesions must be scabbed over with no oozing or discharge and no new lesions should have occurred in the preceding 48 h
	(2) Wrestlers require a minimum of 120 h of oral anti-viral treatment, again so long as no new lesions have developed and all lesions are scabbed over	(2) Wrestlers require a minimum of 120 h or five full days of oral anti-viral treatment, again so long as no new lesions have developed and all lesions are scabbed over
	(3) Active herpetic infections shall not be covered to allow participation	

[50, 51]

Suppressive antiviral therapy should be limited to athletes with a history of recurrent herpes to reduce the risk of reactivation during the sport season (Table 18.1). Valacyclovir 500 mg to 1 g daily has also been studied in wrestlers ages 13–31 and appears to suppress recurrent outbreaks [52].

Specific Investigations Recommended

For diagnosis
Viral culture
Polymerase chain reaction
Direct fluorescent antibody
Tzanck smear
Skin biopsy of atypical lesion
Serologic testing

Table 18.21 First line therapies

Oral acyclovir	E [48]
Valacyclovir	A [51, 52]
Famciclovir	E [48]

Varicella Zoster Virus

Clinical Features

Varicella or chickenpox is caused by varicella zoster virus (VZV), a member of the herpesvirus family. It is a highly communicable disease transmitted by aerosolized droplets or direct person-to-person contact. The typical incubation period is 10–14 days and it is infectious from 48 h prior to the onset of rash until skin lesions have crusted over.

Clinical features include a prodrome of fever, chills, malaise, headache, and arthralgias, with subsequent development of a generalized vesicular exanthem within 24–48 h. These pruritic vesicles initially appear on the scalp, face, and trunk, and then spread to the extremities (Figs. 18.6 and 18.7). New vesicle formation generally stops within 4 days, and most lesions have fully crusted by day 6. "Breakthrough varicella" can occur after a single dose of the varicella vaccine and subsequent exposure to VZV. Clinical features include absent to low fever, <50 macules and papules, and a shorter duration of illness.

Varicella tends to be more severe in infants, adolescents, and the immunocompromised. Potential complications include secondary bacterial superinfection of skin lesions, pneumonia, nervous system involvement (encephalitis, cerebellar ataxia, aseptic meningitis), thrombocytopenia, glomerulonephritis, and hepatitis. Reye syndrome was a common complication before the association with salicylates was understood. Herpes zoster (shingles) represents delayed sequelae of varicella and will be discussed in a subsequent section.

Management Strategies

In the United States, a two-dose live, attenuated vaccine program is recommended for all healthy individuals 12 months of age or older without evidence of immunity [53]. For children 12 months to 12 years, a first dose is recommended at age 12–15 months and a second dose at age 4–6 years. The second dose may be administered at an earlier age, provided the time interval between the first and second dose is >3 months. For adolescents >13 years without evidence of

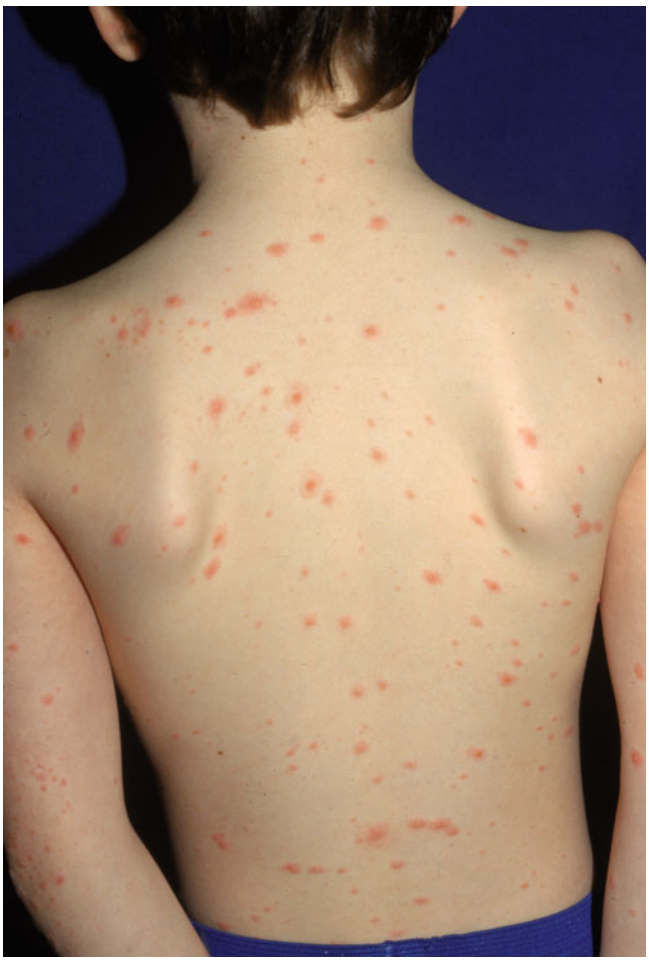

Fig. 18.6 Numerous truncal edematous papules in a child with varicella zoster

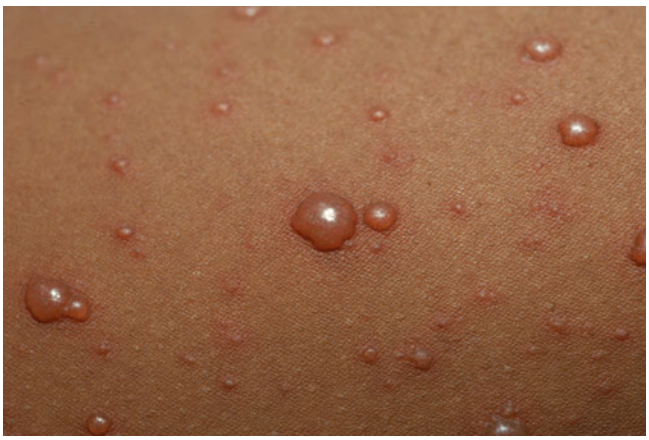

Fig. 18.7 Characteristic "dewdrop on a rose petal" demonstrating a vesicle on an erythematous base seen with chickenpox

varicella immunity, two doses of the vaccine should be administered at least 4–8 weeks apart.

In healthy children below the age of 12 years, treatment is usually symptomatic for itch, pain, and prevention of secondary superinfection. This includes antihistamines, acetaminophen, and topical care including cool compresses, oatmeal baths, calamine lotion, menthol-camphor (Sarna) lotion, and mupirocin. Fingernails should be clipped to avoid excoriation and bacterial superinfection. Salicylates should be avoided given the risk of Reye syndrome. Antiviral therapy is not recommended for routine use in otherwise healthy children [54].

According to the American Academy of Pediatrics, oral acyclovir or valacyclovir should be considered in (1) children older than 12 years without evidence of immunity, and in children of any age with (2) chronic cutaneous or cardiopulmonary disorders, (3) on long-term salicylate therapy, (4) on short, intermittent systemic, or aerosolized courses of corticosteroids, and (5) secondary infections by a household member, as the disease is usually more severe than the index case [55, 56]. Table 18.22 contains antiviral dosing recommendations [57]. Antivirals have a limited window of opportunity to affect clinical course, and should be started within 24 h of the rash developing.

Intravenous acyclovir is recommended for immunocompromised children, including those treated with chronic steroids [58, 59]. Therapy initiated within 24 h of rash onset maximizes efficacy, but individuals should be treated even if this time window has passed. Some experts have used valacyclovir in selected immunocompromised patients believed to be at lower risk of developing severe varicella, but this should be reviewed on a case-by-case basis. Foscarnet should be used to treat infections caused by acyclovir-resistant VZV strains, which are typically limited to immunocompromised hosts (Table 18.22) [60].

In the setting of VZV exposure, immunization may prevent or modify disease if given to otherwise healthy children within 72–120 h after varicella exposure [61]. Acyclovir is not recommended for prophylactic use in either the immunocompetent or immunocompromised. Varicella-Zoster Immune Globulin (VZIG; 125 units/10 kg, maximum 625 units) is recommended in immunocompromised children with no history of varicella and/or negative serologic testing as soon as possible within 10 days of exposure [62]. If VZIG is not available, IVIG (400 mg/kg administered once) is a potential alternative [63]. Immune globulin preparations are not effective once symptoms are present. Potential varicella exposures include an infected member of the household, playmate (face-to-face indoor contact), hospital roommate, or healthcare worker. Varicella can be contracted from those with zoster, but requires intimate contact (touch or hugging) before the lesions are crusted [55].

In neonates, varicella infection has a higher case-fatality rate when the mother develops varicella from 5 days before to 2 days after delivery. This is secondary to immature neonatal cellular immunity and insufficient development and transplacental transfer of VZV-specific maternal immuno-

Table 18.22 Varicella anti-viral dosing recommendations for immunocompetent and immunocompromised

Antiviral	Population	Route	Age	Dosing
Acyclovir[a,b]	Varicella in immunocompetent host	Oral	≥2 years	80 mg/kg per day in 4 divided doses for 5 days; maximum dose 3,200 mg/day
Acyclovir[a,b]	Varicella in immunocompetent host requiring hospitalization	IV	≥2 years	30 mg/kg/day in 3 divided doses for 7–10 days; maximum dose 3,200 mg/day
Acyclovir[a,b]	Varicella in immunocompromised host	IV	<1 year	30 mg/kg per day in 3 divided doses for 7–10 days
Foscarnet[a,b]	VZV infection resistant to acyclovir	IV	Adult dose	120 mg/kg/day, divided every 8 h, up to 3 weeks
Valacyclovir[a,b]	Varicella in immunocompetent or immunocompromised host	Oral	2 to <18 years	20 mg/kg per dose 3 times daily for 5 days, not to exceed 1 g per dose 3 times daily

Dosing guidelines derived from: [208]
[a]Dosing should be decreased in patients with impaired renal function
[b]Refer to *AAP Red Book* and *Harriet Lane* as referenced above for further details regarding administration and side effects

globulin G antibodies. VZIG is recommended in this population and is also recommended in a hospitalized preterm infant (28 weeks or more gestation) whose mother lacks evidence of immunity against varicella, and a hospitalized preterm infant (less than 28 weeks gestation or birth weight of 1000 g or less) regardless of maternal immunity [55, 62].

VZIG is not indicated for healthy term infants exposed postnatally to varicella, even in those whose mother develops a rash more than 2 days after delivery. However, some would advise VZIG for exposed newborns within the first 2 weeks of life whose mothers do not have evidence of VZV immunity.

Specific Investigations Recommended

For diagnosis
Polymerase chain reaction
Direct fluorescent antibody
Viral culture
Tzanck smear
Serologic (acute and convalescent IgM and IgG antibody titers)

Table 18.23 First line therapies

Symptomatic therapy	D [54]
Acyclovir	A [54, 55, 59]
Valacyclovir	B [55]

Table 18.24 Second line therapies

Foscarnet	E [60]

Table 18.25 Prophylaxis

Live attenuated varicella vaccine	A [53, 61]
Varicella zoster immune globulin	B [62]
Intravenous immunoglobulin	C [63]

Herpes Zoster

Clinical Features

Herpes zoster or shingles is caused by reactivation of varicella zoster virus (VZV) in the dorsal root ganglia. VZV establishes latency during primary varicella infection or following varicella vaccine. Although pediatric zoster is most common among immunocompromised children and those exposed in utero or within the first year of life, it can occur in children without these risk factors. Childhood zoster tends to be milder and less associated with postherpetic neuralgia. The classic presentation is an acute, unilateral vesicular eruption in a dermatomal distribution along one or more sensory nerves (Figs. 18.8 and 18.9). Patients may complain of pain, hyperesthesia, and tenderness before cutaneous findings. Crusting of the vesicles and healing occurs within a few days to 1 week. Zoster may become disseminated in immunocompromised children, with visceral complications including encephalitis, pneumonia, and hepatitis.

Management Strategies

Treatment includes symptomatic therapy and antivirals [64]. Symptomatic care includes cool compresses, calamine lotion, antihistamines, and analgesics. Fingernails should be kept short to avoid superinfection and excoriation.

Acyclovir is the only antiviral agent for zoster with specific pediatric dosing guidelines; famciclovir and valacyclovir do not have sufficient clinical data for pediatric zoster (Table 18.26). Ideally, antiviral therapy should be given within 72 h of exanthem onset to decrease acute neuritis, vesicle formation, and time to crusting [65]. Immuncompromised patients as well as those with serious complications or disseminated disease should be treated with intravenous acyclovir [66].

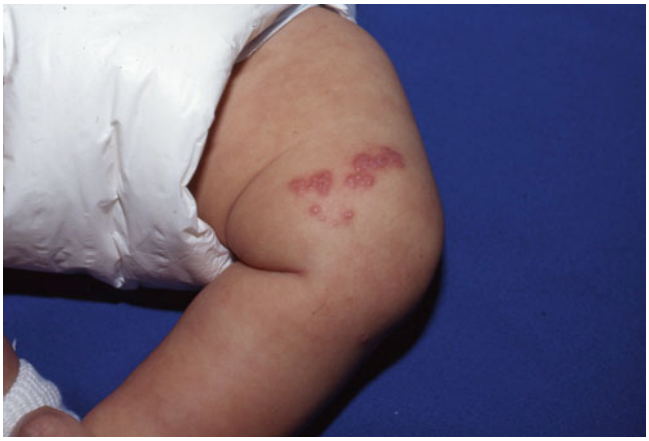

Fig. 18.8 Clustered vesicles in a dermatomal distribution in an infant with herpes zoster. The mother had chicken pox late in pregnancy

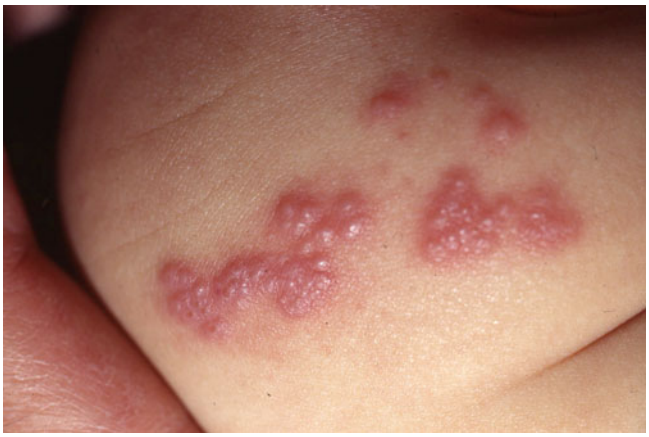

Fig. 18.9 Close-up of the infant in Fig. 1.8, showing vesicles grouped on an erythematous base with shingles

Specific Investigations Recommended

For diagnosis
Polymerase chain reaction
Direct fluorescent antibody
Viral culture
Tzanck smear
Serologic (acute and convalescent IgM and IgG antibody titers)

*Refer to reference [67] for discussion of these methods

Table 18.27 First line therapies

Symptomatic therapy	D [64]
Acyclovir	A* [64–64]

Epstein-Barr Virus/Infectious Mononucleosis

Clinical Features

Infectious mononucleosis (IM) is one of the most recognized syndromes of Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV4). IM is caused by primary EBV infection in older children or adolescents, and consists of fever, pharyngitis, lymphadenopathy, and fatigue. Cutaneous manifestations are nonspecific and usually appear as a morbilliform copper-colored eruption on the trunk and extremities (Figs. 18.10 and 18.11). Administration of antibiotics, particularly penicillins such as ampicillin and amoxicillin, will lead to development of a morbilliform, scarlatiniform, or petechial eruption in the majority of patients with IM. This is thought to represent an enhanced reaction to drugs or their metabolites rather than a true allergy. Systemic complications include encephalitis, upper airway obstruction (due to

Table 18.26 Oral and intravenous antiviral dosing guidelines for herpes zoster in the immunocompetent and immunocompromised host

Antiviral	Population	Route	Age	Dosing
Acyclovir[a,b]	Herpes zoster in immunocompetent host	Oral	≥12 years	4,000 mg/day in 5 divided doses for 5–7 days
Acyclovir[a,b]	Herpes zoster in immunocompetent host	IV (if requiring hospitalization)	<1 year	30 mg/kg per day in 3 divided doses for 7–10 days
Acyclovir[a,b]	Herpes zoster in immunocompromised host	IV	<12 years	30 mg/kg per day in 3 divided doses, for 7–10 days
Acyclovir[a,b]	Herpes zoster in immunocompromised host	IV	≥12 years	30 mg/kg per day in 3 divided doses, for 7–10 days
Famciclovir[a,b]	Herpes zoster	Oral	Adult dose	1,500 mg/day in 3 divided doses for 7 days
Valacyclovir[a,b]	Herpes zoster	Oral	Adult dose	3 g/day in 3 divided doses for 7 days

Dosing guidelines derived from: [207, 208]
[a]Dosing should be decreased in patients with impaired renal function
[b]Refer to *AAP Red Book* and *Harriet Lane* as referenced above for further details regarding administration and side effects

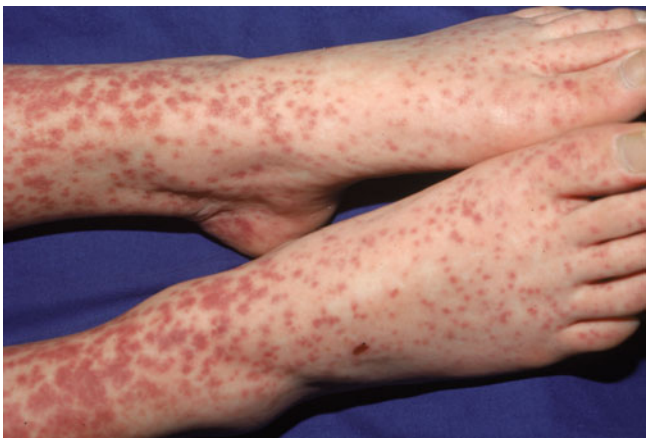

Fig. 18.10 *Brownish red* or *copper*-colored macules and papules seen with the rash of infectious mononucleosis from EBV

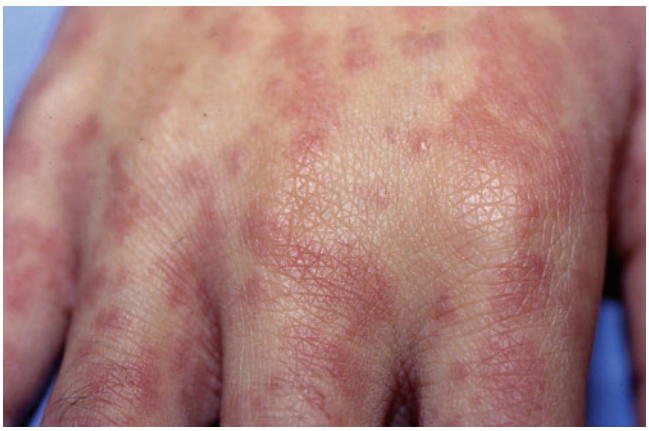

Fig. 18.11 *Purple-red* macules and papules of EBV infection

tonsillar hypertrophy), mild acute hepatitis, lymphocytosis with atypical lymphocytes, thrombocytopenia, hemolytic anemia, splenomegaly and, rarely, splenic rupture.

Another dermatologic manifestation of EBV involves large, painful, symmetric genital ulcers, particularly in adolescent females, on the labia minora and majora. Most patients then develop symptoms of infectious mononucleosis.

Initial laboratory evaluation should include a complete blood count with differential, hepatic function panel, and heterophile antibody test (or Monospot test). Monospot may be negative in the early stages and in children less than 4 years of age. Further serologic testing including EBV IgM, and IgG antibodies against viral capsid antigens, early antigens, and nuclear antigen proteins may be pursued in those who are Monospot-negative.

Management Strategies

Management is mainly supportive. Rest, hydration, antipyretics, and analgesics are recommended. Patients should avoid exertion and participation in sports for a minimum of 3 weeks. Amoxicillin and ampicillin should not be prescribed. Systemic corticosteroids may be helpful in managing more severe complications including upper airway obstruction, hemolytic anemia, and thrombocytopenia [68–70].

Specific Investigations Recommended

For diagnosis
Complete blood count with differential
Hepatic function panel
Heterophile antibody test/Monospot test (may be negative in early infection and in children under age 4)
EBV PCR
Viral serologies: EBV IgM and IgG against viral capsid antigens, early antigens, nuclear antigen proteins

Table 18.28 First line therapies

Antipyretics	E
Analgesics	E
Hydration	E
Avoidance of sports for 3 weeks (due to risk of splenic rupture)	E

Table 18.29 Second line therapies

Systemic corticosteroids (especially for complications such as upper airway obstruction, hemolytic anemia)	B

Warts

Clinical Features

Warts or verrucae are a common dermatologic condition in children and adults, with a variety of presentations. They may be cobblestoned or filiform as in the common wart (verruca vulgaris) (Fig. 18.12); flesh-colored, flat-topped plane warts (verruca plana); or hyperkeratotic warts on soles (verruca plantaris) or palms (verruca palmaris). A study of wart incidence by age range showed warts were most common among 9- and 10-year-olds, with 8.61 % having warts [71]. In children, verrucae are typically benign and more of a cosmetic concern. Pain and functional impairment may occur if warts proliferate on soles, hands, or periorificially.

Verrucae are caused by the human papillomavirus (HPV), with different strains of HPV being more common in different types of warts. Verruca vulgaris is most commonly associated with HPV strains 1, 4, 27, and 57 while palmoplantar warts are thought to be caused by HPV 2 [72].

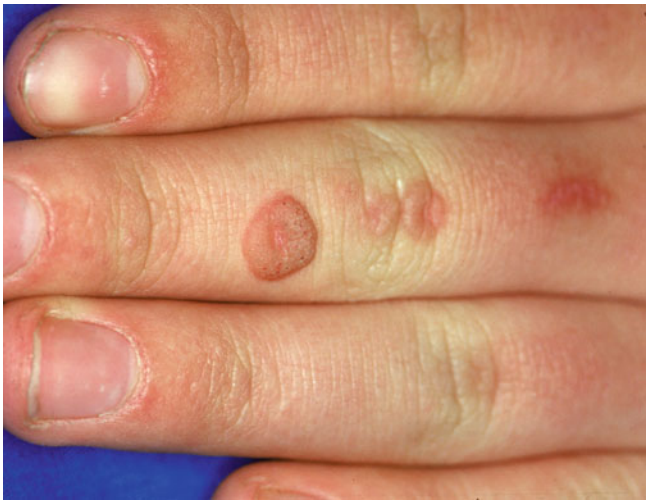

Fig. 18.12 Verrucous cobblestoned papule of verruca vulgaris

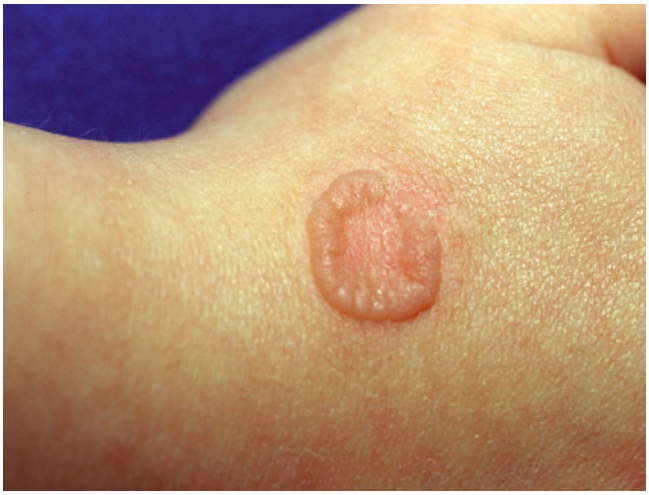

Fig. 18.13 Ring wart after cryotherapy

Management Strategies

Warts are benign, and immunocompetent children will eventually clear the infection [73]. Treatment strategies for warts in children should focus on minimizing discomfort and progression of lesions, while avoiding painful treatment modalities. Verruca plantaris should be treated to minimize functional impairment and discomfort. Management is similar to verruca vulgaris, with possible need to move to second- and third-line therapies sooner, given the potential symptomatic nature of plantar warts. With any painful treatment modality, encouraging the patient's family to pretreat with acetaminophen or ibuprofen can help lessen the patient's pain and make him or her a more willing treatment partner.

HPV is ubiquitous in the environment, and children with warts do not represent a significant infectious risk to others. Children are more likely to auto-inoculate and spread the virus to other parts of their skin. Families should be counseled on this potential for auto-inoculation. Children should be dissuaded from their natural tendencies to touch, bite, pick, or otherwise manipulate warts.

First-line therapies to treat warts include observation, salicylic acid, and occlusion with duct tape [73–75]. While requiring patience on the part of the patient and family, these options are typically well-tolerated by children and are a good initial choice for asymptomatic verrucae that are not cosmetically disturbing to the patient.

More advanced wart therapies involve various degrees of local irritation and immunomodulation to the wart. Topical prescription creams such as 5-fluorouracil and imiquimod and in-office application of a combination of tricholoroacetic acid, podophyllin, and Cantharidin 0.7 %, are well-tolerated [76, 77]. Liquid nitrogen cryotherapy can be effective, and is better tolerated in older children and teenagers [75] (Fig. 18.13). Isolated case reports have described clearance of recalcitrant verrucae after patients received the HPV vaccination, despite the fact the serotypes covered in the vaccine are not those typically associated with common warts [72]. Squaric acid, diphenylcyclopropenone, intralesional bleomycin, intralesional candida antigen, and laser treatments are other advanced wart therapies that may require additional cooperation and pain tolerance on the part of the patient [78–87].

Specific Investigations Recommended

For diagnosis
Scraping with #15 blade to visualize pinpoint capillaries and interrupted dermatoglyphics
Biopsy if appears atypical

Table 18.30 First line therapies

Observation only	Children will typically clear warts without sequelae in 1–2 years	B [73]
Salicylic acid	OTC impregnated bandages, 17 % liquid, or stick applicator	B* [75]
	Surrounding skin may become macerated	
Duct tape occlusion	May require frequent reapplication if patient has significant sweating	B [74]

Table 18.31 Second line therapies

5-fluorouracil cream/ solution	Daily application of thin layer followed by occlusion	B [77]
In-office liquid nitrogen cryotherapy	Two freeze-thaw cycles	B* (adults and children older than 12) [75]
OTC cryotherapy with dimethyl ether and propane	Cannot achieve same level of cooling as liquid nitrogen	E [75]
35 % tricholoroacetic acid, 25 % podophyllin, cantharidin 0.7 %	Painless application	E (author's experience)
	Thin layers applied in office	
	Patient washes off in 6–8 h	

Table 18.32 Third line therapies

Oral cimetidine	40 mg/kg/day divided BID or TID, maximum 2.4 g/day	A [104]
	Randomized controlled trials have not shown efficacy over placebo	
HPV vaccine	FDA approved for females and males ages 9–26	D* [72]
Squaric acid dibutyl ester	Requires formulation by compounding pharmacy	B [82, 84, 85]
	Pre-treatment sensitization on upper arm required, with 2 % squaric acid	
	Treatment concentration 0.2 % squaric acid and adjusted based on clinical response	
	Pre-treatment with 50 % trichloroacetic acid may increase the efficacy of squaric acid	
Diphenylcyclopropenone (DPCP)	Requires sensitization prior to treatment with 0.1–0.25 %	B [79]
Candida antigen, intralesionally	0.1 mL of candida antigen injected into wart	B [81]
	May treat up to 3 warts at one time with maximum dose 0.3 mL	
	May require 2–3 treatments spaced 4–6 weeks apart	
Topical cidofovir	1–3 % cidofovir applied daily to every other day	B (children and adults) [83]
Long-pulse Nd:YAG laser	May require multiple sessions for clearance	B* (one patient in study was a child) [80]
Pulsed dye laser	Requires patient cooperation and may leave post-treatment ecchymosis	B* [78]
Bleomycin, intralesionally	Requires pre-treatment with topical or intralesional anesthesia	B* (adults and children older than 12) [86]
	Requires multiple injections into one wart	
	Patient likely will experience discomfort	

Condyloma

Clinical Features

Condyloma or anogenital warts are pink-gray, polypoid verrucous-surfaced papules along vulvar, penile, perineum, or peri-rectal skin. Condyloma result from infection with human papillomavirus (HPV) on genital skin, primarily with HPV strains 6 and 11 with the incubation period ranging from a few weeks to several months [88]. Adjacent skin folds may have "kissing" lesions representing spread of the virus through skin-on-skin contact. Multiple studies have suggested peri-rectal is the most common location for condyloma. Lesions may be asymptomatic or associated with pruritus, discomfort, or bleeding.

A child may acquire condyloma through several modes of transmission: vertically from mother to child perinatally, auto-inoculation by the child from a non-genital verruca, direct transmission from a caregiver during diapering or bathing, or inoculation from fomites [89]. Suspicion for transmission via sexual abuse is higher in older children (3 years and above) who do not have non-genital verruca in themselves, relatives, or other caregivers. When sexual abuse is a concern, careful history-taking by trained providers and the involvement of child protection agencies are the crucial first steps. A detailed physical exam for any other signs of abuse is key, but many patients who have experienced sexual abuse have no pertinent findings on exam.

Management Strategies

The location and persistence of lesions can make treating condyloma a prolonged and potentially uncomfortable process. Condyloma may be treated with topical preparations applied in-office or at home. Destructive modalities, such as cryotherapy, excision, or laser treatments, are alternative treatment strategies that may be more painful and require more cooperation [90, 91].

With the growing use of HPV vaccines, condyloma management now starts with prevention [92–94]. The quadrivalent HPV vaccine available in the US (Gardasil™) covers HPV strains 6, 11, 16, and 18 [92, 95]. Gardasil-9 is a new expanded version of the original vaccine and covers HPV strains 6, 11, 16, 18, 31, 33, 45, 52, and 58. Both are FDA-approved for females and males aged 9–26 years. A bivalent vaccine (Cervarix™) covers HPV strains 16 and 18 and is FDA-approved for girls aged 9–26 years [92, 95]. The vaccines are given as a series of three intramuscular injections into the deltoid muscle.

Cryotherapy has a clearance rate that varies from 27 % to 88 % depending on technique [88]. Two applications of liquid nitrogen—delivered from cryo-canister, cold forceps, or cotton-tipped application—for at least 15 s or until a rim of frost covers the entire lesion with a 1 mm border, should be separated by sufficient time to allow the lesion to thaw without external re-warming. Cryotherapy should be repeated every 2–4 weeks. Podofilox (Condylox) and podophyllotoxin are plant-derived anti-mitotic medications that may be used topically on condyloma [90, 91, 96, 97].

For second-line therapies, imiquimod applied three to five nights a week is usually well-tolerated by patients [90–98]. Symptomatic smaller condyloma may be excised under local or general anesthesia. Initial clearance rates for excision range from 35 % to 70 %, with recurrence rates around 20 % [88].

Numerous additional destructive and immunomodulatory treatments have been tried for condyloma [99–102]. Cimetidine is an H_2 receptor antagonist whose efficacy against condyloma and verruca vulgaris as demonstrated in open-label studies and case series has not been duplicated in randomized controlled trials [103, 104]. In adults, the application of 5-aminolevulinic acid (ALA) following by photodynamic therapy has produced clearance of condyloma, and could be considered for older children able to tolerate the procedure and discomfort [105]. Sinecatechins (VEREGEN or Polyphenon E) are green tea-based polyphenols with immunomodulatory properties, and may appeal to families who prefer a more plant-derived, less medicalized approach [106]. Cidofovir and interferon are treatments used for extensive condyloma in immunosuppressed patients [107].

Specific Investigations Recommended

For diagnosis
HPV PCR (rarely)
Biopsy if atypical appearing
For treatment
Sexually transmitted disease screening if appropriate

The diagnosis of condyloma is typically based on clinical exam and history. Biopsy and HPV PCR are rarely used as means of differentiating condyloma from potential mimics such a molluscum contagiosum and psuedoverrucous perianal papules when the clinical exam is not sufficient.

Table 18.33 First line therapies

Medication	Details	Level of evidence
HPV vaccination	FDA approved for females and males ages 9–26 years old	B [92, 93, 94]
Cryotherapy	Needs to be repeated every 1–4 weeks for several sessions	A [90]
	Requires patient who is able to tolerate discomfort	
Podofilox/ podophyllotoxin	CDC guidelines state total surface area treated with podophyllotoxin should not exceed 10 cm^2 and no more than 0.5 mL applied on a daily basis	A*-D (pediatric series) [90, 91, 96, 97]
	Podofilox was used as 0.05 % gel up to BID for 3 days a week in pediatric series	

Table 18.34 Second line therapies

Medication	Details	Level of evidence
Imiquimod	Strengths from 3.75 to 5 % have been used nightly for up to five nights per week	A (patients 12 and older) [96, 97, 98]
	A systematic review in adult condyloma patients found imiquimod was minimally superior to placebo in achieving complete or partial clearance of condyloma	
Surgery/scissor excision	Initial clearance rates 35–70 %	B* [91]
	Recurrence rates 20 %	
Potassium hydroxide 5–10 %	Daily use, applied carefully with application until point of irritation	B* [100]

Table 18.35 Third line therapies

Medication	Details	Level of evidence
Oral cimetidine,	20–40 mg/kg/day	E–A*(patients were 16 and older) [103, 104]
	Case study describing resolution with adjunctive use, but double-blinded placebo trials in older teenagers and adults found no benefit over placebo	
5-fluorouracil cream/solution	Meta-analysis of 5-flurouracil in anogenital warts in adults found topical use had therapeutic benefit, but its efficacy could not be quantified	A* [99]
Topical cidofovir	1 % cidofovir gel applied daily for up to 5 days a week showed improved rates over placebo	A* [107]
Trichloroacetic acid	An 80 % TCA mixture applied in-office every 2 weeks for 3 treatments to the condyloma of a pediatric patient led to significant clinical improvement	E [101]
ALA-photodynamic therapy	Case report of urethral meatus-obstructing condyloma treated with 20 % ALA incubated for 3 h followed by treatment with 630 nm helium-neon laser light	E [105]
Squaric acid dibutyl ester	Patients initially sensitized with 3 %, then treated twice weekly with concentrations ranging from 0.0003 to 3 %	C (adult and pediatric patients) [102]
Sinecatechins 10–15 % ointment	TID application showed better clearance than placebo in a manufacturer-sponsored trial	A* [106]

Epidermodysplasia Verruciformis

Clinical Features

Epidermodysplasia verruciformis (EDV) is a congenital or acquired susceptibility to beta-human papilloma viruses (HPV) that results in numerous flat-topped papules, often on the face and arms, resembling flat warts. EDV may be considered a type of "generalized verrucosis" with widespread eruption of verrucous lesions [108]. EDV is most commonly associated with HPV strains 5 and 8, with other studies describing the involvement of strains HPV 9, 12, 14, 15, 17, and 19 through 25.

Congenital EDV is associated with mutations in the *EVER1* and *EVER2* genes that code for transmembrane channel-like proteins 6 and 8 (TMC6 and TMC8) in the endoplasmic reticulum; these act as transmembrane proteins involved in the regulation of zinc levels [108]. Congenital EDV most often has an autosomal recessive mode of inheritance [108]. Acquired EDV has also been reported in immunosuppressed HIV and transplant patients. Patients with EDV are at a much higher risk of developing squamous cell carcinomas (SCC), given the oncogenic properties of HPV 5 and 8 and their decreased immune response to the virus [109, 110].

Management Strategies

Many of the therapies for EDV are similar to those for verruca vulgaris, including topical 5% imiquimod, glycolic acid, and cidofovir [108–112]. Oral cimetidine has also been explored [113]. For second- and third-line therapies, oral isotretinoin, acitretin with interferon, excision, photodynamic therapy, and combination treatment with curettage and trichloracetic acid have been used [109, 114–119]. HIV-infected patients with EDV do not typically improve with the initiation of HAART [120]. Some HIV patients may first experience lesions of EDV after the initiation of HAART as part of immune reconstitution [108].

Specific Investigations Recommended

For diagnosis
Biopsy
HPV PCR
HIV if suspected

Biopsy is often helpful to distinguish EDV from verruca vulgaris and verruca plana. Histologically, EDV displays characteristic hypergranulosis and keratinocytes with blue-gray cytoplasm in the upper epidermis [119]. With increased susceptibility to HPV infections, patients with EDV are at increased risk for squamous cell skin carcinoma and should receive routine complete skin exams [108, 115].

Table 18.36 First line therapies

Medication	Details	Level of evidence
Imiquimod 5%	Applied daily 3–5 times a week	E [110, 111]
HAART for HIV+ patients	Case series of adults with HIV and EDV showed no improvement in lesions after HAART initiation	D*-E [110, 120]
	Pediatric HIV+ patient did improve after HAART initiation	

Table 18.37 Second line therapies

Medication	Details	Level of evidence
Glycolic acid 15%	Pediatric HIV+ patients showed flattening of EDV lesions with once-daily application, increased to twice daily after 2 weeks	B [112]
Topical cidofovir 1%	BID application improved EDV in small case study of adults with HIV	D* [109]

Table 18.38 Third line therapies

Medication	Details	Level of evidence
Isotretinoin	Clearance after 12 months of 0.8 mg/kg/day followed by maintenance dose of 0.3 mg/kg/day	E* [118]
Acitretin or etretinate	Adult patient had improved EDV lesions and reduction in SCC with 0.2 mg/kg/day of acitretin plus 1 mcg/kg/week interferon 2 pediatric patients with EDV had impro vement of lesions with 1-1.5mg/kg/d etr etinate but were lost to follow-up.	E* [115, [211]
	Requires strict contraception in females of child-bearing potential for 3 years after discontinuation	
Oral cimetidine	40 mg/kg/day for 12 weeks showed improvement in a 16 year-old	E [113]
Curettage and 35% tricholoroacetic acid	Curettage followed by a brief application of TCA	D* [116]
Photodynamic therapy and systemic retinoids	20% 5-aminolevulinic acid allowed to incubate for 6 h followed by photodynamic therapy	E* [117]
	Clearance for several months in adult patient	
Excision	Reserved for severe cases with functional impairment	E* [114]

Molluscum Contagiosum

Clinical Features

Molluscum contagiosum are pink to flesh-colored dome-shaped papules with central umbilication. These often appear as multiple clustered lesions in intertriginous areas such as the popliteal fossae and axillae (Figs. 18.14 and 18.15). Caused by a poxvirus, *Molluscipoxvirus*, molluscum may trigger an eczematous dermatitis in surrounding skin or a generalized eczema flare in children with atopic dermatitis. Molluscum can also produce a hypersensitivity type reaction locally with circular or annular erythema [121] (Fig. 18.16). Children will typically clear molluscum in 6–18 months, but some may have a prolonged course for 2–3 years [122].

Management Strategies

Given molluscum lesions are benign and ultimately self-resolving, providers should focus their treatment strategies on symptomatic or cosmetically disturbing lesions, with a preference for less painful treatment modalities. A 2009 systemic review of molluscum treatments did not find any one modality superior to others, but the review was limited in its number of studies and randomized controlled trials [123].

Children with molluscum should not be barred from normal activities, such as school, daycare, or swimming, given the ubiquitous nature of the poxvirus. *Molluscipoxvirus* is transmitted through direct personal contact and fomites; so children with molluscum should use dedicated towels at

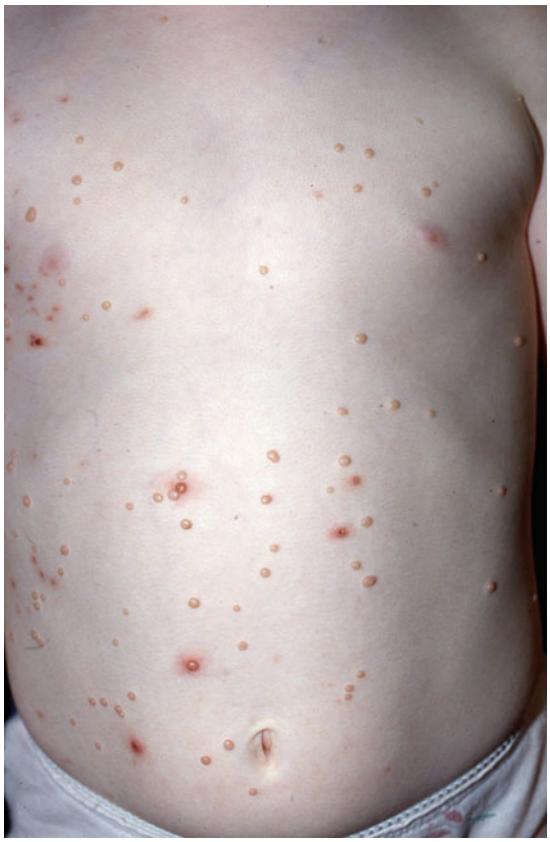

Fig. 18.14 Numerous umbilicated papules, some with inflammation, with molluscum contagiosum

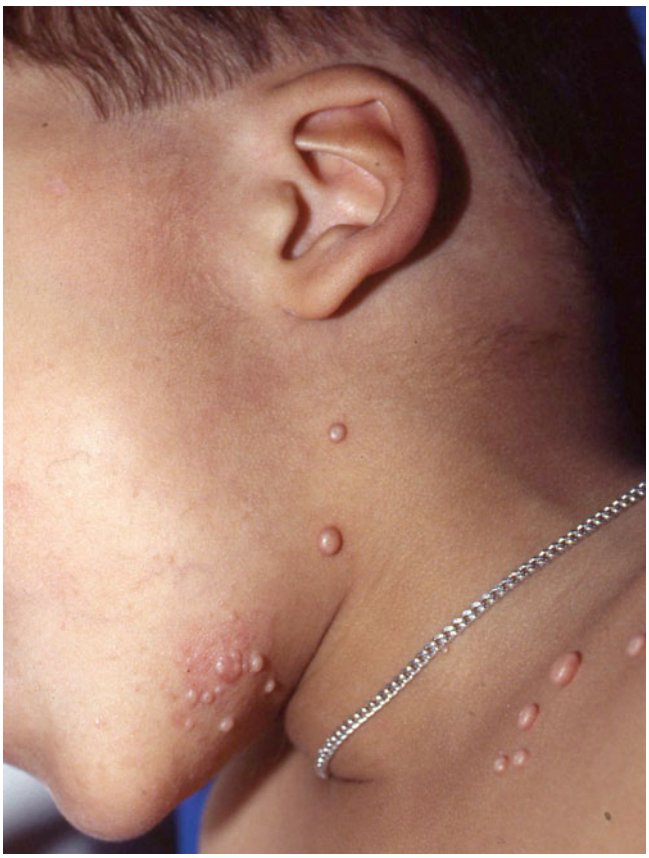

Fig. 18.15 Umbilicated dome-shaped papules of molluscum contagiosum

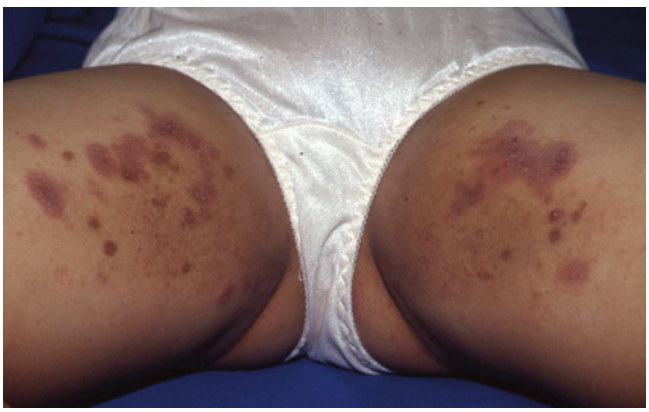

Fig. 18.16 Hypersensitivity reaction to molluscum demonstrating circular erythematous plaques

home and avoid activities with close physical contact, such as wrestling.

Families need forewarning of the potential for molluscum abscesses—warm, tender, erythematous nodules—that may develop after a molluscum lesion is treated, or may appear spontaneously as the lesion is about to resolve. Butala et al. described highly inflamed molluscum that is often mistaken for secondary cellulitis as "BOTE" sign or "beginning of the end" sign [124]. This inflammatory reaction before resolution can unfortunately trigger work-up and treatment for presumed cellulitis. Parents should be reassured that molluscum abscesses are not cellulitis. Analgesics and warm compresses are useful to help to treat associated discomfort.

Children will typically clear molluscum without any intervention. Unless the lesions are symptomatic or distressing to the child, observation is an appropriate management option for uncomplicated molluscum. Children with atopic dermatitis may have a flare of their eczema adjacent to any molluscum, or a generalized flare of eczema on non-adjacent sites. Any concurrent flare of atopic dermatitis should be treated with emollients and topical steroids to prevent further spread of the molluscum [121].

Treating molluscum lesions serves two purposes: to locally destroy the specific lesions, and to hasten the ultimate resolution of all lesions by triggering a systemic anti-molluscum inflammatory response. Cryotherapy can be effective, but is uncomfortable for the child [125]. The treated areas may hypo- or hyperpigment if aggressive cryotherapy is performed. Adapalene and tretinoin creams are potential at-home, relatively painless, molluscum treatments [126]. Once used for molluscum, imiquimod is no longer recognized as effective against molluscum, based on data showing a lack of efficacy in pediatric patients [125, 127, 128].

Numerous other destructive and immunomodulatory techniques have been used to treat molluscum [129–136]. Cantharidin, produced from an extract of the blister beetle, is a non-FDA approved irritant that is applied to molluscum lesions and then washed off in 6–8 h [137, 138]. A variant on curettage, extracting a molluscum's core, will trigger the resolution of the lesion [139]. Some parents may be able to apply gentle lateral pressure during a warm bath and successfully extract this core. Often, the large numbers of molluscum lesions and the need for a cooperative child make this a less feasible treatment option. In patients with AIDS/HIV, topical cidofivir has been found helpful in speeding the resolution in this population at risk for more widespread and recalcitrant disease [140].

In sexually active teenagers, genital molluscum is a sexually transmitted disease, and the American Academy of Pediatrics (AAP) recommends screening for other sexually transmitted diseases in these patients [141]. Genital molluscum in younger children is most likely caused by auto-inoculation and, per the AAP, does not necessarily denote sexual abuse [141].

Specific Investigations Recommended

For diagnosis
Tzanck prep of core contents looking for Henderson-Patterson bodies
Biopsy if atypical-appearing or to confirm
Screen for other sexually transmitted diseases if genital molluscum in sexually active patient

Table 18.39 First line therapies

Medication	Details	Level of evidence
Observation only	Children will typically clear molluscum without active intervention in 6–18 months	C [212]
Treat molluscum dermatitis	Emollients, topical steroids and avoidance of irritating substances should be used for dermatitis around molluscum lesions	E [121]

Table 18.40 Second line therapies

Medication	Details	Level of evidence
Cantharidin 0.7 %	Cantharidin is not U.S. FDA-approved for use and must be ordered from a compounding pharmacy	B [137, 138]
	Drop liquid onto the molluscum and then allow to dry for 2–3 min	
	Patient should wash off area in 4–6 h	
	May require repeat treatment in 4–8 weeks	
Cryotherapy	Liquid nitrogen applied in a two-step freeze-thaw- cycle repeated weekly for 2 weeks	A [125]
	May cause discomfort and post-treatment pigmentary change	
Salicylic acid 12 % gel	Salicylic acid 12 % gel applied two times a week	A [134]
Salicylic and lactic acid	Film containing 16.7 % salicylic acid and 16.7 % lactic acid applied to molluscum three times a week	B [213]
	High rate of local irritation	
Retinoids, topical	Adapalene and tretinoin may be of benefit	E [126]
	Parents should be cautioned to avoid overuse and potential irritation	

Table 18.41 Third line therapies

Medication	Details	Level of evidence
Potassium hydroxide 2.5–10 %	Applied BID until lesions become inflamed	A [136]
	May cause stinging	
Oral cimetidine	40 mg/kg/day divided bid/tid, given for 8–12 weeks has shown to faster clearance in some studies; other studies have shown no benefit over observation, affects CYP450	A [131]
Curettage/ extraction	Topical anesthetic may be used before curettage to lessen discomfort for patient	B [139]
	Some use a fine gauge needle to puncture molluscum's surface before removing the core	
Pulsed dye laser	Single pulse of pulsed dye laser to molluscum resulted in 84.3 % remission rate after a single treatment	C [130]
Diphencyprone	Sensitized with 0.5 % diphencyprone	B [133]
	Treatment with weekly concentrations of 0.0001 %, titrating up to 0.1 % if there was no clinical irritation	
Cidofovir	Topical 3 % cidofovir daily for 5 days per week for 2 months helped resolve refractory molluscum in two pediatric HIV patients	D [140]
Intralesional Candida antigen	Injecting 0.1 mL per lesion for total dose of up to 0.3 mL may speed resolution of molluscum	B [132]
Tricholoroacetic acid 20–35 %	Narrow-tipped applicator was used to apply TCA to facial molluscum	D [129]
	Pigmentation and discomfort may occur	
Duct tape occlusion	Continual occlusion by duct tape may trigger an inflammatory response	E [135]

Cowpox

Clinical Features

Cowpox is a rare zoonotic infection demonstrating pustules, vesicles, or necrotic ulcerations on the hands or face [142]. Edema and erythema often surround the lesions, with necrotizing lymphadenitis and cellulitis being frequent secondary complications [143]. Systemic, flu-like symptoms of malaise, fatigue, and fever may accompany the skin lesions.

Cowpox is caused by an orthopoxvirus and is transmitted from contact with infected animals such as cats, dogs, horses, and rats [144–146]. Cowpox outbreaks among European pet rat owners have occurred in recent years [144, 146]. Pet rats often sit on their owner's shoulder, making shoulder, neck, and ear common sites of cowpox ulcers [146].

With similarities between vaccinia and cowpox viruses, the smallpox vaccine is thought to offer some protection against other orthopoxviruses like cowpox and monkeypox [142]. Smallpox vaccination efforts concluded in the late 1970s, leading to a possible increase in the incidence of cowpox cases in the coming years, as the percentage of vaccine-naïve patients in the population grows [142].

Management Strategies

Cowpox is a limited, self-resolving condition, but can have significant secondary lymphadenitis and cellulitis. A handful of more widespread cases in patients with atopic dermatitis have been described [147]. Once the definitive diagnosis of cowpox is made by PCR and electron microscopy, observation and reassurance are reasonable first-line management strategies for uncomplicated cases. Patients and their families should receive anticipatory guidance that cowpox ulcerations and eschars may take 2–3 months to resolve and will often leave scars [142]. Severe complications, such as keratitis and corneal erosions, may result from cowpox infections of the eye; any suspected eye involvement necessitates an immediate ophthalmology referral [142, 148].

Household pets, such as cats and rats, are the most likely vectors for the transmission of cowpox to humans, and any suspected infected pet should receive a veterinary evaluation [142, 143, 145, 146].

Specific Investigations Recommended

For diagnosis
PCR of biopsy specimen or blister fluid
Electron microscopy to detect characteristic viral inclusions in keratinocytes
IgM serology
Wound and blood cultures to rule out bacterial abscess
CBC to check for leukocytosis
CRP
For treatment
Evaluation of household pets for possible source of cowpox
Urgent ophthalmology referral for any ocular involvement

Table 18.42 First line therapies

Observation	E [142, 146]
Antibiotics for secondary cellulitis	E [143, 144, 146, 148]

Table 18.43 Second line therapies

Intravenous cidofivir	E [148]
Topical steroids	E [146]
Oral steroids	E [146]

Table 18.44 Third line therapies

Hyperbaric oxygen	E [143]
Surgical debridement	E [143, 144]

Orf

Clinical Features

Orf, also known as ecthyma contagiosum or contagious pustular dermatitis, typically demonstrates an isolated ulcerative nodule on the finger or hand of a patient who has had contact with sheep, goats, or reindeer [149]. It is caused by a parapox virus and its characteristic nodules have six distinct stages: macular, targetoid, ulcerative, regenerative, papillomatous or verrucous, and regressive. Despite the appearance during the draining ulcerative phase, most lesions heal with minimal scarring.

Children contract orf after being exposed to the virus-containing saliva of farm animals. Orf nodules may appear on non-hand sites such as the face or arm if the child is licked on that site. In adults, orf exposure is occupational in nature, with most affected patients being farmers, butchers, or veterinarians. Individuals slaughtering livestock as part of religious observances have also contracted orf. The orf vaccine for livestock is another potential route of viral exposure for humans.

Management Strategies

In humans, orf is self-limiting and resolves within 1–2 months in immunocompetent patients with minimum sequelae. These patients only require supportive care, with wound management and analgesics, until the nodule resolves. Observation with supportive care and possible treatment of any suspected secondary infections is an appropriate first-line strategy. Immunocompromised patients may have larger lesions that require active intervention [150–154].

Specific Investigations Recommended

For diagnosis
PCR
Biopsy
Bacterial culture if secondary infection suspected

Table 18.45 First line therapies

Medication	Details	
Observation	Nodules typically resolve spontaneously in 1–2 months	E [154]
Treatment of secondary infection	Nodules may become secondarily infected requiring antibiotics	E [213]

Table 18.46 Second line therapies

Medication	Details	
Imiquimod 5 %	Three times per week application in immunosuppressed patients	E* [149, 150, 152]
Cryotherapy	Two cycles given weekly for 60 s resolved recurrent nodule in adult renal transplant recipient	E* [151]

Table 18.47 Third line therapies

Medication	Details	
Cidofovir 1 % cream	Applied daily for 5 days and none for 5 days in repeating cycles for 2 months in immunocompromised patient with resolution	E* [153]

Smallpox

Clinical Features

Smallpox is caused by variola major virus and was declared eradicated in 1980. Variola virus is currently legally retained in two high-security laboratories: the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and the State Research Center of Virology and Biotechnology (VECTOR) in Koltsovo, Russia. Smallpox is transmitted via respiratory droplets, direct contact, and fomites (clothing and bedding). After an incubation period of 7–17 days, symptoms of high fever, fatigue, headache, myalgias, and vomiting appear. This prodromal phase is followed by an enanthem of erythematous macules on the oral mucosae. The exanthem starts 1–2 days later as a morbilliform eruption on the face that spreads to the arms, legs, hands, and feet. Infectivity is highest at the onset of the exanthem. Macules and papules evolve into vesicles and pustules, which crust and form scabs that fall off in 3–4 weeks, leaving behind pitted scars. Complications include secondary bacterial infection, arthritis, encephalitis, pneumonia, and blindness from viral keratitis. Variola major has a mortality rate of 30 %. Much higher mortality rates are observed in hemorrhagic and malignant forms of variola, which are characterized by a severe prodrome, petechiae, and cutaneous and mucosal hemorrhage. Variola minor, a less severe variant that is more common among patients previously vaccinated against smallpox, has a mortality rate of 1 %.

Although smallpox has been declared eradicated, the threat of bioterrorism with smallpox by rogue nations or terrorist groups remains. Vaccination using vaccinia virus is the main method of preventing an epidemic in a bioterrorism attack. Routine smallpox vaccination among civilians has not been performed in the United States since 1972 due to the rarity of the disease, the contagious nature of vaccinia, and significant adverse reactions of the vaccine. Adverse

reactions include headache, myalgias, fever, secondary bacterial infections, vaccinia necrosum, eczema vaccinatum, generalized vaccinia, erythema multiforme, and encephalitis. The most common serious adverse events in children are generalized vaccinia and eczema vaccinatum.

Generalized vaccinia involves the spread of lesions from the vaccination site to other areas of the body in individuals without a history of eczema. Eczema vaccinatum is a generalized spread of lesions throughout the body in individuals with active or a past history of eczema. Local immune dysregulation and disrupted skin barrier function in eczema patients permit viral dissemination. Bacterial superinfection with *S. aureus*, and supraglottic edema are potentially fatal complications of eczema vaccinatum. Therefore, a history of eczema or close contact with an individual with eczema are exclusion criteria for elective smallpox vaccination. The current strategy for managing a smallpox outbreak involves vaccination of first responders and isolation, vaccination, and surveillance of identified cases and their contacts.

The CDC has established major and minor criteria for the diagnosis of smallpox, and patients at high risk must meet all three major criteria including: (1) a febrile prodrome and at least one of the following: prostration, headache, backache, chills, vomiting, or severe abdominal pain; (2) classic smallpox lesions of firm vesicles or pustules; and (3) lesions in the same stage of development. Any suspected case of smallpox should be reported to the state health department and the CDC. Vesicular and pustular fluid, blood, and tonsillar swabs must be sent to the CDC. Methods for confirming the diagnosis include electron microscopy, polymerase chain reaction (PCR), serologies, and cell cultures. Patients at low or moderate risk of smallpox per CDC criteria should be tested for varicella or other suspected illnesses.

Management Strategies

Management consists of isolation, vaccination, and intensive supportive care with hydration and nutrition. Broad-spectrum antibiotics should be administered in patients with secondary bacterial infections [155]. The antiviral therapy cidofovir has shown efficacy against various poxviruses in vitro and may be useful [155–159].

Specific Investigations Recommended

For diagnosis
Vesicular or pustular fluid (on cotton swab) or crusts; blood; tonsillar swabs (collected in sealed vacutainer tubes enclosed in watertight container) to send to the CDC
Tzanck smear, viral culture, DFA (to rule out HSV and VZV)

Table 18.48 First line therapies

Vaccination (using vaccinia)	D
Isolation, airborne and contact precautions	D
Supportive care, hydration	D
Broad-spectrum antibiotics for secondary bacterial infection	E
Cidofovir 5 mg/kg	E

Table 18.49 Second line therapies

Intravenous vaccinia immune globulin 6,000 IU/kg for 3 doses	E
ST-246 (tecovirimat) 5 mg/kg daily (with goal plasma level 1,000 ng/mL)	E

Rubeola

Clinical Features

Rubeola, commonly known as measles, is caused by an RNA virus in the Paramyxoviridae family. It starts with a prodrome of the three Cs (cough, conjunctivitis, and coryza), fever, and Koplik spots, which are pathognomonic whitish gray papules on the buccal mucosa. This is followed 2–4 days later by the appearance of pink macules and papules around the hairline and behind the ears. This prototypical morbilliform eruption spreads in a cephalocaudad direction (Fig. 18.17) before resolving in the same order by which it appeared. Vesicles or hemorrhagic features may be seen. Complications include pneumonia, otitis, gastroenteritis, myocarditis, encephalitis, and subacute sclerosing panencephalitis, which can occur years later.

Management Strategies

Specific antiviral therapy does not exist, and treatment of uncomplicated measles is supportive. The World Health Organization recommends vitamin A for all children with measles in developing countries because low serum vitamin A levels are associated with increased morbidity and mortality. In 2012, Sudfeld et al. found that measles mortality was reduced by 62 % when two doses of vitamin A were given to infants and children over 1 year, at doses of 100,000 IU and 200,000 IU, respectively [160].

In 1963, a live-virus vaccine, MMR, was created and is now given at 12–15 months and 4–6 years of age in the United States. This dramatically decreased the incidence in the United States, but measles remains a significant problem worldwide. In a 2012 Cochrane review of 64 comparative retrospective or prospective trials, one dose of the MMR vaccine was at least 95 % effective in preventing measles and 92 % effective in preventing secondary cases of measles in

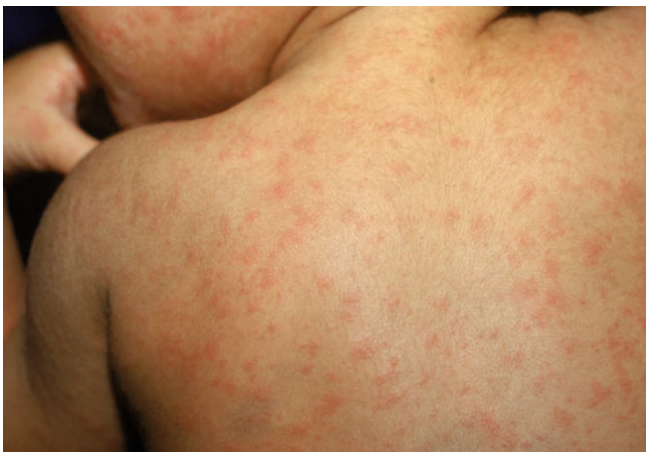

Fig. 18.17 Pink papules spreading in a cephalocaudad distribution of rubeola

household contacts. Two doses were 95 % effective in preventing secondary cases. Although aseptic meningitis, febrile seizures, and idiopathic thrombocytopenic purpura may be seen in the weeks following vaccine administration, there was no association with autism, asthma, leukemia, hay fever, type 1 diabetes, gait disturbance, Crohn disease, demyelinating disease, or infections [161]. Despite the development of a safe and effective vaccine, measles outbreaks continue to occur, even in developed countries. Administration of the live vaccine within 72 h of exposure is preferred over passive immunization with immunoglobulin, unless the patient is under 1 year of age, immunocompromised, or pregnant.

Passive immunization has been used to prevent measles in non-immunized individuals who have been exposed to the virus; however, estimates of immunoglobulin efficacy are variable. A 2014 Cochrane review of 13 randomized, quasi-randomized, and cohort studies found that when given to non-immunized individuals within 7 days of exposure, passive immunization with immunoglobulin reduced the risk of measles by 83 % and mortality by 76 %. No serious adverse effects were reported [162]. If no contraindications exist, the live vaccination should also be given no sooner than 6 months after the intramuscular form or 8 months after the intravenous form of immunoglobulin.

Although not routinely used, ribavirin may decrease the severity and duration of measles symptoms. In 2011, Pal performed a randomized controlled trial in patients with serology-confirmed measles. The group treated with ribavirin and supportive care were found to have reduced duration of fever, malaise, cough, coryza, conjunctivitis, and other constitutional symptoms, as well as a shorter hospital stay and fewer complications when compared to controls who were treated with supportive care only [163].

Diagnosis of measles is usually clinical, but serology, PCR, and virus isolation are available. Serum IgM antibody testing has near 100 % sensitivity when measured 6 or more days after the onset of fever, and is considered the gold standard in countries with a high prevalence of measles. However, false-negatives do occur, and testing should be repeated if done early after symptom onset. In countries with a low prevalence of measles, paired acute and convalescent IgG and IgM sera should be performed, with a fourfold or more increase indicative of current infection. Although less widely used, reverse transcription-PCR in peripheral blood mononuclear cells (PBMC) may be more effective in diagnosing measles than measurement of serum IgM. RT-PCR can also be done on nasopharyngeal secretions or urine samples, and are appealing as a less-invasive method in children. Virus isolation is not routinely done in clinical settings because sensitivity is low.

Specific Investigations Recommended

For diagnosis
Serology (IgM or paired acute and convalescent IgM and IgG)
RT-PCR (from nasopharyngeal secretions, PBMC or urine)
Virus isolation (not recommended)

Table 18.50 First line therapies

Vaccination (at 12–15 months and 4–6 years of age)	A
Report to state health department	
Isolation for 4 days after rash onset	B

Table 18.51 Second line therapies

Medication	Details	
Immunoglobulin	Postexposure prophylaxis (0.5 mL/kg IM with max 15 mL for non-immunized infants <12 months; 400 mg/kg IV for immunocompromised patients regardless of immunization status; 400 mg/kg IV for non-immunized pregnant women)	B
Vitamin A	In developing countries given once daily for 2 days at 50,000 IU for age <6 months; 100,000 IU for 6–11 months; 200,000 IU for >11 months	B
Ribavirin	15 mg/kg/day [164]	A

Rubella

Clinical Features

Rubella, or German measles, is caused by an RNA virus in the Togaviridae family. Half of cases may be asymptomatic. In adolescents and adults, it often begins with a prodrome of low-grade fever, headache, and upper respiratory symptoms. There may be accompanying lymphadenopathy of the

occipital, posterior cervical, and posterior auricular nodes. This is followed up to 5 days later by an exanthem of rose-colored macules and papules that begin on the face and spread in a cephalocaudad direction. This typically fades over 2–3 days in the same order as it appeared, and is occasionally followed by fine desquamation in severely affected areas. Forchheimer's spots, consisting of petechial macules on the soft palate, may be present and are characteristic of rubella. Joint pain develops in about half of females, and may take weeks to resolve or become chronic. Other complications include anemia, neutropenia, thrombocytopenia, encephalitis, myocarditis, pericarditis, and hepatitis.

Management Strategies

While rubella is usually mild with a self-limited course, it can cause miscarriage, stillbirth, and congenital rubella syndrome, especially when transmitted during the first 16 weeks of gestation. Congenital rubella syndrome is characterized by cataracts, deafness, heart defects, microcephaly, and a "blueberry muffin rash," which is caused by extramedullary hematopoiesis in the skin.

In 1969, the first rubella vaccine was licensed. It is now given in a combined live vaccine with measles and mumps viruses at 12–15 months and 4–6 years of age in the United States. There is a high degree of variability in the individual response to vaccination with live rubella virus. In 2000, Davidkin et al. found that after the first dose of the MMR vaccine, 98.5 % of patients had rubella seropositivity. Eleven years after the second MMR dose, 99 % of patients had rubella seropositivity. At 15 years, almost one-third of patients vaccinated at 14–18 months and 6 years had low antibody levels, putting them at risk for rubella infection during their reproductive age. In contrast, only 9 % of patients vaccinated at 6 and 12–13 years had low antibody levels at 15 years. These results bring into question the ideal timing of MMR vaccination in preventing congenital rubella syndrome [165].

A measles, mumps, rubella, and varicella (MMRV) vaccine was licensed in the United States in 2005. Initially, use of the MMRV was preferred; however, post-licensure studies reviewed by the CDC showed that one additional febrile seizure per 2,300–2,600 children occurred 5–12 days after the first dose when given the MMRV vaccine, in comparison to separate MMR and varicella vaccines at the same visit. There was no increased risk of febrile seizure after the second dose of MMRV. In 2010, the Advisory Committee on Immunization Practices (ACIP) updated their recommendations to reflect this new information, recommending that if there is no parental preference, separate MMR and varicella vaccines be given for the first dose and the MMRV vaccine be used for the second dose [166]. By 2005, the United States had successfully eliminated endemic rubella transmission; however, rare cases continue to occur in non-immunized individuals born in other countries.

Diagnosis is usually based on serology or virus detection, as rubella can be difficult to distinguish from other viral exanthems clinically. An elevated IgM level or at least a fourfold rise between acute and convalescent IgG levels taken 7–21 days later makes acute rubella infection likely. Serum IgM level may be negative if taken in the first 4 days of infection and should be repeated after day 5, if negative. Serologic testing methods vary between laboratories, with enzyme immunoassays (EIAs) being the most common. Virus detection can also be done using reverse transcription-PCR (RT-PCR) from nasal, blood, urine, or cerebrospinal fluid specimens, but those from the throat are preferred.

Rubella immunity should be determined by maternal IgG level at all first prenatal visits, given the severity of congenital rubella syndrome. Historically, prenatal diagnosis of fetal rubella infection has been done through detection of fetal serum IgM level. In 2004, Macé et al. reported the sensitivity and specificity of RT-PCR using amniotic fluid in 45 pregnant women with confirmed primary infection were 83 % and 100 %, respectively. Sensitivity increased to 95 % when samples collected less than 6 weeks after maternal infection or early in gestation were excluded. RT-PCR of amniotic fluid is less invasive and may be a desirable alternative to fetal IgM detection in the prenatal diagnosis of congenital rubella [167].

Given its self-limited course, treatment of rubella is primarily supportive. Pregnant women susceptible to rubella may be given prophylactic IM/IVIg if exposure is suspected, but vaccination is contraindicated during pregnancy. In 2002, Krause et al. found that all of five commercially available IVIg preparations analyzed by enzyme immunoassay had high activity against rubella virus. This supports the use of IVIg in the prevention and treatment of rubella, especially in patients without an adequate immune response [168].

Specific Investigations Recommended

For diagnosis
Serology (IgM or acute and convalescent IgG)
RT-PCR of nasopharyngeal secretions or amniotic fluid

Table 18.52 First line therapies

Vaccination (at 12–15 months and 4–6 years of age)	A
Antipyretics/analgesics	E
Hydration	E
Contact isolation or school/work avoidance for 7 days after rash onset	

Table 18.53 Second line therapies

IM/IVIg	E

Parvovirus B19

Clinical Features

Parvovirus B19 is a small single-stranded DNA virus that infects only humans. Although 20 % of cases are asymptomatic, it can also cause illness, and erythema infectiosum is the most common. Erythema infectiosum, also known as fifth disease or "slapped cheek" disease, is most common in school-aged children between 4 and 10 years old. Community epidemics may occur every 3–6 months. Erythema infectiosum begins with a prodrome of fever, headache, and respiratory symptoms. This is followed 2–3 days later by bright red macular erythema on the cheeks, with sparing of the nasal bridge, and circumoral pallor. Up to 4 days later, pink macules and papules appear on the extremities (Fig. 18.18) and to a lesser extent, the trunk. Central clearing results in a characteristic lacy or reticular pattern. This cutaneous eruption lasts 1–3 weeks, and may worsen with sun or heat exposure.

Arthralgias are seen in only 10 % of patients overall, but up to 30–60 % of adult women. This usually affects the small joints of the hands, wrists, knees, and ankles, and is self-limited over a period of a few weeks. Some authors have suggested an association with rheumatoid arthritis, connective tissue disease, and juvenile idiopathic arthritis. Parvovirus B19 also causes reticulocytopenia, which is usually mild, but can lead to an aplastic crisis in susceptible individuals with sickle cell anemia or other hemoglobinopathies. Rare complications of parvovirus B19 include cardiac involvement, neurologic problems, hepatitis, and hemophagocytic syndrome. If infection occurs during pregnancy, anemia may occur, with a small chance of fetal hydrops, miscarriage, or stillbirth; however, the majority of infants will be asymptomatic. Risk to the fetus is greatest during the first 20 weeks' gestation.

Less commonly, parvovirus B19 infection causes papular-purpuric gloves and socks syndrome (PPGSS). Unlike erythema infectiosum, this is most commonly seen in young adults. PPGSS begins with acute onset erythema and edema of the hands and feet (Fig. 18.19) There is often a petechial or purpuric component. A prodrome or enanthem may also be present. Other reported causes of PPGSS include coxsackievirus B6 and human herpesvirus 6.

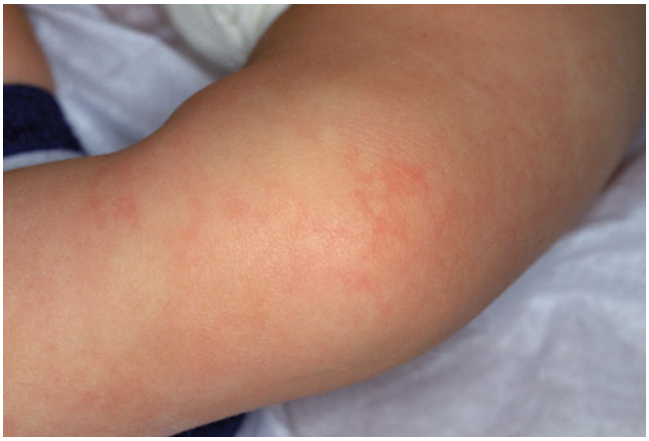

Fig. 18.18 Lacy, reticulated erythema of fifth disease

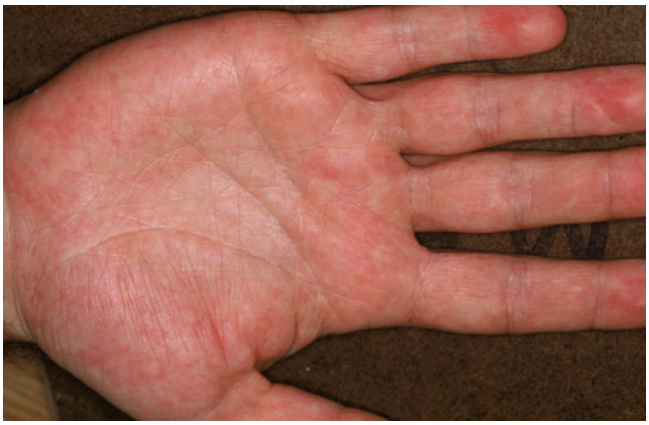

Fig. 18.19 Palmar erythema and edema of papular purpuric gloves and socks syndrome

Management Strategies

There is no specific antiviral therapy available for parvovirus B19 infection, and symptoms are usually mild and self-limited. Cidofovir is known to have broad activity against DNA viruses. In 2015, Bonvicini et al. found cidofovir to have dose-dependent inhibitory activity on parvovirus B19 replication using two cell lines generated from peripheral blood mononuclear cells [170].

Treatment of parvovirus B19 is symptomatic. Despite a lack of specific studies to support their use, nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to treat associated arthropathy. In 2015, Lallement et al. successfully treated chronic arthralgia with high-dose ascorbic acid at 10 g by mouth daily for 10 days after the patient had minimal improvement with oral prednisone and NSAIDs. She relapsed 3 weeks after treatment, but fully recovered after 3 weeks of additional treatment at the same dose [171].

Transfusions may be indicated for anemia. In 2014, Sekiguchi et al. successfully treated recurrent autoimmune hemolytic anemia associated with pure red cell aplasia and hemophagocytic syndrome with 1,000 mg of pulsed oral methylprednisolone daily for 3 days, followed by 60 mg of daily prednisolone with a gradual taper [172]. In 2015,

Drwila et al. used IVIg to treat biopsy-proven viral myocarditis with clinical improvement seen after 3 days of treatment [173].

When fetal infection is suspected, serial ultrasounds should be performed, with in utero transfusions when indicated. Termination of pregnancy is rarely indicated because parvovirus B19 is not teratogenic. Anemia is the major manifestation of fetal infection, and intrauterine transfusion should be considered for any fetal hemoglobin <10 g/dL. In 2007, Hsu et al. successfully treated fetal ascites and hypertrophic cardiomyopathy with 2 weeks of intrauterine digitalization therapy with 0.25 mg of digoxin every 12 h. IVIg has also been used in the postnatal period, with resolution of viremia and improvement of anemia [174].

Parvovirus B19 infection is usually a clinical diagnosis; however, laboratory testing can be performed when confirmation is needed. The preferred method is measurement of serum IgM, which becomes detectable 8–10 days after the onset of infection and stays elevated for 2–4 months. The rise in IgM level coincides with appearance of the erythema infectiosum rash, so patients are not considered contagious after this point. Serum IgG level is positive in about 60 % of adults and is generally not useful in diagnosing acute infection, unless there is a fourfold or greater increase from acute to convalescent sera. Distinguishing recent and previous parvovirus B19 infections based on IgM and IgG enzyme immunoassays (EIAs) alone can be prone to error. Detection of IgG avidity may be a useful addition, as low avidity correlates with more recent infection.

PCR may also be used, and is particularly useful in immunocompromised patients; however, viral DNA may persist for months, or even years, after acute infection. A panel of 78 sera was tested by Maple et al. in 2015. Both PCR and EIAs showed high overall agreement with consensus determination of recent or past infection [175]. In 2015, Ishikawa et al. used PCR to measure parvovirus B19 DNA levels in maternal and fetal serum, and amniotic fluid samples taken between 16 and 27 weeks' gestation. The concentration of DNA in amniotic fluid was found to be at least 100 times higher than that of maternal serum and corresponded with that of fetal serum. Amniotic fluid may be used as a substitute for fetal serum in quantification of parvovirus B19 infection in early pregnancy [176].

Specific Investigations Recommended

For diagnosis
Serology (IgM or paired acute and convalescent IgG)
PCR
For treatment
CBC
Serial fetal ultrasounds

Table 18.54 First line therapies

Antipyretics/NSAIDs	E
Hydration	E
Emollients	E

Table 18.55 Second line therapies

Blood transfusion	E

Table 18.56 Third line therapies

IVIg	E
Systemic steroids	E
Ascorbic acid	E
Intrauterine digoxin	E
Cidofovir	E

Roseola

Clinical Features

Roseola infantum, also referred to as exanthem subitum or sixth disease, initially appears in an otherwise healthy infant with 3–5 days of high fevers of up to 41 ° C. Febrile seizures are common during this period. As the fever defervesces, blanchable rose-pink macules and papules appear on the trunk and proximal extremities and spread centrifugally (Fig. 18.20). Accompanying features may include eyelid edema, bulging of the anterior fontanelle, cervical lymphadenopathy, mild upper respiratory symptoms, injection of the tympanic membranes, diarrhea, and Nagayama spots (erythematous papules on the soft palate and uvula).

Roseola is more common in the spring, and is thought to be caused by infection with HHV-6 or, less often, HHV-7. While the majority of children become HHV-6 positive during their first few years of life, less than one-third of them will have classic signs of roseola. Of note, HHV-6 and HHV-7 have also been linked to pityriasis rosea and drug-induced hypersensitivity syndrome (DIHS).

Management Strategies

Roseola resolves spontaneously over a period of a few days, usually without sequelae. Therefore, treatment is primarily supportive. Rarely, encephalopathy and encephalitis have been reported in both immunocompromised and immunocompetent patients, and can result in long-term morbidity. Ganciclovir, foscarnet, and cidofovir have anti-herpesvirus activity and have been investigated in the treatment of HHV-6 and HHV-7 in immunocompromised hosts.

Ganciclovir has activity against HHV-6 in vitro, but activity in vivo has not been well characterized. In 2002, Tokimasa

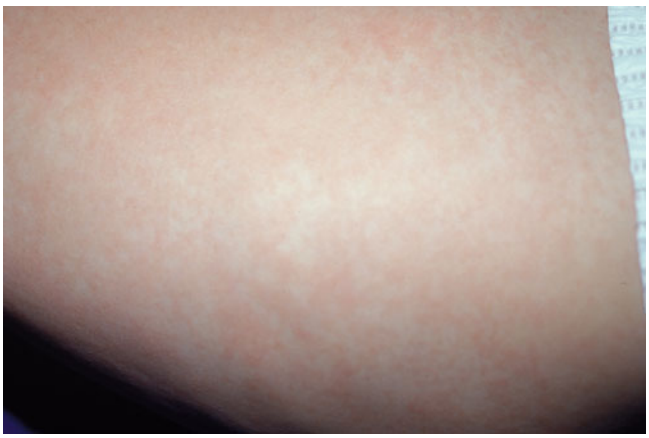

Fig. 18.20 Ill-defined pink macules on the trunk of a child with roseola

et al. did a retrospective comparison of pediatric allogeneic stem cell transplant recipients showing that HHV-6 reactivation rate was lower in those treated with prophylactic ganciclovir at 3 weeks (0/13 vs. 11/28). Patients with HHV-6 reactivation had improvement in symptoms and/or reduction in HHV-6 copy number when treated with ganciclovir [178]. In 2002, another study by Zerr et al. showed that after 3 weeks of treatment with ganciclovir and/or foscarnet, HHV-6 viral load decreased in the CSF of hematopoietic stem cell recipients with HHV-6 encephalitis or other CNS disease. Use of cidofovir is limited by nephrotoxicity. Hexadecyloxylpropyl cidofovir is a lipid conjugate form of cidofovir [181]. In 2013, Bonnafous et al. found activity against HHV-6 was higher than standard cidofovir in both cidofovir-sensitive and -resistant strains. Furthermore, nephrotoxicity was less than with standard cidofovir because it does not accumulate in the kidney tubules [177].

While its characteristic presentation makes routine laboratory diagnosis of roseola unnecessary, it can be of value in severe cases or immunocompromised patients. This is best done using serologies, PCR, or viral culture. Traditionally, paired IgG sera taken within the first week of illness and 10–14 days later has been the gold standard for diagnosis, with a fourfold or more increase indicative of active infection. There is some cross-reactivity between HHV-6 and HHV-7 but this will show HHV-6 seroconversion in an HHV-7 negative individual or vice versa. Antibody avidity tests may be needed to distinguish primary HHV-7 infection in the setting of previous HHV-6 infection [179]. Serum IgM detection is less reliable. Current techniques use qualitative and quantitative PCR to confirm positive serologies; however, these do not reliably distinguish primary infection from latent or reactivated virus. Reverse transcription-PCR may help distinguish between active and latent HHV-6 infection [180]. HHV-6 can be cultured from peripheral blood mononuclear cells (PBMC), but this test is not always available.

Specific Investigations Recommended

For diagnosis
None typically
HHV-6 serology (paired acute and convalescent IgG)
PCR (serum, plasma, or CSF)
Viral culture (PBMC)

Table 18.57 First line therapies

Antipyretics	E
IV hydration	E
Antiepileptic for seizure >5 min	E

Table 18.58 Second line therapies

Ganciclovir	B
Foscarnet	D

Table 18.59 Third line therapies

Cidofovir	E

Gianotti-Crosti Syndrome

Clinical Features

Gianotti-Crosti syndrome (GCS), also known as papular acrodermatitis of childhood, is characterized by a papular or papulovesicular eruption following various infections or vaccinations [184–192]. Lesions are comprised of asymptomatic or mildly pruritic erythematous monomorphic papules and papulovesicles (Fig. 18.21). Unlike classic viral exanthems that mostly involve the trunk, GCS is distributed symmetrically over the face, buttocks, and extensor upper and lower extremities. Mucous membranes are not involved. Typical preceding symptoms include a low-grade fever, upper respiratory symptoms, diarrhea, and axillary or inguinal lymphadenopathy [184]. Hepatomegaly and splenomegaly are uncommon. The eruption appears approximately 1 week later and resolves without scarring in 3–4 weeks, although longer courses have been described. Relapses are rare.

GCS predominantly affects children 1–6 years of age, and there is an increased incidence in children with a history of atopy. Although GCS was initially described in association with Hepatitis B virus (HBV) in the 1960s, many other viruses, including Epstein-Barr (EBV), influenza, and molluscum contagiosum, have since been implicated. HBV is a rare cause in the United States, and EBV is now the most common cause. Bacterial infections may rarely trigger GCS [186]. GCS is also associated with immunizations, and has been reported to occur after measles-mumps-rubella (MMR), *Haemophilus*, oral polio, and diphtheria-pertussis-tetanus

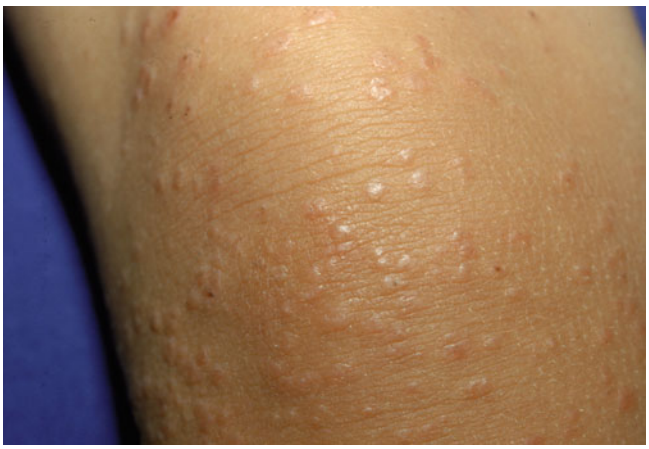

Fig. 18.21 Flat-topped monomorphic papules on the extremities of Gianotti-Crosti syndrome

vaccines [190]. Despite the connection between HBV and GCS, immunization against HBV rarely causes GCS [182].

Diagnosis is made clinically. A thorough physical examination, including lymph node and abdominal exams to assess for hepatosplenomegaly, should be performed. Histopathologic features are nonspecific and include acanthosis, hyperkeratosis, spongiosis, and a lymphohistiocytic perivascular infiltrate. Hepatitis serologies and liver function studies should be checked if there is strong clinical suspicion of hepatitis.

Management Strategies

Gianotti-Crosti syndrome is self-limited and treatment is supportive. Lesions are usually asymptomatic, but if pruritus is present, oral antihistamines or topical anti-pruritics may be helpful. Topical and systemic corticosteroids can be used, but their efficacy has not been well-established [182]. If associated infections such as Lyme, streptococcal, or hepatitis B are confirmed, therapy with oral antibiotics or antivirals may be warranted [183].

Specific Investigations Recommended

For diagnosis
Liver enzymes (if gastrointestinal symptoms present and strong clinical suspicion of hepatitis)
Viral serologies: Epstein-Barr virus, hepatitis B surface antigen

Table 18.60 First line therapies

Topical antipruritics	E
Topical corticosteroids	E
Emollients	E
Systemic antihistamines	E
Systemic corticosteroids	E

Table 18.61 Second line therapies

Systemic antibiotics	E
Systemic antivirals	E

Unilateral Laterothoracic Exanthem/ Asymmetric Periflexural Exanthem of Childhood

Clinical Features

Unilateral laterothoracic exanthem (ULE), also known as asymmetric periflexural exanthem of childhood (APEC), is a mildly pruritic eruption that begins unilaterally near the axilla or inguinal crease, and spreads centrifugally to become bilateral and asymmetric. Early lesions are 1–2 mm erythematous coalescing papules with a surrounding pale halo. Over time, papules become more scaly and eczematous, with a central dusky color (Fig. 18.22) The lesions resolve with fine desquamation and postinflammatory pigmentation in 5 weeks. Children ages 1–5 years are typically affected during the winter or spring. Preceding or concomitant symptoms of fever, upper respiratory symptoms, vomiting, diarrhea, or lymphadenopathy (consisting of an enlarged lymph node where the exanthem starts), are often present [195–198]. For this reason, although there is no clear viral cause, a viral etiology has been suspected. Viral infections including adenovirus [198], parainfluenza 2 and 3, parvovirus B19 [196], human herpesvirus 6 and 7, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) have been associated with ULE. Recent reports have suggested that a postzygotic mutation in embryogenesis may change the cutaneous epitopes on one side of the body and cause an altered responsiveness of the skin to infections, leading to a mosaic presentation [198].

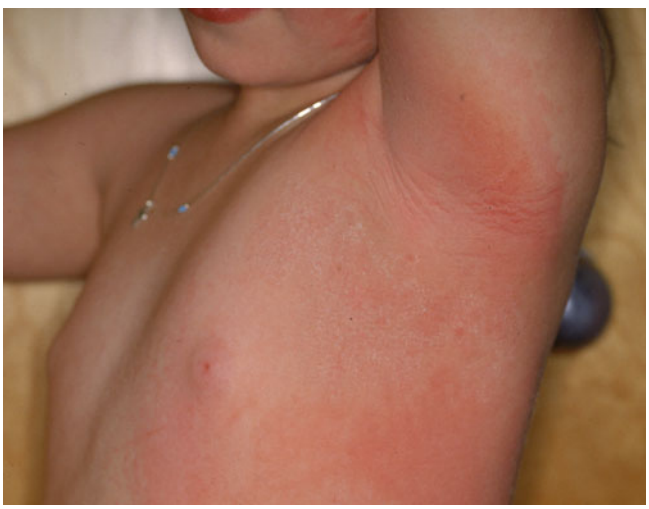

Fig. 18.22 Confluent fine erythematous papules of unilateral laterothoracic exanthem

Diagnosis is based on clinical presentation, and further investigations are not necessary. Histopathologic features show lymphocytic infiltration of blood vessels and eccrine ducts, and exocytosis of lymphocytes into the acrosyringium.

Management Strategies

ULE spontaneously resolves typically in 3–4 weeks, but can take up to 8 weeks. Treatment is aimed at symptom management. Pruritus is mild in most cases and can be treated with topical emollients, topical antipruritics, and oral antihistamines. Topical corticosteroids have shown mixed results [193, 194].

Specific Investigations Recommended

For diagnosis
Consider checking viral serologies: EBV, parvovirus B19, adenovirus

Table 18.62 First line therapies

Topical emollients	D
Topical antipruritics	D
Oral antihistamines	D

Table 18.63 Second line therapies

Topical corticosteroids	D

Enteroviral Exanthems

Clinical Features

Enteroviruses comprise a subgroup of picornaviruses that cause a wide spectrum of disease. The human enterovirus group includes polio, echoviruses, coxsackieviruses A and B, and enteroviruses 68–71. Transmission occurs via the fecal-oral route, often in swimming pools, in the summer and fall. Enteroviruses may cause severe infections such as neonatal sepsis, meningitis, myocarditis, and polio. Polioviruses, which do not cause exanthems, have largely been eliminated from the world. Most infections caused by enteroviruses are benign, self-limited, febrile illnesses. There are a variety of exanthems and enanthems associated with non-polio enteroviruses, which will be elaborated on in more detail [204].

Non-polio enteroviruses cause a broad spectrum of symptoms including fever, malaise, vomiting, diarrhea, pharyngitis, respiratory symptoms, aseptic meningitis, myositis, hemorrhagic conjunctivitis, and exanthems. The typical exanthem consists of nondescript erythematous macules and papules in a morbilliform pattern. Petechial, purpuric, urticarial, scarlatiniform, and vesicular lesions have also been described.

Hand-foot-and-mouth disease (HFMD) is a common enteroviral exanthem that frequently affects children younger than 5 years. Clinical features may include fever, malaise, upper respiratory symptoms, and odynophagia. The characteristic exanthem consists of triangular or elliptical-shaped vesicles surrounded by erythema on the palms, soles, dorsal hands and feet, and buttocks (Figs. 18.23 and 18.24). More widespread vesicular exanthems have also been reported [206]. The associated enanthem involves painful vesicles and erosions on the buccal surfaces, tongue, uvula, tonsillar pillars, and hard and soft palates (Fig. 18.25). Onychomadesis is common following

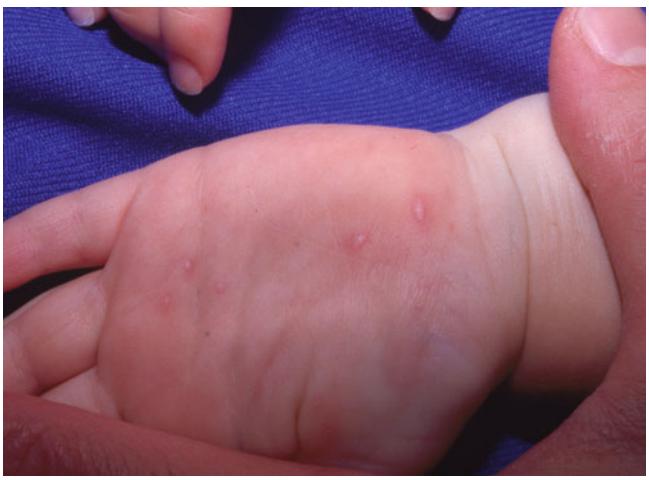

Fig. 18.23 Elliptical-shaped vesicles with surrounding erythema in a toddler with hand-foot- mouth disease

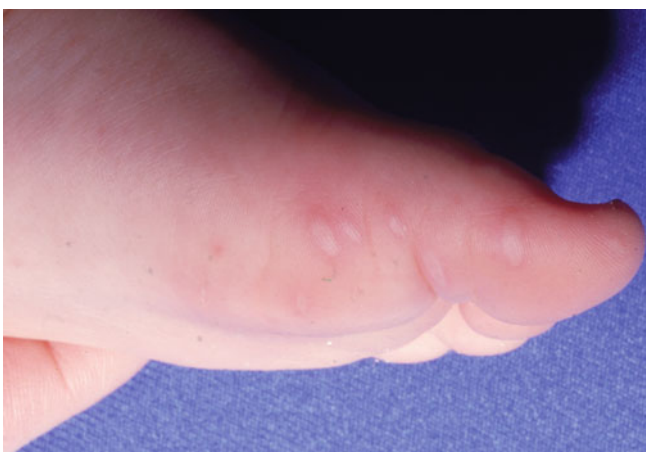

Fig. 18.24 "Football"-shaped vesicles on the foot of a toddler with hand-foot-mouth disease

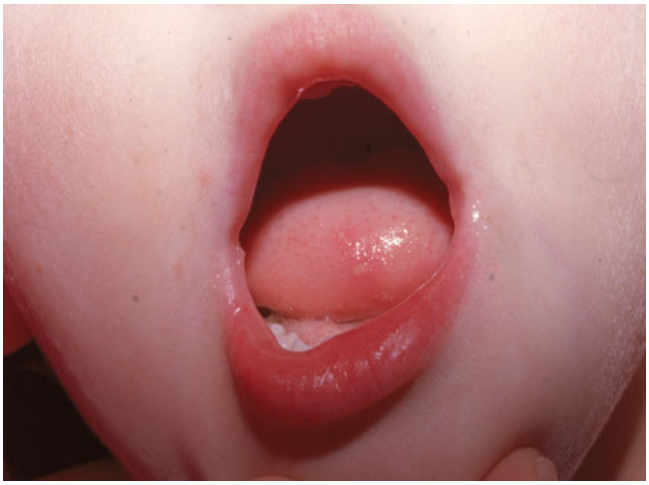

Fig. 18.25 Erosion on the tongue in the toddler with hand-foot-mouth disease

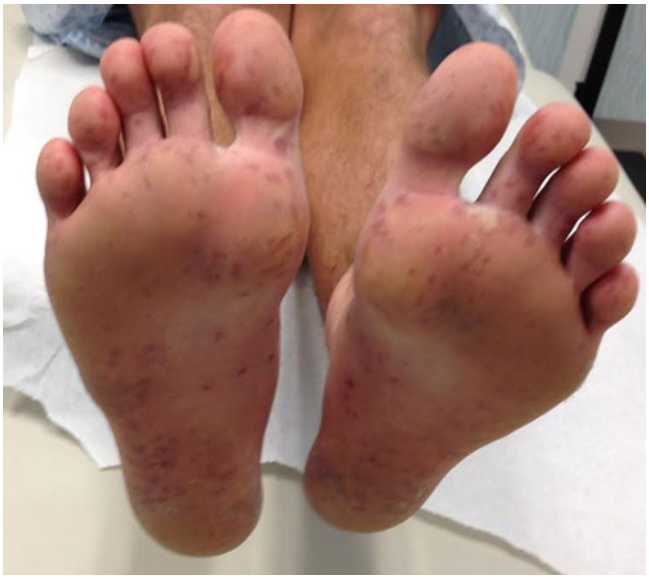

Fig. 18.26 Petechial and purpuric macules on the plantar surface of a teenager with presumed Coxsackie A6 eruption

HFMD as a result of temporary nail matrix arrest related to viral infection. HFMD is most commonly associated with coxsackievirus A16, but has also been caused by coxsackieviruses A5, A7, A9, A10, B1, B2, B3, B5, and enterovirus 71. Epidemics caused by enterovirus 71 led to several deaths due to pulmonary edema and hemorrhage, meningitis, myocarditis, and flaccid paralysis in 1998. Since 2011, an atypical form of HFMD caused by coxsackievirus A6 has been increasingly reported in the United States [202]. This atypical HFMD is characterized by fever and a widespread erythematous papulovesicular eruption that extends beyond the classic distribution of palms and soles. Vesicles, bullae, hemorrhagic bullae, erosions, papules, and petechiae (Fig. 18.26) tend to have a predilection for the perioral region and sites of atopic dermatitis, similar to eczema herpeticum. It has therefore been labeled as "eczema coxsackium [203]." Diagnosis is made clinically based on physical examination in most cases of typical HFMD. In cases of atypical HFMD, laboratory confirmation with viral polymerase chain reaction (PCR) and culture, both of vesicle fluid, may be necessary. PCR can also be performed on oropharyngeal (throat swab) or stool specimens (bulk stool or rectal swab).

Herpangina is an enanthem characterized by fever, sore throat, and painful vesicles and erosions involving the soft palate, uvula, and tonsillar pillars. It is typically caused by coxsackieviruses A, but other causes include coxsackieviruses B, and echoviruses. Lesions are similar to herpetic gingivostomatitis, but more frequently affect the posterior oral cavity rather than the lips [202].

Echoviruses cause an array of exanthems with morbilliform, vesicular, urticarial, erythema multiforme-like, and petechial morphologies. There are often concomitant systemic symptoms of fever, upper respiratory symptoms, and gastrointestinal symptoms. Echoviruses 7, 11, 19, and 30 have been associated with outbreaks in neonatal units. Echovirus 6 has been reported to cause a dermatomal vesicular zoster-like eruption. Echovirus 9 has caused epidemics of aseptic meningitis with petechiae similar to meningococcemia. Echovirus 16 has been associated with a roseola-like exanthem. Echoviruses 25 and 32 have been linked to *eruptive pseudoangiomatosis*, an enteroviral exanthem marked by acute hemangioma-like lesions [199].

Management Strategies

Most enterovirus exanthems run a benign, self-limited course and resolve within a few weeks. Treatment is supportive, and consists of adequate hydration and pain control [199]. For more severe enterovirus infections associated with meningitis and septicemia in neonates [205] or immunocompromised populations, systemic treatment with intravenous immunoglobulin (IVIg) or pleconaril, an antiviral drug that prevents enterovirus attachment, entry and uncoating, can be considered [199–201].

Specific Investigations Recommended

For diagnosis
DFA from floor of intact vesicle to exclude HSV or VZV infection
Enterovirus PCR from vesicle fluid, oropharyngeal (throat swab), stool specimen,or rectal swab
Acute (IgM) and convalescent (IgG) enterovirus serologies and viral culture (although yield is suboptimal)

Table 18.64 First line therapies

Antipyretics	E
Analgesics	E
Hydration	E

Table 18.65 Second line therapies

Intravenous immunoglobulin 750 mg/kg	C
Pleconaril 5 mg/kg TID for 7–10 days	B

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Bites and Infestations

19

Tina S. Chen

Introduction

Bites and infestations are a common and important cause of skin findings in children. They may cause mechanical, chemical, allergic, and infectious damage to the skin. They are most often caused by the phylum Arthropoda, which contains more species than all the other species in the world combined. Arthropods are invertebrates with a segmented exoskeleton comprised of chitin, a modified polysaccharide, and are comprised of three different classes: Arachnida, Insecta, and Myriapoda. Arachnids have eight legs and include mites, ticks, spiders, and scorpions. Insects have six legs and include lice, flies, mosquitoes, fleas, bugs, bees, wasps, ants, caterpillars/moths, and beetles. Centipedes and millipedes belong to the class Myriapoda and have multiple pairs of legs. Lastly, this chapter will also include cutaneous larva migrans, as well as some common marine causes of skin disease.

Class Arachnida

The class Arachnida includes mites, ticks, spiders, and scorpions. Adults and nymphs have four pairs of legs while larvae have three pairs of legs. Arachnids cause human disease by puncturing and feeding on tissue fluids, and some are important vectors of infectious diseases as well.

Order Acarina

The order Acarina is comprised of mites and ticks. These are arachnids that commonly cause cutaneous findings. Scabies is the most common mite infestation in humans, affecting approximately 300 million people worldwide [1]. Scabies has been infecting humans worldwide for over 2,500 years. Besides scabies, several other mites are important vectors of cutaneous disease. They are small arachnids (0.1–2 mm in size) and usually not found specific to any host. Adhesive tape stripping or vacuum cleaner filters may sometimes help to capture and identify mites, though the actual offending creature is often not found. They uniformly puncture and feed on tissue fluids, commonly leading to papular, papulovesicular, bullous, urticarial, or morbilliform eruptions. Ticks are blood-sucking arachnids that may not only cause cutaneous symptoms but also transmit a myriad of diseases.

Scabies

Clinical Features

Scabies is a very common mite infestation caused by an obligate human parasite (*Sarcoptes scabiei* var. *hominis*) that can only survive away from human epidermis for 72 h. The mite is transmitted via direct contact with an infected individual or fomites, and incubates on average for 1 month prior to the development of cutaneous symptoms. Repeat infestations tend to have a shorter incubation period. Scabies is more commonly found in young children, as well as those in situations of overcrowding, poor hygiene, poor nutritional status, homelessness, dementia, and sexual contact [2].

The hallmark for scabies infestation is pruritic, excoriated papules, nodules, burrows, vesicles, and/or pustules, that is often more symptomatic at night or when the patient feels warm (for example, after a hot bath). Lesions are commonly found in the Circle of Hebra, the ring drawn from the main sites of involvement: axillae, elbows, wrists, hands (especially interdigital spaces and palms), and

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genitals. Other frequently affected sites include the waist, soles, and postauricular skin, and in women, the areolae and nipples. The infestation does not tend to affect the face and scalp in adults, but the scalp can be affected in infants. Infants may also demonstrate poor feeding and irritability.

A very high number of mites may result in an extremely contagious condition known as crusted scabies (Norwegian scabies), which clinically resembles a scaly eczematous dermatitis. Crusted scabies can be lichenified and is more often found in immunocompromised individuals. All presentations of scabies can be secondarily infected. Symptoms of infestation may persist for weeks after successful therapy, due to hypersensitivity to the mites, a condition referred to as post-scabietic pruritus.

Investigations Recommended

For diagnosis
Clinical examination for classic-appearing burrows, often with a vesicle or small pustule at the end of a burrow
Skin scraping with mineral oil for microscopic identification of mites, ova (eggs) or scybala (scabies feces)
Biopsy if diagnosis is uncertain
High-magnification videodermatoscopy or PCR of scale can confirm diagnosis, though very rarely necessarily

Management Strategies

Treat all close contacts to limit spread of disease
Wash clothing, sheets and towels in hot water (140 °F, 60 °C) and dry with high heat [3]
Vacuum and clean living quarters
Put stuffed animals, other toys and fomites in a plastic bag for 72 h
Of note, pets do not need to be treated since they cannot harbor these mites

Therapies [3–14]

In general, the face and scalp do not need to be treated unless the patient is an infant or immunocompromised. Resistance to topical therapies has begun to emerge.

Table 19.1 First line therapies

Permethrin 5 % cream, applied from the neck down and rinsed off after 8–14 h, repeat in 1 week	A
Contraindicated in infants under 2 months of age	
In pregnant women, shorten the application to 2 h prior to rinsing off	
Ivermectin 200 μg/kg per dose, taken orally for one dose; repeat in 2 weeks:	A
Off-label use	
Consider in severe cases, crusted scabies or immunocompromised individuals	
Not recommended in children under 15 kg of weight or in pregnant or nursing women	
Malathion 0.5 % lotion to dry hair for 8–12 h then rinsed off; repeat in 7–9 days:	C
FDA approved over 6 years of age	
Flammable	

Table 19.2 Second line therapies

Sulfur 6–10 % ointment compounded into petrolatum or mineral oil applied from the neck down 1–2 times daily for 3–5 days and rinsed off 24–48 h after the final application	B
Can be used in pregnant women and infants	
Ivermectin 1 % lotion to applied at a dose of 400 μg/kg, repeated in 1 week	A
Crotamiton 10 % cream applied from the neck down 1–2 times daily for 5 consecutive days and rinsed off 24 h after the final application; repeat one overnight application 1 week after initial day of application:	B
Resistance common	
Intralesional corticosteroids for nodular lesions	E
Topical steroids and antihistamines for post-scabietic pruritus	E

Table 19.3 Third line therapies

Benzyl benzoate 25 % lotion applied from the neck down every other night for 3 applications:	B
Should not use in infants and young children	
Not available in the United States	
Lindane 1 % lotion applied from the neck down and rinsed off after 8–12 h neck, repeat in 1 week:	A
Avoid under 2 years of age as well as pregnant or nursing women given possible neurotoxicity	
Banned in California	
Resistance common	
American Academy of Pediatrics does not recommend its use in children	
Monosulfiram soap	C*
Topical thiabendazole solution	B*
Co-trimoxazole	D*
Natural pyrethrins	C
Topical dimethicones	A

Chiggers (Harvest Mites, Jiggers, "RED BUGS")

Clinical Features

Chiggers, *Trombicula alfreddugesi*, are unique in that only the six-legged larvae, and not the eight-legged adults or nymphs, affect humans and animals. Found most commonly in the southern United States, the larvae are found in vegetation, and attaches to those who pass by. Chigger infestation is self-limited, usually seen in the summer and fall, and presents as intensely pruritic, grouped, edematous, erythematous 1–2 mm papules or papulovesicles, with a hemorrhagic punctum at sites of constricted clothing (elastic in socks, edges of underwear, belts at the waist) [15]. In boys and men, chiggers can also be found on the penis, causing "summer penile syndrome" with symptoms of penile swelling, pruritus, and dysuria. The larvae inject an irritating substance into the skin, causing the pruritus, before falling off the skin or being scratched off. Secondary infection may develop.

Investigations Recommended

Investigations recommended
None

Management Strategies

Permethrin on clothing for prevention
Washing immediately after exposure may help prevent symptoms

Therapies [16]

Supportive care with antipruritics (camphor, menthol), cool compresses, topical anesthetics (pramoxine), topical or intralesional corticosteroids, and oral antihistamines	E*
Vinegar (5 % acetic acid) may help with post-exposure prophylaxis and symptomatic relief of pruritus	E*

Cheyletiella (Walking Dandruff)

Cheyletiella are relatively larger non-burrowing mites (approximately 0.4 mm in length) caused by animal-specific mites. They are found on dogs, cats, and rabbits and are caused by *Cheyletiella yasguri*, *Cheyletiella blakei*, and *Cheyletiella parasitivorax*, respectively. Affected animals have fine, flaking scale, but may not exhibit any symptoms of infestation. These mites do not live on human skin; they quickly bite a nearby human and return to their animal hosts, causing grouped pruritic papules, vesicles, bullae, and wheals.

Investigations Recommended

For diagnosis
Have pets evaluated by a knowledgeable veterinarian
Brushings from animal's hair and place in a plastic bag with alcohol where mites will float while hair and scales sink
For treatment
None

Management Strategies

Management strategies
None

Table 19.4 Therapies

Supportive care	E*
Dips and shampoos from veterinarians for pets, including fipronil, permethrin, and amitraz	E*

Grain and Avian Mites

Clinical Features

As the name suggests, grain mites are found in grain and straw. Bites from these mites result in intensely pruritic macules, papules, vesicles, or pustules followed by urticarial wheals without burrows. Fever and purpura may develop in more severe cases. Avian mites (also known as fowl mites or bird mites) are rarely found on humans, but instead are found in nearby birds, nests, clothing, and bedding. Two different

genera of avian mites cause accidental skin eruptions, termed gamasoidosis in humans: *Dermanyssus* and *Ornithonyssus*. Eruptions are typically a widespread pruritic papular dermatitis with a morbilliform appearance, with possible vesicles and urticarial wheals without burrows. Eruptions from either type of mite are self-limited.

Investigations Recommended

For diagnosis
Search for avian mites on clothing, bedding, nests and nearby birds

Management Strategies

Management strategies
None

Table 19.5 Therapies

Supportive care	E*

Demodex

Clinical Features

Demodex mites, *Demodex folliculorum* and *Demodex brevis*, are normally found in human pilosebaceous units of the head and neck. In some susceptible individuals, they may cause a pruritic folliculitis on the face and/or trunk comprised of both papular and pustular lesions, occasionally with a perioral affinity resembling rosacea. *Demodex* often may affect the eye as well, leading to blepharitis, chalazions, and other findings. This eruption is more common in adults and, in children, may suggest immunocompromise.

Investigations Recommended

For diagnosis
A skin biopsy may be helpful when diagnosis is uncertain

Management Strategies

Management strategies
None

Table 19.6 Therapies [17–22]

Permethrin 5 % cream applied to affected area, wash off in 8–14 h, and repeat in 1 week if needed	E*
Crotamiton 10 % to affected areas twice daily until improved	E*
Benzoyl peroxide 2–10 % wash or gel to affected area daily until improved	E*
Oral metronidazole 15 mg/kg/day or 750 mg/day in divided doses for 2–3 weeks	E*
Oral ivermectin 200 μg/kg per dose, taken orally for one dose; can be taken in conjunction with oral metronidazole	B*
Topical ivermectin 1 % cream daily for 12 weeks, metronidazole 0.75 % or 1 % gel or cream, sulfur, sodium sulfacetamide, benzoyl benzoate, lindane, hexachlorocyclohexane or camphor oil have also been reported	E*

Ticks

Clinical Features

Ticks are round arachnids with specialized mouth parts for sucking blood. There are three categories of ticks: hard ticks (Ixodidae), soft ticks (Argasidae), and Nuttalliellidae. Only hard and soft ticks bite humans; however, hard ticks transmit the majority of diseases because they can remain attached to human skin, whereas soft ticks do not. Most tick bites are painless, and transmission of diseases usually result only after 24 h of tick attachment. Tick-borne diseases often have specific vectors, and more than one disease can be transmitted at a time. *Ixodes scapularis* and *I. pacificus* transmit Lyme disease, babesiosis, human granulocytic ehrlichiosis (human anaplasmosis), and in Europe, may cause viral encephalitis. The *Dermacenter* ticks, *D. variabilis* (the American dog tick) and *D. andersoni* (the Rocky Mountain wood tick), are major vectors for Rocky Mountain Spotted Fever in the eastern and western United States, respectively. *D. andersoni* also transmits Colorado tick fever, Q fever, and tularemia. *Amblyomma americanum* (the lone star tick) is a vector for human monocytic ehrlichiosis. Ornithodoros soft ticks transmit borrelial relapsing fever. *Ixodes* ticks tend to bite the torso; *Amblyomma* ticks, the lower legs, buttocks and groin; *Dermacentor* ticks, the head, neck, and upper trunk.

Patients may present with the offending tick still attached, often thinking that it is a new mole, as the attached tick slowly engorges itself with blood before falling off up to 2 weeks later. Hypersensitivity reactions to bites may cause erythematous papular, nodular, bullous, and ulceronecrotic lesions that are usually pruritic. A classic sign of tick bites is the "comet" sign, where many bites spread from initial points in the distal areas of the ankles and legs [23].

Tick bites may lead to secondary infection, alopecia, cutaneous lymphoid hyperplasia, and granulomas (possibly related to retained mouthparts). "Tick bite pyrexia" may develop in some patients, causing fever, chills, vomiting, headache, flu-like illness, and abdominal pain. Systemic symptoms usually resolve within 36 h of tick removal. Notably, *Dermacentor* ticks hidden in the scalp may potentially cause life-threatening tick paralysis. This condition is more common in children, and resembles Guillain-Barré syndrome with a reversible ascending flaccid paralysis. The mortality rate is 10 % due to respiratory failure. Removal of tick parts leads to rapid resolution.

Investigations Recommended

For diagnosis
Thorough clinical examination for evidence of tick bites, attached ticks, or residual tick parts; if found, removal of entire tick including mouth parts and attachment cement, and without squeezing its abdomen
Lyme serology when appropriate
Rickettsial immunofluorescence and immunoperoxidase studies when appropriate
ELISA, PCR, and immunofluorescence available for some viruses such as West Nile

Management Strategies

Clothing to try to prevent bites:
Light-colored and long-sleeved clothing
Close-toed shoes
Tuck pants into socks
Insect repellents:
DEET or picaridin to exposed skin
Permethrin applied to clothing
Control of tick populations is important:
Exclusion of animal hosts
Removal of leaf debris
Treatment of ticks on animal populations and pets

Table 19.7 Therapies

Supportive care	E*
Potent topical or Intralesional corticosteroids for the tick bite reaction, if needed	E*
Diseases are treated specifically and beyond the scope of this chapter, though most tick-borne diseases such as Rocky Mountain Spotted Fever respond to doxycycline, which is the first-line therapy even in children and pregnant women; in pregnant women, if the disease appears to be mild, chloramphenicol may be an alternative choice of therapy	

Order Araneida

Spiders are found worldwide and play an important role in controlling insect populations. Spiders tend to bite out of self-defense and bites are common, though the offending spider is usually not identified. The two most clinically relevant species in the United States are the black widow (*Latrodectus mactans*) and brown recluse (*Loxosceles reclusa*) species and will be discussed here.

Black Widow Spider (*Latrodectus Mactans*)

Clinical Features

The black widow spider is a black- or brown-colored spider with a reddish hourglass visible on the ventral abdomen, and is found throughout the North American continent and Cuba. It has a potent depolarizing neurotoxin, alpha-latrotoxin, and female spiders are more dangerous due to their larger size. A black widow spins webs in cool, dark places and tends to bite only if threatened. Bites appear as two red marks with surrounding edema, and are normally seen on exposed skin, buttocks, or genitalia. The bites result in severe pain within minutes, and over the course of hours, chills, vomiting, muscle cramps, abdominal rigidity, and partial paralysis may ensue. A morbilliform eruption may sometimes be present, and several reports of resulting priapism exist in the literature [24]. Children may develop profuse sweating and become more agitated and irritable. Most black widow bites run a self-limited course, though a small minority of bites may be lethal.

Investigations Recommended

For diagnosis
Identification of the offending spider, when possible

Management Strategies

Management strategies
Medical observation if any systemic symptoms develop

Table 19.8 Therapies [25–28]

Specific antivenin, given up to 90 h after the bite	A*
Pain control, possibly requiring intravenous opiates	E*
Benzodiazepines (diazepam) as needed, though they do not shorten duration of symptoms and may have side effects	E*
Calcium gluconate as needed for associated tetany	E*
Antibiotics if secondarily infected	E*

Brown Recluse Spiders (*Loxosceles reclusa*)

Clinical Features

Many species of *Loxosceles* spiders can be found throughout the world. *Loxosceles reclusa*, the brown recluse spider, is found hidden in dark, dusty areas, such as attics and basements, predominantly in the Southeastern, Midwestern, and Southwestern United States. It is a brown spider with a dark-brown, violin-shaped mark on the dorsal cephalothorax measuring around 1 cm in size. The primary toxic enzyme is sphingomyelinase D, which has numerous hematologic effects, including red blood cell lysis and skin necrosis due to neutrophil activation. Other enzymes found include alkaline phosphatase, esterase, ATPase, and hyaluronidase. The spider tends to bite only in self-defense, and these slow-healing bites are usually found on the extremities. Mild cases result in a self-resolving urticarial reaction. Classically, a bite causes localized pain, pruritus and erythema within 6 h and progressively becomes more painful, ulcerated, and necrotic over the subsequent 18 h. Lymphangitis and gangrene may develop over the following week, occasionally together with a generalized petechial or morbilliform eruption, as well as fever, chills, nausea, and arthralgias. Serious systemic findings are rare, but may include necrotizing fasciitis, severe hemolysis, renal insufficiency, pulmonary edema, disseminated intravascular coagulation, and shock.

Investigations Recommended

For diagnosis
Identification of the offending spider, when possible
Complete blood count and fibrin split products

Management Strategies

Management strategies
Seek medical attention unless mild symptoms only

Table 19.9 First line therapies

Rest, ice, and elevation of bite site	E*
Tetanus prophylaxis, if needed	E*
Antivenin, if available	E*
Conservative debridement if necrotic and no longer spreading	E*

Table 19.10 Second line therapies

Sulfone (dapsone) 100–300 mg PO daily	E*
Antibiotics if secondarily infected	E*
Aspirin, antihistamines (cyproheptadine) and tetanus vaccination can be considered	E*
Intravenous fluids and systemic corticosteroids (1–2 mg/kg/day) if severe skin lesions, systemic symptoms and in small children, though controversial	E

Table 19.11 Third line therapies [23, 27, 29, 30]

Dapsone, colchicine, hyperbaric oxygen, vasodilators, heparin, topical nitroglycerin, electric shock, curettage, and surgical excision have been reported as possible therapies, but have variable results	E*

Order Scorpionida

Scorpions

Clinical Features

Scorpions are nocturnal, tropical arachnids with a stinger containing venom at the end of a curved, elongated tail. They are found worldwide, and in the United States, *Centruroides exilicauda* is the most common species, found most commonly in the southern states. Scorpions tend to hide in dark places and sandboxes, and sting only by accident or in self-defense. Stings deposit two toxins, a hemolytic toxin and a neurotoxin, typically leading to pain and paresthesias often out of proportion to the erythema and edema seen, accompanied by tachycardia and hypertension. Locally, other cutaneous findings that may be seen include petechiae, purpura, bullae, necrosis, and lymphangitis. The deposited neurotoxin may potentially cause salivation, vomiting, colicky abdominal cramps, psychomotor agitation, convulsions, cardiac arrhythmias, acute pulmonary edema [23] and, rarely, respiratory paralysis and death. In general, children are at higher risk for severe envenomation, as most fatalities from scorpion stings are reported in children younger than 10 years old [31, 32]. Notably, stings from the Egyptian scorpion lead to death from respiratory failure in 50 % of children.

Investigations Recommended

Investigations recommended
None

Management Strategies

Management strategies
Observe children after stings closely for at least 4 h, given higher risk of severe reaction to venom

Table 19.12 Therapies [23, 33–39]

Apply a tourniquet proximal to the area of sting, when possible, though controversial	E*
Local anesthetics (1–2 mL lidocaine 2 % or bupivacaine 0.5 %) without vasoconstrictors repeated every 30–60 min for up to 3 injections or application of ice to the bite	E*
Anti-venom, if available, best given within 4 h	B
If severe, admission to the Intensive Care Unit: intravenous fluids, sedation (intravenous or oral midazolam 0.05–2 mg/kg), anti-arrhythmics, anti-hypertensives (prazosin 30 µg/kg orally every 6 h for 48 h or until clinical improvement), and calcium-channel blockers as needed	E
Intravenous corticosteroids no longer recommended	E

Class Insecta

Insects have three body parts—a head, thorax and abdomen—and have three pairs of legs. This class of bugs is very clinically important, since approximately 25 % of reports of anaphylaxis are due to insect stings. Often times, only one family member may be bitten, even when all are exposed to the same environment.

Order Phthiraptera, Suborder Anoplura

Lice (or louse, if singular) are wingless, `flat-bodied insects that have been infesting humans worldwide for thousands of years. Three types of lice are clinically important—head lice (*Pediculus humanus* var. *capitis*), body lice (*Pediculus humanus* var. *corporis*), and pubic lice, also known as head crab or crab lice (*Phthirus pubis*). Lice are obligated to live off human blood, and measure 1–4 mm in size. Head and body lice are elongated and similar in appearance, whereas crab lice resemble a miniature version of the food.

Pediculosis Capitis (Head Lice)

Clinical Features

In children, head lice cause the most common of the lice infestations, and are most frequently seen in children ages 3–12 and their parents. It affects all races, though African-American children are less often infected. Head lice usually cannot survive away from the human host more than 36 h. Adult lice are approximately 1–3 mm in size and feed on the scalp every 4–6 h. Females live for approximately 1 month and lay five to ten eggs daily. Eggs, called nits, are 0.8 mm in size, and viable nits are usually found cemented by a proteinaceous matrix to the hair within 0.6 mm of the scalp, but can be farther away in warmer climates. Nits develop into adult lice over the course of 2 weeks. Bites from head lice are painless, and the hallmark of disease, intense scalp pruritus, usually manifests within 2–6 weeks of infestation. The diagnosis is made by identifying the louse or nits in the scalp. Erythematous macules, papules, excoriations, scaliness or secondary bacterial infection can sometimes be seen on the scalp. Cervical or suboccipital lymphadenopathy may also be present.

Investigations Recommended

For diagnosis
Thorough clinical examination for lice and nits
Mount on a glass slide for microscopic evaluation if needed
Dermoscopy may be of benefit

Management Strategies

Screen all close contacts and treat those found to have lice or nits simultaneously; empirically treat if any close contacts share a bed or comb
Clean hats and headgear
Vacuum living quarters
Over-the-counter permethrin 0.5 % spray for fomites (furniture, etc.)
Manual removal of nits with a fine-toothed nit-removal comb on damp hair; vinegar may help to loosen the cement
The American Academy of Pediatrics recommends against no-nit policies since they have not been found to be effective [40]
Wash clothing, sheets, and towels hot water (at least 122 °F, 50 °C) or on high heat in the dryer for a minimum of 10 min; place items not appropriate for laundering in a plastic bag for 1–2 weeks

Therapies

Of note, there is increasing resistance to some of these therapies, particularly permethrin and lindane. No therapies are reliably ovicidal, so repeat treatment in 1 week is recommended for all of the following. This also helps to fight growing resistance, which has already been reported with permethrin, pyrethrins, lindane, and malathion. Until safety is established for the following therapies, only mechanical removal of lice and nits is recommended for children under 2 years old, except for permethrin 1 % cream, which is FDA approved down to 2 months of age [3, 4, 13, 41–53].

Table 19.13 First line therapies

Over-the-counter permethrin 1 % lotion or cream rinse to damp hair and rinse off in 10 min without subsequent shampooing of hair for at least 24 h	A
Permethrin 5 % cream applied to hair and scalp overnight for 8–14 h and rinsed off in the morning	E*
Pyrethrins 0.3 % +/– piperonyl butoxide 4 % shampoo or mouse applied for 10 min then rinsed off:	A
Avoid in patients allergic to chrysanthemums and related plants such as ragweed	

Table 19.14 Second line therapies

Malathion 0.5 % lotion to dry hair for 30 min to 12 h then rinsed off; repeat in 7–9 days:	A
FDA approved over 6 years of age	
Flammable	
Spinosad 0.5–1 % topical suspension applied to dry hair for 10 min then rinsed off; repeat in 7 days:	A
Do not use in neonates and in lactating women	
Benzoyl alcohol 5 % lotion to dry hair for 10 min then rinsed off:	A
FDA approved over 6 months of age	
Can be used in pregnant or lactating women	
Ivermectin 200–400 μg/kg per dose, taken orally for one dose:	A
Off-label use and not recommended in children under 15 kg of weight or in pregnant or nursing women	
Ivermectin 0.5–1 % lotion to dry hair and scalp and rinse out with water in 10 min applied only once	A
Crotamiton 10 % lotion twice daily for 5 days	E
Topical occlusion therapy with petroleum jelly, dimethicones, or other occlusive agents	A
Mechanical removal (wet combing) of lice and nits every 3 days for 2 weeks	A

Table 19.15 Third line therapies

Lindane 1 % shampoo or lotion to dry hair for 4 min (shampoo) or overnight (lotion) then rinsed off; applied only once and not repeated:	A
Avoid under 2 years of age as well as pregnant or nursing women given possible neurotoxicity	
Banned in California	
American Academy of Pediatrics does not recommend its use in children	
Carbaryl 0.5 % lotion or shampoo for 8–12 h then rinsed off:	B
Not approved in the United States	
1,2-octanediol 1 % spray twice weekly to washed and dried hair for 6 weeks	A
Tocopheryl acetate 20 % spray to dry hair for 20 min, then washed	A
Oral trimethoprim-sulfamethoxazole 8–10 mg/kg/day divided BID for 10 days (alone or together with permethrin 1 %):	B
Off-label and mixed data	
Alternative considerations though not studied well:	E
Greasy occlusion of the scalp with Cetaphil Gentle Skin Cleanser, petrolatum jelly, styling gels, and various oils	
Shaving the head	
Hot air to the scalp for 30 min	
Herbal shampoos	

Pediculosis Corporis

Clinical Features

The body louse measures 2.4–4 mm in length and is most often found in areas of poor hygiene, poverty, and overcrowding. Unlike the other two types of lice, body lice are vectors of several human diseases, including epidemic typhus (*Ricketssia prowazekii*), relapsing fever (*Borrelia recurrentis*), trench fever, and bacillary angiomatosis (*Bartonella quintana*). The louse is rarely found on human skin, but rather, resides in the seams of clothing, where its nits can also be found, and it survives for up to 1 month away from the host. Bites from the body louse are usually painless, and result in erythematous or copper-colored macules, pinpoint papules or wheals, with a hemorrhagic punctum. Excoriations, secondary bacterial infections, furuncles, and lymphadenopathy may be found. Unlike scabies, the hands and feet are not typically involved.

Investigations Recommended

For diagnosis
Examine clothing for identification of body louse

Management Strategies

Wash clothing in hot water (at least 122 °F, 50 °C) or on high heat in the dryer for 30 min, and iron all seams
Treat clothing and fomites with permethrin 0.5 % spray, malathion 1 % powder, or dusting powders containing DDT
Abandon infested mattresses and other fomites for 1 month, or discard
Treat all household and close contacts
Improve personal hygiene as able

Table 19.16 First line therapies

Permethrin 5 % cream applied from the neck down and rinsed off after 8–14 h, repeat in 1 week:	E*
Contraindicated in infants under 2 months of age	
Pyrethrins 0.3 % +/− piperonyl butoxide 4 % shampoo or mousse applied for 10 min then rinsed off:	E*
Avoid in patients allergic to chrysanthemums and related plants such as ragweed	

Table 19.17 Second line therapies

Malathion 0.5 % lotion to dry hair for 8–12 h then rinsed off; repeat in 7–9 days:	E*
FDA approved over 6 years of age	
Flammable	
Ivermectin 200–250 μg/kg per dose, taken orally for one dose; repeat in 1–2 weeks:	E*
Off-label use and not recommended in children under 15 kg of weight or in pregnant or nursing women	

Table 19.18 Third line therapies [3]

Lindane 1 % lotion applied from the neck down and rinsed off after 8–12 h, repeat in 1 week:	E*
Avoid under 2 years of age as well as pregnant or nursing women, given possible neurotoxicity	
Banned in California	
Resistance common	
American Academy of Pediatrics does not recommend its use in children	
Carbaryl 0.5 % lotion or shampoo for 8–12 h then rinsed off:	E*
Not approved in the United States	

Pediculosis Pubis

Clinical Features

Crab lice are 1 mm in length and are usually considered a sexually transmitted disease, though can be non-sexually transmitted via close contact or contaminated clothing and bedding. They can be found in the hair, eyelashes (phthiriasis palpebarium) or eyebrows, especially in children. The infestation is most often diagnosed in males between 15 and 40 years of age. Patients classically present with pruritus in the pubic area, and the characteristic skin finding is maculae ceruleae, and asymptomatic gray-blue macules on the lateral abdomen and inner thighs due hemosiderin deposition. Erythema can often been seen around hair follicles, and excoriations, secondary infection, and local lymphadenopathy may be present. When the eyelashes are infested, the lice may appear like flecks of mascara.

Investigations Recommended

Investigations recommended
None

Management Strategies

Screen for other sexually transmitted diseases
Wash clothing, sheets, and towels

Table 19.19 First line therapies

Permethrin 1 % lotion or cream rinse to damp hair and rinse off in 10 min without subsequent shampooing of hair for at least 24 h (B*)	B*
Permethrin 5 % cream applied from the neck down and rinsed off after 8–14 h, repeat in 1 week (E*):	E*
Contraindicated in infants under 2 months of age	
Pyrethrins 0.3 % +/– piperonyl butoxide 4 % shampoo or mousse applied for 10 min then rinsed off:	A*
Avoid in patients allergic to chrysanthemums and related plants such as ragweed	
On eyelashes, occlusion with petrolatum jelly twice daily for 8 days followed by mechanical removal of nits	E*
Physotigmine 0.25 % or 1 % ointment for eyelashes	E*

Table 19.20 Second line therapies

Malathion 0.5 % lotion to dry hair for 8–12 h then rinsed off; repeat in 7–9 days:	E*
FDA approved over 6 years of age	
Flammable	
Ivermectin 200–250 μg/kg per dose, taken orally for one dose; repeat in 1–2 weeks:	E*
Off-label use and not recommended in children under 15 kg of weight or in pregnant or nursing women	

Table 19.21 Third line therapies [3]

Lindane 1 % shampoo; not approved for extensive body surface due to toxicity (B*):	B*
Avoid under 2 years of age as well as pregnant or nursing women, given possible neurotoxicity	
Banned in California	
American Academy of Pediatrics does not recommend its use in children	
Other reported but less well-studied therapies:	B*
Trimethoprim/sulfamethoxazole	
Oral tetracycline	
Pyrethrin ointment compounded in petroleum jelly (1:8)	
Cryotherapy	
Laser therapy	

Order Diptera

Mosquitoes and two-winged biting flies belong to the order Diptera. Bites from these insects are common, and usually of no significant consequence. Bites from adult mosquitoes and flies can be vectors of important human diseases. The treatment of these specific diseases is beyond the scope of this chapter. Fly larvae may cause a condition called myiasis, which is also briefly discussed below.

Mosquitoes

Clinical Features

Bites from mosquitoes (*Culicidae*) are the most common insect bites found in infants and children, though they can bite all individuals. They are attracted to bright clothing, moisture, heat, carbon dioxide, lactic acid, estrogen, and specific odors, which can be found in skin and hair products and perfumes. Bites typically cause pruritic, erythematous papules or wheals, often with a central punctum. Nodular, vesicular, bullous, and hemorrhagic reactions may also be seen, and secondary bacterial infection may occur.

Lesions are characteristically grouped with seasonal variation, typically occurring less often in colder months. Children tend to have more severe local reactions to bites compared to

adults. Mosquitoes are important vectors for several diseases around the world including, but not limited to, malaria, dengue, yellow fever, filariasis, and encephalitis (West Nile).

Investigations Recommended

Investigations recommended
None

Management Strategies

Prevention of bites is best, with long-sleeved, darker clothing and repellents
Minimize skin and hair products and perfumes
Reduce mosquito populations with insecticides and ultrasonic electronic devices

Table 19.22 Therapies [27]

Supportive care: oral antihistamines, cool compresses, topical antipruritic agents (calamine), and topical corticosteroids	E*
Oral corticosteroids if severe reactions	E*

Flies

Clinical Features

Noteworthy biting flies that cause human diseases include *Phlebotomus* flies (sand fly; transmits leishmaniasis, sandfly fever, and verruga peruana), *Lutzomyia* flies (sand fly; transmits leishmaniasis and Carrion's disease), *Mucosidae* flies (tsetse fly; transmits African trypanosomiasis), and *Simulidae* flies (black fly; transmits onchocerciasis). Bites are most common on exposed skin and are often painful, resulting in a pruritic papule or nodule, sometimes with overlying vesicles. Lesions typically self-resolve within several days.

Investigations Recommended

Investigations recommended
None

Management Strategies

Protective clothing and insect repellents
Reducing fly populations

Table 19.23 Therapies

Supportive care: oral antihistamines, acetaminophen, cool compresses, topical antipruritic agents (calamine), and topical corticosteroids	E*

Myiasis

Clinical Features

Myiasis is the result of fly larvae infestation in human skin. The human botfly *Dermatobia hominis* larvae may cause painful furuncles, sometimes accompanied by a "crawling" sensation in the skin, when eggs are accidentally deposited into human skin. Infestations with *D. hominis* are more commonly seen after travel to Central and South America. Larvae of the *Gasterophilus* fly may cause creeping myiasis, where larvae wander aimlessly intradermally. Clinically, this may appear as a tortuous line, ranging 1–30 cm in length.

Investigations Recommended

Investigations recommended
None

Management Strategies

Management strategies
None

Table 19.24 Therapies [54]

Extraction through occlusion with tape, nail polish, glue, petrolatum jelly, or paraffin	E*
Surgical excision	E*
Cryotherapy	E*
Application of irritant such as chewing tobacco or camphor oil to the skin	E*

Order Siphonaptera

Fleas belong to the order Siphonaptera. They have laterally compressed bodies with large hind legs. They are ubiquitous culprits for insect bites among humans and animals, and show little specificity to hosts. Control of flea populations may be important, as they are also vectors for several diseases, including bubonic plaque, endemic typhus, brucellosis, erysipeloid, and tungiasis. Of these diseases, only tungiasis will be briefly discussed in this chapter.

Flea Bites

Clinical Features

Flea bites are extremely common in humans. The most important fleas to cause bites in humans are the human flea

(*Pulex irritans*), cat flea (*Ctenocephalides felis*), and dog flea (*Ctenocephalides canis*). Interestingly, the cat flea is the most common flea found on domestic dogs. Flea bites appear as intensely pruritic papulovesicles or wheals, often with a hemorrhagic punctum. In children, tense bullae may form. Bites are most often found on the lower legs, and to a lesser extent, on other exposed skin such as the forearms. They tend to be multiple in number, and are sometimes found in zigzagging or linear clusters, as fleas tend to jump instead of fly.

Investigations Recommended

For diagnosis
Seek evaluation by a veterinarian for pets

Management Strategies

Eliminate fleas on pets with agents such as lufenuron
An exterminator may need to clear living quarters of fleas with pesticides

Table 19.25 Therapies

Supportive care: oral antihistamines, topical antipruritic agents (calamine), and topical corticosteroids	E*

Tungiasis

Clinical Features

Tungiasis is caused by the burrowing of the female sand flea (also known as the chigoe or jigger flea; *Tunga penetrans*) into the dermis. *T. penetrans* is the smallest flea in the world and is found in South and Central America as well as parts of the Caribbean, Africa, and India. As the name suggests, the condition tends to be in sandy or beach areas and is most often seen on the feet near the great toe. A typical lesion resembles a pea-sized, pruritic, painful abscess, sometimes with a central punctum, ulceration, and skin necrosis or secondary infection.

Investigations Recommended

Investigations recommended
None

Management Strategies

Infestation may be avoided by wearing shoes
Pesticides to infested regions if needed for population control of fleas

Table 19.26 First line therapies

Extraction of the flea with a sterile needle, curettage or excision	D*
Oral ivermectin 200–300 μg/kg daily ×1–2 days in a row, especially if multiple lesions	A*
Tetanus prophylaxis, if needed	E*
Treatment of secondary infection, if warranted	E*

Table 19.27 Second line therapies [13, 54–57]

Cryosurgery:	E*
Though often painful in young children	
Occlusion/suffocation of the lesion	E*
Oral thiabendazole 25 mg/kg/day	E*
Oral niridazole 30 mg/kg/day	A*
Topical dimethicones	B
Other reported topical therapies: ivermectin, metrifonate or thiabendazole	A*

Order Hemiptera

This group contains insects that are commonly known as "bugs." Examples include bed bugs, water bugs, stink bugs, and reduviid bugs (also known as kissing bugs, assassin bugs). Only bed bugs will be discussed here.

Bed Bugs (Cimicosis)

Clinical Features

Bed bugs are nocturnal, blood-sucking, wingless insects that have a flat, oval body, usually measuring 3–7 mm in size. The most common in the United States is *Cimex lectularius*, though *C. hemipterus*, found in more tropical climates, also commonly affects humans. It has not been proven whether bed bugs transmit diseases such as HIV, hepatitis B, and Chagas' disease. Over the past three decades, there has been an increased incidence of bed bug infestations within homes, now not limited only to overcrowded areas. They hide in cracks and crevices and bite exposed skin at night, classically biting in a somewhat linear pattern in groups of three, commonly referred to as "breakfast, lunch, and dinner." Lesions typically appear as pruritic, erythematous papules, wheals, or bullae. Systemic reactions are rare, but may include diffuse urticaria, angioedema, asthma, and anaphylaxis.

Investigations Recommended

For diagnosis
Inspect headboards, mattresses, and cracks and crevices in the walls for bed bugs

Management Strategies

Bed bugs are notoriously difficult to eradicate, as they can travel from one house to another and survive without food for a year
Eliminate any visible cracks or crevices and treat with dichlorvos, pyrethroids, malathion or permethrin, though these insecticides may cause illnesses, including one fatality [58]
Long-sleeved sleepwear
Vacuum hiding areas and wash linens with hot water
Permethrin-impregnated bed nets
Inspect and treat domestic animals, if infested
Inspect and rid nearby bats and birds, as they may harbor bed bugs

Table 19.28 Therapies [4, 54]

Supportive care: oral antihistamines, topical antipruritic agents (calamine), and topical corticosteroids	E*
Topical antibiotics if superinfected	E*
Systemic corticosteroids rarely needed	E*

Order Hymenoptera

All can cause dermatologic findings, including Wells syndrome (eosinophilic cellulitis). The most notable insects in this order are bees, wasps and ants, which are discussed below.

Bees, Wasps (Hornets, Yellow Jackets) and Ants

Clinical Features

Bees, wasps, and ants fall under the order Hymenoptera [54]. They all have four wings and six legs and tend to live and work together in colonies. Bees are found throughout the world, except the North and South Poles. They are the only insects that produce a food consumed by humans: honey. They are generally docile and only tend to sting when startled or threatened. Wasps help to keep fly, caterpillar, and other insect populations under control. Though some live in solidarity, wasps often live together in colonies and can be extremely aggressive if their nests are bothered. Yellow jackets tend to sting repeatedly and are the most common cause of allergic reactions and stings in the United States. Bee and wasp stings cause local burning pain, pruritus, and edema that may last for several days. Serum sickness can occur 1 week after the sting and, rarely, seizures, severe anaphylaxis, or even Kounis syndrome (allergic myocardial ischemia) may ensue [59]. Anaphylactic reactions may be fatal within minutes, leading to at least 40 deaths in the United States annually. A high number of bee stings at the same time may lead to multiple organ failure.

The most notable species of ants causing dermatologic symptoms is the fire ant *Solenopsis richteri and invicta*, which is most commonly found in the southern United States. Fire ants help control tick populations by eating their eggs, but also cause damage to livestock and crops. Their bites and stings on humans are particularly painful compared to those of other ants, and they often attack by both biting and stinging simultaneously without warning. Fire ants may leave eight bites in a circular pattern, and the painful erythematous, edematous papules classically evolve to become pruritic sterile pustules over hours. Anaphylaxis is rare but can be fatal. Bullet ants (*Paraponera* species) cause the most painful stings of the Hymenoptera order.

Investigations Recommended

Investigations recommended
None

Management Strategies

Management strategies
Those with known allergy to stings and bites should carry an EpiPen (or EpiPen Jr for kids)

Table 19.29 Therapies

Supportive care: oral antihistamines (dexchlorpheniramine), topical antipruritic agents (calamine), ice packs, and topical corticosteroids	E
Oral prednisone, beginning at 1 mg/kg/day or 30 mg daily in older children, for massive envenomation	E
Epinephrine 0.3 mL intramuscularly (and possibly repeated every 10 min), oral antihistamines, promethazine and systemic corticosteroids for anaphylaxis	E

Order Coleoptera

Blister Beetles

Clinical Features

Several types of blister beetles fall under this group, including the families *Meloidae*, *Oedemeridae*, and *Staphylinidae*. *Meloidae* and *Oedemeridae* exude cantharidin, while *Staphylinidae* exude pederin, a different vesicating agent. The most relevant blister beetle in dermatology is the Spanish fly *Lytta vesicatoria* (previously named *Cantharis vesicatoria*), belonging to the family Meloidae. When it is threatened or compressed, it exudes cantharidin, the chemical frequently used to treat molluscum contagiosum and warts in children. Contact with cantharidin or pederin causes an immediate burning or tingling sensation, with bullae formation often in

a linear pattern (dermatitis linearis) in the subsequent 24–48 h. The chemical agent may cause corneal erosions if it comes contact with the eye. Severe manifestations from contact with cantharidin may lead to fever, nausea, and vomiting. Ingestion by children may cause oral blisters, vomiting, abdominal pain, and renal failure.

Investigations Recommended

For diagnosis
Ophthalmology consultation if the eye is affected

Management Strategies

Avoidance of contact with these beetles (mosquito nets, decreased use of artificial lighting)
Clinical monitoring for systemic symptoms if ingested

Table 19.30 Therapies [54]

Supportive care: drainage of bullae, cool compresses and topical antibiotics as needed	E*
Washing areas of contact with soap and water or iodine soon after contact may be of benefit	E

Order Lepidoptera

Butterflies and moths, as well as their larvae, caterpillars, belong to this category. Only caterpillars and moths cause cutaneous symptoms.

Caterpillars and Moths

Clinical Features [60, 61]

In the United States, the most common offending creatures of caterpillar dermatitis (lepidopterism) are the brown-tail moth (*Euproctis chrysorrhoea*) and the puss caterpillar (*Megalopyge opercularis*). The brown-tail moth is found throughout Europe and along the coast of Maine and Cape Cod; the puss caterpillar is found in the southeastern states and is responsible for the severe stings in the United States. Another common caterpillar to cause cutaneous symptoms is the Io moth (*Automeris io*), which is found primarily in Southern Canada and the eastern United States. With a few rare exceptions of moth species, caterpillars and moths do not bite humans, but can cause cutaneous disease when the hairs or scales from the creatures or their eggs and cocoons come in contact with the skin. The hairs often cause mechanical damage, but can also impregnate toxins containing histamine, and other vasoactive substances such as kinins and plasminogen activators, into the skin. Caterpillars and moths cause a wide range of clinical findings, from mild eczematous dermatitis to life-threatening systemic symptoms. Typically, the hairs cause pruritic, erythematous macules, papules, vesicles, or wheals. Hairs on clothing can lead to diffuse lesions. Irritating hairs in contact with the eye may result in severe conjunctivitis, ocular pruritus, and ophthalmia nodosa (an immediate toxic response followed by granulomatous inflammation secondary to foreign bodies). Oral exposure in children usually leads to drooling accompanied by a mild, self-limited lip or mucosal irritation. Ingestion can cause lesions along the gastrointestinal tract and may require endoscopy for removal of the hairs. Serious systemic symptoms are uncommon but may include fever, nausea, numbness, arthralgias, cramps, pharyngitis, malaise, diaphoresis, headaches, dizziness, seizures, renal failure, anaphylaxis, and life-threatening intracranial hemorrhage [62]. These findings are mostly seen with some species of caterpillars and moths outside the United States.

Investigations Recommended

Investigations recommended
None

Management Strategies

Clinical monitoring if severe systemic symptoms
Removal of embedded hairs with forceps or tape stripping
Manual removal of caterpillars and cocoons

Table 19.31 Therapies

Supportive care: corticosteroids (topical, intralesional or oral depending on severity), cool compresses, antipruritic topical agents (calamine), pramoxine and local anesthesia as needed	E*

Class Myriapoda

Centipedes and millipedes belong to the Myriapoda class. Centipedes belong to the order Chilopoda; millipedes, to the order Diplopoda [23].

Centipedes

Clinical Features [63]

Centipedes have 17 or more segments and may be up to 25 in. in length (*Scolopendra* genus), causing some to report

having been bitten by a snake. Centipede bites are most common in tropical and subtropical regions, and most bites occur indoors at night and involve an extremity [64]. A centipede bite normally runs a benign, self-limited course and may be painful or painless, depending on the species. The two large tusks cause bites to appear as a pair of hemorrhagic marks forming a chevron shape accompanied by pain, edema, and erythema at the bite site and possible pruritus, lymphangitis, and paresthesias as a result of the neurotoxic venom. The bites may occasionally be accompanied by constitutional symptoms or the development of Wells syndrome, a recurrent granulomatous dermatitis with eosinophilia. Rarely, rhabdomyolysis, coronary ischemia, proteinuria, or acute renal failure may transiently develop due to severe reactions to bites or to ingestion of centipedes by children. There have been very few reports of death caused by centipede bites in humans.

Investigations Recommended

Investigations recommended
None

Management Strategies

Management strategies
None

Table 19.32 Therapies

Supportive care for symptoms, including rest, ice, elevation, antihistamines (D*), and anesthesia such as local lidocaine (D*) as needed	D*
Tetanus immunization if needed	E*
Oral corticosteroids for severe reactions [65]	D*
Antibiotics as needed	D*
Topical or intralesional corticosteroids for Wells syndrome	E*

Millipedes

Clinical Features

Unlike centipedes, millipedes do not bite, but rather cause a self-limited chemical burn or dermatitis due to a secreted toxin. Millipedes commonly cause ocular burns from squirting the toxin. On the skin, the toxin may cause an erythematous or pigmented curved-shaped patch or plaque, sometimes with overlying vesicles. Prolonged exposure to a millipede may mimic a blue toe syndrome [66]. The strange appearance of the toxic burn may sometimes be confused as child abuse.

Investigations Recommended

Investigations recommended
None

Management Strategies

Wash off toxin as soon as possible with alcohol or ether
Ophthalmology consultation if eyes are involved

Table 19.33 Therapies

Supportive care for symptoms, including topical corticosteroids and anesthesia as needed	E*

Papular Urticaria

Clinical Features [4, 67]

This is a nonspecific hypersensitivity reaction that is most often and commonly seen in children ages 2–10 years old in response to insect and arthropod bites. It is not seen in infants, as it takes time to develop the type I hypersensitivity to bites. The eruption tends to occur most often in the late spring and summer seasons, and flea are the most common offenders. Clinically, papular urticaria may present as recurrent, pruritic red papules or urticarial wheals that occasionally lead to vesicles, bullae, nodules (including prurigo nodules), and secondary bacterial infection. This eruption may be localized to the area where bites occur, or may become generalized. Anaphylaxis may seldom occur.

Investigations Recommended

For diagnosis
Find offending agent to prevent recurring bites, if possible
Skin biopsy if needed to prove diagnosis to parents

Management Strategies

Prevention of bites with clothing and repellents such as DEET and picaridin
EpiPen Jr 0.3 mL of epinephrine 1:2,000 or EpiPen 0.3 mL of epinephrine 1:1,000 when necessary

Table 19.34 Therapies [4]

Supportive care: topical corticosteroids, cool compresses, antipruritic topical agents (calamine, menthol, camphor, pramoxine), oral antihistamines	E
Intralesional triamcinolone 10–40 mg/mL for nodules	E*
Oral prednisone tapered from 1 mg/kg for 10 days for severe cases	E

Insect Repellents

DEET (N,N-diethyl-3-methylbenzamide) is the most widely used, safest, and most effective insect repellent used worldwide [68]. It can be applied to both skin and cotton or wool clothing, but should not be applied under clothing. It is effective against mosquitoes, flies, chiggers, fleas, and ticks. Concentrations of 10–35 % are generally adequate, and concentrations of greater than 50 % are not recommended, given a plateau in clinical benefit. There is concern for rare toxic reactions including hypotension, seizures, respiratory distress, syncope, anaphylaxis, possible neurotoxicity, and even death [69]. Therefore, DEET is not to be used in infants under 2 months of age, and lower concentrations are recommended for children (10 % should be effective, and not to exceed 30 %). Apply DEET only sparingly to the face, and not on the hands, of young children. A high level of DEET can cause local irritation to the skin, including erythema and bullae.

A newer synthetic repellent that is equally efficacious and safe is picaridin. Picaridin is effective against mosquitoes, biting flies, and ticks, and concentrations of up to 20 % can be found. Unlike DEET, picaridin does not damage plastics or fabrics. It may also be less irritating to the skin. No reports of significant toxicity have been reported in medical literature. Permethrin 0.5 % can be spayed on tents and clothing to repel against several insects and arthropods, including mosquitoes, flies, and chiggers.

Second-line insect repellents may be helpful, but not necessarily as effective as DEET. These include other synthetic agents such as IR3535, as well as botanical repellents including soybean oil (Bite Blocker for Kids), citronella oil/candles, neem oil, fennel oil, cedar, eucalyptus, lemongrass, and geraniol. Some have also used ingested garlic or vitamin B1 with some efficacy as well.

Other Cutaneous Infestations

Cutaneous Larva Migrans (Creeping Eruption)

Clinical Features

Cutaneous larva migrans is a self-limited skin eruption caused by the larvae of dog and cat hookworms, *Ancylostoma caninum* and *Ancylostoma braziliensis*, respectively. The infection is most frequently found in tropical countries, but within the United States, is most commonly seen in the southeastern states. The offending worms live within the intestines of infected animals, and eggs are deposited in the soil with feces. Larvae from hatched eggs burrow into human skin and usually begin migrating with days of penetration. The larvae cannot complete their life cycles in humans as they cannot penetrate the dermis, and as a result, wander aimlessly in the epidermis for months. The eruption typically begins as pruritic erythematous papules on the extremities, buttocks, or genitalia, and evolves to serpiginous, raised, erythematous plaques that are 2–3 mm in width and migrate approximately 1–2 cm/day. Bullae may form, though rare. The lesions may become secondarily infected or ulcerated from scratching. Affected individuals usually exhibit no systemic symptoms, but may have eosinophilia or Löffler syndrome (pulmonary eosinophilia due to parasitic infestation) [70].

Investigations Recommended

Investigations recommended
None

Management Strategies

Management strategies
Control of dog and cat hookworm infections

Therapies

Use antihelminthic medications cautiously in children, as they are not very well studied in this population. Ultimately, eruptions resolve spontaneously in 2–8 weeks [71, 72].

Table 19.35 First line therapies

Ivermectin 150 μg/kg in children as a single dose or 200 μg/kg PO in adults daily for 1–2 days	D

Table 19.36 Second line therapies

Albendazole 15 mg/kg/day PO divided BID in children or 200–400 mg PO BID ×5–7 days in adults; rare side effects	D
Thiabendazole 25 mg/kg/day PO divided BID ×2–5 days; side effects include headache, dizziness, and gastrointestinal symptoms	D
Topical thiabendazole 500 mg/5 mL QID 2–3 weeks	D

Table 19.37 Third line therapies

Cryotherapy:	E
Often not effective and is painful for children	

Marine Eruptions

Marine parasites contain some of the most potent toxins known to man. Avoidance of these parasites is best, as accidental contact with these parasites may cause a wide

spectrum of clinical features, ranging from mild self-limited eruptions to drowning after loss of consciousness from systemic symptoms. Three of the more common eruptions caused by venom from marine organisms include cercarial dermatitis, seabather's eruption, and jellyfish stings.

Cercarial Dermatitis (Swimmer's Itch)

Clinical Features

Cercarial dermatitis, also known as swimmer's itch, is most often due to the *Trichobilharzia* species. In the United States, cercarial dermatitis is most commonly found in the mid- and southwestern states. Schistosomes are small parasites found in freshwater lakes and aquariums. Within these aquatic environments, snails serve as intermediate hosts, releasing cercariae into the water. Cercariae accidentally infect humans and usually die within hours in human skin. Infestation causes erythematous papules and papulovesicles on exposed skin. These lesions may become secondarily infected, and post-inflammatory hyperpigmentation is common. In some, sensitization occurs on initial exposure, and the eruption may only be present upon subsequent contact with cercariae.

Investigations Recommended

For diagnosis
PCR water analysis when necessary

Management Strategies

Management strategies
Avoidance of infested waters when possible

Table 19.38 Therapies [73]

Supportive care with topical corticosteroids, oral antihistamines and cool compresses as needed	E*
Systemic corticosteroids if severe	E*

Seabather's Eruption ("SEA LICE")

Clinical Features

Seabather's eruption is not a true infestation, but is included here because it can often be confused with cercarial dermatitis (swimmer's itch). The eruption is the result of a hypersensitivity reaction to stinging nematocysts of cnidarian larvae, most commonly *Linuche unguiculata* (thimble jellyfish) and *Edwardsiella lineata* (sea anemone). These larvae are transported to shore via ocean currents. Individuals swimming in the Caribbean and Gulf of Mexico are most likely to acquire this eruption, though the nematocysts can also be found off the coast of Southeast Asia, Brazil, and New York. Seabather's eruption presents with very pruritic erythematous papules, papulovesicles, or urticarial plaques, usually limited to the areas under swimming garments and in intertriginous areas. Rarely, systemic symptoms including fever, chills, headache, and nausea may accompany the pruritic rash. Symptoms usually begin within hours of exiting the water, but can range from minutes to 2 weeks after exposure.

Investigations Recommended

Investigations recommended
None

Management Strategies

Management strategies
Removal of bathing suits prior to rinsing with fresh water to try to prevent or reduce the eruption. Of note, fresh water may cause further discharge of toxins from the nematocysts

Table 19.39 Therapies [74]

Supportive care with topical corticosteroids and oral antihistamines as needed	E*
Vinegar to the affected areas may help to deactivate remaining nematocysts	E*

Jellyfish Stings

Clinical Features

Jellyfish belong to the phylum Cnidaria, and are marine invertebrates with toxic fluid found on their bodies and tentacles. Similar to seabather's eruption, the stings are not true infestations, but are included here as they are responsible for the most frequent ocean-related stings to humans. Jellyfish stings may cause a wide range of cutaneous manifestations, including erythema, pruritus, intense burning, urticaria, papules, papulovesicles, plaques, dermatitis, and local necrosis in a somewhat linear pattern, or even on digits. These are seen predominantly on the extremities. Secondary infection, post-inflammatory hyperpigmentation, and scarring may ensue. In less than 10% of cases, an affected individual may develop regional lymphadenopathy, thrombophlebitis, angioedema, an id reaction, erythema nodosa, ocular edema, conjunctivitis, panic attacks, or muscle spasms [75]. Rarely, a sting may

cause a life-threatening reaction such as anaphylaxis, cardiac arrest, or loss of consciousness leading to drowning. True jellyfish (schyphozoans) are responsible for the majority of stings and typically cause mild, self-limited irritation. Three of the most dangerous jellyfish include the Portuguese man-of-war (*Physalia physalis*) found in the Atlantic, Pacific and Indian Oceans; the major box jellyfish (*Chironex fleckeri*) found in northern Australia; and Irukandji jellyfish (*Carukia barnesi*). Contact with any of these can be lethal.

Investigations Recommended

Investigations recommended
None

Management Strategies

Immediate management
Remove victims from water
Remove tentacles
Wash sting site with saltwater, 4–6 % acetic acid (household vinegar), ammonia, or a baking soda slurry (50 % in saltwater); avoid alcohol or fresh water, as these may cause further discharge from nematocysts, though there is conflicting evidence in literature regarding these measures [75, 76]
Soak in hot water after rinsing with saltwater or vinegar; ice packs if hot water is not available
Prevention
Wearing stinger suits or nets in infested waters (helpful only for large jellyfish)
Safe Sea cream (may cause nematocyst discharge in some species)

Table 19.40 Therapies [76, 77]

Supportive care: topical and oral corticosteroids and antihistamines as needed	E*
Pain control:	A*
Hot water	
Ice if hot water is not available	
Pain control:	E*
Lidocaine	
EpiPen for anaphylaxis	E*
Seek medical attention if severe and may require cardiac monitoring	

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Hypersensitivity Syndromes

20

Marjon Vatanchi and Adelaide A. Hebert

Urticaria

Clinical Features

Urticaria is a transient allergic reaction of the dermis characterized by pruritic, well-demarcated erythematous wheals, with or without central pallor (Figs. 20.1, 20.2, and 20.3). The intracutaneous edema is manifest clinically by erythema and localized to widespread primary lesions. The hallmark of urticaria is that no single lesion persists longer than 24 to 36 hours and most persist in a focal location for only 30 to 90 minutes. The incidence is 5 % of the population, and hives occur in females twice as often as males. Most cases of urticaria are idiopathic. Common causes include drug reactions, infection, and food. Angioedema is a deep, dermal swelling that commonly occurs on the face, typically periocular or perioral Angioedema may be mast- cell mediated or kinin-related. Current understanding of angioedema attribute causation to idiopathic, C1 inhibitor deficiency or hereditary forms with normal C1-INH. Chronic cases of are defined by symptoms lasting longer than 6 weeks.

Management Strategies

Differential diagnoses include viral exanthema, contact dermatitis, drug eruptions, insect bites, and erythema multiforme. Acute urticaria in children has been largely seen following a viral or bacterial infection. Many children receive antibiotics after a bacterial infection and then develop urticaria, rendering it difficult to attribute cutaneous findings to an infection versus a drug reaction. In angioedema without urticaria, the clinician should think of other disorders such as drug-induced angioedema, idiopathic angioedema, or hereditary and acquired C1 inhibitor deficiency. Initial management should be targeted on relieving pruritus and angioedema, if present. Two-thirds of cases of urticaria are self-limiting [1]. For this reason, the treatment options have not been extensively studied for acute cases. Many of the treatments are anecdotal recommendations from studies of chronic urticaria.

Specific Investigations Recommended

For diagnosis
Clinical
CBC with differential, urinalysis, ESR, LFTs
Allergy-specific IgE antibody

A diagnosis of urticaria can be made clinically with a good history and cutaneous findings of transient, pruritic wheals. To address the underlying cause, a basic laboratory work-up may be conducted to include a cell blood count (CBC) with differential, urinalysis, erythrocyte sedimentation rate (ESR), and liver function tests (LFTs). If a certain allergy is suspected, an allergy-specific immunoglobulin E (IgE) antibody may be performed.

Biopsy is not indicated unless the case is atypical. Histopathology demonstrates a mild, lymphocytic perivascular infiltrate with marked dermal edema [2].

Table 20.1 First line therapies

Second-generation H_1 antihistamines	B
Combining H_1 and H_2 antihistamines	B

Most commonly, the recommended therapy will be second-generation H_1 antihistamines, as they are non-sedating [3]. Doses can be prescribed as following: cetirizine 5 to 10 mg daily for children >6 years; 2.5 to 5 mg for children 2–5 years; 2.5 mg for children 6 months to 2 years. Alternatives include levocetirizine, loratadine, desloratadine,

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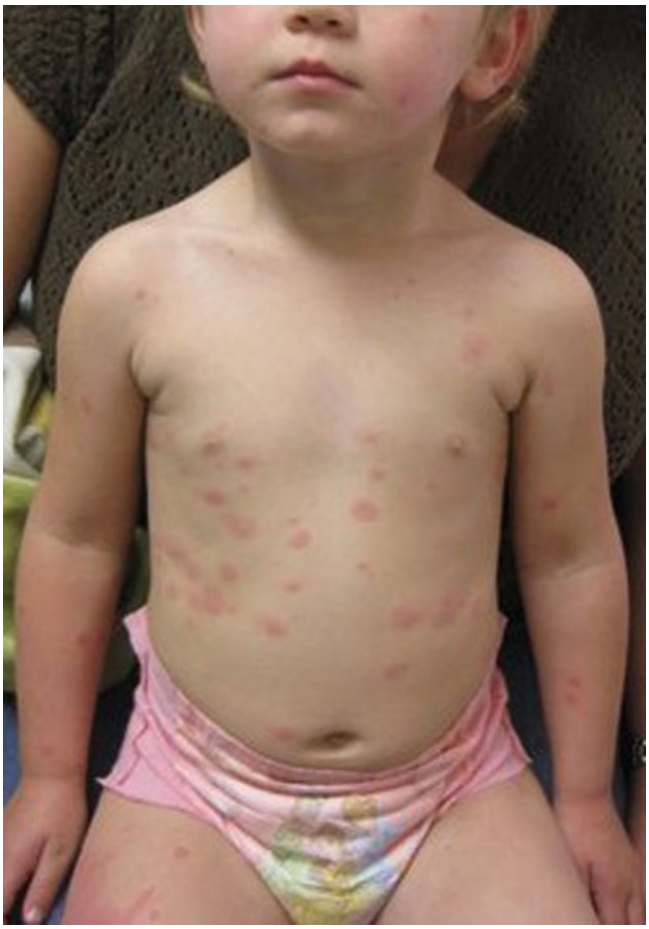

Fig. 20.1 Urticaria (Courtesy of Adelaide A. Hebert, MD)

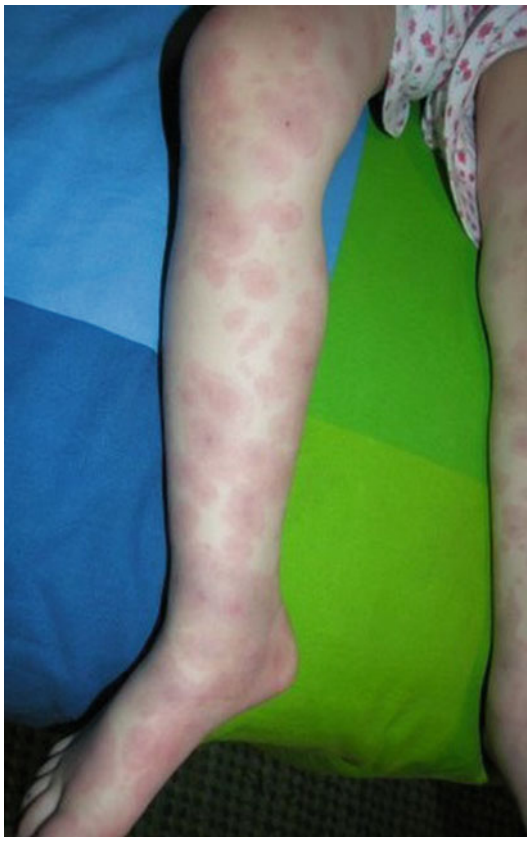

Fig. 20.2 Urticaria (Courtesy of Adelaide Hebert,MD)

and fexofenadine. Combining H_1 and H_2 antihistamines for patients with acute urticaria has been shown to produce a better response [4]. than use of H1 antihistamines alone (in some published studies). H_2 antihistamines include ranitidine, nizatidine, and famotidine.

In an emergency room setting, parenteral dosing of first-generation H_1 antihistamine is available: diphenhydramine 0.5–1.25 mg/kg (up to 50 mg per dose) IV/IM every 6 h as needed or hydroxyzine 0.5–1 mg/kg (up to 50 mg per dose) IM every 6 h as needed.

Table 20.2 Second line therapies

First-generation H_1 antihistamines	D
Systemic Glucocorticoids	E

First-generation H1 antihistamines are still used to treat urticaria. despite the fact that this class of medications can they cross the blood-brain barrier and cause a sedating side effect.

Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, has been used to treat patients with recurrent angioedema and chronic urticaria within 1–2 weeks [5].

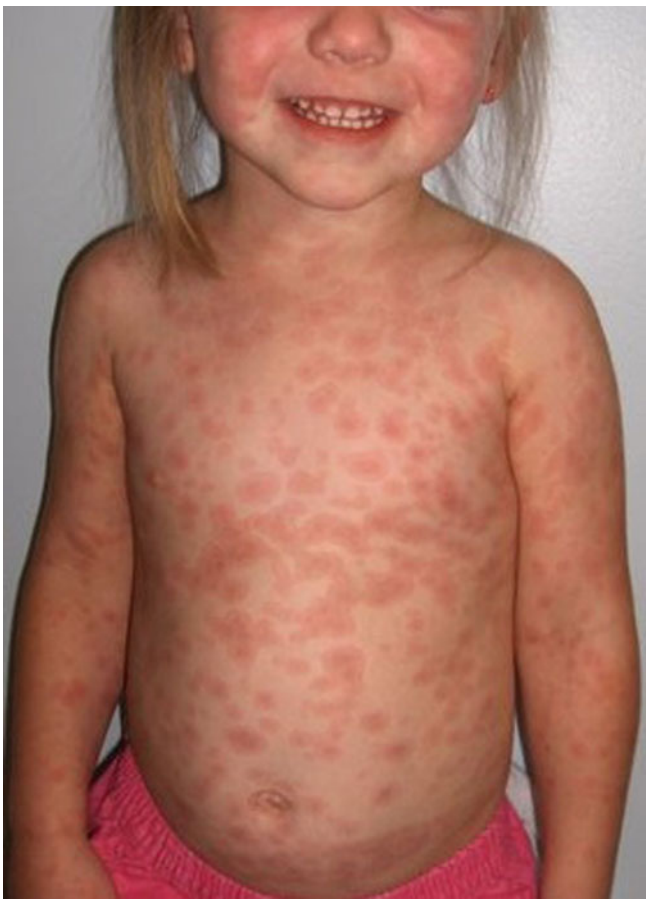

Fig. 20.3 Urticarial multiforme (Courtesy of Adelaide Hebert, MD)

Table 20.3 Third line therapies

Omalizumab	A
Ecallantide (Kalbitor) ®[a]	A
Antileukotriene agents	B
Cyclosporine	D

[a]Treatment for patients with acute hereditary angioedema

A randomized, double-blind clinical trial was conducted on patients ages 12–75 who continued to be symptomatic while on antihistamines. Subcutaneous omalizumab was effective in decreasing pruritus [6]. Ecallantide (Kalbitor®), a kallikrein inhibitor, blocks the production of bradykinin and therefore its effects. Multiple randomized, double-blind clinical trials were performed in different age groups which showed that ecallantide was effective in relieving acute hereditary angioedema attacks. This medication is administered subcutaneously in a hospital setting or infusion center, to monitor for possible side effects. In clinical trials, 4 % of patients experienced anaphylaxis [7]. Antileukotriene agents (montelukast) have not been studied in acute cases; however, this agent has been used in chronic cases of urticaria. These medications are not demonstrably more effective than combining H_1 and H_2 antihistamines. Cyclosporine has been used with to treat chronic disease with positive results; however, patients are still susceptible to relapses [8].

Drug Hypersensitivity Reaction

Clinical Features

Drug hypersensitivity reactions, also known as exanthematous drug eruptions, are type IV, T-cell mediated immune reactions that are the most common type of adverse drug reaction. Patients develop erythematous macules or small papules that appear 7–14 days after drug exposure [9]. This classic drug-induced skin eruption predominantly involves the trunk and proximal extremities. Typically, there is no mucosal membrane involvement. Cutaneous drug reactions are morbilliform 95 % of the time, with 5 % being urticarial (Figs. 20.4 and 20.5). Synonyms include morbilliform or maculopapular drug eruption.

Management Strategies

Differential diagnosis includes viral and bacterial exanthems, contact dermatitis, psoriasis, and other eruptions associated with systemic diseases. The cutaneous signs of a drug eruption are self-limiting. Treatment is targeted toward symptom relief such as pruritus. In severe disease with mucosal or genital involvement, suspect drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN). A thorough medical history is impera-

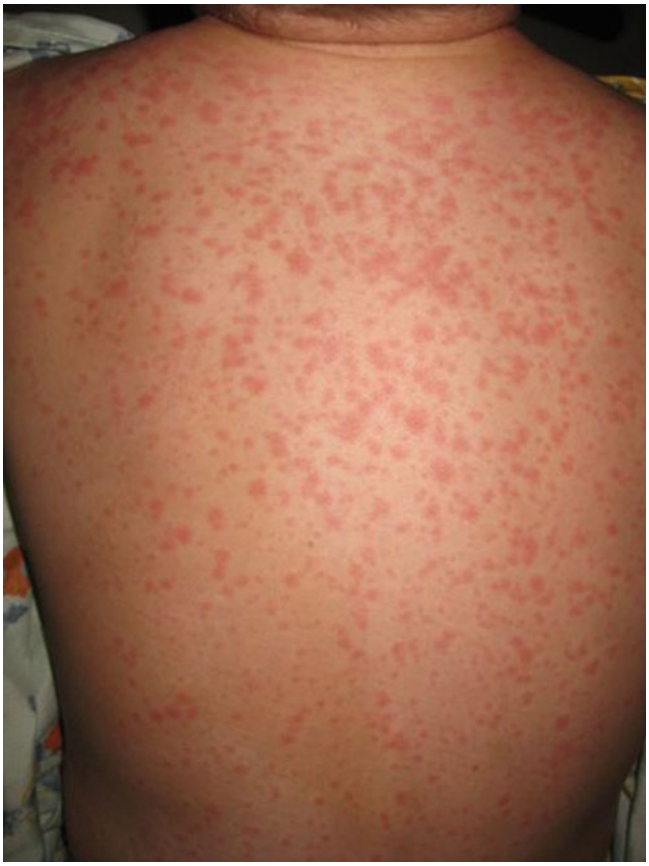

Fig. 20.4 Drug hypersensitivity reaction (Courtesy of Adelaide Hebert, MD)

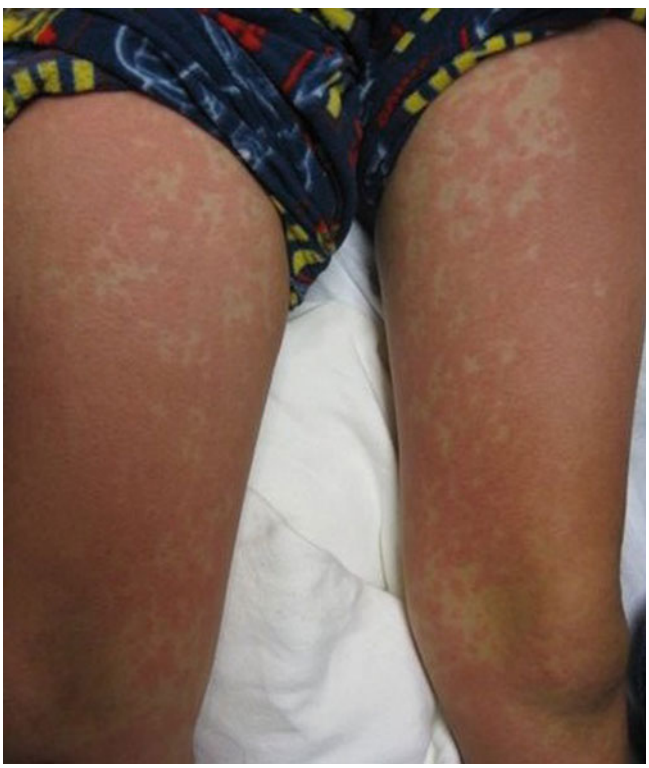

Fig. 20.5 Drug hypersensitivity reaction (Courtesy of Adelaide Hebert, MD)

tive in order to identify a chronological relationship between drug exposure and symptoms. Next, discontinuation of the offending agent (when deemed feasible) is advised. Even with discontinuation, cutaneous findings and symptoms may persist and take up to 7–14 days, or longer, to begin to improve. In patients with serious drug eruptions who take several medications, the nonessential drugs should be discontinued, if possible. Laboratory tests are only necessary if the diagnosis is not clear from the history and the clinical correlation.

Specific Investigations Recommended

For diagnosis
CBC with differential
LFT and Renal panel
ANA (antinuclear autoantibody)
Skin biopsy
For treatment
Patch Testing 1–6 months after symptoms

CBC with differential is performed to identify eosinophilia, changes in white blood cell count, and alteration of platelets. LFT and renal panel can be performed to identify systemic involvement, especially if DRESS is suspected. If an autoimmune connective tissue disease is in the differential, ANA and other studies directed at discovery of the suspected autoimmune disorder should be performed.

A skin biopsy is often not necessary, and only warranted if a severe hypersensitivity reaction is noted. Biopsies may be considered in patients with systemic symptoms such as fever, signs of systemic involvement, or mucous membrane involvement, or if the cutaneous symptoms evolve to erythroderma, blistering, or pustule formation. The histopathology of most drug eruptions display interface dermatitis with dyskeratotic keratinocytes along the dermoepidermal junction and scattered eosinophils.

Patients complain of moderate to severe pruritus; therefor, topical corticosteroids with medium to high potency are suggested (group 1–3 on the corticosteroid potency chart). In order of increasing strength, these include: triamcinolone acetonide 0.5 % cream (Triderm), fluocinonide 0.05 % cream (Lidex-E), betamethasone dipropionate 0.05 % cream (Diprolene), or clobetasol propionate 0.05 % cream (Temovate). A wide variety of topical steroids are available. A list of topical steroids in a wide variety of formulations (creams, ointments, foams, gels, solutions, tape) separated by strength and class is available on the National Psoriasis Foundation website at: https://www.psoriasis.org/about-psoriasis/treatments/topicals/steroids.

Antihistamines (sedating and non-sedating) can be used to treat pruritus systemically. These include diphenhydramine, hydroxyzine, and non-sedating cetirizine (Table 20.5). Hydroxyzine and cetirizine are administered until the pruritus subsides.

Table 20.4 First line therapies

Avoid offending agent	D
Topical corticosteroids	B
Oral antihistamines	B

Table 20.5 Antihistamine dosing

Medication	Age	Dose
Diphenhydramine (Benadryl)	2–5 years	6.25 mg every 4–6 h
	6–11 years	12.5–25 mg every 4–6 h
	≥12 years	25–50 mg every 4–6 h
Hydroxyzine (Atarax, Vistaril)	<6 years	1–2 mg/kg/day divided into 6–8 h
	≥6 years	12.5 to 25 mg every 6–8 h
Cetirizine (Zyrtex, Reactine)	6–12 months	2.5 mg daily
	12 months to <2 years	Start at 2.5 mg daily, may increase to 2.5 mg twice daily or 5 mg daily
	2–5 years	2.5 mg daily, may increase to 2.5 mg twice daily or 5 mg daily
	≥6 years	10 mg daily

Table 20.6 Second line therapies

Systemic corticosteroids	E

Systemic corticosteroids are not recommended unless the patient has systemic involvement or severe cutaneous symptoms [10]. In these cases, a short course of prednisone 1–2 mg/kg/day may be beneficial.

Table 20.7 Third line therapies

Desensitization	B

Desensitization can be used to decrease the allergic response to a necessary medication. In patients who do not require a certain medication or are able to substitute for another medication, then desensitization is not necessary. However, in the subset of the population who have an exanthematous drug eruption to a medication that is necessary, this is a viable option [11, 12]. Desensitization is typically carried out in a hospital setting, with adequate support to

handle any urgent medical need should one arise during the process of desensitization.

Fixed Drug Eruption

Clinical Features

A fixed drug eruption (FDE) is a specific cutaneous drug reaction that recurs in the same area when re-exposed to an offending medication. Acute FDE typically presents as a single plaque or a small cluster of dusky red, violaceous plaques that appear 30 min to 8 h after drug administration (Fig. 20.6). Sometimes this cutaneous finding can take several days to evolve. Typical plaques of a fixed drug eruption are well-demarcated, round to oval, and with edematous skin changes with or without vesiculation (Fig. 20.7). These fixed skin lesions can occur anywhere on the body, but are seen most commonly on the lips, genitalia, perianal area, hands, feet, and/or any site of previous trauma [13, 14]. Mucosal involvement can be a manifestation of a fixed drug eruption. Upon resolution of the fixed drug eruption, plaques can leave behind post-inflammatory hyperpigmentation. Rarely, patients can have atypical variants of severe FDE, which include multiple plaques, non-pigmenting lesions, or generalized bullous lesions that may appear similar to more serious diseases such as Stevens-Johnson syndrome (Fig. 20.8).

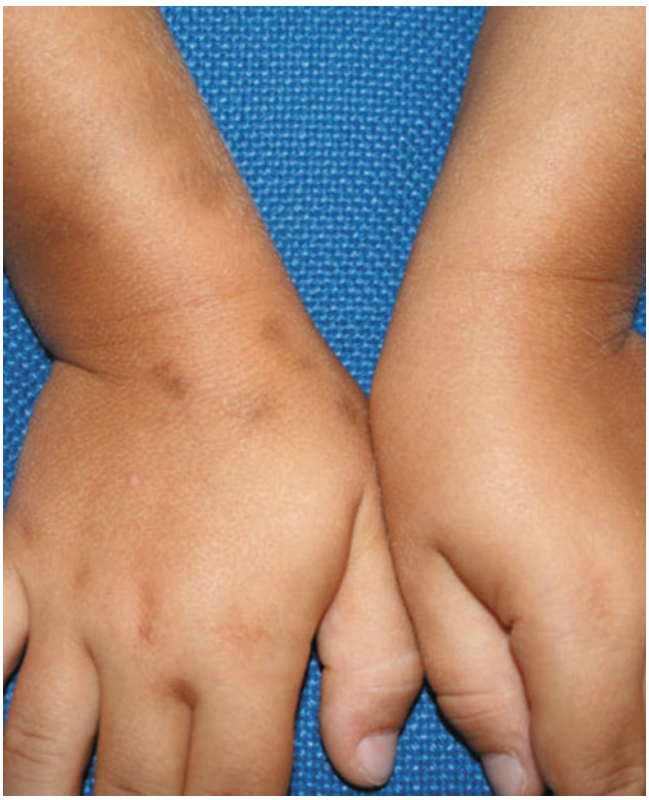

Fig. 20.7 Fixed drug eruption (From Bonifazo E. Differential Diagnosis in Pediatric Dermatology. In: *Allergic Diseases*. Springer; 2013. p. 95. Used with kind permission from Springer Science and Business Media)

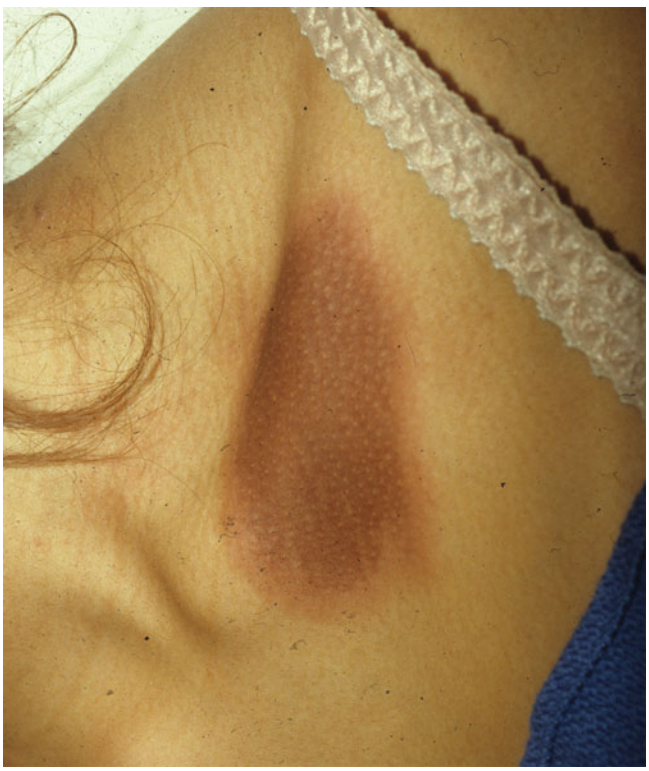

Fig. 20.6 Fixed drug eruption (Courtesy of Adelaide Hebert, MD)

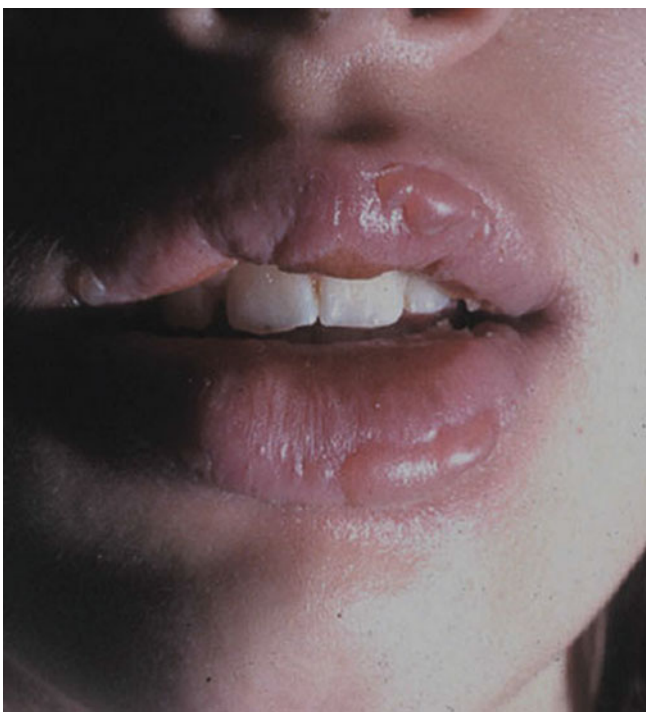

Fig. 20.8 Fixed drug eruption (From Bonifazo E. Differential Diagnosis in Pediatric Dermatology. In: *Allergic Diseases*. Springer; 2013. p. 95. Used with kind permission from Springer Science and Business Media)

The hallmark of FDE is that lesions reappear at the same site when patients are re-exposed to the offending agent. New lesions can occur in new sites as well. Cross-reactivity is possible from medications that have a similar chemical structure than the offending medication.

Pruritus is a common finding in fixed drug eruptions, although other systemic symptoms are typically absent. In the pediatric population, FDEs account for 14–22 % of cutaneous drug reactions [15]. The localized response of FDE is attributed to intraepidermal CD8+ T cells [16]. When these cells are activated, they release interferon-γ and cytotoxic granules [17]. The most common culprits of FDEs include antibiotics (trimethoprim, sulfamethoxazole, tetracycline, and penicillins), NSAIDs, acetaminophen, phenolphthalein, barbiturates, and antimalarials.

Management Strategies

Differential diagnosis includes erythema multiforme (EM) and SJS/TEN for the generalized bullous FDE variant. Diagnosis is made after history and identification of lesion morphology. Having a recurrence of the fixed dusky plaque at the same anatomic site is very supportive for the diagnosis of FDE. Once the offending agent is identified, immediate discontinuation of the offending agent is recommended. After this is done, the classic skin lesion will persist for 7–10 days, leaving behind a patch of post-inflammatory hyperpigmentation.

Specific Investigations Recommended

For diagnosis
Clinical
Biopsy
Oral challenge
Patch testing

Diagnosis is typically clinical; however further investigation is warranted when this is not obvious. FDE on histology will display hydropic degeneration of the basal layer, pigmentary incontinence, dyskeratotic cells, and dermal lymphocytic infiltrates.

An oral challenge test or patch testing can be performed to identify the offending agent. Oral challenge test is not recommended if the patient has ever developed a generalized FDE. In a study of 450 patients who received the oral challenge test with the medication believed to be causing their symptoms, 10 % developed pruritus, 0.9 % had a fever, and 0.7 % developed generalized urticaria. No severe reactions were noted [18]. During an oral challenge test, patients do not get tested with the full dose of the presumed offending medication. In patients with a history of generalized FDE, patch testing is a valid option. There are different methods to perform a patch test. In one study, 1–5 % of the therapeutic dose combined with a diluting agent such as white soft paraffin was applied to the patients' skin. The suspected medication is applied to an old FDE lesion to elicit a local reaction as well as to normal tissue to compare. If no reaction is witnessed, the dose can be titrated upwards. As this testing methodology is not considered to be systemic, this test is considered safe for patients with previous history of FDE. More methods of performing a patch test are to mix the implicated drug with petrolatum or dilute in water at 10–20 % concentration and then apply it to the skin. A reaction is considered positive when erythema occurs within 24 h and lasts at least 6 h [19].

Table 20.8 First line therapies

Discontinue offending drug	D
Topical corticosteroids	B
Systemic antihistamines	B

The first step in treatment of FDE is to withdraw and avoid the offending agent, and avoid all drugs that are chemically related. Patients should be provided with a list of medications to avoid that includes the generic name, trade names, and medications that cross-react. Similar to drug hypersensitivity reactions, FDE is self-limiting once the offending agent is discontinued. Therapy is targeted to treat pruritus and educate the patient regarding both what to expect during the resolution of the FDE and how to potentially avoid this skin reaction in the future. For small or single FDE lesions, topical corticosteroids (group 1–3) can be applied daily for 7–10 days. For diffuse pruritus, oral H_1 antihistamines are prescribed (Table 20.5).

Table 20.9 Second line therapies

Systemic corticosteroids	–

In cases of generalized FDE, or when systemic systems are present, a short course of moderate dose systemic corticosteroids may be beneficial. This has yet to be proven in randomized, double-blind trials; however, numerous clinicians attest to the effectiveness of this therapeutic approach through clinical experience. The administration of prednisone (Rayos, Sterapred) 0.5–1 mg/kg/day for 3–5 days can alleviate pruritus and potentially hasten the resolution of the FDE.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Clinical Features

SJS and TEN (erythema multiforme major) are severe mucocutaneous adverse reactions that are part of the same disease continuum, and are distinguished by the disease severity and

extent. Patients develop fever, cutaneous discomfort, and extensive epidermal detachment and necrosis. This skin reaction is typically attributed to a medication or an infectious agent. Bullous erythema multiforme (EM) is a milder reaction with only cutaneous symptoms. This is characterized by flat or slightly raised target lesions with epidermal involvement less than 10 % body surface area (BSA).

In SJS, patients develop widespread macules or target lesions also less than 10 % BSA, and the mucous membranes are involved in over 90 % of patients with presentation in at least two distinct sites (oral, ocular, and genital). When epidermal necrosis and detachment is between 10 % and 30 % BSA, this is diagnosed as an overlap SJS-TEN, and when BSA is greater than 30 %, TEN is diagnosed (Fig. 20.9). TEN has the same incidence of mucosal involvement as SJS, with over 90 % of patients having the mucous membranes affected. As SJS and TEN are in the same continuum, these two potentially life-threatening cutaneous disorders will be discussed together.

Patients typically complain of fever and flu-like symptoms preceding the mucocutaneous symptoms by 1–3 days. Physicians should suspect SJS/TEN in patients who have fever, skin tenderness, blistering, and mucosal inflammation [20]. Cutaneous findings begin with ill-defined, coalescing erythematous macules with pruritic centers. Lesions start on the face and thorax before spreading to rest of body. Scalp, palms, and soles are rarely involved. As disease progresses, vesicles and bullae form and skin begins to slough. Patients will have a positive Nikolsky sign. The skin surface will resemble that of a burn patient. Most patients develop painful, hemorrhagic erosions of the oral mucosa and vermillion border (Figs. 20.10, 20.11, and 20.12)

Malnutrition and dehydration can develop, due to painful stomatitis and mucositis. Many affected patients also develop severe conjunctivitis with purulent discharge. Amongst survivors, long-term ocular complications such as corneal damage or conjunctival scarring puts them at risk for vision loss. Pharyngeal mucosa and urogenital involvement is common [21].

Medications attributing most in pediatric patients include sulfonamide antibiotics, phenobarbital, carbamazepine, lamotrig-

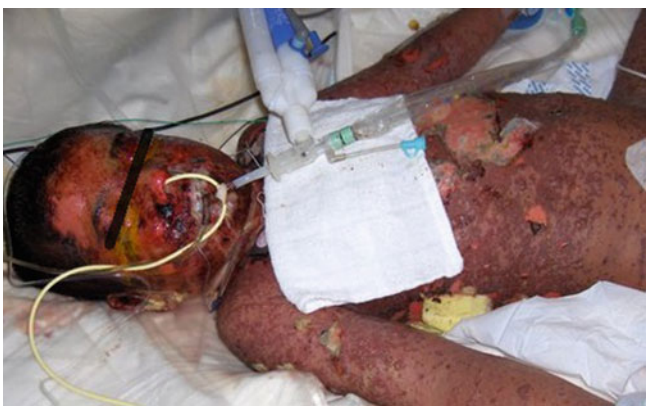

Fig. 20.9 Toxic epidermal necrolysis (Courtesy of Adelaide Hebert, MD)

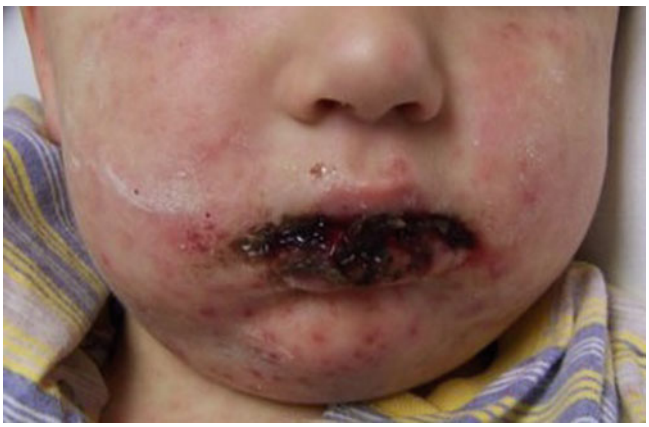

Fig. 20.10 Steven Johnson Syndrome (Courtesy of Adelaide Hebert, MD)

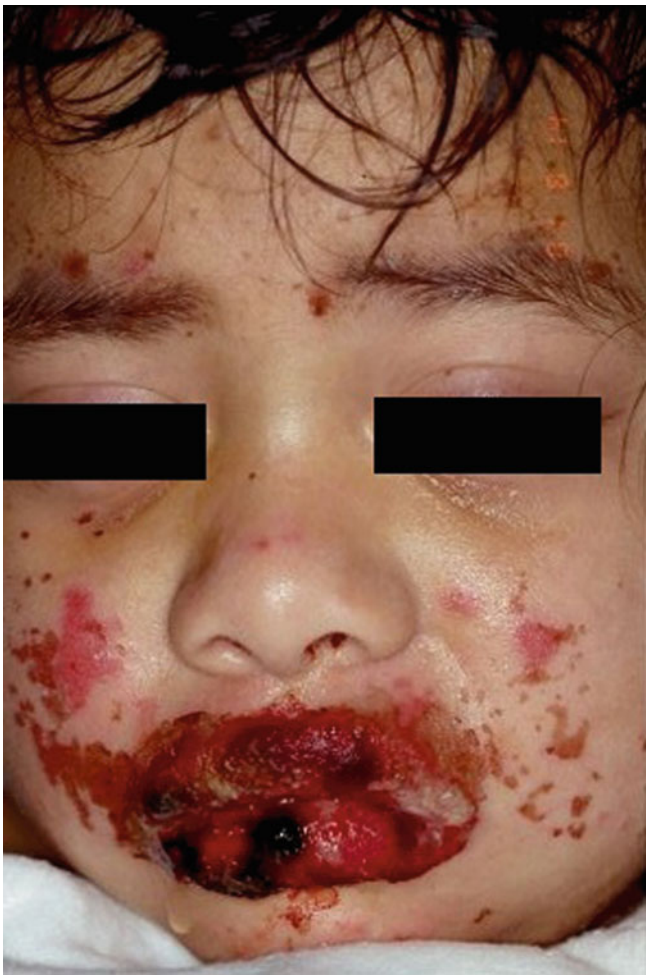

Fig. 20.11 Steven Johnson Syndrome (Courtesy of Adelaide Hebert, MD)

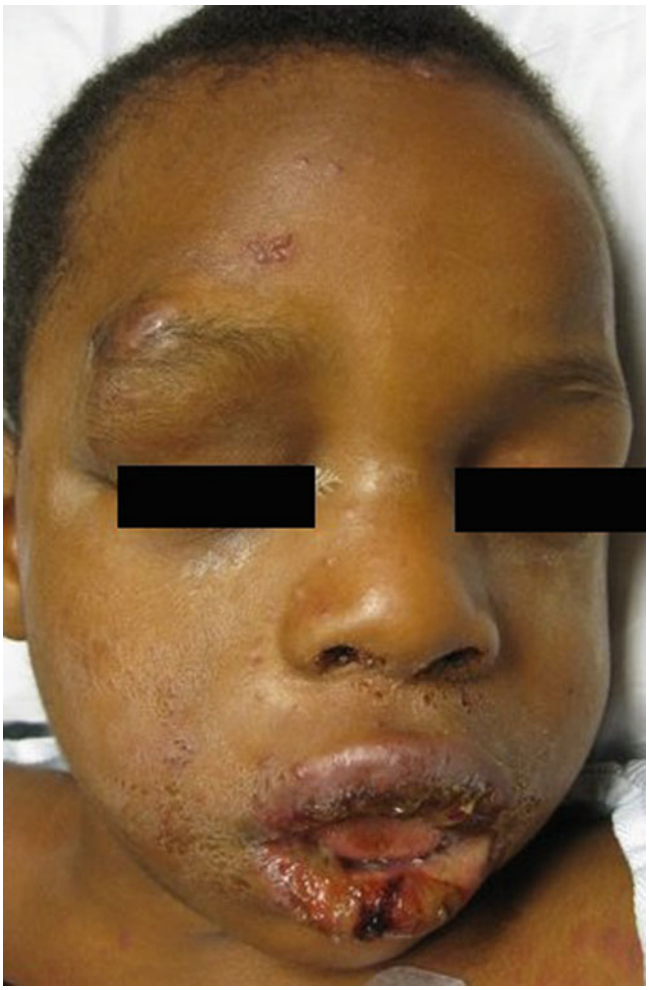

Fig. 20.12 Steven Johnson Syndrome secondary to Herpes Simplex Virus infection (Courtesy of Adelaide Hebert, MD)

ine, and acetaminophen (Paracetamol) [22]. While medications are the most likely cause of these conditions, greater than 25 % of pediatric cases cannot be clearly linked to a medication. The most common infectious causes are *Mycoplasma pneumonia* (especially if fever, cough, and mucositis is present) and cytomegalovirus [23]. On very rare occasions, vaccines have been known to cause SJS and TEN [24].

Medications stimulate the immune system by binding to major histocompatibility complex I (MHC-I) and T-cell receptors. This immune response leads to clonal expansion of cytotoxic T-cells that are drug-specific. These cells kill keratinocytes directly, and ultimately recruit cells that release cytokines.

Management Strategies

All suspected cases of SJS or TEN should be considered for hospital/intensive care unit admission. Once the diagnosis is verified, severity should be assessed and management initiated, including placement of the patient on a non-stick bedding and dressing such as ExuDry®. Differential diagnosis for SJS/TEN includes: EM, erythroderma (due to radiation toxicity or other causes), erythematous drug eruptions, acute generalized exanthematous pustulosis, phototoxic eruptions, and Staphylococcal Scalded Skin Syndrome. The management of SJS/TEN starts with immediate removal of the offending agent, IV antibiotics (treatment or prophylaxis), hospitalization, nutritional and supportive care, and wound care.

Adults have a higher mortality rate than children when afflicted with TEN; however 50 % of children have long-term sequelae as a result of this severe cutaneous disease. In a series of 55 children with SJS/TEN, 10 had recurrence up to 7 years after their initial episode. Recurrence was mostly attributed to *Mycoplasma pneumonia* infection, herpes simplex virus, or antiepileptic drugs [25]. This demonstrates that patients can have a long-term immunosensitivity to certain medications, and should indefinitely be classified as hypersensitive/allergic to offending agents and medications with the same chemical structure.

There is a wide array of sequelae that can develop after recovery from SJS/TEN. Patients can develop irregular pigmentation patterns, alopecia, abnormal nail growth, xerostomia, gingival synechiae, long-term vulvovaginal dryness, urinary retention, chronic bronchitis/bronchiolitis, and multiple ophthalmologic problems such as photophobia or visual impairment.

Specific Investigations Recommended

For diagnosis
SCORTEN
CBC, LFT, Renal panel
Cultures
Mycoplasma pneumoniae serology
Biopsy
For treatment
Cultures (wound and lines) during hospitalization

Due to the severity of this group of skin disorders, basic laboratory work-up and cultures are necessary, both initially and as the patient is managed over the course of their disease progression. Patients develop anemia and lymphopenia. One-third of patients have neutropenia. which is correlated with a poor prognosis [26]. Major fluid loss can lead to increased BUN, hyperglycemia, hypoalbuminemia, and electrolyte imbalance. Mild elevations in serum aminotransferases of about two to three times the normal limit are present in half of TEN patients. There is a high risk of bacterial superinfection and sepsis; therefore, cultures should be taken from the blood, cutaneous wounds, and mucosal wounds. *Mycoplasma pneumonia* serology is also

obtained in the early stage of the disease and 3 weeks following.

Table 20.10 First line therapies

Immediate discontinuation of offending agent	B
Wound care	B
Supportive care	–
Transfer to burn center	B

A skin biopsy should be performed in most cases to verify the suspected diagnosis. The hallmark of SJS/TEN on histopathology is partial or full-thickness keratinocyte necrosis of the epidermis, typically without inflammation [27].

A 10-year observational study of 203 adult patients with SJS or TEN concluded that early withdrawal of the offending agent decreased mortality, especially if withdrawn before the presence of blistering [28]. The administration of supportive care, inclusive of wound care, fluid and electrolyte management, nutritional support, and pain control, are essential to assure an optimized outcome. Even with meticulous care, a large number of severely affected patients succumb to adverse events from the disease. Multiple studies have been conducted comparing different wound care techniques: debriding wounds versus leaving detached skin intact, or using nonadherent dressings with silver versus petrolatum. None of the studies found one technique to be superior to another in regard to rates of survival or reepithelialization.

Although controversial to some, prognosis is improved when patients with severe cutaneous and systemic symptoms are transferred early to burn centers [29]. Room temperatures should be raised to prevent excessive caloric loss due to uncontrolled muscle shaking to help maintain core body temperature. Nasogastric feeding may be necessary to endure adequate calories for the stress of the disease and to promote cutaneous recovery. Bronchial injury and hypersecretions should be managed by a trained respiratory therapist, with chest physical therapy and pulmonary toileting. Extra care should be taken when passing the feeding tube, to avoid further damage to affected mucous membranes.

All patients who are admitted to the hospital should get immediate eye exams by an ophthalmologist because the ocular inflammation and damage can develop quickly. Genitourinaryexaminations should be conducted for both males and females to evaluate for complications such as phimosis, urethral strictures, or vaginal or labial adhesions. In patients with intravaginal ulcers, a moderate-potency topical corticosteroid gel can be applied intravaginally twice daily. Topical or systemic antifungals can be used concomitantly to prevent vaginal candidiasis.

Table 20.11 Second line therapies

Systemic antibiotics	E

Once cutaneous symptoms are present, care should be provided in a manner similar to the technique used in a burn unit. Skin and line cultures should be considered every 48 h. Systemic antibiotics are not necessary, unless the patient displays symptoms such as fever or general deterioration with evidence of infection. Infections with gram negative rods, especially Pseudomonas, can be especially problematic and should be dealt with promptly.

Table 20.12 Third line therapies

Intravenous immunoglobulin	D
Systemic corticosteroids	D
Hemoperfusion	C
Cyclosporine	E

There have been many retrospective and a few controlled studies evaluating the use of intravenous immunoglobulin (IVIG) and systemic corticosteroids in adults. Overall, the data shows decreased rates of mortality with both medications when used alone or together. In an adult meta-analysis, IVIG doses ≥2 g/kg significantly decreased mortality in both SJS and TEN [30]. In pediatric patients, the use of IVIG and/or systemic corticosteroids has been reported in case studies and still used anecdotally based on the data in adult studies. Given the side effects of these medications, there use can be controversial. Theoretically, they increase the risk of sepsis and decrease the rate of epithelialization. If considering these agents, therapeutic interventions should be given made on a case-by-case basis.

A preliminary study from 2014 introduced the benefits of hemoperfusion in ten pediatric patients who failed glucocorticoid and IVIG therapy. The patients received three to five hemoperfusion sessions before the disease process began to halt and their general health improved. Hemoperfusion may serve as a new adjunct treatment [31].

A few case reports and a case series in adults administered cyclosporine 3–5 mg/kg/day suggest that cyclosporine may slow the progression of SJS/TEN. Many of these patients developed adverse side effects, including hypertension and increase in infections. Few case reports of children treated with cyclosporine for SJS/TEN have appeared in the medical literature.

Erythema Annulare Centrifugum

Clinical Features

Erythema annulare centrifugum (EAC) is a cutaneous eruption with annular, migratory, erythematous papules/plaques that have central clearing, raised borders, and are non-pruritic (Fig. 20.13). This condition can appear at any age, and is present in both males and females equally. EAC develops

secondary to a reaction to drugs, foods, or infections, or stems from an immunologic/autoimmune cause.

The eruption appears as papules or plaques ranging from 1 to 10 cm on the trunk, buttocks, or lower legs. Lesions can be pink, red, or purple, and appear annular, oval, semiannular, or as targets (Fig. 20.14). There is a characteristic rim of scale along the inner borders of the lesion (Fig. 20.15). Once the eruption appears, it begins to spread centrifugally over 1–2 weeks. The duration of EAC is quite variable; new lesions can develop in the succeeding months, or patients can have a recurrence after years.

Management Strategies

Differential diagnosis of EAC includes pityriasis rosea, erythema multiforme, dermatophyte infections, urticaria, granuloma annulare, psoriasis, or any other eruption with an annular morphology. Treatment depends on etiology; however, discontinuation of the offending agent is usually curative. Medications can be prescribed to manage associated symptoms which are typically few.

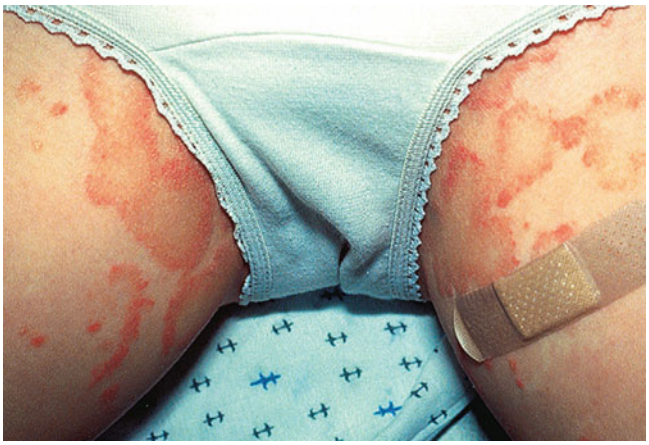

Fig. 20.13 Erythema Annulare Centrifugum (Reprinted from *Pediatric Dermatology*, 4th Ed., Cohen BA. China: Saunders; 2013. p. 190; with permission from Elsevier)

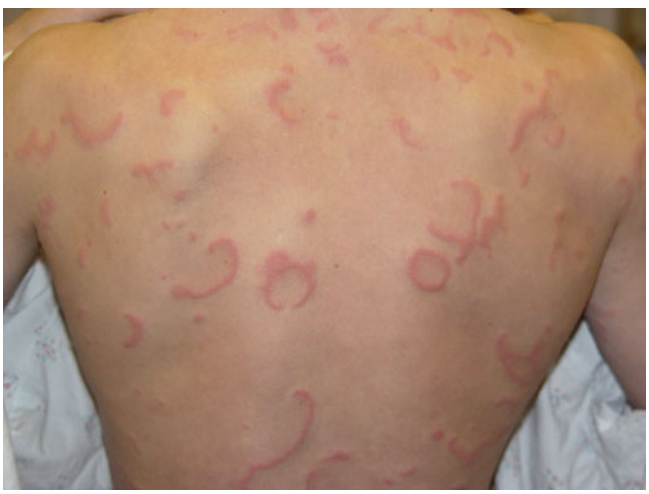

Fig. 20.14 Erythema Annulare Centrifugum (Reprinted from *Pediatric Dermatology*, 4th Ed., Cohen BA. China: Saunders; 2013. p. 190; with permission from Elsevier)

Specific Investigations Recommended

For diagnosis
Clinical
Punch biopsy

Histology displays parakeratosis, mild papillary edema, spongiosis, and focal infiltration of lymphocytes surrounding dermal blood vessels and adnexal structures in a "coat-sleeve" pattern [2].

Table 20.13 First line therapies

Discontinue offending agent	D
Topical corticosteroids	B
Antihistamines	B
Topical antipruritics	E

Moderate-potency topical corticosteroids can be applied until the lesions resolve. Patients do not generally complain of pruritus; however, antihistamines of topical antipruritics can be administered for relief. Topical antipruritics include calamine or menthol 1 % cream [32].

Table 20.14 Second line therapies

Topical tacrolimus	E
Topical calcipriol	E

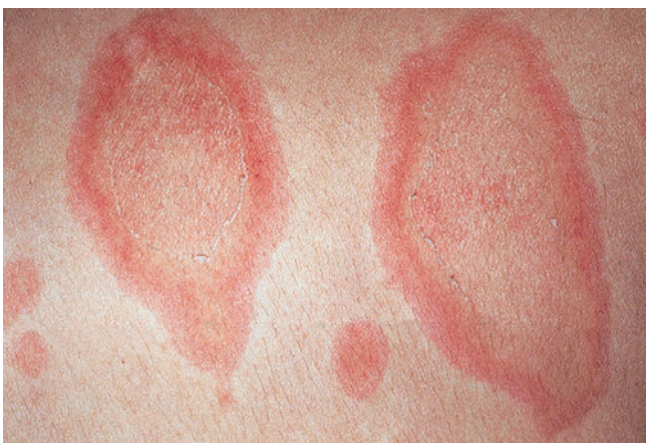

Fig. 20.15 Erythema Annulare Centrifugum (Reprinted from *Pediatric Dermatology*, 4th Ed., Cohen BA. China: Saunders; 2013. p. 190; with permission from Elsevier)

Topical tacrolimus 0.1% ointment may be applied twice daily (off label) until complete clearance of the EAC. Patients begin to notice fading of lesions within weeks one to three of treatment. Vitamin D analogues have been used to treat EAC refractory to topical corticosteroids. Topical calcineurin inhibitors do not carry the potential side effects of atrophy or adrenal suppression that corticosteroids may induce if overused.

Table 20.15 Third line therapies

Systemic metronidazole	E

There are case reports of adult and pediatric patients who were treated successfully with systemic metronidazole and subcutaneous interferon-α respectively. Use of metronidazole in the pediatric population is not common and anecdotal. For interferon-α, a severe side effect is spastic diplegia; therefore treatment with this medication is not recommended [33].

Erythema Nodosum

Clinical Features

Erythema nodosum (EN) is a cell-mediated, delayed-type hypersensitivity reaction that causes painful red or purple nodules on the legs. Forty percent of cases are idiopathic, and the second most common cause is streptococcal pharyngitis. Other possible triggers include infections (mycoplasma and tuberculosis), medications (estrogens or birth control pills, sulfonamides, penicillin), pregnancy, diseases (Crohn's, ulcerative colitis), or internal malignancy. This form of septal panniculitis typically affects patients above 15 years of age and favors women to men 3:1.

Patients complain of warm, tender, red nodules on the pretibial area (Fig. 20.16). Nodules can also appear on the trunk, thighs, and upper extremities; however absence over the pretibial area is rare. Nodules are round, palpable, and range from 1 to 5 cm (Fig. 20.17). Lesions progress to become purple or brown and last about 3–6 weeks without scarring (Fig. 20.18). Fever, malaise, or polyarthralgia may also be present. Symptoms can recur, especially after reinfection [2].

Management Strategies

Differential diagnosis includes multifocal cellulitis, ecchymosis, deep fungal infections, insect bites, thrombophlebitis, erythema induratum, and other panniculitides. Like most hypersensitivity syndromes, identification and removal of the

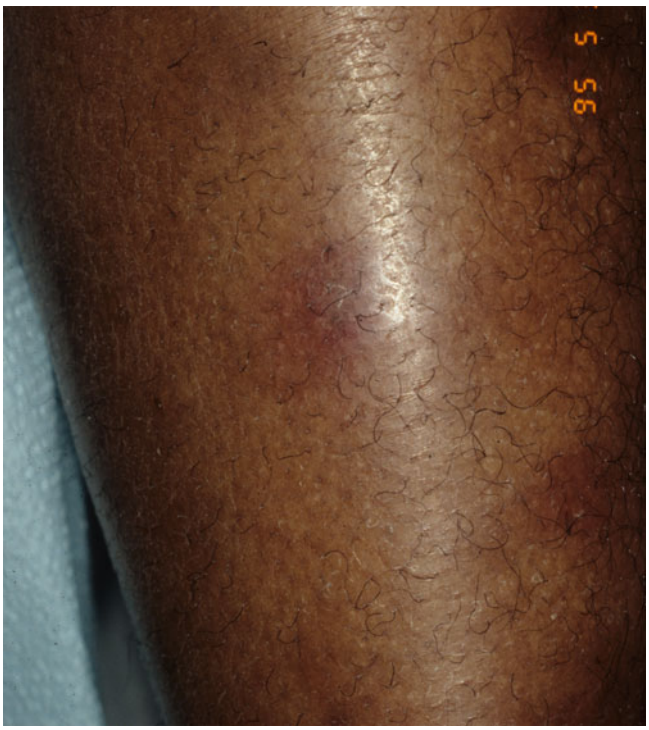

Fig. 20.16 Erythema Nodosum (Courtesy of Adelaide Hebert, MD)

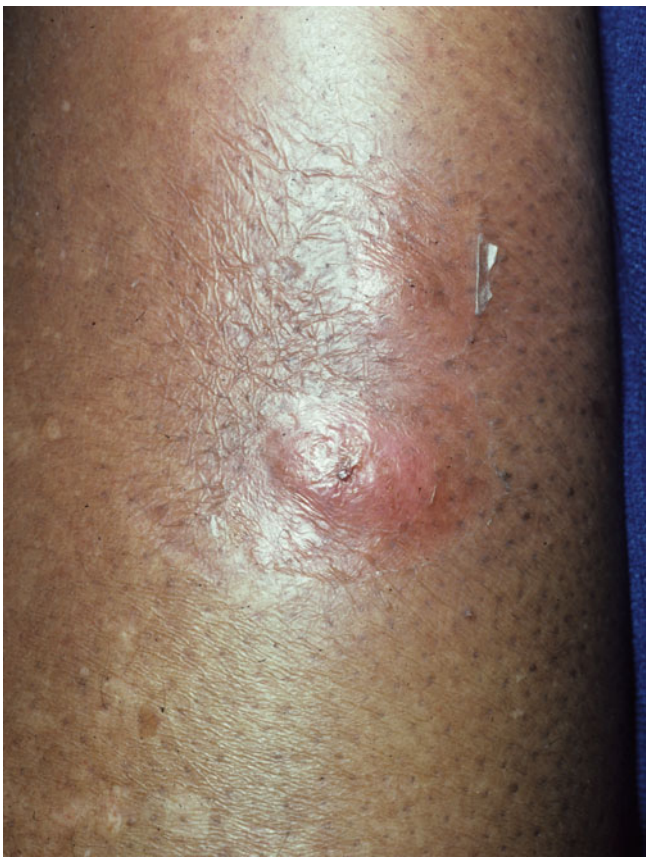

Fig. 20.17 Erythema Nodosum (Courtesy of Adelaide Hebert, MD)

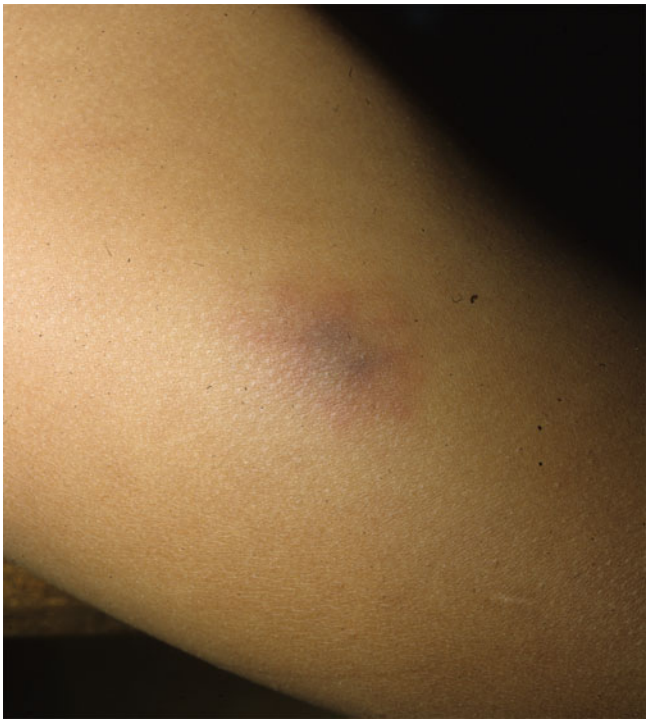

Fig. 20.18 Erythema Nodosum (Courtesy of Adelaide Hebert, MD)

offending agent is the first step. Next, perform a diagnostic work-up to identify any infectious cause. EN can be an early manifestation of a connective tissue or inflammatory disease; therefore, when medications or infections are ruled out, a further work-up may be necessary. Symptoms resolve spontaneously; however, treatment with local or systemic medications can be used to alleviate the presence of nodules [2].

Specific Investigations Recommended

For diagnosis
Streptococcal throat culture or Antistreptolysin-O titer
Deep incisional biopsy
CBC with differential, LFTs, bilirubin, albumin, renal panel, ESR
CXR
PPD test

At initial investigation, a detailed medication history is necessary. Recommended work-up includes a streptococcal throat culture or antistreptolysin-O titer at diagnosis and 2–4 weeks later to assess for antecedent streptococcal infection. Diagnosis is mostly clinical; however, a biopsy can be performed in atypical cases. A deep incisional biopsy would be necessary because a punch biopsy may produce an inadequate sample. Histology shows panniculitis with inflammation of septa in the subcutaneous fat tissue and associated vasculitis. A further work-up consisting of labs to assist in diagnosing infection versus inflammatory disease, chest X-ray (CXR) to rule out sarcoidosis, and a purified protein derivative (PPD) test for tuberculosis (TB) are recommended. When EN is present with hilar adenopathy on CXR, sarcoidosis is favored.

Table 20.16 First line therapies

Leg elevation	–
NSAIDs[a]	D
Intralesional steroids	E
Antibiotics	E

[a]Contraindicated in patients with IBD

Symptoms can be improved with bed rest, leg elevation, and compressive dressings. Over-the-counter pain-killers such as nonsteroidal anti-inflammatory drugs (NSAIDs), naproxen, or indomethacin, can help alleviate pain, unless symptoms are secondary to irritable bowel disease (IBD) [34]. NSAIDs are known to flare bowel symptoms in such patients. Antibiotics can be administered for a positive bacterial culture or streptococcal titer, and should be administered in patients who are symptomatic. It is important to keep in mind that titers can be positive even if the patient has passed the active phase of the infection; therefore, antibiotics may not be helpful in all situations.

When the etiology is unknown and infectious causes have been ruled out, intralesional steroids can be administered into the nodules.

Table 20.17 Second line therapies

Potassium iodide	D (adult)
Colchicine	E
Hydroxychloroquine	E
Cyclosporine	E

Potassium Iodide was discovered to treat EN after reports of success with other panniculitides [35]. Other treatment options include colchicine and Hydroxychloroquine, which have had beneficial outcomes in case reports. There are, however, conflicting reports regarding the benefits of cyclosporine in adults. More research is necessary in pediatric populations.

Henoch-Schonlein Purpura

Clinical Features

Henoch-Schonlein purpura (HSP) represents a small-vessel vasculitis in children with an IgA-mediated reaction to an

upper respiratory infection. IgA complexes deposit in the small vessels of the dermis, gastrointestinal tract, glomeruli, lungs, and CNS. This results in complement activation leading to vascular damage. One to 2 weeks following a respiratory infection, there is acute-onset purpura, joint pain, and abdominal pain with or without renal involvement. Abdominal pain occurs in 85 % of patients. Cutaneous findings include petechiae and palpable purpura on the lower extremities (especially calves) and buttocks (Figs. 20.19, 20.20, and 20.21) [2].

Management Strategies

Differential diagnosis includes acute rheumatic fever, disseminated intravascular coagulation, Rocky Mountain Spotted Fever, and meningococcal septicemia. HSP is self-limiting; however treatment is available for atypical cases and may be required for patients with renal involvement or abdominal pain [2].

HSP resolves over weeks to months. Recurrence occurs in 5–10 %. Mortality is 1–3 % and typically due to renal or GI complications. The younger the patients, the less severe the disease. Young children have less systemic symptoms and complications.

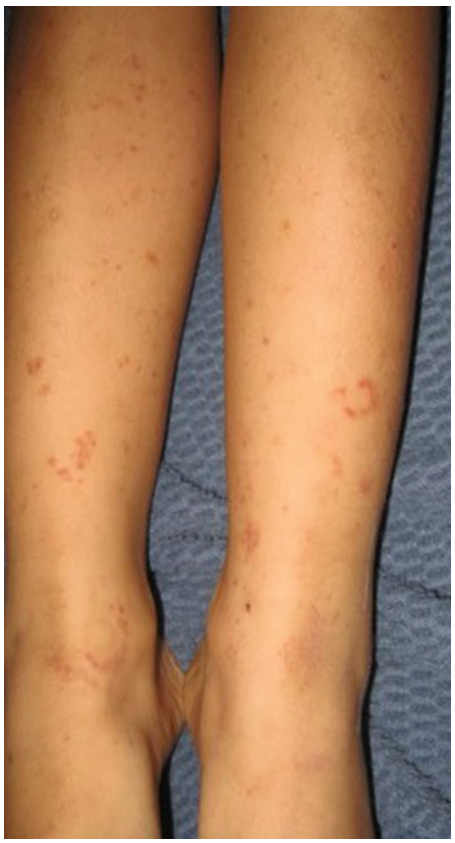

Fig. 20.20 Henoch-Schonlein Purpura (Courtesy of Adelaide Hebert, MD)

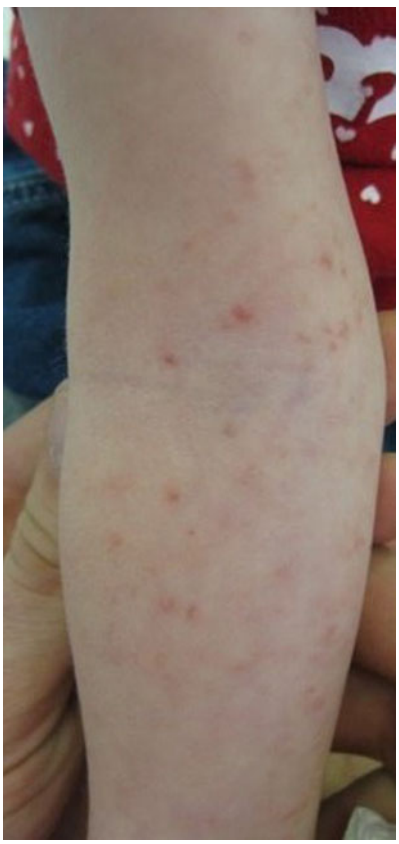

Fig. 20.19 Henoch-Schonlein Purpura (Courtesy of Adelaide Hebert, MD)

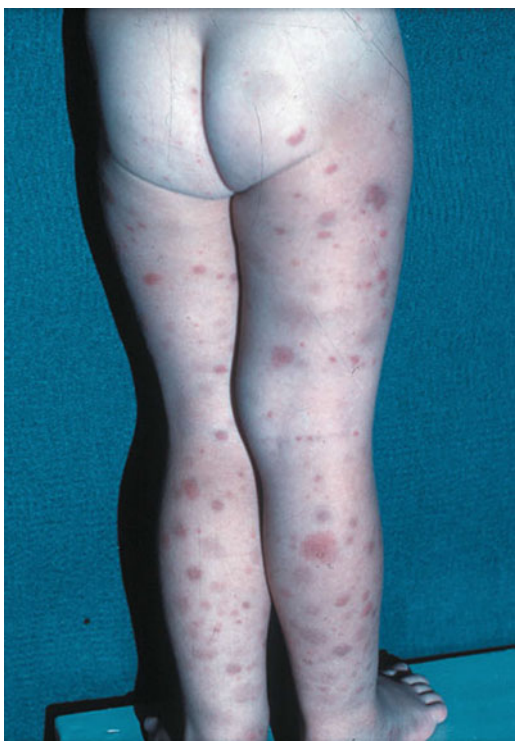

Fig. 20.21 Henoch-Schonlein Purpura Eruption (From Bonifazo E. Differential Diagnosis in Pediatric Dermatology. In: *Allergic Diseases*. Springer; 2013. p. 101. Used with kind permission from Springer Science and Business Media)

Specific Investigations Recommended

For diagnosis
Biopsy
Immunofluorescence
Urinalysis
CBC, ESR
Streptococcal throat culture or anti streptolysin screen
Stool guaiac test

Histology reveals leukocytoclastic vasculitis with fibrinoid degeneration of small dermal vessel walls, perivascular and intramural infiltration of neutrophils/lymphocytes, and RBC extravasation with hemosiderin deposits. On immunofluorescence, deposition of IgA, C3, and fibrin is present. Urinalysis is positive for hematuria, proteinuria, and red cell casts. Patients can develop leukocytosis, anemia, or elevated ESR. Also, a streptococcal throat culture may still be positive at time of diagnosis. Some patients will have positive guaiac tests as well [2].

Table 20.18 First line therapies

Antibiotics	–
Cyclosporine factor XIII	B
Systemic corticosteroids	C
Azathioprine	C
Factor XIII	D

While antibiotics do not treat HSP; they may be necessary to treat an upper respiratory tract infection, if still present. There have been case reports of children with HSP who are factor XIII deficient. Factor XIII concentrate can benefit these patients, especially those with severe GI symptoms.

In patients with renal or internal organ involvement, corticosteroids, cyclosporine, or azathioprine may be used. In one clinical trial of 24 patients, cyclosporine was effective in resolving nephrotic-range proteinuria in 100% of patients randomized to that medication [36]. Methylprednisolone has also been effective in ameliorating progression of disease. This medication can be administered at 1–2 mg/kg/day to prevent life-threatening complications such as gastrointestinal bleeding and proteinuric nephritis [37, 38]. Azathioprine can been administered with methylprednisolone to increase efficacy [39, 40].

Table 20.19 Second line therapies

IVIG	E
Plasmapheresis	E
Aminocaproic acid	E
Mychophenolate mofetil	C

There have been anecdotal case reports showing benefits of intravenous immunoglobulin (IVIG), plasmapheresis, and aminocaproic acid. IVIG is a viable alternative to corticosteroids in patients with significant gastrointestinal symptoms [41]. Plasmapheresis is used in patients with renal dysfunction. Risk of immunosuppression should be evaluated [42]. Aminocaproic acid has been used as an adjunct therapy to corticosteroids, and mychophenolate mofetil in treating patients with nephrotic-range proteinuria [43].

Table 20.20 Third line therapies

Dapsone	D
Plasma exchange therapy	D

A case series utilizing Dapsone has proved beneficial in treating HSP; however, more research is necessary to evaluate for efficacy [44]. In patients with severe gastrointestinal symptoms, plasma exchange has been used with beneficial results [45].

Polyarteritis Nodosa

Clinical Features

Polyarteritis nodosa (PAN), also known as macroscopic polyarteritis or classic polyarteritis nodosa, is a multisystem, necrotizing vasculitis of medium-sized arteries. This condition occurs in pediatric and adult populations; however, it is more severe and life-threatening in pediatric cases. Patients develop aneurysms of the small- and/or medium-sized arteries and multisystemic involvement. Symptoms include fever, malaise, weight loss and, in severe cases, renal disease, CNS involvement, and fatal coronary disease. Cutaneous findings occur in 15% of patients, and can vary from erythematous macules or nodules to purpura and ulcers (Fig. 20.22). Symptoms appear in a livedo pattern on the trunk or extremities, with lower legs being the most commonly affected location (Fig. 20.23) [2, 46].

Management Strategies

Differential diagnosis includes autoimmune connective tissue disease, microscopic polyangiitis, Churg-Strauss syndrome, and other vasculitis. Pediatric PAN has a chronic relapsing course, with a poor prognosis secondary to cardiac failure. Management consists of aspirin, NSAIDs, and IVIG. There are secondary options available for patients refractory to initial therapies. If left untreated, PAN has a high mortality rate secondary to fulminant deterioration, or by progression of

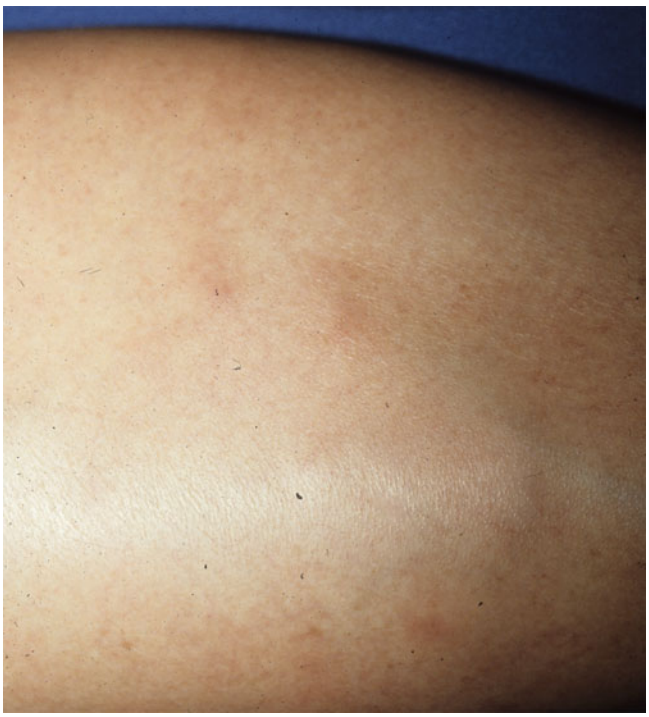

Fig. 20.22 Polyarteritis Nodosa (Courtesy of Adelaide Hebert, MD)

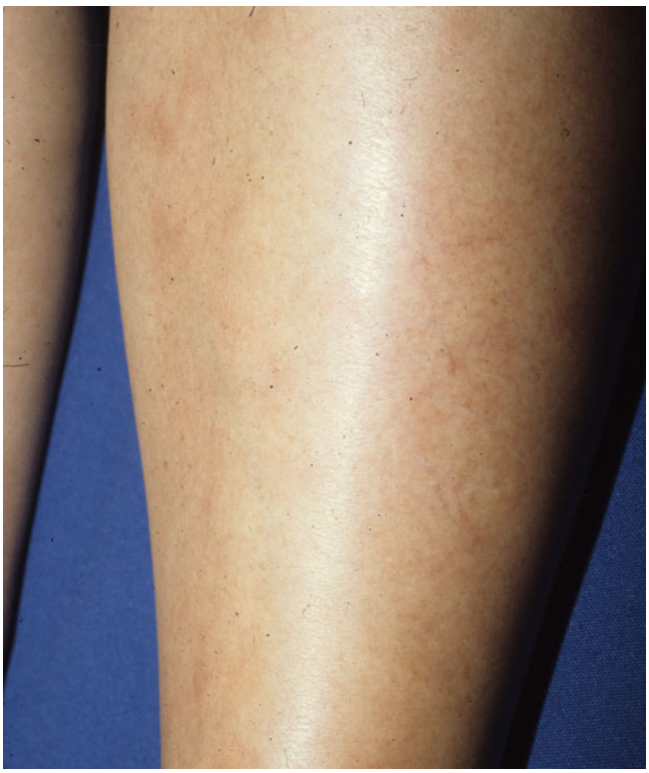

Fig. 20.23 Polyarteritis Nodosa (Courtesy of Adelaide Hebert, MD)

disease after recurrent episodes. Mortality results from renal or cardiovascular failure, bowel perforation, or intractable hypertension. Treatment decreases mortality rate by 50 % [2].

Specific Investigations Recommended

For diagnosis
Biopsy
Immunofluorescence
CBC with differential, renal panel, ESR
Arteriography

Unfortunately, it can be difficult to diagnose PAN from cutaneous symptoms alone. Biopsy with appropriate technique and depth of tissue can be very helpful. Histology displays necrotizing vasculitis of medium-sized vessels, with polymorphonuclear neutrophils infiltrating all layers of the vessel wall and perivascular area. If there is occlusion, thrombosis, or infarction of the vessel, fibrinoid necrosis will be present. Immunofluorescence displays deposits of C3, IgM, and fibrin within the vessel walls.

PAN patients typically develop leukocytosis, eosinophilia, anemia, elevated ESR, and elevated BUN/Creatinine. To diagnose an aneurysm, arteriography is recommended to evaluate the renal, hepatic, and visceral vasculature [2].

Table 20.21 First line therapies

Aspirin	E
NSAIDs	E
IVIG	E
Colchicine	E
Dapsone	E
Systemic corticosteroids	E

As vasculitis classification evolves, PAN is becoming diagnosed less and treatment is determined secondary to etiology. Therefore, clinical studies are few, and research on treatment options are anecdotal. Current management recommendations include a less aggressive therapy with NSAIDs, colchicine, or dapsone. In addition, primary PAN is treated with immunosuppressants, and hepatitis B-induced PAN is treated with antiviral therapy and plasmapheresis.

IVIG is a treatment option in patients with a prolonged course, or as treatment prior to considering systemic corticosteroids [47]. Corticosteroids can be used alone or in conjunction with immunosuppressants. Therapy with methylprednisolone pulses and cyclophosphamide doses has been reported [48].

Table 20.22 Second line therapies

Cyclophosphamide	E
Methotrexate	E (adults)
Plasma exchange	E
Pentoxifylline	E

Low-dose methotrexate has been reported in adults to be beneficial [49]. Plasma exchange has been used in patients with organ dysfunction with favorable effects; however, clinical trials are still necessary to evaluate further [50]. Pentoxifylline has been used as an adjunct treatment in PAN [51].

Serum Sickness

Clinical Features

Serum sickness is a type III, immune-complex allergic reaction that was originally witnessed after treatment with horse or rabbit antiserum. Today, it is more commonly seen with medications or vaccinations. Cardinal features are cutaneous eruption, fever, polyarthralgia, or polyarthritis that develop 1–2 weeks after exposure to an offending agent. During the acute stage, patients are febrile and ill-appearing. Patients develop polycyclic wheals and edema similar to urticaria on the face, trunk, and extremities (Figs. 20.24 and 20.25). Fifty percent get arthralgias, and they can also get lymphadenopathy, peripheral neuritis, cerebral edema, or glomerulonephritis [2]. In children with arthritic pain, serum sickness should be ruled out.

Recurrence can develop and may be more rapid or severe if a previously immunized patient is re-exposed to the culprit agent. Rather than the 1–2 weeks to symptom presentation (due to development of IgG), patients can induce an IgM response in 12–36 h.

Serum-sickness-like reactions are used to describe reactions to medications that can clinically resemble serum sickness; however the pathogenesis does not involve deposition of immune complexes. The patient with this condition typically lack lymphadenopahty, fever and proteinuria. The exact mechanism is not well understood. The most common culprits in the past were cefaclor (Ceclor) and amoxicillin. While serum sickness is more common in adults, serum-sickness-like reactions are more common in children [52].

Management Strategies

Differential diagnosis includes urticaria, angioedema, viral exanthema, TEN, Kawasaki's disease, or subacute bacterial endocarditis. Serum sickness is self-limited and prognosis is good once the offending agent is removed [2]. Treatment options are provided in severe cases; otherwise, it is only for symptom relief.

Specific Investigations Recommended

For diagnosis
CBC with differential, ESR, CRP
Serum chemistry, LFTs
Urinalysis
Complement studies: CH50, C3, C4
Hepatitis panel
Biopsy

In patients without a clear etiology, a laboratory work-up should always be performed. In serum sickness, the CBC displays neutropenia and mild thrombocytopenia with or without eosinophilia. Acute phase reactants (ESR, CRP) are elevated. Creatinine can also be elevated up to twice the

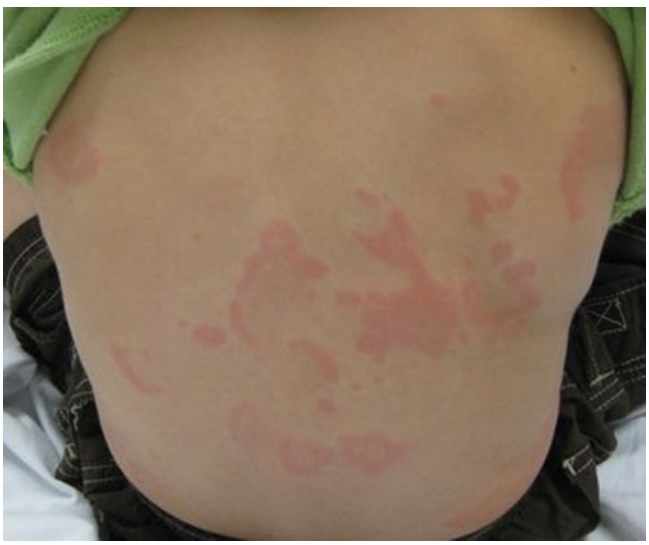

Fig. 20.24 Serum sickness (Courtesy of Adelaide Hebert, MD)

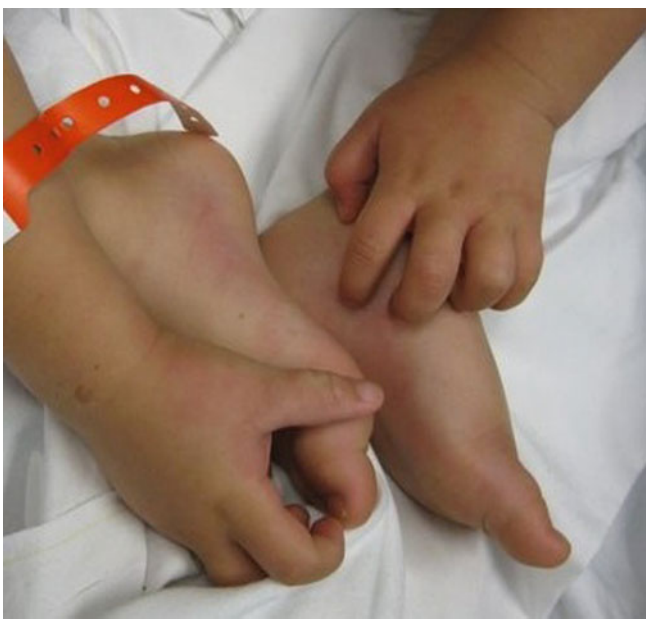

Fig. 20.25 Serum sickness (Courtesy of Adelaide Hebert, MD)

baseline, however this can resolve in a few days. Progression to glomerulonephritis is rare. In serum sickness, patients can have a urinalysis positive for mild proteinuria and hematuria, while in serum-sickness-like this is not present. During severe episodes, complement CH50, C3, and C4 can be lowered secondary to consumption. Extra tests can be performed to exclude infectious causes such as a hepatitis panel to rule out acute hepatitis B infection.

Although not necessary, a skin biopsy can be helpful in confirming the diagnosis. Histopathology can be similar to urticaria with mild perivascular infiltration of lymphocytes and histiocytes. Direct immunofluorescence demonstrates IgM and C3.

Table 20.23 First line therapies

Discontinuation of offending agent	D
Antihistamines	D
Systemic glucocorticoids	D
NSAIDs	E
Analgesics	E

Treatment of serum-sickness is variable. Those with mild disease do not require treatment. In these patients, once the offending agent is removed, fever and arthralgia begin to resolve. Within 48 h, they stop producing new lesions. A retrospective study was conducted looking at treatment practices of emergency room pediatricians and found that the most common practice included discontinuation of offending agent combined with antihistamines and glucocorticoids [53]. NSAIDs and analgesics can also be provided for symptom relief.

In patients with high fever and severe arthritis/arthralgias, prednisone is administered orally at 0.5–1.0 mg/kg/day. In those who appear acutely ill or are very uncomfortable, intravenous methylprednisolone can be administered at 1–2 mg/kg/day in one or two divide doses. Duration of therapy is typically less than 1 week and can be tapered [54].

Table 20.24 Second line therapies

Plasmapheresis	E (adult)

Plasmapheresis has seldom been used in adults who could not be taken off the offending agent, such as a diabetic who is insulin-dependent.

Graft-Versus-Host Disease

Clinical Features

Graft-versus-host disease (GVHD) is an immune disorder caused by the response of histoincompatible, immunocompetent donor cells against the host tissue as a complication of hematopoietic cell transplant (HCT). Acute GVHD occurs within 100 days of HCT, and chronic GVHD occurs after 100 days, although other findings have been used to distinguish the difference. Multiple criteria have been use to stage GVHD based on liver, gastrointestinal, or cutaneous involvement. Cutaneous GVHD is manifest by the following cutaneous findings:

Acute GVHD

- Stage 1 – Maculopapular eruption of <25 %
- Stage 2 – Maculopapular eruption of 25–50 %
- Stage 3 – Maculopapular eruption >50 %
- Stage 4 – Erythroderma with bullae

Chronic GVHD

- Stage 1 – Lichenoid
- Stage 2 – Sclerodermoid

In acute GVHD, patients develop maculopapular eruptions, with or without bullae, that are generalized or present on acral surfaces, pinna, cheeks, neck, or upper back (Figs. 20.26 and 20.27). Oral manifestations include mucositis, erosions, ulcers, lichenoid lesions, xerostomia, and oral pain.

In chronic GVHD, patients have more lichenoid or sclerotic papules, plaques, and ulcers. Lesions can be hypopig-

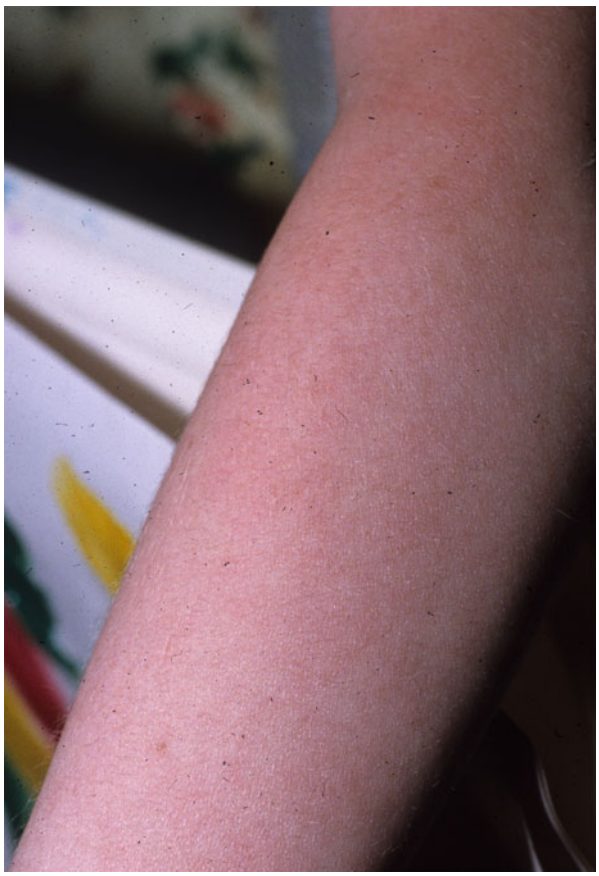

Fig. 20.26 Acute graft-versus-host disease (Courtesy of Adelaide Hebert, MD)

mented or purple and present on the dorsal hands and forearms (Fig. 20.28). Sclerosis is typically seen on trunk, buttocks, hips, and thighs (Figs. 20.29, 20.30, and 20.31). Patients can also have alopecia, anhydrosis, oral lichen planus-like lesions, erosive stomatitis, esophagitis, bronchiolitis obliterans, and muscle wasting.

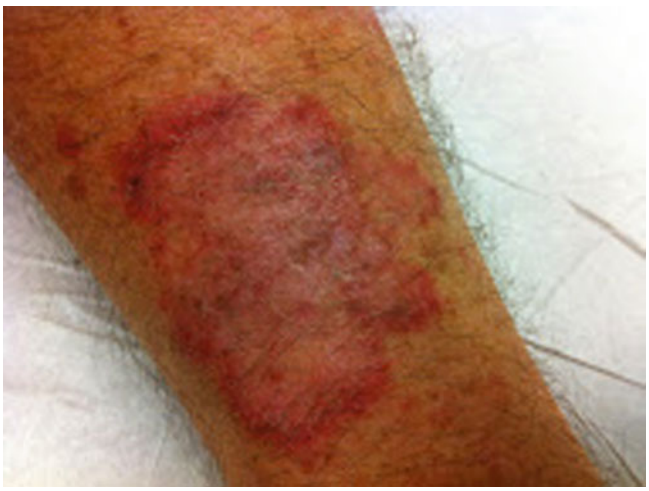

Fig. 20.27 Acute graft-versus-host disease (Courtesy of Adelaide Hebert, MD)

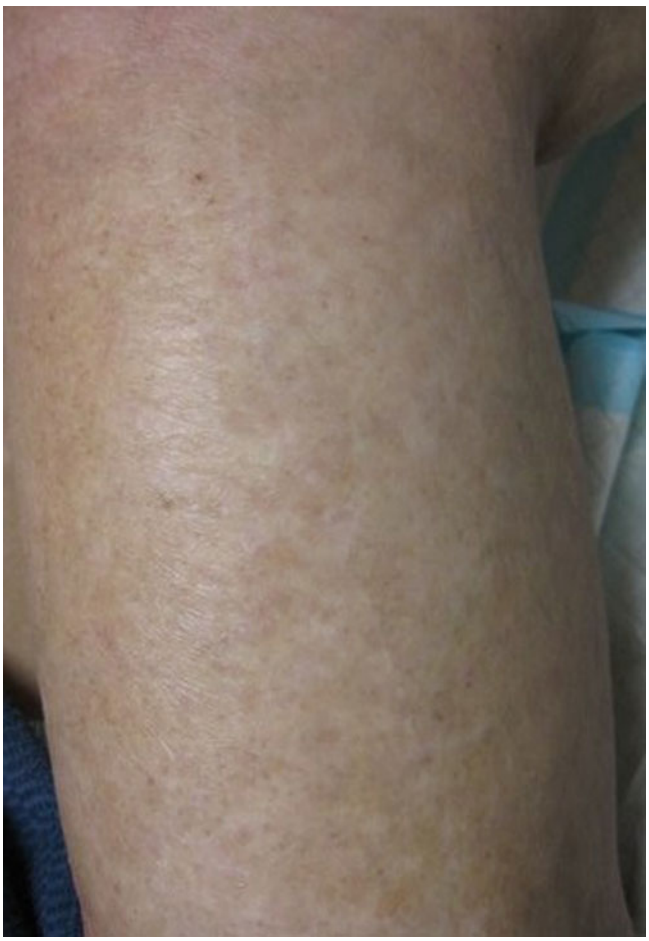

Fig. 20.28 Chronic graft-versus-host disease (Courtesy of Adelaide ebert, MD)

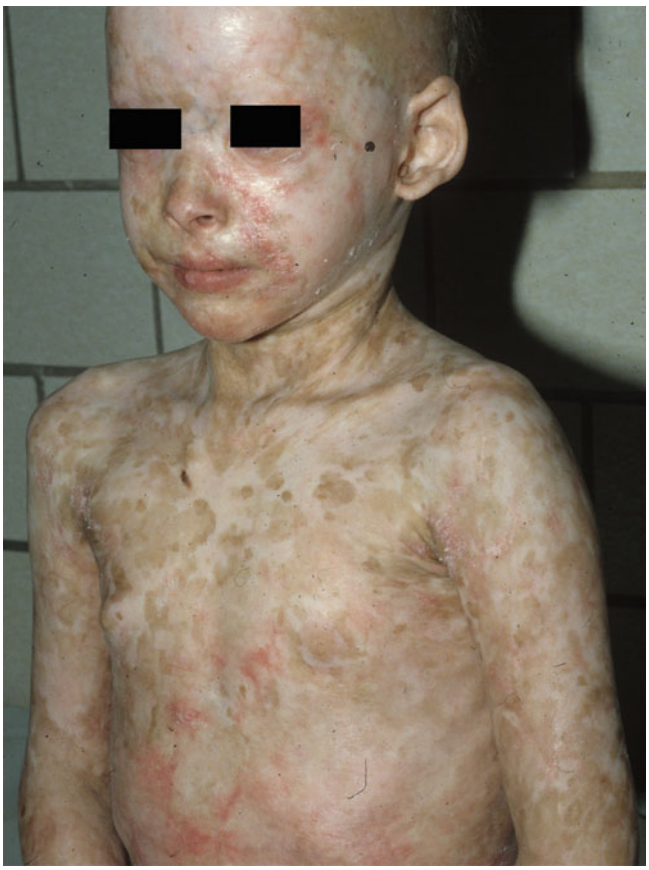

Fig. 20.29 Chronic graft-versus-host disease (Courtesy of Adelaide Hebert, MD)

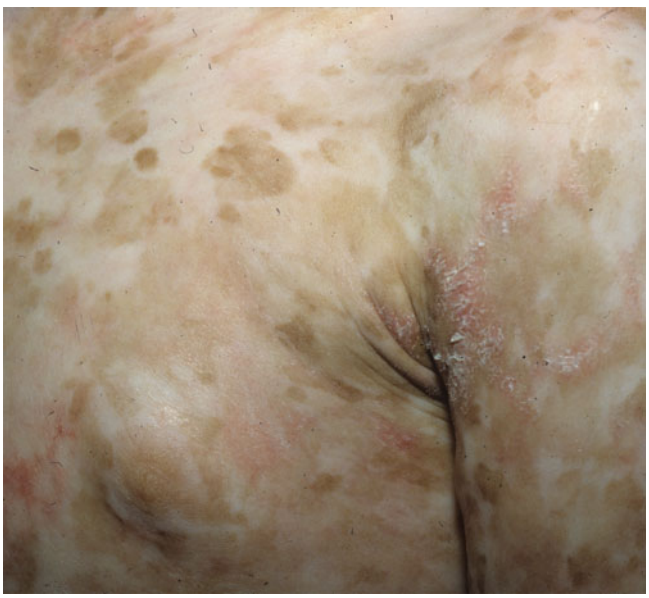

Fig. 20.30 Chronic graft-versus-host disease (Courtesy of Adelaide Hebert, MD)

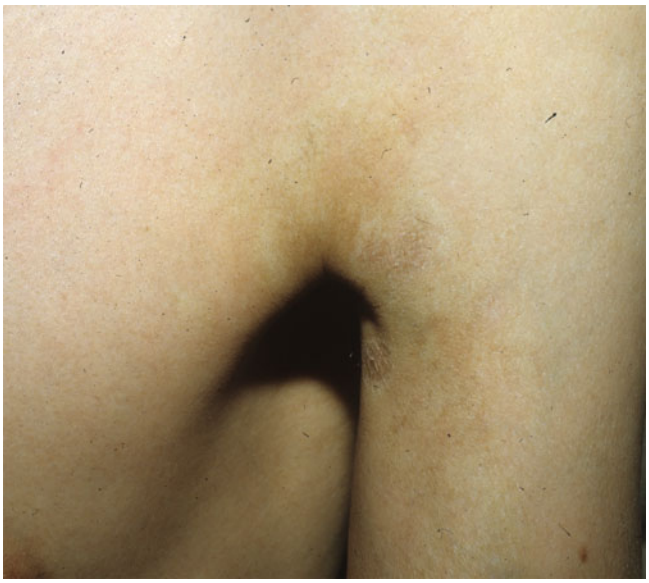

Fig. 20.31 Recovery of hypopigmentation and cutaneous sclerotic changes in patient with chronic graft-versus-host disease (Courtesy of Adelaide Hebert, MD)

Management Strategies

Differential diagnosis includes drug eruption, viral exanthema, eruption of lymphocyte recovery, acral erythema, TEN, radiation dermatitis, and erythema multiforme. While it can be difficult to diagnose GVHD because patients post-HCT are on concomitant treatments and chemotherapy, this diagnosis warrants consideration in this population. As clinical findings can be nonspecific, a skin biopsy may be helpful in producing a definitive diagnosis.

Specific Investigations Recommended

For diagnosis
Punch biopsy
CBC with differential, chemistry, renal panel, LFTs, ESR
Complement levels
MRI
For treatment
Serial photography
Range of motion assessment

Biopsies of the skin taken early in the disease course may be nonspecific; however, once a patient's disease progresses, a skin biopsy may be very informative [55]. Histopathology of acute GVHD displays interface dermatitis, lymphocytic infiltrate in the superficial dermis, vacuolization of the basal layer of the epidermis, and epidermal apoptotic keratinocytes (which may also be present in the follicular epithelium as well). There can also be presence of satellite cell necrosis. Fulminant lesions display subepidermal clefting and full-thickness necrosis of the epidermis [56].

Labs are typically not beneficial in diagnosing GVHD; however the following have been noted: leukopenia or mild leukocytosis, eosinophilia, elevated ESR, mild proteinuria or hematuria, transient elevation of serum creatinine, and decreased C3 and C4.

In chronic GVHD, the histopathology varies depending on the type of skin involvement. In lichen planus-like lesions there is hyperkeratosis, hypergranulosis, acanthosis, saw-tooth rete, interface dermatitis, dyskeratotic keratinocytes, and sometimes periadnexal inflammation [57]. In sclerotic lesions there is epidermal atrophy and edema. In lesions that are more morpheaform, thickened collagen bundles are present with loss of adnexal structures.

If subcutaneous involvement or fasciitis is suspected, an MRI can be beneficial. In patients with chronic sclerotic changes, serial pictures and range of motion assessments are good tools for assessing progression.

Systemic therapies and phototherapy are the mainstay of treatment for cutaneous lesions. High-potency corticosteroids can provide improvement in patients with cutaneous manifestations and no internal involvement. Phototherapy is an additional option for cutaneous symptoms. In a retrospective study in adults, psoralen plus UVA (PUVA) and narrow-band UVB improved skin findings in patients that were refractory to glucocorticoid therapy [58]. Patients with high fever, severe arthritis/arthralgias, or extensive eruptions may be treated with a short course of corticosteroids. Prednisone 0.5–1.0 mg/kg/day is recommended or in severe cases methylprednisolone 1–2 mg/kg/day [54].

Table 20.25 First line therapies

Discontinuation of offending agent	D
Systemic corticosteroids	D
Phototherapy	D
Topical antipruritic agents	E
Oral antihistamines	D
Topical corticosteroids	D
Oral anesthetics	D

Patients with chronic cutaneous GVHD should be provided with supportive care. The National Institute of Health set up preventative care guidelines to include: photoprotection, regular emollient use, topical steroid adverse event monitoring, and wound management [59]. Daily emollient use can reduce pruritus as well as topical antipruritic agents such as hydrocortisone with pramoxine or menthol-

contacting creams. Patients with more severe symptoms may need systemic antipruritics such as diphenhydramine, hydroxyzine, or doxepin for stronger relief. When using topical corticosteroids, high-potency agents are recommended, however, patients should be monitored for signs of skin atrophy, telangiectasia, stria distensae, and ecchymosis. For the face and intertriginous folds, lower potency corticosteroids are recommended.

For oral mucosal involvement, supportive measures can provide pain relief and comfort. Viscous lidocaine can used judiciously assist in oral intake. Patients with xerostomia benefit from salivary stimulants such as sugarless gum or candy.

Currently there are no recommended secondary or tertiary options for GVHD, as many physicians discontinue the offending agent and prescribe systemic corticosteroids and antihistamines. There is a need for randomized clinical trials to evaluate for more treatment options.

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Photosensitivity and Photoreaction

21

Yuan Yu Michael Huang and Reagan D. Hunt

Solar Urticaria

Clinical Features

Affected patients develop erythema, itch, and urticarial wheals on exposed skin rapidly after brief exposure to UVA, UVB or visible light (Fig. 21.1). In some patients, systemic symptoms develop concurrently, including headache, gastrointestinal distress, wheezing, or syncope.

Management Strategies

General management of solar urticaria includes use of protective clothing, broad spectrum UVA/UVB sunscreens, and avoidance of exposure to the wavelengths of light/UV radiation to which the individuals are sensitive. For those with solar urticaria provoked by visible light or longer wavelength UV-A, exposure avoidance may be challenging. Treatment with H1 antihistamines is helpful, and is generally regarded as first-line therapy. Phototherapy to induce tolerance may also be a useful treatment strategy.

Investigations Recommended

For diagnosis
Phototesting to UVA (320–400 nm), UVB (290–320 nm), visible light (400–800 nm)
Consider ANA, anti-Ro, anti-La, plasma and RBC porphyrins to help exclude connective tissue disease and porphyria
Consider total serum IgE; IgE level may be helpful in treatment-refractory solar urticaria cases for which omalizumab is considered

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- This review article provides an excellent overview of the pathogenesis, diagnosis, and treatment of photodermatoses [1].

Table 21.1 First line therapies

H1 antihistamines	C

- In this retrospective case series of 57 patients, which includes 14 patients between the ages of 9 and 20 years, H1 antihistamine daily reduced intensity of wheals and erythema in 63 % of patients. Antihistamine dosing was as follows: terfenadine 60 mg twice daily, astemizole 10 mg once daily, cetirizine 10 mg once daily, and loratadine 10 mg once daily. Patients who did not respond to scheduled antihistamine treatment were treated with oral PUVA as discussed below. Almost half of the patients were disease free within 5 years [2].
- Seven patients (mean age 28 years, included one 17-year-old) with documented solar urticaria to visible light were treated with cetirizine 10 mg daily for 4 weeks. During weeks 3 and 4 of treatment, they were encouraged to expose themselves gradually to natural light. Symptomatic relief and increased minimal urticaria doses (MUD) were noted in all participants after 15 days of cetirizine [3].
- A 2-year-old girl with solar urticaria on photoprovocative testing to UVB, UVA, and visible wavelengths up to 500 nm had resolution of symptoms while taking loratadine 10 mg daily [4].

Table 21.2 Second line therapies

Phototherapy based hardening (narrow band UVB, broad band UVB, UVA, PUVA)	B
H1 antihistamines and Leukotriene receptor antagonist	C

- This retrospective case series of 57 cases includes 14 children and adolescents between the ages of 9 and 20 years. Patients who did not respond to scheduled antihistamine treatment were treated with oral PUVA three times weekly

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× 4 weeks (oral administration of psoralen 0.6–0.8 mg/kg followed by UVA irradiation 2 h later), and 26 % of these patients achieved complete suppression of wheal formation and erythema with phototesting, rendering MUD undetectable [2]

- Narrowband UV-B phototherapy controlled solar urticaria in 39 adult patients. Individuals <18 years of age were excluded in this study, however, given that narrowband UVB is a well-tolerated therapy for many childhood skin disorders, and that narrowband UVB is efficacious in solar urticaria in adults, it is reasonable to consider as an alternative to PUVA in children and adolescents, although specific data in the pediatric population is lacking [5].
- This review article discusses phototherapy management of solar urticaria [6].
- This prospective study treated eight patients with verified solar urticaria to visible light and UVA who were assigned to one of two treatment arms based on disease severity. Those with higher minimal urticaria doses (less photosensitive) were started on combination therapy with desloratadine 5 mg twice daily and montelukast 10 mg once daily. Those with lower minimal urticaria doses (more photosensitive) were started on desloratadine 5 mg twice daily, fexofenadine 120 mg twice daily, cetirizine Hcl 10 mg twice daily, and montelukast 10 mg once daily. The study included four children (ages 5–16 years). Doses were adjusted to standard pediatric dosing for these children. Partial remission was noted in one child (who was in the more aggressive arm), and full remission was noted in the other three children and all four treated adults. The medications were well tolerated [7].

Table 21.3 Third line therapies

Omalizumab	E

- This case report describes a 16-year-old boy with solar urticaria to UV-A and UV-B treated with omalizumab. The patient failed to improve with antihistamines, including loratadine (30 mg/day), cetirizine (20 mg/day), and diphenhydramine (up to 200 mg/day), and was noted to have an elevated serum IgE (851 IU/ml), so he was started on a trial of omalizumab 400 mg every other week for 3 months. He demonstrated partial improvement after six omalizumab treatments, with an increase in the minimal urticaria dose for UV-B, and delayed response time from 1 to 15 min for post-exposure erythema in both UV-A and UV-B spectrum [8].
- This case report describes a 16-year-old girl with solar urticaria to UV-B spectrum exposure. She failed to improve with broad spectrum sunscreen use and the combination of cetirizine 10 mg/day, desloratadine 5 mg/day and hydroxyzine 25 mg/day, as well as with the combination of cetirizine 20 mg/day, ranitidine 150 mg/day and montelukast 10 mg/day. Five-day courses of prednisone (25 mg daily) were ineffective. Her IgE was mildly elevated (228 IU/ml). She was treated with 375 mg omalizumab every other week for 6 months, then dosing was reduced. Omalizumab treatment induced remission of her solar urticaria, which remained inactive 4 months after treatment was discontinued. Phototesting at end of therapy and at 4 months after discontinuation was negative [9].

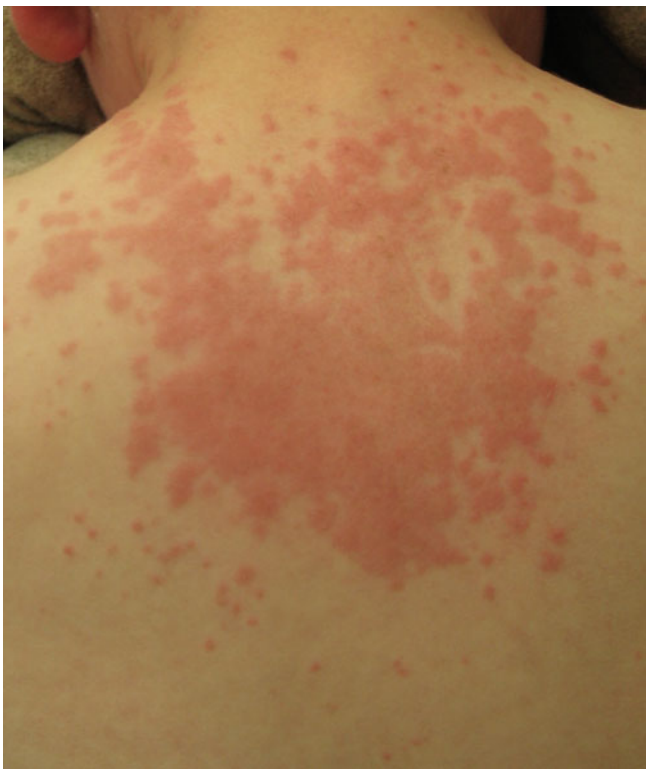

Fig. 21.1 Solar urticaria on back soon after sun exposure

- This case report describes a 6-year old boy with recurrent episodes of solar urticaria associated with angioedema. The action spectrum for his solar urticaria was found to be limited to the visible light range on provocative phototesting to UV-A, UV-B, and visible light. He failed to respond to antihistamine treatment of desloratadine 5 mg twice daily, fexofenadine 120 mg twice daily, cetirizine 5 mg in morning and 10 mg at night, and montelukast 4 mg once daily. He had an elevated IgE (2004 IU/ml) and was treated with omalizumab, which was gradually escalated to 300 mg once every 2 weeks. Once remission occurred, dosing was spaced to monthly to maintain remission while antihistamines and leukotriene receptor antagonists were weaned [10].

Non-standard Therapies Not Studied or Reported for Children/Adolescents

Intravenous immunoglobulin (IVIG)	E
Extracorporeal photopheresis	E
α-melanocyte-stimulating hormone analogue [Nle4-D-Phe7]-α-MSH	C

- This case series describes two adult women with solar urticaria who were successfully treated with 2 g/kg of IVIG divided over 5 days, and remained in remission post-IVIG for greater than 1 year (13 months and 4 years at time of report) [11].
- This case report describes a 54-year-old-man with solar urticaria who failed to improve with oral antihistamines, hardening (with UVA, UVB, visible light, or oral PUVA), and oral cyclosporine. He was treated with nine extracorporeal photopheresis cycles, and his minimal urticaria dose (MUD) increased and symptoms decreased [12].
- Five patients with solar urticaria were treated with α-melanocyte stimulating hormone analogue afamelanotide. The mean age of participants was 34 years, and the youngest patient was an 18-year-old. All five subjects had a solar urticarial response to UV-A, and some had overlapping response to UV-B or visible light. Subjects were treated with a single 16 mg afamelanotide implant in winter. In all subjects, increased melanocytic pigmentation was noted, along with a decreased urticarial response and reduced MUD at 30 and 60 days post implant. No serious adverse effects occurred, and no concerning changes in nevi were noted [13].

Polymorphous Light Eruption

Clinical Features

Although more prevalent in young adults, polymorphous light eruption (PMLE) also develops during childhood, and is the most common photosensitivity disorder among children. Pruritic skin lesions develop in photo-exposed areas within hours to days after sunlight exposure, and may have many different morphologies, with the most common being papules or papulovesicles (Fig. 21.2). The eruptions occur most often in late spring to early summer, as "hardening" occurs, and affected individuals experience decreased photosensitivity after gradual sun exposure over time. In some cases, presumably due to the hardening phenomenon, the face and dorsal hands may be spared, whereas lesions develop on areas which were covered in the preceding winter months, such as the upper chest and extensor arms.

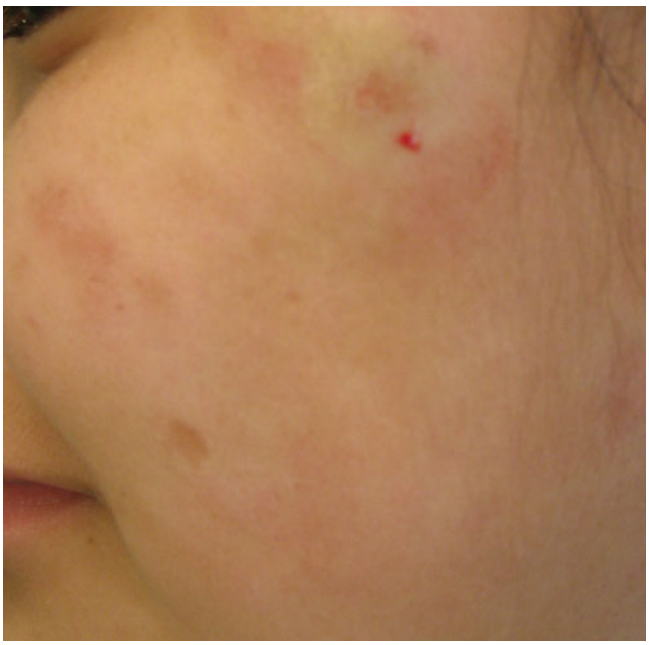

Fig. 21.2 Polymorphic light eruption on the face

Management Strategies

Prevention is the first-line therapy for patients with PMLE. Affected individuals should avoid exposure to sunlight, wear protective clothing, and use sunscreen with high sun protection factor UVA/UVB coverage.

In those with recurrent eruption, despite diligent sunlight protection and avoidance, phototherapy to induce hardening in spring can be effective in preventing eruption in up to 90 % of the patients.

In patients with an acute flare of PMLE, topical corticosteroids and oral antihistamines can reduce inflammation and alleviate itch. In more severe cases, treatment with oral prednisone, antimalarial medications, beta-carotene, nicotinamide, cyclosporine, and dietary fish oil can be considered. Further, azathioprine and thalidomide have been reported as possible alternative therapies.

Lastly, several experimental prevention strategies have been reported, including extract of polypodium leucotomos, topical DNA repair enzymes, topical vitamin D, and flavonoids. These approaches may be promising as potential alternative therapies for patients unable or unresponsive to phototherapy treatment.

Investigations Recommended

For diagnosis
Phototesting
Skin biopsy
ANA, anti-Ro, anti-La to help exclude connective tissue disease

- This retrospective study reports successful phototesting in 92 children between the ages of 4 and 16 years. Of the participants, 56 had a photosensitivity disorder and 22 were diagnosed with PMLE. The average age of the PMLE patients was 11 years. Among them, photosensitivity for UVB was found in 32 %, UVA 28 %, and both UVA and UVB in 40 % [14].

Table 21.4 First line therapies

Behavioral sunlight avoidance with use of high-protection level UVA/UVB broad-spectrum sunscreen	C
Narrowband or Broadband UVB phototherapy	C
PUVA	D

- Twelve adults with PMLE were tested by photoprovocation after applying placebo or sunscreen with high protection level against UVB/UVA, containing methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M), bis-ethylhexyloxyphenomethoxyphenyl triazine (Tinosorb S) and butyl methoxydibenzoylmethane. PMLE symptoms were elicited after photoprovocation on the placebo-treated arm in 10 of 12 subjects, but were not replicated in any of the subjects on the UVA/UVB sunscreen-protected arm in individual subjects [15].
- When applied at a concentration of 2 mg/cm^2, all 15 female patients (ages 18–45 years) treated with high UVA protection sunscreen (SPF45, UVA protection factor 25) showed no PMLE skin eruptions upon exposure provocation 15 min after sunscreen application. In comparison, only 4 of 15 (27 %) patients were protected when using lower UVA protection sunscreen (SPF45, UVA protection factor 5) [16].
- Among 51 patients (ages 5–82 years) treated with PUVA (three times weekly for 3–4 weeks in the spring), 64 % reported total protection from PMLE symptoms during the summer after treatment completion, 26 % reported partial protection, and 10 % reported no change. Development of the eruption during active treatment occurred in 22 % of the patients, but was usually mild and did not interfere with treatment [17].
- In eight of ten patients (ages 18–74), photohardening with narrow-band UVB was successful, even in patients refractory to UVA and broadband UVB phototherapy [18].

Table 21.5 Second line therapies

Oral prednisone	A
Beta-carotene, lycopene, *Lactobacillus johnsonii supplement*	A
Anti-malarial medications	A
Thalidomide	B
Nicotinamide	B
Dietary fish oil	C
Azathioprine	E

- In eight patients, 25 mg prednisone daily for 7 days was superior to placebo in management of acute PMLE. This suggests that a short course of prednisone is reasonable for patients planning sunny vacations [19].
- In 60 patients (ages 18–50 years), treatment with one capsule per day for 12 weeks of a commercially available nutritional supplement (verum) containing 2.5 mg lycopene, 4.7 mg of beta-carotene, and 5.10^8 cfu of the probiotic *L. johnsonii* (Inneov Sun Sensitivity, Laboratoires Innéov, Asnières sur Seine, France) resulted in reduced PMLE lesion induction compared to control group [20].
- For PMLE, 63 patients (all >18 years) were treated with hydroxychloroquine 400 mg/day for 1 month, and 200 mg/day for a second month, whereas 54 patients received treatment with chloroquine 500 mg/day for 1 month, and 250 mg/day for a second month. Hydroxychloroquine was marginally more effective than chloroquine in managing acute flares [21].
- 22 of 25 patients (adult and pediatric) treated with 100–200 mg/day thalidomide experienced improvement without notable side effects [22].
- 25 out of 42 (60 %) subjects (ages 16–56 years) were treated successfully with oral nicotinamide 3 g daily for 2 weeks that led to the absence of symptoms, despite extensive sun exposure. The dose was reduced to 2 g daily after 1 week of treatment, and 12 of the 25 patients developed PMLE relapse [23].
- 13 patients (ages 21–81 years) were treated for 3 months with fish oil capsule twice daily containing 18 % eicosapentaenoic acid, 12 % docosahexaenoic acid, both w-3 fatty acids, and saturated fatty acids. The patients showed decreased prostaglandin increase after UVA provocation. Nine of 13 patients showed reduced sensitivity to photo induction [24].
- Two patients (ages 49 and 50 years) who typically had year-round photosensitivity triggered by as little as 1–2 min of sun exposure, and unresponsive to all standard treatments, were treated with 0.8–2.5 mg/kg of azathioprine daily for 3 months, with complete remission of symptoms and normal sun tolerance [25].

Table 21.6 Third line therapies

Oral polypodium leucotomos extract	B
Topical DNA repair enzyme	A
Topical vitamin D3	A
Flavinoid antioxidant, vitamin E and sunscreen (SPF 15)	A

- In 20 of 25 patients (80 %) ages 21–68 years, oral daily 480 mg polypodium leucotomos extract provided improvement in tolerance to sun exposure without developing polymorphous light eruptions. Seven (31 %)

showed complete normalization, four (13 %) showed clear improvement, and nine (36 %) showed slight improvement [26].

- 14 patients treated with after-sun lotion containing DNA-repair enzymes from *Anacystis nidulans* and *Micrococcus luteus* extract prevented PMLE lesion induction through UV radiation significantly as compared to those treated with placebo lotion. All patients treated with SPF30 broad-spectrum sunscreen completely avoided polymorphic light eruptions [27].
- 13 subjects (ages 22–50 years) were pretreated with calcipotriol cream twice daily for 7 days before start of phototesting. The pretreatment resulted in a lower severity and frequency of PMLE eruption in up to 83 % of the patients [28].
- In 30 patients ages 20–45 years, treatment with preparation consisting 0.25 % alpha-glucosylrutin (a natural, modified flavonoid), 1 % tocopheryl acetate (vitamin E), and a broad-spectrum SPF15 sunscreen was more effective in preventing PMLE compared to sunscreen alone or placebo [29].

Juvenile Spring Eruption

Clinical Features

Juvenile spring eruption (JSE) is a distinct photodermatosis characterized by erythema and itch of light-exposed areas on the ears that begins hours after sun exposure and progresses to nearby erythematous papules and vesicles over 24–48 h. Lesions may crust and tend to heal with minimal or no scarring in 1–2 weeks. Additional extra-auricular skin lesions have been noted on the hands, face, and legs in less than 5 % of reported cases. JSE most commonly occurs in young boys in the early spring, and may recur each year in the same individual. Outbreaks occur on cool, sunny days. Although the pathogenesis has not been completely elucidated, JSE is considered to be a localized variant of polymorphous light eruption.

Management Strategies

JSE typically resolves within 2 weeks with minimal intervention. Topical corticosteroids effectively treat symptoms during flares. In one report, oral antihistamines used concurrently with topical corticosteroids resulted in clinical improvements in two patients. Preventative strategies consist of sunlight avoidance behaviors, wearing longer hair or caps, and application of broad-spectrum sunscreens to reduce frequency and severity of future episodes. As this condition is uncommon and self-limited, there are no large or randomized clinical intervention trials to direct evidence-based treatment.

Investigations Recommended

For diagnosis
If history and physical exam strongly support diagnosis, no other studies needed. If diagnosis unclear, consider the following tests
Provocative phototesting
Skin biopsy
ANA, anti-Ro, anti-La to help exclude connective tissue disease
Porphyrin screening to help exclude erythropoietic protoporphyria and other cutaneousporphyrias

- Lesional skin of JSE shows histological features consistent with polymorphous light eruption [30].
- All four patients showed normal minimal erythema dose response to UVA and UVB wavelengths. Upon provocative testing with daily 20 J/cm^2 UVA dosage on the ears for 3 days, three patients showed no response, while one patient had generalized diffuse erythema without papulovesicles. This differs from polymorphic light eruption and hydroa vacciniforme, which typically produces characteristic lesions upon repeated daily provocative phototesting with UVA [31].
- Provocative phototesting is often negative in juvenile spring eruption (JSE). This case report describes a boy with JSE who had a positive phototest reaction 24 h after exposure to a single dose of UV-A radiation (4.8 J/cm^2) on the back [32].

Table 21.7 First line therapies

Broad-spectrum sunscreen use and sunlight avoidance	C

- 18 patients using prophylactic broad-spectrum sunscreen reported reduction in frequency and severity of attacks [30].
- Four patients were advised to use broad-spectrum sunscreens, and no relapse occurred over a year [31]
- Two patients managed with broad-spectrum sunscreen reported no recurrence of eruptions in the next 6 months [33].

Table 21.8 Second line therapies

Topical steroids	E

- Case report describes one patient with severe JSE who was treated with topical betamethasone valerate 0.12 % ointment for 6 weeks, with scars upon resolution [32].

Table 21.9 Third line therapies

Oral antihistamines	E

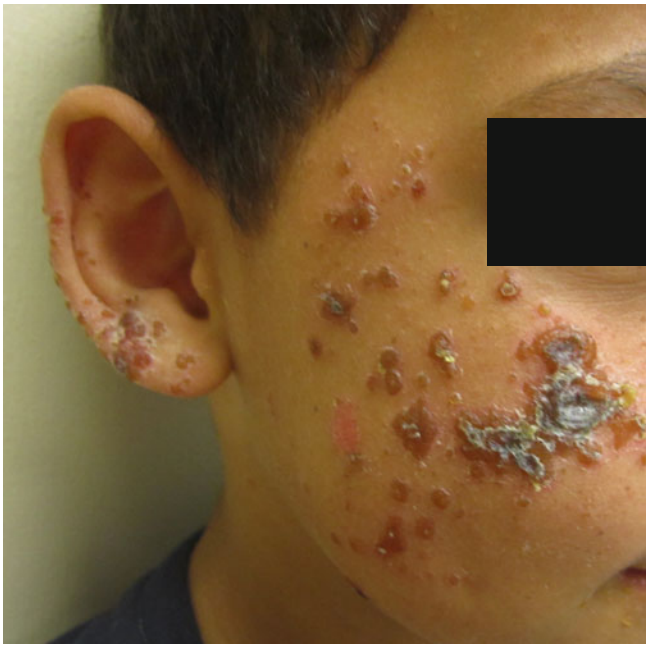

Fig. 21.3 Actinic Prurigo on the face

- Two patients treated with oral antihistamine and topical steroids leading to clearing of lesions after 2 weeks [33].

Actinic Prurigo

Clinical Features

Actinic prurigo (AP) is an uncommon, immunologically mediated photosensitivity disorder that mainly affects individuals of Native American descent in North and Latin America. It usually manifests in childhood with photodistributed pruritic papules, plaques, and nodules which are present year-round, but are more severe during summer months. Fewer similar lesions may be found on areas of skin that are routinely covered by clothing. In contrast to polymorphous light eruption, skin lesions tend to persist more than 4 weeks, and sometimes scar. Prominent cheilitis and ocular findings, including conjunctivitis, photophobia, and pseudopterygium, are often present (Fig. 21.3). AP is diagnosed based on history and physical exam findings. Phototesting and HLA typing may be helpful to provide additional data in cases of diagnostic uncertainty.

Management Strategies

Therapy for AP centers around limiting sun exposure, with emphasis on use of protective clothing and broad-spectrum, high sun-protection factor sunscreens. UVA and UVB protective films may be helpful to reduce sun exposure through window glass. High-potency topical corticosteroids may alleviate itch. Phototherapy hardening treatments may offer some benefit. Thalidomide, an anti-TNF–α agent, is very effective for managing symptoms of AP, however, the potential for teratogenicity and peripheral neuropathy may limit its use. Pentoxifylline, which demonstrates some anti-TNF-α properties, has shown promise in one uncontrolled study. Other treatments such as tetracycline, Vitamin E, antimalarial medications, oral corticosteroids, and beta-carotene may lead to clinical improvement, although the efficacy of these agents is unclear. In patients with ocular manifestations, cyclosporine eye drops have been effective in several cases.

Investigations Recommended

For diagnosis
HLA-typing
Provocative Phototesting
Skin biopsy is not required for diagnosis, but may support the diagnosis; in AP, lip cheilitis shows well-formed lymphoid follicles on histopathology

- This article reviews diagnosis and treatment of actinic prurigo AP. It notes that photoprovocation with repeated exposure to UVA (2.5 J/cm^2/day for 10 days) or UVB (3–5 mJ/cm^2/day for 15 days) reproduces characteristic actinic prurigo lesions in most cases (75 %–100 %), and that specific HLA types have been noted in patients with AP, including HLA-DR4(DRB*0407), HLA-DR4(DRB1*14), HLA-Cw4, HLA-A24, HLA-A28, HLA-B39(B16). In one study, polymorphous light eruption (PMLE) was not associated with any particular HLA type, suggesting that HLA typing may help distinguish between PMLE and AP [34].
- Follicular cheilitis has sensitivity of 74.3 % and specificity of 36.4 % for AP [35].

Table 21.10 First line therapies

Sunlight avoidance – behavioral and environmental avoidance, protective clothing, topical broad spectrum, high sun-protection factor sunscreen	C
Phototherapy (narrow band UVB, PUVA)	C

- Of 21 patients who completed the clinical trial, 18 had "good to excellent results" after management with broad-spectrum UVA/UVB sunscreen. One patient reported that treatment with PUVA was useful [36].
- In this open clinical trial, six patients were treated with weekly narrow-band UVB for 5 weeks in spring.

On follow-up, patients reported that treatment was worthwhile and well tolerated, except for transient erythema [37].
- One child was treated with systemic PUVA with clearing symptoms; however, improvement was not sustained at 4-month follow-up [38].

Table 21.11 Second line therapies

Thalidomide	B
Potent topical corticosteroids	C

- 11 AP patients (ages 15–59 years) were treated with thalidomide for 1 month; all stopped having active pruritic lesions [39].
- In this clinical trial, seven of eight patients (four of whom aged <18 years) were successfully treated with intermittent 3 to 14-day courses of topical 0.05 % clobtasol 17-proprionate cream or ointment, applied once or twice a day. All patients previously failed to improve after treatment with less-potent topical steroids [40].

Table 21.12 Third line therapies

Pentoxifylline	C
Tetracycline	C
Vitamin E	C
Cyclosporine	C
Cyclosporine eye-drops	E
Oral corticosteroids	E
Anti-malarial medications	E
Cimetidine	E
Beta-carotene	E

- In this 6-month open-label, uncontrolled study, all ten participants (thrree of whom were <18 years) over 15 years old (>45 kg) received pentoxifylline at a daily dose of 1200 mg (400 mg three times a day) and younger patients (<45 kg) received 800 mg pentoxifylline (400 mg twice a day) for 6 months. Clinical improvement was documented after 1 month of treatment and was maintained at 6 months [41].
- Eight patients were treated with tetracycline (1.5 g daily) and another group of eight with vitamin E (100 IU daily). Both drugs used were effective in reducing signs and pruritus in AP, with no significant difference in efficacy between the two medications [42].
- In this clinical trial, 18 of 19 patients (mean age of 17 years) showed significant improvement after a 2-month course of cyclosporin A 2.5 mg/kg/day, with effects lasting for at least 6 months after completion of therapy [43].
- One 14-year-old girl was treated with 2 % cyclosporine eye drop at 1 drop/8 h. The patient improved 2 weeks later, but relapsed and required maintenance at 1 % cyclosporine eye drop 1 drop every 12 h [44].
- Among 21 AP patients (ages 4.5–64.9 years), most had been treated with antihistamines (fexofenadine, loratadine) with little to no improvement. In 11 patients, oral prednisolone (12.5–25 mg/day) was beneficial in providing temporary relief in acute exacerbations. Hydroxychloroquine (200 mg twice daily for 3 months) was moderately effective in one patient, but was ineffective at 200–400 mg daily for 3–6 months in three other patients. Cimetidine 600 mg/day reduced itch, but not skin findings or photosensitivity, in one patient. Of three patients treated with beta-carotene (20 mg twice daily), one had limited improvement while the others had no improvement after a 3-month course [45].

Hydroa Vacciniforme

Clinical Features

Hydroa vacciniforme (HV) is an uncommon, idiopathic photosensitivity disorder (estimated prevalence 0.34 cases per 100,000 per year). It predominantly affects children and frequently resolves spontaneously by early adulthood. Classic HV presents as recurrent pruritic papules and vesicles within hours to days after sun exposure, which appear on the nose, cheeks, and ears. Subsequently, lesions crust then slowly resolve over a period of 1–6 weeks, with characteristic varioliform scarring. In some cases, ocular and oral disease occurs. Ophthalmic complications include photophobia, keratoconjunctivitis, and corneal erosions. Oral complications included aphthous stomatitis and ulcerative gingivitis.

Severe HV-like eruption is an HV-like eruption with larger, deeper lesions, and is associated with NK-T-cell lymphoproliferative disorders, worse prognosis, and potentially fatal outcome.

The precise pathophysiology of HV is unknown, but UVA is thought to play an important role, as the characteristic lesions of the disease can be reproduced by artificial UVA exposure. Additionally, several studies have reported an association between HV and latent Epstein-Barr virus (EBV) infection, as EBV-encoded small nuclear RNA has been found in cutaneous infiltrates in both typical and severe HV-like patients.

Management Strategies

Strict restriction of sun exposure, appropriate protective clothing, and regular use of broad-spectrum UVA/UVB sunscreen is critical for management of HV. Courses of narrowband UVB phototherapy or UVA photochemotherapy

(PUVA) prophylactically to decrease photo-sensitivity may help in some cases. Other treatments such as anti-malarial medications, oral glucocorticoids, beta-carotenes, and dietary fish oil may offer some clinical improvement, though none appear to be reliably effective. In patients with EBV-associated HV with a high EBV DNA load, antiviral treatments with acyclovir or valacyclovir may help. Immunosuppressive agents, such as azathioprine, have been helpful in some patients. Evidence for treatment is limited and largely derives from small case series or single case reports.

Investigations Recommended

For diagnosis
Skin biopsy
Screening for EBV infection and detection of EBV-infected cells by T-cell receptor gene rearrangement with polymerase chain reaction
Photoprovocation test with daily UVA
Porphyrin screening to help exclude erythropoietic protoporphyria and other porphyrias
Antinuclear antibody and extractable nuclear antigen to rule out lupus erythematosus and other connective tissue disease
Absence of aminoaciduria excludes Hartnup disease

HV can be diagnosed from clinical exam and/or histopathology. Histology of HV lesions is distinctive. Early lesions show spongiosis, focal keratinocyte degeneration, and a perivascular lymphohistiocytic infiltrate; older lesions demonstrate intra-epidermal vesicles, confluent epidermal necrosis, and ulcerations.

Photoprovocation generates characteristic lesions when using daily low-dose UVA, but not a single large exposure to UVA nor daily low-dose exposure to UVB. Patients typically demonstrate a normal minimal erythema dose (MED) to UVA. The action spectrum of 320–390 nm characteristically induces the skin lesions.

Bullous lupus erythematosus, porphyria (erythropoietic protoporphyria, congenital erythropoietic porphyria and childhood porphyria cutanea tarda), and Hartnup disease may clinically mimic HV. Consider testing as above as needed to confirm the diagnosis.

Screening for EBV is required only if lymphoma is suspected, but recommended given the association between EBV infection and HV and the association between chronic EBV infection and lymphoproliferative disorders.

- Successful photoprovocation response occurred in four HV patients after repeated daily exposure to a small dose of UVA, but not a large single exposure to UVA or UVB [46].
- Eight of 15 HV patients were sensitive to UVA provocation tests, 6 of whom developed papulovesicular lesions [47].
- In 29 of 33 patients with typical HV and 15 of 15 patients with severe variant HV-like eruption, EBV DNA levels in peripheral mononuclear cells were elevated, with the DNA load being higher in those with severe variant. In 43 of the overall 48 patients, EBV+ T cells and reactive EBV- cytotoxic T cells were detected in cutaneous infiltrates [48].

Table 21.13 First line therapies

Broad-spectrum sunscreen (UVA/UVB), protective clothing and sunlight avoidance	C

- Hydroa vacciniforme was satisfactorily controlled in 9 of 15 patients using broad-spectrum sunscreen and strict sunlight avoidance [47].
- In one patient with ocular lesions accompanied by HV, wearing protective sunglasses prevented additional eye symptoms, despite recurrence of skin disease [49].

Table 21.14 Second line therapies

Narrowband UVB phototherapy	C
PUVA	E

- In an open clinical trial in which four HV patients were treated on average ten times daily, two reported increased tolerance to sunshine from 1 to 3–6 h [50]
- Two HV patients were successfully treated by narrowband ultraviolet B phototherapy, but disease relapsed within 3–6 weeks after completed course of treatment [51].
- Five of 15 HV patients who did not respond to conservative management were treated with narrowband UVB phototherapy. Three of the five patients exhibited good to moderate disease control. In the remaining two patients, phototherapy did not offer any improvement [47].
- One 14-year-old boy with HV was successfully treated with PUVA therapy [52].

Table 21.15 Third line therapies

Anti-malarial medications	D
Antivirals	E
Beta-carotene ± canthaxanthin	E
Azathioprine	E
Dietary fish oil	E
Topical corticosteroids	E

- Four HV patients were treated with either 100 mg/day hydroxychloroquine (two patients) or 100–125 mg/day

cholorquine (two patients). Those on hydroxychloroquine showed no improvement, but the two patients on chloroquine had a reduction in severity of their disease [53].

- Four patients with EBV-associated HV were treated with acyclovir/valacyclovir therapy 28–72 mg/kg/24 h for 1–3 weeks with good clinical response [54].
- One HV patient treated successfully after 2 months' treatment with sunscreen coverage and oral administration of carotenoids (10 mg of beta-carotene and 15 mg of canthaxanthin in a capsule, 1 capsule/20 kg/day) [55].
- Two HV patients were treated with 60 mg/day beta-carotene and demonstrated increased sunlight tolerance after completed course [56].
- Three HV patients who failed standard therapies were treated with five 1 g capsules of dietary fish oil (MaxEPA) daily for 3 months. All three showed reduced sensitivity to UVA photoprovocation testing. A mild-to-good improvement was seen in two patients, but no improvement in the third. The latter patient responded to Azathioprine treatment [57].
- This case report describes one HV patient whose skin lesions improved with 1-week treatment of topical methylprednisolone [58].

Pellagra

Clinical Features

Pellagra is a nutritional disorder that results from niacin deficiency. It is prevalent in countries with high malnutrition rates, especially in areas where millet and maize are the major dietary staples. Pellagra may develop in adolescents and children with poor diets. Aside from poor nourishment, niacin deficiency can be caused by gastrointestinal malabsorption, anorexia nervosa, carcinoid tumor, Hartnup disease, and drugs such as isoniazid. Pellagra is characterized by the clinical triad of photosensitive dermatitis, dementia, and diarrhea. Untreated pellagra ultimately leads to death from multi-organ failure. In infants and children, the classic symptoms of pellagra may not be well developed and may be more difficult to recognize. Approximately one-third of patients have only skin lesions at the time of diagnosis.

The skin eruption is associated with a burning sensation and consists of symmetric, well-demarcated erythematous patches in sun-exposed areas (dorsal hands, face, neck, upper chest) that evolves into hyperpigmented plaques in chronic lesions. Characteristic skin lesions on the neck are referred to as "Casal's necklace."

Detailed history, including dietary history, and physical examination are sufficient for this clinical diagnosis. Additionally, given the rapid improvement of pellagra with niacin therapy, response to treatment can be a confirmatory diagnostic criterion. There are no tests which can definitively diagnose pellagra, and histopathological evaluation is often unspecific. However, tests such as urinary niacin metabolite concentration may indicate niacin deficiency, and aid in diagnosis.

Management Strategies

Patients with pellagra should be treated with niacin in the form of nicotinic acid or nicotinamide to correct the vitamin deficiency. Nicotinamide may be more desirable because it is not associated with the side effects of uncomfortable flushing, vasomotor instability, and hyperuricemia observed with some cases of nicotinic acid administration. Typically, improvement with treatment is rapid, and symptoms resolve over a few days to a week.

Given that pellagra patients often have coexisting vitamin deficiencies, vitamin supplementation such as vitamin B complex, pyridoxine, and zinc, along with niacin, are also recommended. Several cases reported successful treatment of pellagra with tryptophan, and this may serve as an alternative treatment for those who are not tolerant of niacin therapy. Topical management of skin lesions with emollients and sunlight avoidance may reduce discomfort. Lastly, one should evaluate for and treat underlying causes for pellagra such as Hartnup disease, carcinoid syndrome, use of isoniazid and other offending drugs, or poor dietary intake in anorexia nervosa or alcoholism.

Investigations Recommended

For diagnosis
Spot urine sample for Niacin metabolite
Urinary amino acid testing to rule out Hartnup disease
Skin biopsy (may be non-specific)
Phototesting

- In 34 patients with pellagra, whole blood NAD and NADP concentration and NAD:NADP ratio were not significantly depressed. However, concentration of niacin urinary metabolites 1-methyl-2-pyridone-5-carboxamide (2-PYR) and 1-methylnicotinamide (1-MN) were lower in pellagra patients, and markedly higher following treatment. The use of the combined cut-offs (2-PYR <3.0 micromol/mmol creatinine and 1-MN <1.3 micromol/mmol creatinine) gave a sensitivity of 91 % and specificity of 72 % for detecting pellagra. Thus, spot urine sample for 2-PYR and 1-MN is an effective method of detecting niacin deficiency in pellagra patients [59].
- The most common histological changes observed among seven pellagra patients were hyperkeratosis of the

epidermis and dilation of the superficial vascular plexus associated with extravagated red blood cells in the dermis. Intradermal blisters occurred due to excessive ballooning of keratinocytes, but subepidermal blistering was observed in three cases. This study concludes that histological features of pellagra vary throughout the course of the disease and may be nonspecific [60].

Table 21.16 First line therapies

Nicotinic acid or Nicotinamide	B
Balanced, protein sufficient diet	D

- In 23 patients with pellagra, administration of 200–300 mg daily nicotinic acid resulted in rapid improvement in symptoms. Vitamin B1 is recommended as a supplement, as its deficiency often coexists in patients with pellagra [61].
- In this retrospective survey, all pediatric patients with pellagra (ages <15) were treated successfully with 50-mg nicotinamide supplement and B-complex tablet three times daily for 15 days. Additionally, all patients received weekly 400 g food supplements consisting of corn soy blend, oil, and sugar [62].
- In two orphanages with previous pellagra outbreaks, modification of diet with increased fresh meat and leguminous protein foods (compared to previous diet composed mostly of cereal, vegetables, and canned food) led to no report of further pellagra cases over the course of 1 year [63].

Table 21.17 Second line therapies

Vitamin B complex supplement	D
Sunlight avoidance and skin emollient	E

- In addition to 50-mg nicotinamide, pediatric patients with pellagra were also given B-complex supplemental tablets three times daily [62].
- One 48-year-old patient with isoniazid-induced pellagra was treated with nicotinamide 300 mg/day successfully. The use of moisturizer, sunscreen, and sunlight avoidance helped alleviate the acute symptoms of the skin disease [64].

Table 21.18 Third line therapies

Zinc	C
Tryptophan	E
Topical nicotinamide	E

- In this clinical study, 14 patients with alcoholic pellagra (ages 21–45 years) were placed on a diet that excluded tryptophan, zinc, and niacin. In seven who received 220 mg zinc sulfate orally, their urinary niacin metabolites levels (1-MN and 2-PYR) were significantly higher compared to patients who did not receive zinc supplementation. Thus, zinc may play a role in niacin metabolism, and may serve as an alternative method in preventing pellagra lesions [65].
- One 30-year-old patient with worsening pellagra was treated successfully using 6 g/day tryptophan for 6 days, leading to remission of all symptoms. This suggests that pellagra is not simply a disease of niacin deficiency but, perhaps more appropriately, of abnormal tryptophan metabolism [66].
- In a 30-year-old patient, topical application of 1 % nicotinamide in cetomacrogol 1000 topical cream twice daily leads to substantial improvement of the rash within 7 days. The patient's neurological symptoms also improved. This suggests that percutaneous absorption of nicotinamide may help treat niacin-deficiency [67].

Cutaneous Porphyrias

Clinical Features

Porphyrias are metabolic disorders that result from specific defects in the heme/porphyrin biosynthetic pathway. Cutaneous porphyrias refer to the subset of porphyrias that have associated skin complications, and include erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), congenital erythropoietic porphyria (CEP), hepatoerythropoietic porphyria (HEP), and porphyria cutanea tarda (PCT).

EPP and XLDPP manifest with acute photosensitivity. Patients complain of a painful burning sensation of skin within minutes of sun exposure, and erythema and edema may develop a few hours after extensive sun exposure (Fig. 21.4). In some cases, waxy skin thickening or scarring may be noted on the nose or dorsal hands. Rarely, liver failure may occur in these patients, and regular liver function screening is recommended.

CEP, HEP, and PCT are characterized by bullous eruptions on photo-exposed skin. Increased skin fragility, milia, and hypertrichosis can be seen. The skin findings in CEP tend to be severe. CEP is a rare autosomal recessive multisystem disease associated with hematologic abnormalities in which the bullous skin disease may develop into extensive photo-distributed scarring, with possible nasal distortion, ectropion, and cicatricial alopecia. HEP, also inherited in an autosomal recessive manner, is even more uncommon. Similar to CEP, the bullous lesions on photo-exposed skin may be mutilating, however, hematologic abnormalities in HEP are infrequent. PCT can be inherited in an autosomal dominant fashion or acquired, often in the context of liver

disease or hereditary hemochromatosis. In children, it is more likely to be genetically inherited.

Additionally, hereditary coproporphyria (HCP) and variegate porphyria (VPO), which are classified as acute porphyrias, sometimes also demonstrate bullous skin photo-distributed eruptions. These skin lesions may appear episodically with the characteristic "acute attacks" of abdominal pain, gastrointestinal distress, and neurological symptoms, or they may occur in isolation.

Management Strategies

The action spectrum of cutaneous porphyrias includes visible light as well as some wavelengths of UV-A, so strict sunlight avoidance and physical protection from sunlight is critical. Interventions aimed at increasing epidermal pigmentation, such as beta-carotene, phototherapy hardening, and afamelanotide may offer some benefit. Correct diagnosis of porphyrias presenting with cutaneous features and monitoring for potential systemic complications is critical.

Investigations Recommended

For diagnosis
Biochemical testing for porphyria is diagnostic; skin biopsy is not required, but may have supportive histopathological features
Plasma fluorescence emission [EDTA-preserved whole blood protected from light]
Peak ≥623 nm: EPP/XLDPP, VP
Increased erythrocyte free protoporphyrins rule in EPP/XLDPP
Peak <623 nm: PCT, HCP, or CEP
Urinary and fecal porphyrin profiles differentiate
No plasma fluorescence emission peak with active skin symptoms excludes porphyria

For monitoring
For EPP/XLDPP (annually)
Liver function tests
Erythrocyte protoporphyrin
Monitor for changes in photosensitivity
For PCT (annually once in remission)
Liver function tests
For CEP
Every 6–12 months depending on severity: complete blood counts, liver function tests
Every 2–3 years: splenic ultrasound and bone density study

- This detailed review article discusses diagnosis and management of cutaneous porphyrias [68].

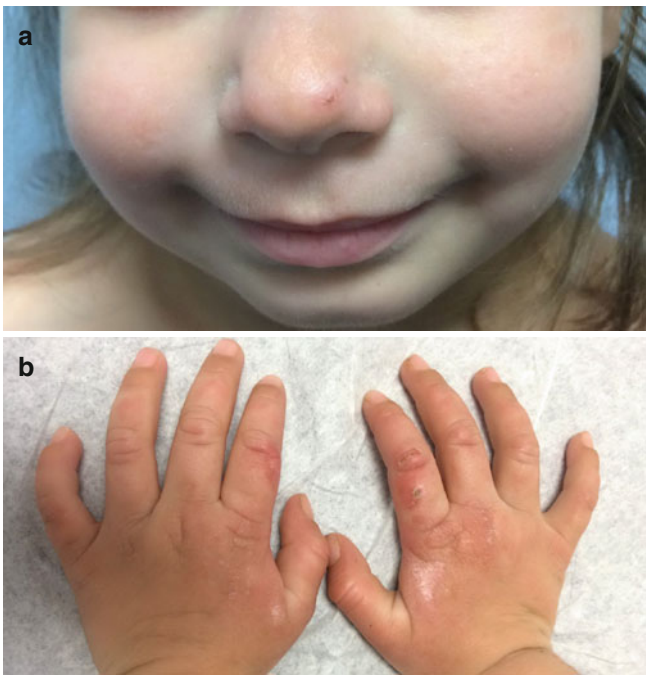

Fig. 21.4 (**a**) EPP on the face. (**b**) EPP on the hands

Table 21.19 First line therapies

Sunlight avoidance and physical photoprotection	D

- Of 223 EPP patients included in a cohort study (ages 5–87 years), 92% indicated that daily activities were disrupted on sunny days. Sun avoidance and protective clothing were cited as helpful by the majority. Reported sunscreen use (including reflectant sunscreen preparations) was variable [69].

Table 21.20 Second line therapies

Beta-carotene	D
Phototherapy hardening (narrow band UVB, PUVA)	D
Cimetidine	E
Hydroxychloroquine	E
Vitamin E	E
Vitamin C	A

- In a cohort of 223 EPP patients (age range 5–87 years), 187 patients had been prescribed beta-carotene, but two-thirds of these patients discontinued it [69].
- Caucasian girl with EPP demonstrated improvement in photosensitivity of face and forearms, but not hands, after 3-month trial of beta-carotene (90–180 mg/day) [70]
- Three children had rapid improvement of photosensitivity a few weeks after starting systemic cimetidine. The treatment appears to be well tolerated [71]

- Only 2 of 12 CEP patients who were treated with beta-carotene (15–120 mg daily, mean duration of treatment 13.6 years) reported improvement in photosensitivity or decreased blistering. Half of them self-discontinued the medication due to perception of inefficacy [72].
- Fifteen of 20 photosensitivity patients (among whom 8 had various cutaneous porphyrias) who underwent narrow band UVB hardening in Spring reported that phototherapy was helpful. Adverse effects included erythema in a subset [37].
- A 4-year-old girl with childhood-onset porphyria cutanea tarda was treated with hydroxychloroquine 3 mg/kg twice daily and vitamin E (200 U/day) with reduction of blistering noted after 6 weeks [73].
- Among 12 patients with EPP treated with 1 g daily of vitamin C for 4 weeks versus placebo in crossover trial, there was a non-statistically significant trend toward improvement in self-reported photosensitivity during the period of vitamin C treatment. Nine of the 12 patients were also taking beta-carotene concurrently throughout the trial [74].

Table 21.21 Third line therapies

Afamelanotide for erythropoietic protoporphyria	A

- In this double-blind trial, pain-free time with sun exposure in EPP patients at 6–9 months' post-implant was reduced in afamelanotide implant-treated patients as compared to placebo controls. Quality-of-life improvement was noted after treatment with afamelanotide, and serious adverse medication reactions were not attributed to the drug. The trial only enrolled adult subjects (>18 years) [75].
- Quality-of-life scores increased among EPP patients treated with afamelanotide. Minor side effects such as nausea were reported [76].

Bone marrow transplant for severe congenital erythropoietic protoporphyria	D

- This retrospective clinical study evaluates patient data and suggests a clinical management algorithm for CEP. This study includes clinical data on six children with CEP who were treated with bone marrow transplantation, and five of the six remained with no evidence of disease at 11.5 years post-transplantation. Bone marrow transplantation can be curative, and the authors propose that it should be considered in cases of CEP with progressive symptomatic transfusion-dependent anemia and/or thrombocytopenia, progressive photomutilation, or in patients with specific uroporphyrinogen III synthetase genotypes which are associated with poor outcomes [72].

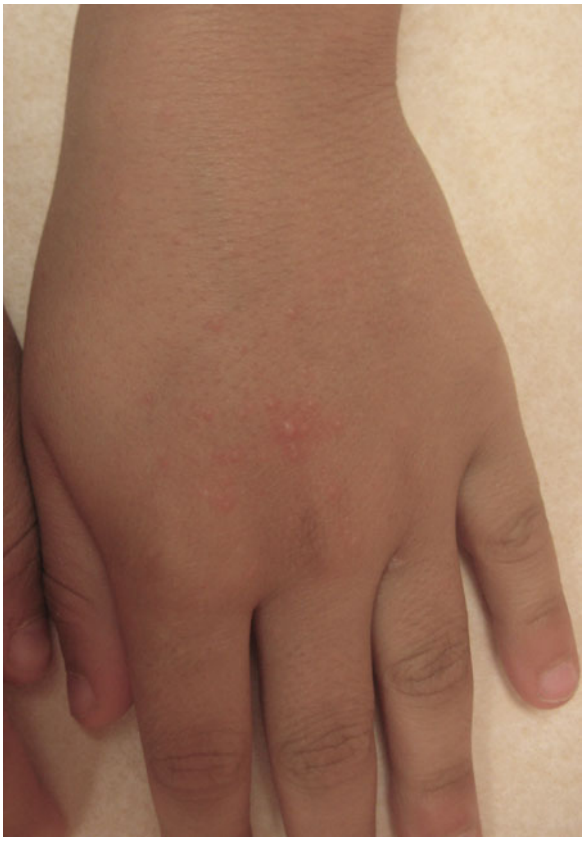

Fig. 21.5 Pseudoporphyria on the hand

Pseudoporphyria

Clinical Features

In pseudoporphyria (PP), photodistributed bullous lesions develop in erythematous patches after a trigger is encountered. Bullae, vesicles, milia, and fragile skin most commonly appear on the sun-exposed dorsal hands (Fig. 21.5), but may also develop on the fingers, extensor legs, upper chest, and face. In tanning bed-related PP, bullae and vesicles have been noted on dorsal knees, pre-tibial surfaces, and dorsal feet. Some children with PP have been noted to have pitted and angular facial scarring reminiscent of erythropoietic protoporphyria (EPP), and in many of them, no history of frank blistering can be obtained. Individuals with fair skin types appear to be more susceptible to PP. Hypertrichosis, hyperpigmentation, and sclerodermoid changes are absent in PP. Whereas the clinical and histopathological features of PP partially overlap with those of porphyria cutanea tarda (PCT), PP patients have normal red blood cell, serum, urine, and stool porphyrin profiles.

Triggers associated with PP include certain medications, ultraviolet (UV) light exposure (especially UV-A), and chronic renal failure with or without dialysis. In children, most reported cases of PP are associated with naproxen use.

Tanning bed-associated PP appears to be most common in young women, but teens may be at risk for this complication as well.

Management Strategies

Treatment for PP includes identification and avoidance of suspected triggers, in combination with excellent UV protection (particularly against UV-A wavelengths).

Investigations Recommended

For diagnosis
Biopsy with Direct Immunofluorescence
Red blood cell, serum, urine, and stool porphyrin profiles to rule out biochemical evidence of porphyria

- This review article discusses common triggers, diagnosis, recommended testing, and treatment of pseudoporphyria in children and adults [77].

Table 21.22 First line therapies

Discontinue suspected triggering medications or exposures	E
Broad spectrum UVA-UVB sunscreen and sun avoidance	E

- In this small case series, a 9-year-old girl had continued blistering despite sun protection, so imatinib was discontinued. Dasatinib was started with complete resolution of skin symptoms within 3 months. The other patient discussed is an 18-year-old woman who, despite cutaneous symptoms, continued on imatinib for 4 years until symptoms of ascites developed. Imatinib was reintroduced at a lower dose after ascites resolved, and skin fragility and lesions resolved [78].
- PP in this 50-year-old woman was successfully controlled by broad-spectrum UVA/UVB sunscreen and minimization of sun exposure as voriconazole, the suspected causative agent of her PP, was medically necessary [79].

Therapies Not Studied or Reported for Children/Adolescents

No second-line therapies have been reported or studied for treatment of PP in pediatric patients. Isolated case reports in adults for treatment of PP suggest that glutathione, glutamine, and n-acetylcysteine may offer some benefit.

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Collagen Vascular Diseases

22

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Antiphospholipid Antibody Syndrome

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Clinical Features

Antiphospholipid antibody syndrome (APS) is an autoimmune disorder characterized by increased risk of venous and/or arterial thrombosis. APS is rare in children, but the exact prevalence is unknown. Approximately 60 % of children with APS present with venous events, most commonly lower extremity deep venous thrombosis [1, 2]. Arterial events occur in over 30 % of children, most commonly involving the cerebral arteries and leading to ischemic stroke or transient ischemic attack [1, 2]. Patients can also have a more fulminant presentation, with multiple organ involvement and evidence of small vessel occlusion, which is known as catastrophic APS [3, 4].

APS can be divided into primary and secondary forms. Approximately half of children with APS do not have underlying autoimmune disease or malignancy, and are classified as primary APS [5]. Secondary APS occurs in patients with an underlying systemic disease, most commonly systemic lupus erythematosus (SLE), but other autoimmune conditions or malignancies can be associated [5]. Importantly, 30 % of pediatric patients with APS and SLE initially present with thrombosis alone, and thus were initially thought to have primary APS [1]. Patients with primary APS tend to present at a younger age, with a median age of about 9 years, and have a higher incidence

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of arterial thrombosis and cerebrovascular events [1, 5]. Patients with secondary APS tend to be somewhat older, with a median age of about 13 years, and have a higher frequency of venous thrombosis and skin findings [1, 5]. The female:male ratio in primary APS is approximately equal, while in secondary APS, it is 1.5:1 [5].

Dermatologic manifestations are present in approximately 50 % of patients, though none are specific for APS [6]. Livedo reticularis is the most common skin manifestation [2, 6]. A form of livedo reticularis with a broken, non-contiguous net-like pattern is known as livedo racemosa, and is strongly associated with arterial thrombosis [6]. The clinical triad of livedo racemosa, cerebrovascular accident, and hypertension is known as Sneddon's Syndrome and is rare in children. Other cutaneous manifestations include Raynaud's phenomenon, ulcers, retiform purpura, digital gangrene, superficial thrombophlebitis, nailfold infarcts, and anetoderma [2, 5–7].

Management Strategy

APS should be suspected in children with venous or arterial thrombosis, since thrombotic events are rare in childhood, and APS is a leading cause of childhood thrombosis [2]. Diagnosis is based on presence of vascular thrombosis and laboratory evidence of antiphospholipid antibodies, including anti-cardiolipin antibody, anti-β_2 glycoprotein-1 antibody, and lupus anticoagulant [1, 7] (Table 22.1). A positive antiphospholipid antibody result must be confirmed with repeat testing separated by at least 12 weeks, especially because transient post-infectious antiphospholipid antibodies are common in children [2, 8]. Other inherited or acquired causes of increased thrombotic risk should be sought with a hypercoagulability workup, as many patients with APS have one or more inherited thrombophilia risk factors.

Table 22.1 Proposed criteria for diagnosis of pediatric antiphospholipid antibody syndrome [1, 7]

Clinical criteria	Vascular thrombosis
	Venous or arterial thrombosis may be present
	Thrombosis must be confirmed by imaging studies or by histopathology
Laboratory criteria[a]	1. Anti-cardiolipin antibody
	2. Anti-β_2 glycoprotein-1 antibody
	3. Lupus anticoagulant

Diagnosis of APS is made if one clinical criteria and one laboratory criteria are present

[a]Antiphospholipid antibodies must be present on two or more occasions, separated by at least 12 weeks

Investigation Recommended

Laboratory investigations	Antiphospholipid panel, including anti-cardiolipin antibody, anti-β_2 glycoprotein-1 antibody, and lupus anticoagulant
	ANA and ENA panel to rule out underlying autoimmune condition
	Hypercoagulability panel to assess for inherited thromobophilia risk factors
Imaging studies	Venous duplex if venous thrombosis suspected
	CT or MRI if arterial thrombosis suspected
Skin biopsy	If small vessel thrombosis suspected

Anticoagulation is the mainstay of treatment for a thrombotic event in APS, and does not differ substantially from treatment of a patient without APS. Unfractionated heparin or low molecular weight heparin is typically used as a bridge to warfarin therapy, with a goal INR of 2.0–3.0. In the case of an arterial thrombosis, low-dose aspirin therapy, with or without concomitant warfarin, is recommended [2, 5]. Approximately 20 % of pediatric patients with APS have been documented to have recurrent thrombosis after their initial presentation [1, 5], so long-term anticoagulation and/or antiplatelet therapy is likely to be useful for prevention of recurrent events. The recommended duration of treatment has not been established, however, and the benefits must be weighed against the risk of hemorrhage, especially in active children [2]. In life-threatening situations, such as catastrophic APS, more aggressive treatments such as high-dose systemic steroids, plasmapheresis, intravenous immunoglobulin (IVIg), cyclophosphamide, or rituximab can be considered [2–4, 9]. Of note, precipitating factors such as infection, immobilization, and surgery are commonly seen in patients who develop thrombotic events, and these risk factors should be treated proactively [5, 10].

Table 22.2 First line therapies

Therapy	Dose	Evidence level
Heparin bridge to warfarin (for acute thrombotic event)	Titrate to goal INR 2–3	C
Aspirin (for arterial thrombotic event)	3–5 mg/kg per day, max 325 mg per day	D
Long-term warfarin ± aspirin	Goal INR 2–3, duration and intensity of anticoagulation not defined	D
Modification and/or treatment of risk factors for thrombotic events	D	

Table 22.3 Second line therapies (for life-threatening or catastrophic APS)

Therapy	Dose	Evidence level
High-dose corticosteroids	Methylprednisolone 30 mg/kg (max 1 g) daily for 3 days, followed by prednisone 2 mg/kg/day	E
Intravenous Immunoglobulin	2 g/kg (max 70 g), no defined dosing schedule	E
Plasmapheresis	n/a	E
Cyclophosphamide	750 mg/m^2 per week for 4 weeks	E
Rituximab	375 mg/m^2 per week for 4 weeks	E

Anetoderma

Lauren B. McCaffery, MD and Heather A. Brandling-Bennett, MD

Clinical Features

Anetoderma is a rare, benign condition of the skin characterized by localized patches of flaccid skin which can be macular, depressed (Fig. 22.1 and), or appear as sac-like outpouchings of the skin. On examination, lesions tend to herniate with gentle pressure – an exam finding dubbed the "buttonhole sign." Erythema and fine wrinkling of the overlying epidermis are variably present (Fig. 22.2) [11–14].

Anetoderma can be divided into primary and secondary forms. Primary anetoderma arises in previously clinically normal skin, whereas secondary anetoderma arises at the site of skin previously or concomitantly involved with other dermatoses [14, 15]. Secondary anetoderma has been associated with numerous other conditions, most commonly varicella and acne, but also sarcoidosis, leprosy, human immunodeficiency virus (HIV), tuberculosis, and others [13, 14]. Historically, primary anetoderma was classified into two clinical categories: those associated with a preceding inflammatory stage (Jadassohn-Pelizzary type), and those without an inflammatory stage (Schweninger-Buzzi type). This distinction is primarily of historical interest, as the histologic findings and other clinical features are indistinguishable between these two types [14, 15].

Patients with primary anetoderma typically present with lesions ranging in number from few to over 100, with typical sites of involvement on the upper trunk and proximal extremities. Primary anetoderma can be associated with underlying systemic disease or immunologic abnormalities, most commonly the presence of antiphospholipid antibodies (aPL). Small case series have reported that the majority of patients with primary anetoderma have associated circulating aPL, and approximately

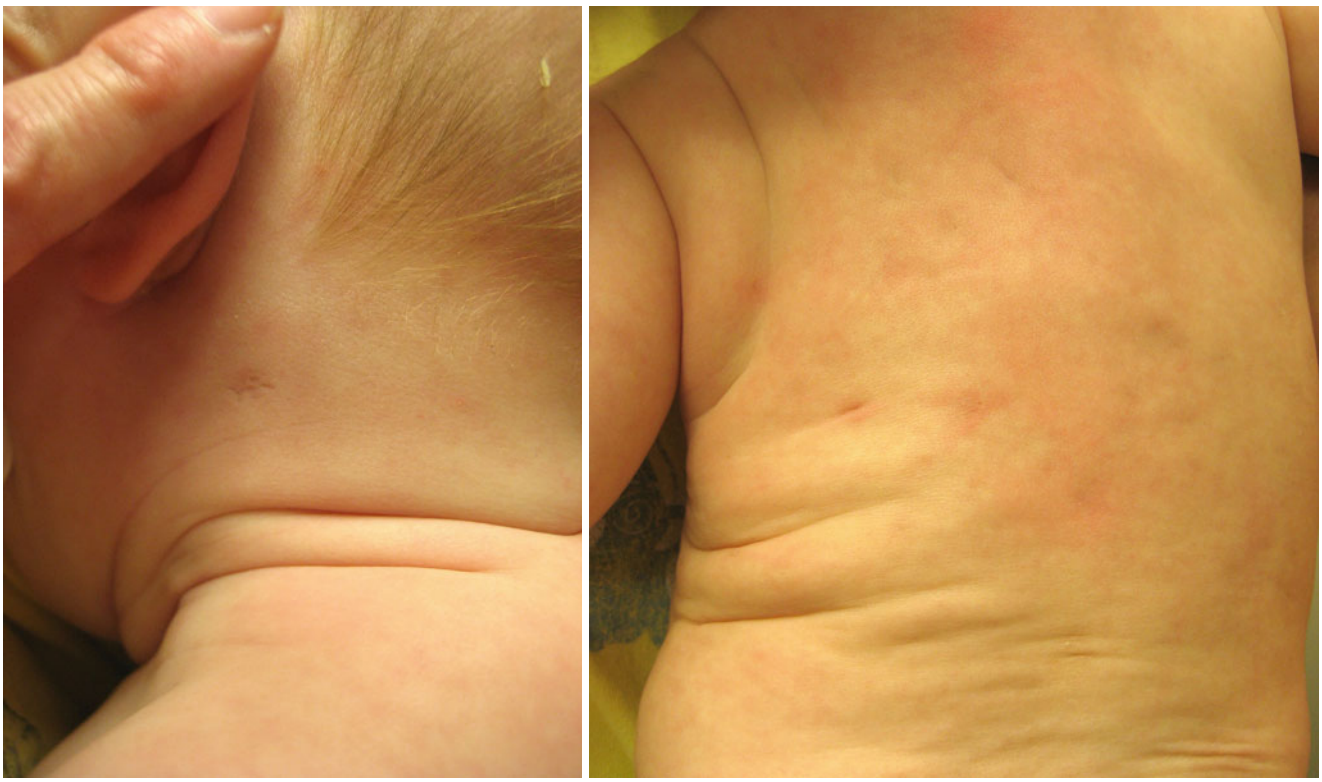

Fig. 22.1 and Fig. 22.2 An eight-month old infant was born with depressed, macular skin on the neck and back

half of these patients ultimately go on to develop full criteria for antiphospholipid antibody syndrome [13, 16, 17].

Anetoderma of prematurity is a distinct form of this disease, which occurs in premature infants receiving care in the neonatal intensive care unit (NICU). Dermatologic findings include the typical localized, flaccid patches of skin, but usually occur at sites of placement on monitoring leads. Accordingly, common sites of involvement include the periumbilical and subclavicular skin. This is thought to occur in immature skin either as a result of local hypoxia resulting from pressure at the site of monitoring leads, or from shearing stress from such leads. The incidence seems to be reduced when leads are placed ventrally on a supine neonate, and vice versa [18, 19].

Management Strategy

The diagnosis of anetoderma is based on typical clinical findings and supportive skin biopsy findings if the clinical diagnosis is in doubt. Anetoderma should be suspected in patients with the typical localized flaccid patches of skin. Histologic findings include focal loss of elastic fibers in the papillary dermis, often with an associated perivascular lymphohistiocytic inflammatory infiltrate [15, 17]. Even in patients with concomitant APS, the present of vascular microthrombi is uncommon [16]. Direct immunofluorescence (DIF) findings are not diagnostic, but can occasionally show overlapping features of a lupus band, with deposition of immunoreactants at the dermo-epidermal junction [16].

Given the high frequency of circulating aPL in patients with anetoderma, screening for aPL is warranted. Any patient with anetoderma and aPL should be monitored closely over time for development of other features of APS or other autoimmune conditions [13, 17].

Treatment for anetoderma has generally been unsatisfactory. Multiple treatments have been unsuccessfully attempted, including intralesional steroid injections, aspirin, phenytoin, dapsone, vitamin E, aminocaproic acid, and nicotinamide [15, 20]. Few case reports have shown success with penicillin or antimalarials [15]. Spontaneous resolution does not tend to occur [18]. For particularly cosmetically bothersome lesions, surgical excision can be performed [14]. Recently, treatment with destructive carbon dioxide (CO2) laser has been reported to lead to significant cosmetic improvement [21].

Investigations Recommended

For diagnostic
Histology
Biopsy of lesionsal skin, with elastic tissue stain
Laboratory
Antiphospholipid antibody panel

Therapy	Dose	Evidence level
First-line therapy		
Observation	N/A	N/A
Second-line therapy		
Penicillin	1800 IU daily for 3 weeks	E
Hydroxychloroquine	3–5 mg/kg/day divided BID, maximum 400 mg/day	E
Surgical excision	N/A	E
Destructive CO2 laser	N/A	E

Atrophoderma of Pasini and Pierini

Regina-Celeste Ahmad, MD, PhD, Alex Fogel BS, and Joyce M.C. Teng, MD, PhD

Clinical Features

Atrophoderma of Pasini and Pierini (atrophoderma) is a benign, asymptomatic, idiopathic dermal atrophy disorder that develops as one or more round-to-ovoid, hyperpigmented, well-demarcated, non-indurated, depressed 1–12 cm patches lacking inflammation (Fig. 22.3) [22, 23]. The affected skin appears thin but feels normal, and the surrounding skin appears and feels normal [23]. Though this condition often arises in young adulthood, it is not uncommon in children, and congenital cases have been reported [24, 25].

Though cases of atrophoderma with isolated lesions have been reported, the disease is typically characterized by multiple, bilaterally symmetric, discrete or confluent lesions [26]. Within a few weeks of arising, the lesions become hyperpigmented, and typically follow a course of slow enlargement over months to years before becoming quiescent [27]. As the lesions evolve, the initial hyperpigmentation may lighten, and the associated skin may become depressed, typically 1–8 mm below the level of the normal surrounding skin, resulting in the classic "cliff-drop" border pattern [28]. While these depressions are visible on side lighting, they are not usually palpable. Importantly, the normalcy of the surrounding skin differentiates atrophoderma from morphea [27].

The patches of atrophoderma typically arise during adolescence or early adulthood on the trunk, chest, arms and/or abdomen, while usually sparing the face, feet and hands [23]. The disease has been observed to co-exist with morphea and lichen sclerosis, and it is often included in differential diagnoses with these conditions, as well as with post-inflammatory hyperpigmentation and anetoderma [27]. Atrophoderma more commonly occurs in Caucasians than in people of darker skin color, in women than in men, and in Europeans

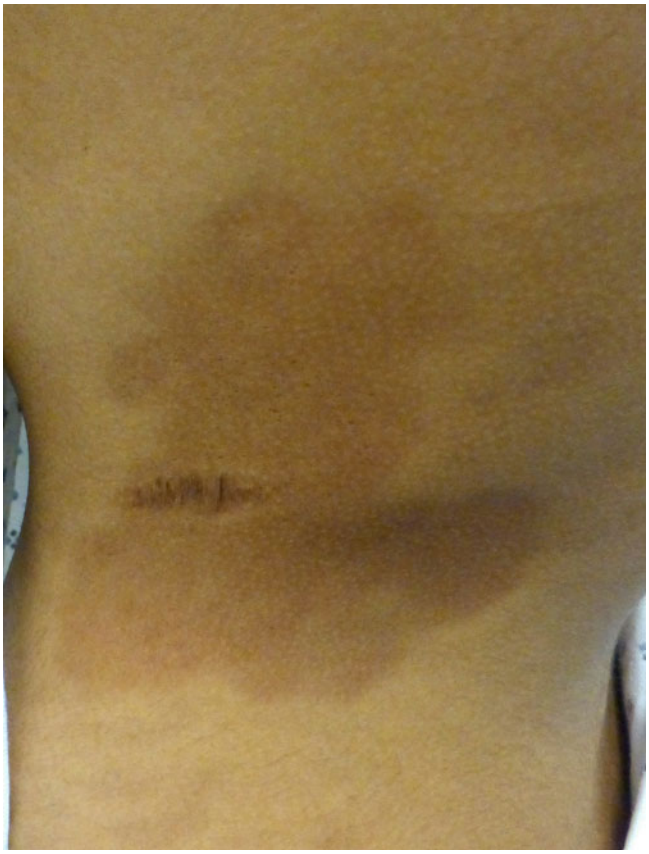

Fig. 22.3 Atrophoderma on the back of a sixteen year old girl. The onset was gradual over 2-3 year period

more than North Americans [23, 25]. Some authors have suggested a relationship between *Borrelia burgdorfi* infection and disease development, but the evidence on this relationship is not definitive [29].

Management Strategy

Atrophoderma is a benign and asymptomatic disorder, with no affect on life expectancy or overall health. The disease typically follows a protracted course with symptoms persisting 10–20 years, though spontaneously self-resolution is not uncommon.

There are currently no accepted standard therapies, due to the rarity of the condition and the absence of good clinical trials. Patient reassurance is thus of primary importance. Patients typically seek treatment to rule out more serious conditions and to alleviate the undesirable appearance.

Sun exposure is believed to darken hyperpigmented lesions in atrophoderma [30]. Photoprotection is therefore recommended to reduce further discoloration of the skin.

Specific Investigations

- Side lighting during physical exam
- Skin Biopsy

Side lighting may be used to observe the characteristic "cliff-drop" borders of atrophoderma. Single lesions have been described as "inverted plateaus" and multiple lesions have been described as having a "Swiss cheese" appearance.

While atrophoderma is a diagnosis of exclusion, skin biopsy may be useful to exclude other conditions. Wedge or elliptical excisions are often recommended over punch biopsy for atrophic conditions to minimize sampling bias. A rim of normal skin should be included in the biopsy sample [28]. Observed histopathological changes in atrophoderma are minimal and non-diagnostic, though specimens often display decreased dermal thickness when compared to normal skin specimens [29].

First-Line Therapies

- Patient counseling and reassurance

Patients should be reassured that atrophoderma is a benign condition without additional associated risk to overall health or life expectancy. Patients should be reassured that the lesions are not infectious, and physicians should palpate the lesions of atrophoderma without gloves. Patient concerns, such as cosmetic appearance, should be understood and used to guide management.

Second-Line Therapies

The following therapies are all level five evidence from adult studies:

- Topical corticosteroids
- Antibiotics
- Antimalarials
- Laser therapy

While no treatment has been shown to be consistently effective for atrophoderma, response to topical corticosteroids, antibiotics and antimalarials have been reported in sporadic cases [23, 31, 32]. There is no agreed-upon dosing regimen. Additionally, the efficacy of antimicrobial therapy in atrophoderma has been primarily observed during treatment of infectious disease [32]. It is therefore unclear whether the drug itself induced improvement in the lesions

of atrophoderma, or whether clearance of the underlying infectious organism resulted in improvement of the lesions [29] More study in this area is needed.

Surgical treatment has not been shown to be effective in restoring the appearance of the affected skin. Laser therapy to reduce hyperpigmentation has been described in one case using a Q-switched alexandrite laser (755 nm) [30]. This therapy induces selective photothermolysis of pigment in the epidermis. However, further research is needed to confirm these findings.

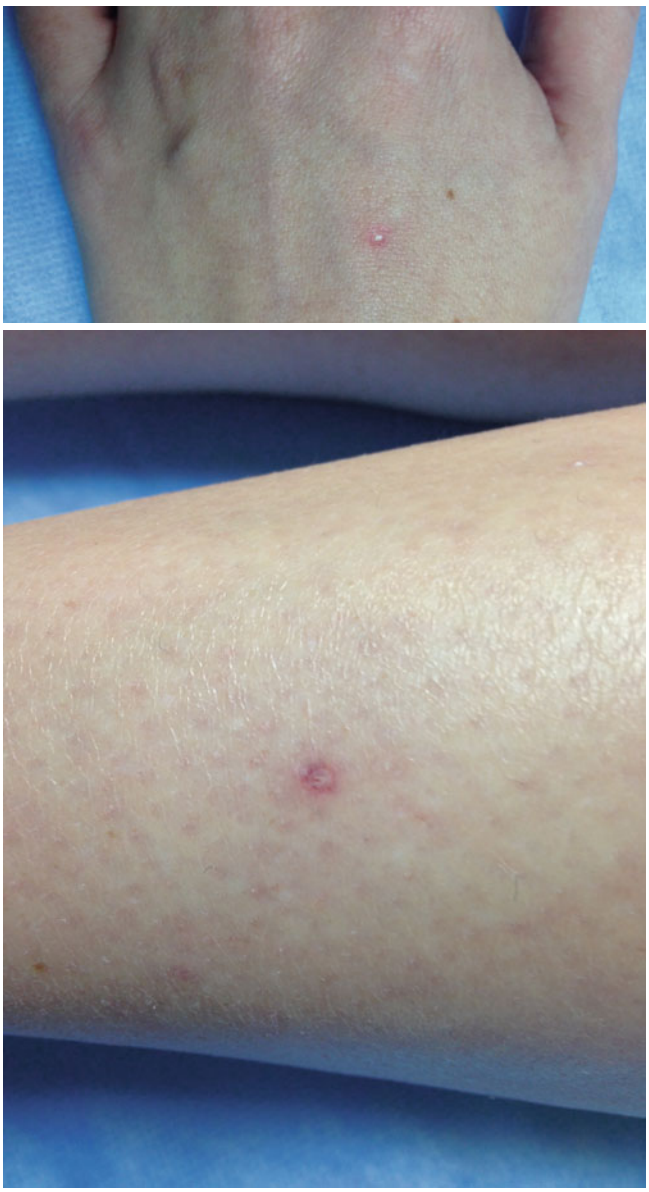

Fig. 22.4 and Fig. 22.5 A seventeen-year old Caucasian female presented with atrophic macules on the dorsal hand and lower extremities. The lesions had white centers and erythematous rims

Degos Disease (Malignant Atrophic Papulosis)

Kate Khorsand, MD, and Heather Brandling-Bennett, MD

Clinical Features

Degos disease, also known as malignant atrophic papulosis, is a rare disorder thought to be caused by a thrombotic vasculopathy. There are two forms of the condition, with one form limited to skin findings and the other with systemic involvement. The systemic form carries a vastly worse prognosis, with rapidly progressive disease that is nearly universally fatal within several years. The skin-limited form can progress into systemic disease months to years later [33]. However, it is possible that the incidence of skin-limited Degos disease is underreported given its benign course. The disease is very rare in children and infants [34, 35].

Degos disease presents with the pathognomonic finding of erythematous papules which develop a pearly, atrophic, porcelain white center often with a telangiectatic rim (Figs. 22.4 and 22.5) [36]. The palms, soles, face and scalp are rarely involved [37]. The gastrointestinal tract and central nervous system are most commonly affected in the systemic form, but other organs may be involved including the pericardium, lungs, eyes, and bladder. Morbidity and mortality is usually caused by sepsis or hemorrhage from bowel or brain infarction. Degos-like lesions may be seen in patients with systemic lupus erythematosus, antiphospholipid antibodies, or dermatomyositis.

The pathophysiology of this disease is unclear, with several hypotheses in existence. The three leading hypotheses at this time favor either inflammation of the vessels, coagulopathy, or primary dysfunction of endothelial cells as the trigger for development of the disease [37].

Management Strategies

Skin lesions suspicious for Degos disease are typically biopsied, and histopathology reveals wedge-shaped dermal necrosis with an overlying atrophic epidermis and hyperkeratosis. There are no diagnostic laboratory markers used, however, coagulation parameters are often abnormal [37]. Patients should be carefully evaluated for any signs of systems of systemic disease, with additional testing performed as indicated below [33]. Patients with skin-limited Degos disease should be followed closely for several years. Unfortunately there is no uniformly effective therapy, and treatment does not seem to prevent progression of the disease from the skin-limited form to the systemic form [37]. The skin-limited form may not be treated, as it is considered a benign process, and immunosuppressive agents can worsen cutaneous lesions.

Investigations Recommended

For diagnosis
Skin biopsy
Fecal occult blood test
Opthalmologic referral and ocular fundus examination
If systemic disease suspected: colonoscopy, brain MRI, echocardiogram

First Line Therapies

Patients with skin-limited disease may be conservatively managed by close monitoring. The first line therapeutic approach for a patient with systemic Degos disease should optimize perfusion and minimize thrombus formation [37]

Therapy	Dose	Evidence
Optimize perfusion, minimize thrombus formation		
Aspirin	325 mg PO daily[a]	E[b]
Pentoxyfylline	400 mg PO three times daily[a]	E[b]
Dipyridamole	75–100 mg PO four times daily[a]	E[b]
Ticlopidine	250 mg PO twice daily[a]	E[b]
Vasodilation, inhibition of platelet aggregation		
Treprostinil	Dose variable	E[b]
Immunosuppression		
Cyclosporine	3.5–5 mg/kg/day	E[b]
Azathioprine	Start 1–3 mg/kg/day with max of 250 mg daily	E[b]
Cyclophosphamide	500–1000 mg/m^2 IV monthly	E[b]

[a]Dose not well established in young children
[b]For evidence only in adults

Second Line Therapy

Several case reports have seen dramatic improvement with eculizumab, a humanized monoclonal antibody acting as a terminal complement inhibitor. This is thought to counteract the complement activation and increased endothelial cell apoptosis leading to thrombotic complications in systemic Degos disease. Unfortunately, this treatment was eventually unable to halt the progression of systemic disease [37, 38].

Dermatomyositis

Nina Washington, MD and Joyce M.C. Teng, MD, PhD

Clinical Features

Juvenile dermatomyositis (JDM) is an autoimmune inflammatory vasculopathy. It classically manifests as symmetric proximal muscle weakness and rash. At diagnosis, constitutional symptoms including fever, fatigue, and weight loss are common [39, 40].

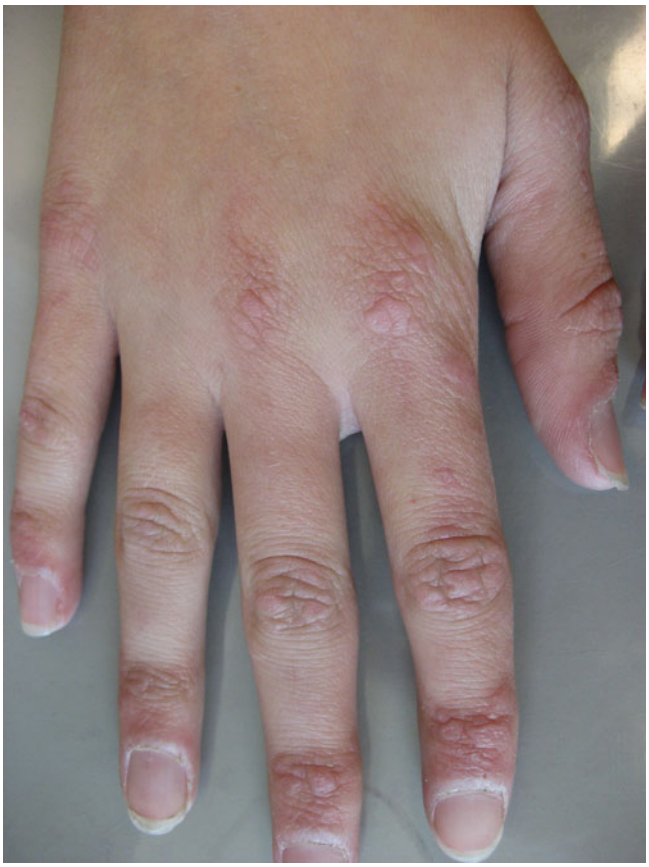

Fig. 22.6 Gottron's papules on the dorsal hand of a teenager with DM. The lesions clustered over the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints

The pathognomonic rash of JDM is the Gottron's Papule – a flat-topped pink to violaceous papule located on the metacarpophalangeal and interphalangeal joints (Fig. 22.6). Classic rashes associated with JDM also include: (1) Heliotrope rash – a violaceous rash of the eyelids often accompanied by periorbital edema and/or erythema; (2) V sign – an erythematous macular rash of the sun-exposed areas of the neck and chest; and (3) Shawl sign – an erythematous macular rash of the back of the neck and shoulders. Patients may also have a malar rash similar to that seen in lupus patients, periungual erythema and telangiectasias of the nail bed capillaries, ulcerations (Fig. 22.7), and erythematous rashes of the extensor surfaces of the knees and elbows (Gottron Sign) [41].

Muscle weakness in JDM is insidious in nature. Patients may have trouble combing or brushing their hair, getting dressed, climbing stairs, or sitting in a chair. Respiratory distress may arise if the diaphragm is affected. Patients may experience dysphagia or hoarseness if the pharyngeal muscles are affected.

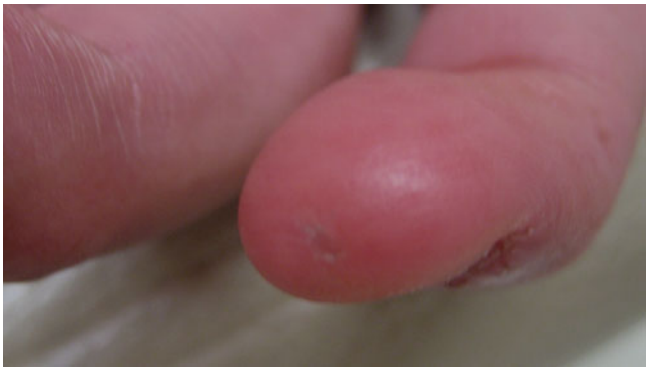

Fig. 22.7 Painful skin ulceration noted on the finger of a teenager with DM

Management Strategies

To date, there have been no randomized, controlled clinical trials (RCTs) solely investigating the treatment of juvenile dermatomyositis; in part due to the rarity and heterogeneity of the disease as well as ethical concerns regarding participation of children in RCTs. Currently, treatment for JDM is divided into topical and systemic therapy, based on consensus guidelines [42, 43] Standard treatment includes corticosteroids and immunosuppressant agents. Methotrexate is overwhelmingly the immunosuppressant of choice amongst providers. Once systemic inflammation is optimally controlled, physical therapy serves to restore muscle strength and conditioning.

Specific Investigations Recommended

In 1975, Bohan and Peter developed criteria for the diagnosis of dermatomyositis [39–41]. Clinical features consistent with a diagnosis included: (1) characteristic skin findings (i.e., Gottron's papules, heliotrope rash, Shawl sign, and malar rash); (2) proximal muscle weakness; (3) elevated muscle enzyme levels; (4) a myopathic pattern on EMG; and (5) evidence of an endomysial, mononuclear inflammatory infiltrate on muscle biopsy. A summary of recommended diagnostic investigations is detailed here.

Diagnostic investigations	
Laboratory	CK, LDH, aldolase, ALT, AST, Anti-Nuclear Antibody, Anti-Jo-1, Anti-Ro/SSA
Imaging	MRI
Functional testing	Nerve Conduction Study (NCS), electromyography
Histology	Muscle biopsy

First Line Therapies

In both consensus publications by the Childhood Arthritis and Rheumatology Research Alliance (CARRA), pediatric rheumatologists agreed that high-dose corticosteroids and methotrexate should be used concurrently as first-line therapy in patients with JDM [42, 43].

Therapy	Dose	Evidence level
Topical therapy		
Topical corticosteroids (e.g., desonide, clobetasol)	Apply to affected areas daily to twice daily	D
Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)	Apply to affected areas twice daily	D
Systemic therapy		
Corticosteroids	Intravenous methylprednisolone – 30 mg/kg/day (max 1 g) for 3 days	D
	Transition to oral prednisone at 2 mg/kg/day for 4 weeks	
	Subsequently tapered by 20 % by treating physician	
	Recommended duration 1 year	
Methotrexate	The lesser of 15 mg/m^2 or 1 mg/kg (maximum 40 mg) once weekly	D
	Subcutaneous route recommended	
	Folic acid supplementation required (1 mg po daily)	

Second Line Therapies

IVIg and Hydroxycholorquine are also effective in the treatment of JDM skin disease [44]. In some protocols, they may be used as first line therapy.

Therapy	Dose	Evidence level
Intravenous immunoglobulin (IVIg)	2 g/kg (maximum 70 g)	C
	Recommend dosing schedules:	
	Every 2 weeks × 3, then monthly	
	Over 2–5 days then 0.4–2 mg/kg/month	
Hydroxychloroquine (Plaquenil)	6–7 mg/kg/day divided bid (maximum 400 mg daily)	E

Third Line Therapies

Third line therapies are used for refractory disease or organ involvement such as interstitial lung disease (ILD).

Therapy	Dose	Evidence level
Cyclosporin A	3.5–5 mg/kg/day	B[a]
Azathioprine (imuran)	1–3 mg/kg/day with max of 150 mg daily	D
Mycophenolate mofetil (CellCept)	20 mg/kg divided twice daily or,	D [45, 46]
	800–1350 mg/m^2/day	
	Total dose of 1–3 g/day	
Tacrolimus (prograf)	0.1–0.2 mg/kg/day divided twice daily	D
Cyclophosphamide (cytoxan)	500–1000 mg/m^2 administered monthly × 6 months	D
Rituximab (rituxan)	BSA ≤1.5 m^2, 575 mg/m^2 at week 0 and week 2	A
	BSA >1.5 m^2, 750 mg/m^2 (up to 1 g/infusion) at weeks 0 and 2	

[a]Study performed in adult DM patients

Non-pharmacologic Therapies

Physical/occupational therapy
Calcium and vitamin D
Sunscreen (minimum SPF 30)
Photoprotective clothing

Eosinophilic Fasciitis

Shelley Yang, MD, Regina-Celeste Ahmad, MD, and Heather A. Brandling-Bennett, MD

Clinical Features

Eosinophilic fasciitis (EF), also known as Shulman's syndrome, is a rare idiopathic fibrosing disorder characterized by inflammation of the fascia resulting in edema and induration of the skin.

EF affects patients of all ages, but is more common in adults with a mean age of onset between 40 and 50. Only a few dozen cases have been reported in the pediatric population. In children, there appears to be a female predominance. Strenuous physical exertion has been reported as a risk factor in multiple case series. Other proposed triggers include trauma, drugs, infection, solid neoplasms, and hematologic disorders.

Presentation is characterized by rapid onset of painful edema and erythema, evolving into induration and fibrosis of the subcutaneous fascia. Distribution is usually symmetrical involvement of the extremities and sometimes the trunk, sparing the face. In children, the hands are frequently affected. The affected skin acquires a bound down, peau d'orange quality. The "groove sign" has been described in reference to an indentation along the course of superficial veins, and is caused by retraction of the subcutaneous tissue. Some children initially diagnosed with EF have evolved into generalized or localized morphea, suggesting EF may be a variant of morphea.

Patients may develop carpal tunnel syndrome, arthritis, and paresthesias. Compared to the adult population, arthritis is less common in children with EF, and there is a lower incidence of hematological abnormalities such as thrombocytopenia, as well as hematologic and solid organ malignancies. Renal involvement, especially IgA nephropathy, has been described in children.

Characteristic laboratory abnormalities include peripheral eosinophilia, hypergammaglobulinemia, and an elevated sedimentation rate.

Management Strategies

Early initiation of systemic prednisone is the mainstay of treatment. Patients usually show a good clinical response with gradual improvement of induration and resolution of laboratory abnormalities. There is also potential for spontaneous remission which can complicate evaluation of treatment response.

Younger onset age (<7 years old) and greater disease severity have been associated with a higher risk of progression and fibrosis refractory to treatment. Therefore, early physical therapy may be an important adjunct to treatment.

Investigations Recommended

There are no published consensus diagnostic criteria for EF. Defining features based on Shulman's original description in 1974 include rapid onset symmetric skin induration along with transient eosinophilia, hypergammaglobulinemia, and marked favorable response to systemic corticosteroids in the absence of Raynaud's phenomenon or any internal manifestations of systemic sclerosis. A deep excisional biopsy down to fascia is recommended for histological diagnosis. Histology reveals fibrosis of the deep fascia and subcutis with a chronic inflammatory infiltrate of lymphocytes, histiocytes, and plasma cells. Eosinophils may be found in the

lower subcutis and fascial layers, but can be only focal and transient, and are not always observed or necessary for diagnosis. Some authors believe a clinical diagnosis based on appearance, labs, and MRI findings are sufficient, without absolute need for surgical biopsy. MRI can be used to localize the optimal anatomic location for a biopsy and monitor response to therapy. Characteristic findings on MRI include superficial fascial thickening, abnormal signal intensity, and contrast enhancement.

Laboratory evaluation typically includes testing for complete blood count with differential and peripheral smear, total immunoglobulin levels, inflammatory markers, muscle enzymes, thyroid studies and autoantibodies. A positive ANA has been found in less than 25 % of patients. Peripheral eosinophilia is present in the majority of patients but is not required for diagnosis and is not an indicator of disease activity. Aldolase, a muscle enzyme, may be a useful measure of disease activity.

First Line Therapies

EF is managed initially with high dose corticosteroids **Evidence level D** [47–49]. Prednisone or prednisolone is typically given at doses of approximately 0.5–1.0 mg/kg/day. Methylprednisolone pulses (500–1000 mg daily for three consecutive days) **Evidence level D**[1] [49] before prednisone treatment has been associated with better outcomes.

Second Line Therapies

Methotrexate at low doses (15–25 mg once weekly) **Evidence level D** [49] is the preferred second-line treatment either alone or in combination with systemic corticosteroids, especially in patients with morphea-like skin lesions or unsatisfactory responses to systemic corticosteroids. In adults, good responses were found to hydroxychloroquine (200–400 mg daily) **Evidence level D**[1] [49] in combination with prednisone.

Third Line Therapies

Third line treatments described in pediatric patients with poor response to systemic corticosteroids include d-penicillamine, mycophenolate mofetil, and infliximab **Evidence level E** [47, 50, 51]. In adults, dapsone, cyclosporine, azathioprine, intravenous immunoglobulin, rituximab, UVA1 phototherapy, and extracorporeal photochemotherapy have been used **Evidence level E**[1] [52–58].

[1]Reported use only in adults.

Juvenile Idiopathic Arthritis

Joy Mombourquette, MD, and Joyce M.C. Teng, MD, PhD

Clinical Features

Juvenile idiopathic arthritis, or JIA, is a general term encompassing several categories of chronic arthritis with onset before the age of 16 years. The instigating cause of JIA is unknown, but the inflammation of the disease is caused by dysfunction of the immune system. Current research suggests that most types of JIA are predominately caused by autoimmunity (dysfunction of the adaptive immune system), with the exception of Systemic JIA, which is thought to be predominately autoinflammatory (dysfunction of the innate immune system).

According to the International League of Associations for Rheumatology (ILAR) criteria, JIA is divided into seven different categories: (1) Oligoarticular JIA, (2) RF negative Polyarticular JIA, (3) RF positive Polyarticular JIA, (4) Systemic JIA, (5) Juvenile Psoriatic Arthritis, (6) Enthesitis-Related Arthritis, and (7) Undifferentiated JIA. Undifferentiated JIA includes chronic arthritis that fulfills criteria for no category or overlaps two or more other categories [59].

Oligoarticular JIA is defined as arthritis in four or fewer joints during the first 6 months of disease. Oligoarticular JIA has a peak onset in the preschool years and affects females more than males. These patients are at higher risk than other categories of JIA for developing chronic uveitis, an inflammatory eye disease that is often insidious in onset.

Polyarticular JIA is arthritis in five or more joints. It also affects females more than males, with two peaks of onset in the preschool years and the later childhood/adolescence years. Polyarticular JIA is divided under the ILAR criteria into rheumatoid factor (RF) positive and negative disease. The arthritis in patients with RF positive disease has a poorer prognosis and tends to occur in older children and adolescents [60].

Systemic JIA is characterized by the classic triad of fever, rash, and arthritis. The fever needs to be present for at least 2 weeks and be quotidian (daily). The classic rash is a salmon-colored, evanescent rash that occurs most often on the trunk and proximal extremities, and usually appears during the times of fevers, with resolution or fading between fevers. The rash can sometimes be induced by heat or by the Koebner phenomenon, can occasionally

be pruritic, and can precede the onset of arthritis by days to years [61]. The arthritis can involve any number of joints, but is typically polyarticular, and needs to be present for 6 weeks to meet diagnostic criteria. Patients often feel ill at times of fever, with return to baseline or near baseline between episodes. Other diagnostic criteria that can be present include hepatosplenomegaly, lymphadenopathy, and serositis.

Enthesitis-related arthritis, or ERA, is a member of the Sponyloarthropathy arthritis family, and involves inflammation of the entheses sites. Common areas of involvement include the sacroiliac joints, the insertion site of the Achilles, quadriceps, and patellar tendons, and the insertion sites of the plantar fascia. The spine can also become involved. This type of arthritis primarily occurs in older children and adolescents, and is more common in males than females. Patients with ERA are more likely to develop an acute type of uveitis that presents suddenly with a painful red eye.

Juvenile psoriatic arthritis has two distinct peaks of onset. The first peak is in the preschool years, and these patients tend to present with polyarticular arthritis and dactylitis. The second peak is in older children and adolescents. These patients tend to have more features of enthesitis and axial joint involvement [62]. Psoriasis does not need to be present to diagnosis psoriatic arthritis, and patients can develop skin disease years after their arthritis features first appear. Additional diagnostic criteria include nail pits, onycholysis, or history of psoriasis in a first-degree relative [59].

Management Strategies

Investigation Recommended

Obtain detailed history about fever, rash and joint symptoms
Radioimaging studies i.e. x-ray or MRI if indicated

Specific Therapies

Treatment of JIA is largely dependent on the type of JIA. The paragraphs and table below provide a brief, concise overview of different medications used in the treatment of JIA. It is strongly recommended that therapy of patients with JIA be administered in conjunction with the recommendations of, and under the supervision of, a pediatric rheumatologist or an adult rheumatologist with experience in the treatment of JIA. Several recommended treatment pathways for the treatment of JIA are available from the American College of Rheumatology and the Childhood Arthritis and Rheumatology Research Alliance (CARRA).

Non-steroidal anti-inflammatory drugs (NSAIDs) are often part of first-line treatment for JIA, but are usually used in combination with a disease-modifying antirheumatic drug (DMARD) and/or biologic medication. There are numerous NSAIDs used in pediatric patients, with varying dose schedules, side effects, and availability of liquid formulations. The most commonly used NSAIDs include ibuprofen, naproxen, meloxicam, diclofenac, indomethacin, and sulindac. In order to achieve anti-inflammatory effects, doses need to be administered on an around-the-clock schedule, and are often administered at higher doses than those used for analgesic effects. For further information on specific NSAID dosing and administration, the author recommends referencing additional resources.

Systemic corticosteroids are generally used sparingly in the treatment of JIA, due to their significant toxicity profile. Doses vary depending on the type of corticosteroid, the level of immunosuppression intended, the route of administration, and the planned duration of treatment. Systemic corticosteroids are recommended as an option for first-line treatment of systemic JIA with or without the use of other medications, but are otherwise not recommended as first-line therapy in other forms of JIA [63]. They can be used acutely during times of disease flare to quickly control inflammation, or to bridge therapy while starting or transitioning DMARDs and biologic medications.

Side effects of systemic corticosteroids include, but are not limited to, increased appetite and weight gain, striae, systemic hypertension, intraocular hypertension, hyperglycemia, mood changes, cataracts, glaucoma, acne, myalgias, growth suppression, osteoporosis, immunosuppression, impaired wound healing, and avascular necrosis. Intra-articular corticosteroid injections are used as treatment in all forms of JIA, and can be used alone or in conjunction with other medications. Intra-articular corticosteroids are useful for providing anti-inflammatory treatment to individual affected joints while avoiding many of the systemic side effects seen with the use of systemic corticosteroids. Injections can be given up to every 3 months as needed for active arthritis, but remission in a joint after injection can last for over 2 years [64]. Side effects of intra-articular corticosteroid injections include skin atrophy and/or hypopigmentation at the injection site, infection, bleeding, or tendon rupture.

Many JIA patients require initiation of a DMARD and/or a biologic at the time of diagnosis or soon after diagnosis, depending on their type of JIA and on their presentation (duration of symptoms, progression of symptoms, signs of articular damage on imaging). The decision of a particular DMARD and/or biologic medication used is based on the type JIA, patient characteristics (ex. presence of uveitis), and features of disease (ex. pattern of involved joints, presence of joint erosions on imaging).

Medication family	Medication	Dose	Common and serious side effects	Lab monitoring	Indications	Level of evidence
Disease-modifying antirheumatic drugs (DMARDs)	Methotrexate [65, 67]	10–20 mg/m^2/week by mouth or subcutaneous injection (max dose 25 mg); subcutaneous injections are recommended for higher doses	Nausea, vomiting, anemia, hepatotoxicity, nephrotoxicity, bone marrow suppression, teratogenicity, immunosuppression	Complete blood count with differential, renal and liver function testing initially and every 1–2 months, spaced out to every 3–4 months once on stable doses	Oligoarticular JIA Polyarticular JIA Systemic JIA ERA Juvenile psoriatic arthritis	A [66]
	Leflunomide [67–69]	All doses given orally: <20 kg: loading dose of 100 mg×1 day, then 10 mg every other day 20–40 kg: loading dose of 100 mg×2 days, then 10 mg daily >40 kg: loading dose of 100 mg×3 days, then 20 mg daily	Rash, nausea, diarrhea, headaches hepatotoxicity, bone marrow suppression, teratogenicity, immunosuppression	Complete blood count with differential, liver function testing and albumin initially and every month for the first 6 months, spaced out to every 6–8 weeks thereafter	Often used interchangeably in patients who cannot tolerate methotrexate	A (studied in patients with polyarticular JIA) [69]
	Sulfasalazine [70–72]	15–25 mg/kg by mouth –twice daily (maximum daily dose 2 g) *Due to side effects, recommend starting at 5 mg/kg twice daily and increasing weekly by 10 mg/kg/day to goal dose	Nausea, vomiting, dyspepsia, anemia/bone marrow toxicity, rash, reversible oligospermia Hypersensitivity reactions: Stevens-Johnson Syndrome and Drug Rash with Eosinophilia and Systemic Symptoms Syndrome (DRESS) Avoid in patients with allergy to sulfa drugs, with Glucose-6-Phosphate Dehydrogenase deficiency, and porphyria	Complete blood count with differential, renal and liver function testing prior to starting therapy, every 2 weeks for the first 3 months, every 4 weeks for the next 3 months, then every 12 weeks while on stable doses	Oligoarticular JIA Polyarticular JIA ERA Juvenile psoriatic arthritis	A (Oligoarticular and polyarticular JIA) [70] A* (Spondyloarthritis with only peripheral articular disease) [71]
	Cyclosporine [73]	2–5 mg/kg/day by mouth, usually divided twice daily	Nausea, vomiting, hypertrichosis, gingival hyperplasia, mucosal lesions, hypertension, renal toxicity, hepatic toxicity, immunosuppression	Blood pressures, complete blood counts with differential, renal and liver function studies, and trough drug levels periodically	Oligoarticular JIA Polyarticular JIA Systemic JIA	D [75]
	Tacrolimus [74, 76, 77]	Systemic JIA (dose from case studies): 0.075–0.11 mg/kg/day by mouth, divided twice daily	Rash, nausea, vomiting, diarrhea, constipation, headaches, paresthesias, hypertension, renal toxicity, hepatic toxicity, hypertriglyceridemia, hyperglycemia, diabetes mellitus, electrolyte abnormalities, immunosuppression	Blood pressures, complete blood counts with differential, renal and liver function studies, electrolytes including magnesium and glucose levels, and trough drug levels periodically	Systemic JIA Polyarticular JIA (Not studied in Oligoarticular JIA, but can be considered in place of cyclosporine)	E (Systemic and polyarticular JIA) [76, 77]

Medication family	Medication	Dose	Common and serious side effects	Lab monitoring	Indications	Level of evidence
Tumor necrosis factor (TNF) alpha inhibitors	Infliximab [78–82]	5–10 mg/kg/dose intravenously; second dose given 2 weeks after the first dose, with subsequent dosing every 4 weeks	Increased risk for the development of opportunistic infections, including invasive fungal infections. Reactivation of latent tuberculosis. Infusion reactions, formation of human anti-chimeric antibodies (HACA), induction of additional autoimmunity, development or worsening of psoriasis, increased risk of malignancy, new-onset or exacerbation of demyelinating diseases and optic neuritis, worsening heart failure in patients with a history of heart failure or decreased left ventricular function	Testing for latent tuberculosis prior to starting treatment and with any high risk exposures to tuberculosis	Oligoarticular JIA Polyarticular JIA Systemic JIA ERA	B (Polyarticular disease in conjunction with methotrexate) [80]
				Complete blood counts with differential, renal and liver function testing every 4–12 weeks	Juvenile Psoriatic Arthritis	A* (Ankylosing Spondylitis and Psoriatic Arthritis) [81, 82]
	Etanercept [83–86]	FDA approved for patients ages 2 years and older: 0.4 mg/kg/dose subcutaneously twice weekly (maximum dose 25 mg). Alternative dosing 0.8 mg/kg once weekly (maximum dose 50 mg)	Increased risk for the development of opportunistic infections, including invasive fungal infections. Reactivation of latent tuberculosis. Injection site reactions, induction of additional autoimmunity, development or worsening of psoriasis, increased risk of malignancy, new-onset or exacerbation of demyelinating diseases and optic neuritis, worsening heart failure in patients with a history of heart failure or decreased left ventricular function	Testing for latent tuberculosis prior to starting treatment and with any high risk exposures to tuberculosis	Oligoarticular JIA	A (Polyarticular JIA) [84]
				Complete blood counts with differential, renal and liver function testing every 4–12 weeks	Polyarticular JIA Systemic JIA ERA Juvenile Psoriatic Arthritis	A* (Ankylosing Spondylitis, Psoriatic Arthritis) [85, 86]
	Adalimumab [87–90]	FDA approved for ages 2 years and older:	Increased risk for the development of opportunistic infections, including invasive fungal infections. Reactivation of latent tuberculosis. Injection site reactions, induction of additional autoimmunity, development or worsening of psoriasis, increased risk of malignancy, new-onset or exacerbation of demyelinating diseases and optic neuritis, worsening heart failure in patients with a history of heart failure or decreased left ventricular function	Testing for latent tuberculosis prior to starting treatment and with any high risk exposures to tuberculosis	Oligoarticular JIA	A (Polyarticular JIA) [88]
		10–15 kg: 10 mg subcutaneously every other week		Complete blood counts with differential, renal and liver function testing every 4–12 weeks	Polyarticular JIA	A* (Ankylosing Spondylitis and Psoriatic Arthritis) [89, 90]
		15–30 kg: 20 mg subcutaneously every other week			Systemic JIA	
		>30 kg: 40 mg subcutaneously every other week			ERA Juvenile psoriatic arthritis	

Medication family	Medication	Dose	Common and serious side effects	Lab monitoring	Indications	Level of evidence
Cytotoxic T lymphocyte antigen immunoglobulin (CTLA-4Ig)	Abatacept [91–93]	Intravenous formulation FDA approved for patients 6 years and older: Weight <75 kg: 10 mg/kg/dose 75 kg–100 kg: 750 mg/dose >100 kg: 1000 mg/dose Dosing: Weeks 0, 2, and 4, then every 4 weeks	Increased risk for the development of opportunistic infections and reactivation of latent tuberculosis and Hepatitis B. Infusion reactions. Headaches, nausea, rash, and hypertension	Testing for Hepatitis B prior to starting therapy. Testing for latent tuberculosis prior to starting treatment and with any high risk exposures to tuberculosis	Polyarticular JIA Extended oligoarticular JIA Systemic JIA	A (Extended oligoarticular JIA, polyarticular JIA, systemic JIA without systemic features) [93]
Anti-CD20 antibody	Rituximab [94–96]	Dosing used in pediatric studies: 375 mg/m^2 IV once weekly for 2–4 doses OR 500 or 750 mg/m^2 IV per dose given 2 weeks apart, for 2 doses Maximum dose of 1000 mg/dose *In pediatric studies, repeat dosing was given ≥24 weeks after the first dose, at the time of reappearance of symptoms	Immunosuppression, reactivation of Hepatitis B infection, infusion reactions, hypogammaglobulinemia. Increased risk of the development of Progressive Multifocal Leukoencephalopathy	Testing for Hepatitis B prior to starting therapy. B cell levels before and 1 month after dosing. Qualitative immunoglobulins every 3 months. Complete blood counts with differentials at regular intervals	Oligoarticular JIA Polyarticular JIA Systemic JIA	B (Oligoarticular JIA, polyarticular JIA, and systemic JIA) [96]
IL-1 inhibitors	Anakinra [97–99]	Typical dosing used in Systemic JIA: 1–2 mg/kg daily, increasing to 4 mg/kg/day as needed for continued uncontrolled disease Dose studied in Polyarticular JIA: 1 mg/kg/day Maximum adult dose: 100 mg/day	Immunosuppression, reactivation of latent tuberculosis, injection site reactions, transaminitis and hepatitis, neutropenia	Testing for latent tuberculosis prior to starting therapy, annually, and with any high risk exposures to tuberculosis. Complete blood count with differential, LDH, and serum creatinine at baseline, weeks 1 and 2, months 1, 2, 6, and 9, and with dose changes	Polyarticular JIA Systemic JIA	A (Systemic JIA and polyarticular JIA) [98, 99]

Medication family	Medication	Dose	Common and serious side effects	Lab monitoring	Indications	Level of evidence
–	Canakinumab [100–102]	FDA approved for children ≥2 years of age and weight ≥7.5 kg: 4 mg/kg/dose every 4 weeks (maximum dose 300 mg)	Immunosuppression, reactivation of latent tuberculosis, injection site reactions, transaminitis and hepatitis, neutropenia and other cytopenias	Testing for latent tuberculosis prior to starting treatment and with any high risk exposures to tuberculosis. Complete blood counts with differentials periodically. Consider obtaining liver function testing periodically	Systemic JIA.	A (Systemic JIA) [102]
–	Rilonacept [103, 104]	4.4 mg/kg (maximum dose 320 mg) × 1, then 2.2 mg/kg (maximum dose 160 mg) once weekly	Immunosuppression, reactivation of latent tuberculosis, injection site reactions, and hyperlipidemia	Testing for latent tuberculosis prior to starting treatment and with any high risk exposures to tuberculosis. Complete blood counts with differentials periodically. Serum lipid levels every 2–3 months after starting therapy and then periodically	Systemic JIA	B (Systemic JIA) [104]
IL-6 receptor inhibitor	Tocilizumab [105–107]	Intravenous dosing FDA approved for children 2 years of age and older:	Immunosuppression, reactivation of latent tuberculosis, infusion reactions, hyperlipidemia, neutropenia, thrombocytopenia, and transaminitis	Testing for latent tuberculosis prior to starting treatment and with any high risk exposures to tuberculosis. Complete blood count with differential and liver function testing with second infusion and every 1–2 infusions thereafter. Serum lipid levels should be obtained every 4–8 weeks initially, then every 6 months	Polyarticular JIA	A (Systemic JIA and polyarticular JIA) [106, 107]
		Weight <10 kg: 10 mg/kg/dose			Systemic JIA	
		Weight ≥30 kg: 8 mg/kg/dose				
		Maximum dose: 800 mg				
		Dosing for Systemic JIA: Every 2 weeks				
		Dosing for Polyarticular JIA: Every 4 weeks				

Lupus Erythematosus

Rebecca Kunder, MD and Joyce M.C. Teng, MD, PhD

Clinical Features

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-organ dysfunction caused by auto-antibody production. Antinuclear antibodies (ANA) are present in nearly all patients with SLE, but also present approximately 10 % of healthy children. Antibodies that are more specific but less sensitive for SLE include antibodies to double-stranded DNA (dsDNA) and particular RNA-associated protein complexes (Smith and U1RNP). About 20 % of patients with SLE present during childhood, mostly during the teenage years, and there is a female predominance. Presenting symptoms can be constitutional such as fever, fatigue, and weight loss. End-organ damage may be present at diagnosis as well. There are two main sets of criteria for SLE diagnosis [108, 109], each of which rely on a combination of immunologic and clinical criteria. The main distinction of the more recent Systemic Lupus International Collaborating Clinics (SLICC) criteria as opposed to the American College of Rheumatology (ACR) criteria is that biopsy-proven lupus nephritis can be used to make the diagnosis under the SLICC guidelines (Tables 22.4 and 22.5).

Table 22.4 ACR criteria (revised 1997)

Requirements: ≥4 criteria (see Hochberg et al. for details)	
Malar rash	Hematologic disorder
Discoid rash	Renal disorder (persistent proteinuria or casts)
Serositis	Immunologic disorder (anti-DNA, anti-Smith, APLs)
Oral ulcers	Neurologic disorder
Arthritis	Abnormal ANA
Photosensitivity	

Table 22.5 SLICC classification criteria

Requirements: ≥4 criteria (≥1 clinical and ≥ immunologic criteria)		
OR		
Biopsy-proven lupus nephritis with positive ANA or anti-DNA		
Clinical criteria		**Immunologic criteria**
Acute cutaneous lupus	Renal disorder	ANA
Chronic cutaneous lupus	Serositis	Anti-DNA
Oral or nasal ulcers	Neurologic disorder	Anti-Smith
Non-scarring alopecia	Hemolytic anemia	APLs
Arthritis	Leukopenia	Low complement
Serositis	Thrombocytopenia	Direct Coombs' test

The clinical manifestations of SLE are protean, but commonly include hematologic, mucocutaneous, musculoskeletal, neurologic and renal pathology. Focusing on the dermatologic manifestations, up to 85 % of patients with SLE have a malar rash or other cutaneous findings at some point. In fact, SLE was so named because the facial rash was thought to resemble the bite of a wolf ("lupus" in Latin). The malar rash is characterized as an area of fixed erythema predominantly over malar eminences which spares the nasolabial folds and often appear to be "butterfly" shaped. It commonly involves the chin and can be either raised or flat. Cutaneous eruption in SLE is often in photo-exposed area, therefore can be used as a diagnostic criterion. Of note, discoid lesions are much less common in SLE than they are in isolated discoid lupus erythematosus (Figs. 22.8 and 22.9). The cutaneous manifestations of SLE, which can be seen in

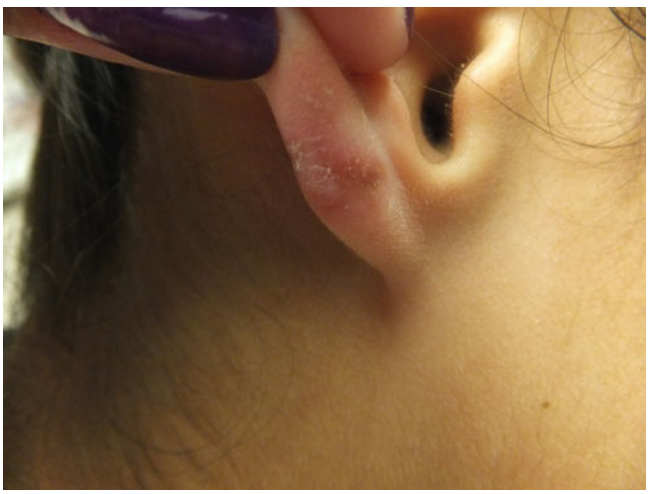

Fig. 22.8 Discoid lesions are common in children with lupus, especially on the ear

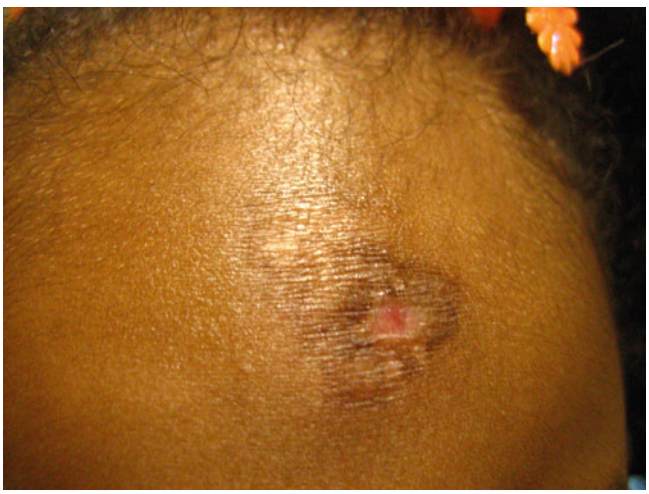

Fig. 22.9 Discoid lesions are common in children with lupus, especially on the head and neck area

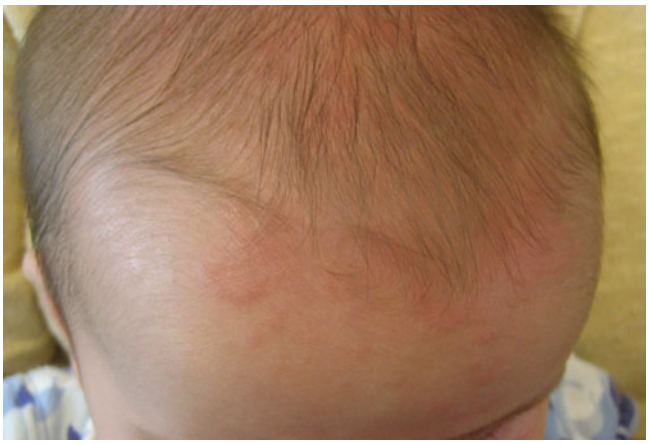

Fig. 22.10 Annular erythematous patches and plaque on the forehead of an infant with neonatal lupus

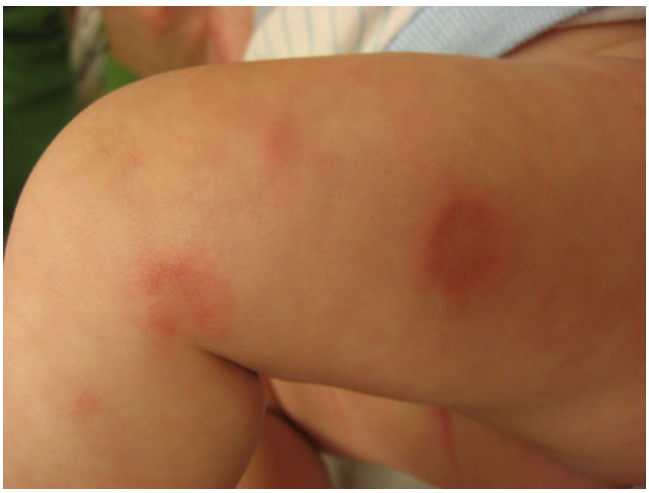

Fig. 22.11 Annular erythematous plaque on the thigh of an infant with neonatal lupus

a variety of autoimmune diseases with a vasculitic component, are often polymorphic. In addition to erythematous patches and plaques in photosensitive area ulcers (both on the skin and the oral mucosa), purpura, as well as color change of the extremities (Raynaud's phenomenon), are also frequent findings in patients with SLE. Importantly, patients who initially have cutaneous findings only can later develop systemic disease; approximately 25 % of SLE patients initially come to medical attention due to rash.

As distinct from SLE, neonatal lupus erythematosus (NLE), is caused by the transfer of specific maternal autoantibodies to the fetus. Antibodies to RNA-associated protein complexes can be passed transplacentally (SS-A/Anti-Ro, SS-B/Anti-La), even in mothers who have not had an autoimmune diagnosis or symptoms. Symptoms in the neonate can include cutaneous lesions, hematologic, hepatic and cardiac pathology, most seriously complete heart block due to scarring of the AV node. Although CNS involvement is less common (8 %), hydrocephalus should be evaluated among those with macrocephaly. Rash is present in approximately 20 % of neonates with NLE, and commonly involves the face and scalp (Fig. 22.10). Peri-orbital involvement, known as "raccoon-eye" or "owl eye" appearance, is characteristic for NLE. The rash can be present at birth or develop up to 3 months of age but typically resolves by 6 months of life when maternal antibodies disappear. A significant percentage of those children may continue to have residue telangiectasia or skin atrophy especially near the temple or scalp (Fig. 22.11). Although rare, hemolytic anemia, thrombocytopenia and neutropenia may occur during the first a few weeks of life.

Management Strategies

As the cutaneous manifestations of NLE resolve over time, treatment of this disease is focused on early diagnosis of fetal heart block, appropriate monitoring, and pacemaker placement in the newborn [110, 111]. The management of SLE, however, is focused on immunosuppression and management of end-organ complications. For children with mild SLE, without renal involvement, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and hydroxychloriquine may suffice. However, the majority of children with SLE require the use of glucocorticoids as well as well as a steroid-sparing agent such as mycophenolate mofetil, azathioprine, or methotrexate. Severe disease with renal or neurologic involvement often requires induction therapy with intravenous cyclophosphamide in conjunction with high-dose glucocorticoids.

Investigations Recommended (Table 22.6)

- For Diagnosis of SLE:
  - Complete physical exam including capillary nailfold microscopy
  - Comprehensive metabolic panel, complete blood count (Coomb's and smear if anemic), urinalysis, ESR, complements (C3 and C4), consider D-dimer
  - Antibodies: ANA, anti-dsDNA, anti-Smith, anti-ribonucleoprotein (RNP), anti-Ro (SS-A), anti-La (SS-B), anti-phospholipid antibodies (APLs), consider ANCAs
  - Consider skin biopsy if diagnosis is unclear
  - If renal involvement, consider renal biopsy
- For Diagnosis of NLE:
  - Comprehensive metabolic panel, complete blood count
  - Antibodies (can be done initially on mother to limit blood drawn from neonate): anti-Ro (SS-A) (>90 % affected neonates), anti-La (SS-B), anti-U1-RNP (both mother and neonate)

Table 22.6 Recommended investigations for diagnosis

Laboratory studies	Antibody testing	Other
Comprehensive metabolic panel	ANA	Physical examination
Complements (C3 and C4)	Anti-DNA	Nail fold microscopy
Urinalysis with UPC	Anti-Smith	Consider skin biopsy
ESR	Anti-RNP	Consider renal biopsy
CBCD (Coombs' and smear if anemic)	Anti-Ro (SS-A) and Anti-La (SSB)	
	APLs	

Table 22.7 Recommended investigations during treatment

Purpose	Tests	Frequency
Track disease activity	CBCD, CMP, Urinalysis, ESR	Range from monthly to every 6 months (depending on disease activity)
	C3, C4, anti-DNA	
Drug levels	For azathioprine: TPMT levels	With medication initiation for dose determination, then at least yearly
	For MMF/MPA: MPA and MPAG levels	
Evaluate for medication toxicity	For DMARDs: CBCD and CMP	For DMARDs: q3 months
	For CYC: CBCD	For CYC: before each dose and at nadir (day 7–14)
	For HCQ or steroids: eye exam	Eye exam yearly

Table 22.8 Recommended first line therapies for systemic diseases

Category	Medication	Details
General therapies	Hydroxychloroquine (Plaquenil)	≤6.5 mg/kg/day, up to 400 mg
		Level of evidence B
	Glucocorticoids	Initial dose up to 2 mg/kg/day (up to 60 mg)
		If severe, IV pulse 30 mg/dose (up to 1 g)
		Taper over several months
Arthritis	NSAIDs	Caution if renal involvement
Steroid sparing agents	Mycophenolate mofeteil (MMF)	Class III, IV or V nephritis (induction and maintenance)
		Level of evidence B
	Mycopholic acid (MPA)	MMF: 600 mg/m^2 BID (up to 1500 mg BID)
		MPA: 720 mg/m^2 BID
	Azathioprine (Imuran)	Hematologic lupus (second line for nephritis)
		1–3 mg/kg/day up to 150 mg daily
	Methotrexate	For musculoskeletal disease
		10–15 mg/m^2/week (PO or SubQ)
	Calcineurin inhibitors	Class V nephritis
Severe disease	Cyclophosphamide (cytoxan)	Class III or IV nephritis, neuropsychiatric lupus
		Level of evidence B
		500 mg/m^2 IV monthly increasing to 1000 mg/m^2 as tolerated with maximum of 1500 mg, given with mesna
		Duration at least 6 months

- Skin biopsy if diagnosis is unclear
- Echocardiography for structural abnormalities and ECG, 24-h holter monitoring for conduction abnormalities.
- MRI if there is sign of macrocephaly (very rare)

– For Treatment of SLE (Table 22.7)
  - Laboratory evaluations as above (except ANA) to track disease activity and medication toxicity (every 3–12 months; the frequency of which depends on disease activity)
  - Drug levels: thiopurine methyltransferase level (TPMT) if on azathioprine, MPA and MPAG levels if on Mycophenolate Mofetil
  - Eye exam (every year if on hydroxychloroquine)

First Line Therapies (Tables 22.8 and 22.9)

– General therapy: steroids (oral or intravenous), antimalarials (hydroxychloroquine) (Evidence level A)
– For skin: photoprotection, smoking-cessation, calcium channel blocker (for Raynaud's), topical corticosteroid, topical calcineurin inhibitor [112–114]

Table 22.9 Recommended first line therapies for dermatologic manifestations

Category	Intervention	Details
General measures	Photo-protection	Broad protection, SPF ≥30
	Hydroxychloroquine (Plaquenil)	≤6.5 mg/kg/day, up to 400 mg
		Level of evidence B
Topical corticosteroids	Low-potency	Flexual skin, face and neck
		Hydrocortisone 1 %, 2.5 %
		Fluocinolone acetonide 0.01 %
	Mid-potency	Trunk and extremities
		i.e. Triamcinolone acetonide 0.025, 0.1, 0.5%
	High-potency	Trunk and extremities
		Fluocinonide, Clobetasol propionate 0.05%
		Level of evidence B
Topical calcineurin inhibitor	Tacrolimus 0.03, 1 % (Protopic)	Level of evidence A
	Pimecrolimus 1 %	Level of evidence D

Table 22.10 Recommended second line therapies

Category	Intervention	Level of Evidence
Refractory dermatologic manifestations	Intralesional corticosteroids	C–E
	Topical or oral retinoids	
	Methotrexate	
	Thalidomide	
Refractory lupus nephritis	Rituximab 750 mg/m2 on days 1 and 14 (up to 1000 mg)	B

– If APLs: aspirin
– For nephritis or cerebritis: steroids, cyclophosphamide, mycophenolate, azathioprine
– For arthritis: steroids, methotrexate (Evidence level A)

Second Line Therapies (Evidence Level E; Table 22.10)

– For skin: intralesional corticosteroids, topical or oral retinoids, thalidomide

For NLE

- Cardiac monitoring depends on the severity of the heart block.
- For cutaneous manifestation, topical steroids may be used for active lesions and laser treatment can be beneficial for persistent telangiectasia later in life.
- Systemic steroids, anti-malarial and immunosuppressive therapies are considered only if there is severe hepatic, neurologic, or hematologic involvement.

Localized Scleroderma/Morphea

Grace Sun Chen, MD and Joyce MC Teng, MD, PhD

Clinical Features

Morphea, also known as "localized scleroderma," is an uncommon autoimmune connective tissue disorder characterized by skin hardening and thickening (Fig. 22.12). This fibrosing condition primarily affects the dermis, but may extend deeper into the subcutaneous tissue, fascia, muscle, or bone. In children, the disease can be particularly disabling, as atrophy of the underlying structures may ultimately lead to growth deformities, including contractures and limb length discrepancies. It is estimated

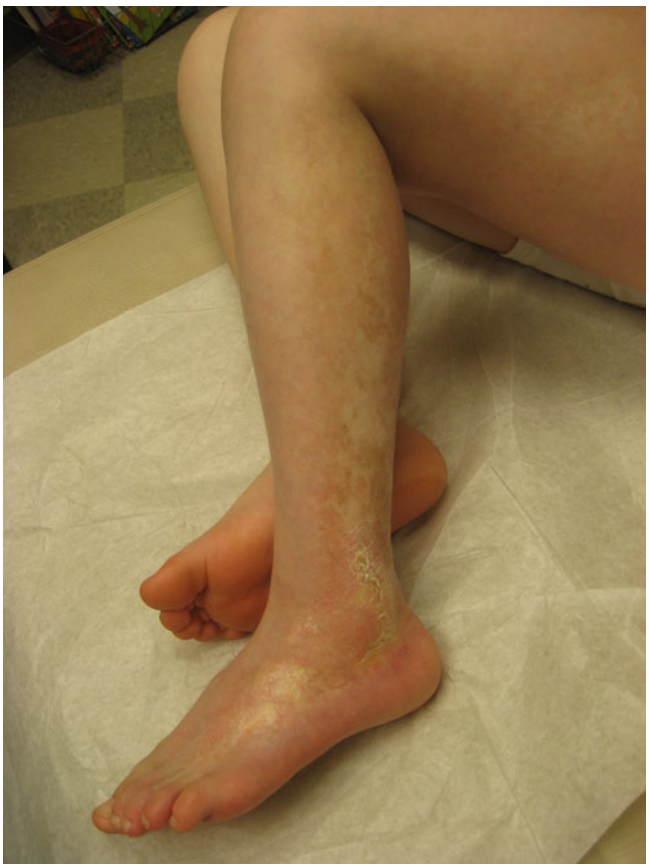

Fig. 22.12 Linear sclerotic plaque on the left lower extremity of an eight-year old boy. The patient also has significant loss of joint movement of his ankle

that two-thirds of all cases of morphea are diagnosed before the age of 18, and up to half of cases undergo skin softening or spontaneous remission from 2.7 to 5.5 years after onset, depending on the type of morphea [115]. The estimated incidence of pediatric morphea is 0.4–1 per 100,000 children [116, 117]. As seen in other autoimmune disorders, morphea has a female-to-male ratio of 2–3:1 and may be encountered in association with other connective tissue disorders including systemic lupus erythematosus, rheumatoid arthritis, Sjögrens syndrome, juvenile dermatomyositis, polymyositis, and eosinophilic fasciitis [118].

Morphea presents as firm, often hyperpigmented, plaques of the skin of varying depth and can occur in any location (Fig. 22.12). Classification of morphea has varied over the years, with a recent classification scheme proposing five types including circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea, and mixed variant morphea. Circumscribed/plaque morphea is subtyped into superficial and deep, depending on involvement of the subcutaneous and deeper tissue, while

linear scleroderma is further classified by location on the trunk/limbs, or head. Linear scleroderma located on the head is further defined as either *en coup de sabre* (ECDS) or progressive hemifacial atrophy [119, 120]. Circumscribed morphea favors the trunk, while linear scleroderma favors the extremities and head. In pediatric patients, linear scleroderma makes up an estimated 65 % of the total cases [120]. Generalized morphea involves 30 % or more of the body surface area. The pansclerotic variant consists of superficial and deep fibrosis extending to the deep underlying structures.

Management Strategies

Treatment for pediatric morphea consists both of topical and systemic therapies, with possible indications for systemic treatment including the potential for morphea to cause significant cosmetic, functional, or growth deformities. There are no strict guidelines outlining criteria for systemic therapy, and the potential for current and future deformity must be weighed against the risks associated with therapy. For linear morphea along a joint, physical therapy is recommended to preserve range of motion. Treatment should be continued until the morphea has burned out and all lesions have become quiescent.

Investigations Recommended

For diagnosis
Punch biopsy if not clinically evident
Anti-nuclear antibody (more common in linear morphea) [121] 42 % positive [122]
Rheumatoid factor (16 %) [122]
Electroencephalography (EEG) for ECDS patients with seizures
MRI/MRA ECDS patients with neurological symptoms
Ophthalmologic exam ECDS patients
For treatment
Complete blood count for MTX, corticosteroids, CSA, MMF
Liver function tests for MTX, CSA, MMF
Basic metabolic panel for CSA, MMF
Lipid panel for CSA
Calcium levels, serum and urine for calcitriol
Blood pressure for CSA
Urinalysis for CSA
Mg for CSA

First Line Therapies

Methotrexate with corticosteroids and UVA1 therapy have the most rigorous studies and are first line treatments [123].

Therapy	Dose	Evidence
Methotrexate (MTX) and corticosteroids	MTX 0.3–0.5 mg/kg/week	A, B, C, D, E
	Prednisone 1 mg/kg/day for 3 months	Most effective
	MTX 15 mg/m^2 max 20 mg for 1 year	
	Prednisone 1 mg/kg/day for 3 months	
	MTX 1 mg/kg/week	
	Prednisone 2 mg/kg/day weaned over 8 weeks to 1 mg/kg/day weaned to 0.25 mg/kg/day for a total of 12 months of steroids	
	MTX 0.3 mg/kg/week Intravenous methylprednisolone 30 mg/kg/day (max 500 mg) for 3 days per months for 3 months	
Ultraviolet A1 light phototherapy (UVA1)	3 times a week starting dose based on skin type, goal dose 20 J/cm^2, 20–50 treatments, decrease frequency with improvement	B, C
Methotrexate	0.2–1 mg/kg/week	D, E
Corticosteroids	Prednisone 1 mg/kg/day	A, D, E
Topicals for mild/stable disease		
Tacrolimus 0.1 % ointment	Twice daily	C, E
Imiquimod 5 % cream	Daily for 5–7 days a week	C, D, E
Calcipotriol 0.005 % ointment	Twice daily	E
Calcipotriene 0.005 % ointment	Twice daily	E

Second Line Therapies

The second line therapies have proven efficacy but are not frequently employed.

Therapy	Dose	Evidence
Psoralen plus Ultraviolet A light therapy (PUVA)	Bath PUVA – 1–26 mg/L methoxypsoralen (8-MOP)	B, C
	Topical 8-Mop 0.0006 % cream	
	Oral 8-MOP 0.4–0.6 mg/kg	
	UVA 3–4 times a week, starting dose based on skin type 0.5–2 J/cm^2, up to 100 treatments	
D-penacillamine	10 mg/kg/day	D, E
Mycophenolate mofetil (MMF)	600-1200 mg/kg/day divided into twice daily dosing	C, E
Cyclosporine (CSA)	3 mg/kg/day	E

Third Line Therapies

The third line therapies are based on case reports or case series and some have questionable efficacy or conflicting results in the literature [124–126].

Therapy	Dose	Evidence
Imantinib, MTX, prednisolone	imantinib 235 mg/m²/day	E
	methotrexate 9.5 mg/m²/week	
	prednisolone 1 mg/kg/day	
D-penacillamine, MTX, prednisolone	D-penacillamine at 10 mg/kg/day	D
	MTX 0.5 mg/kg/week	
	Prednisolone 0.5 mg/kg/day for 1 month and then tapered	
Excimer 308 nm laser	2–3 times a week, standard protocol	E
Calcitriol	1.5 µg/day effective	D
	1.25 µg/day not effective	A
Hydroxychloroquine	200 mg/day, questionable efficacy	D

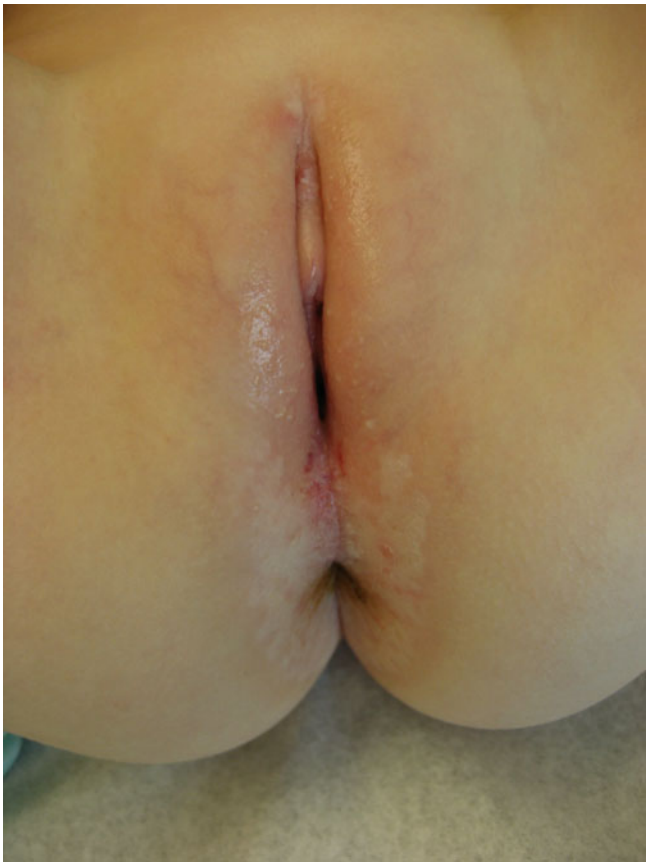

Fig. 22.13 Lichen sclerosis atrophicus in a young Caucasian female. The patient has significant pruritus associated with her disease

Lichen Sclerosus

Clinical Features

Lichen sclerosus (LS), also known as lichen sclerosus et atrophicus, is an autoimmune disorder causing chronic inflammation of the skin particularly in the anogenital region. LS is associated with other autoimmune conditions, such as alopecia areata, autoimmune thyroiditis, vitiligo, and pernicious anemia [127].

In the U.S., the estimated prevalence of LS is about 1:60–1:1000 [128, 129]. LS is more common in women, usually presenting in the fifth or sixth decade of life or during childhood as early as the first few years of life [130]. About 7–15 % of all LS cases occur in children [131, 132]. The bimodal distribution in age of presentation is likely correlated with low estrogen states at these ages [128].

LS in females generally occurs in the anogenital region, presenting as atrophic or ivory white plaques, ecchymoses, and sclerotic and thinned labia minora (Fig. 22.13). In girls, the vulvar purpura may be mistaken for sexual abuse. Chronic pruritus and subsequent excoriation leads to superficial erosions and hyperkeratosis. In young children the discomfort can result in urinary symptoms, constipation, or behavioral problems [133]. As the disease progresses, fissures, superinfection, and symmetric hypermelanosis may also appear [128]. In severe disease, labial scarring and resorption, burying of the clitoris, and narrowing of the introitus. The vaginal introitus scars down, develops adhesions, and becomes susceptible to tearing due to decreased elasticity. Two-thirds of patients with prepubertal LS will improve before the onset of menarche.

In males with LS, the glans, foreskin, and urethra are usually involved, with sparing of the perianal area [134]. LS is associated with phimosis in boys, with one prospective study found LS in 40 % of phimosis cases, with boys between 9 and 11 years old most commonly affected [135].

Adult patients with LS are at risk for developing squamous cell carcinoma (SCC) in the areas affected by LS. In adult females, the risk of developing vulvar SCC is 4–5 % [131]. In males, penile and pseudohyperplastic SCCs occur mostly in uncircumcised patients [136].

Management Strategies

The management of LS focuses on symptom relief and prevention of atrophy, scarring, strictures and malignant transformation. First-line therapies consist of topical

corticosteroids and immune modulators [137]. Preventive measures include moisturizing, gentle soaps, and loose, soft undergarments. Surgical intervention is only necessary when extensive anatomical distortion is observed [130]. In males with early LS, circumcision may be employed to prevent disease progression [138].

Investigations Recommended

- For diagnosis – if clinically ambiguous or recalcitrant to treatment – punch biopsy (not necessary in most of the cases)

First Line Therapies

High potency topical corticosteroids ointments are the first line treatment. Dosing ranges from weekly application to twice daily, and various regimens are recommended [139].

Therapy	Dose/frequency	Evidence
Skin involvement		
Clobetasol 0.05 % ointment	Between 2 weeks to 2 years	B
Mometasone fuorate 0.05 % ointment	5 weeks	A
Clobetasol ointment 0.05 %, triamcinolone 0.1 % ointment and hydrocortisone taper	Clobetasol twice daily for 2 weeks, then daily for 2 weeks, triamcinolone ointment 0.1 % twice daily for 2 weeks, then daily for 2 weeks, hydrocortisone as needed	D
Clobetasol 0.05 % ointment	Once daily for a month, then three times weekly the second month, twice weekly the third month	
Tacrolimus 0.1 % ointment	Daily for 24 weeks	B
Tacrolimus ointment 0.03 %	Daily for 14 weeks	E
Pruritus		
Clobetasol 0.05 % ointment	12 weeks	B
Pimecrolimus 1 % cream	12 weeks	B
Diphenhydramine	Standard dosing	E
Hydroxyzine	Standard dosing	E
Pain		
Tricyclic antidepressants, gabapentin, serotonin reuptake inhibitors	Standard pediatric dosing	E

Topical androgens, estrogen, and progesterone are not effective nor are they recommended for the treatment of LS [140].

Table 22.11 Kasukawa criteria for diagnosing MCTD

Common symptoms:	Raynaud's phenomenon
	Swollen fingers or hands
Presence of anti-U1-RNP	
Mixed findings:	***A. Systemic lupus erythematosus (SLE)-like***:
	Polyarthritis
	Pericarditis/pleuritic
	Lymphadenopathy
	Facial erythema
	Leucopenia/thrombocytopenia
	B. Scleroderma-like:
	Sclerodactyly
	Pulmonary fibrosis
	Esophageal dysmotility
	C. Polymyositis-like:
	Muscle weakness
	High creatine phosphokinase (CPK)
	Myophatic electromyogram (EMG)

Mixed Connective Tissue Disease

Kate Khorsand, MD and Heather A. Brandling-Bennett, MD

Clinical Features

Mixed connective tissue disease (MCTD), first described in 1972, exhibits features of several autoimmune disorders. It is an evolving disease process and variability in presentation makes diagnosis challenging. There are at least three diagnostic criteria (Table 22.11), the most commonly used of which is the Kasukawa criteria [141, 142]. Diagnosis is made based on clinical features of the disease with the presence of anti-U1-RNP antibodies. The most common clinical presenting features include Raynaud's phenomenon, fatigue, polyarthritis, swelling of the hands and finger ('sausage digits'), and muscle weakness [143]. MCTD can involve nearly any organ system, with some of the more serious manifestations including cardiac involvement, pulmonary hypertension, glomerulonephritis, and CNS involvement. Mucocutaneous features are common and include both skin findings, which have significant overlap with other autoimmune conditions, and mucous membrane findings [144]. The most common mucocutaneous findings are listed in Table 22.12.

MCTD is rare in children, representing 0.3–0.6 % of pediatric rheumatology patients in the United States [145]. The median age of onset is 9.5–12 years, with the earliest ages of presentation in the literature ranging from 2 to 5 years [146–148]. There is female predominance of the disorder, but no known ethnic distribution. When compared to the adult population, the pediatric population more frequently exhibits myositis and systemic

Table 22.12 Mucocutaneous features of mixed connective tissue disease

Cutaneous features	Mucus membrane features
Malar rash	Buccal ulcerations
Discoid plaques	Sicca complex
Sclerodactly	Urogenital ulcerations
Calcinosis cutis	Nasal perforation

MCTD is present if: at least one common symptom, with positive anti-U1-RNP antibodies and one or more findings in at least two of three categories A, B, and C

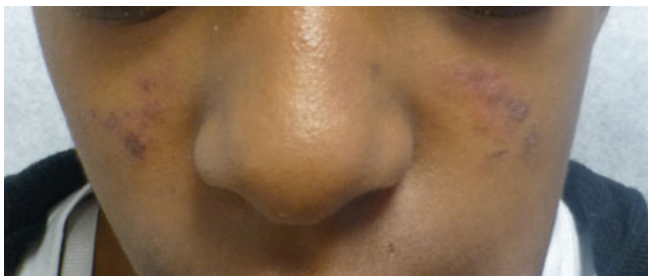

Fig. 22.14 Atrophic hyperpigmented annular patches on the malar cheeks of an African American teenager

lupus erythematous (SLE)-like symptoms than the sclerodermatous symptoms seen more often in adults (Fig. 22.14).

Management Strategies

Management of MCTD is difficult, as there are no consensus treatment guidelines, and data is based on case series or individual case reports. Management has focused on addressing the specific organs involved by the disease in an individual patient, often using therapeutics that are considered to be effective for other autoimmune conditions. Prognosis is variable, and is highly dependent on the severity of internal organ involvement. Most patients do improve after initiation of medications, but long-lasting remission is seen in a minority of patients [142]. The most persistent symptoms appeared to be Raynaud's phenomenon and arthritis, with occasional severe and therapy-resistant thrombocytopenia seen in children, but not adults. Unfavorable outcomes or progressive disease was seen in 15–33 % of patients, however, there is a lower disease-specific mortality in children (0–7.6 %) compared to adults (8.4–23.4 %) [142]. Recent studies have additionally emphasized the impact of MCTD on mental health in pediatric patients [149]. The most common causes of death in children were found to be sepsis, cerebral complications, pulmonary arterial hypertension, heart failure, kidney failure, and GI bleeds [150]. Aggressive treatment of internal organ involvement may ameliorate these serious complications.

Investigations Recommended

Diagnosis of MCTD is made on the basis of clinical features and the presence of anti-U1-RNP antibodies. Additional work-up focuses on identifying and monitoring organ involvement. An initial autoimmune panel should include ANA, ENA panel, anti-ds-DNA, and rheumatoid factor. Perform a complete blood count to screen for hematologic abnormalities such as anemia, leukocytopenia, and lymphopenia, which can correlate with disease activity, and a comprehensive metabolic panel and urinalysis to evaluate for renal or hepatic involvement. Lung and cardiac involvement can be assessed with pulmonary function tests, chest X-ray, high-resolution chest CT, electrocardiogram, and echocardiogram. Other evaluations such as radiologic imaging, electromyography, or muscle biopsy, should be considered based on symptoms or abnormal exam findings.

First Line Therapies

There are no specific recommended treatment regimens for MCTD supported by evidence-based data [151]. The cutaneous eruption usually responds to systemic immunosuppressive medications [145]. Additional therapies are often aimed at specific symptoms or determined by internal organ involvement. For example, calcium channel blockers and preventative measures are often used to treat Raynaud's phenomenon [152].

Therapy	Dose	Evidence level
Systemic corticosteroids	Methylprednisolone 30 mg/kg/day (max 1 g) IV for 3 days or weekly	D
	Prednisone 1–2 mg/kg/day PO	
Hydroxychloroquine	4–6 mg/kg/day (maximum 400 mg daily)	D
Methotrexate	15 mg/m^2 or 1 mg/kg (max 25 mg) SQ or PO weekly	D
	Folic acid supplementation recommended (1 mg PO daily)	
Nifedipine for treatment of Raynaud's phenonemon	Initial dose 0.2–0.5 mg/kg/day (maximum dose 3 mg/kg/day)	A
Amlodipine for treatment of Raynaud's phenonemon	2.5–10 mg daily	A

Second Line Therapies

Other immunosuppressants used in MCTD have less evidence to support their use, and are often used in refractory or severe, life-threatening cases. Case reports focused on treatment of specific organ involvement have also been published, such as immunoadsorption onto protein A combined with corticosteroids and bosentan (a dual endothelin receptor antagonist most often use to treat pulmonary hypertension), which was used successfully in a child with MCTD [153, 154].

Therapy	Dose	Evidence level
Cyclosporine	3.5–5 mg/kg/day	D
Azathioprine (Imuran)	Start at 1–3 mg/kg/day with max of 250 mg daily	D
Mycophenolate mofetil (CellCept)	<1.25 m^2 = 600 mg/m^2/dose bid	D
	40–50 kg or 1.25–1.5 m^2 = 750 mg bid	
	>50 kg or >1.5 m^2 = 1000–1500 mg bid	
Cyclophosphamide (Cytoxan)	500–1000 mg/m^2 IV monthly	D
Rituximab (Rituxan) to treat severe refractory Raynaud's phenomenon	BSA ≤ 1.5 m^2, 575 mg/m^2 at week 0 and week 2	E
	BSA >1.5 m^2, 750 mg/m^2 (up to 1 g/infusion) at weeks 0 and 2	
Plasmapheresis	Not applicable	E
Immunoadsorption onto protein A combined with corticosteroids and bosentan	Not applicable	E
Autologous stem cell transplantation (severe life threatening disease)	Not applicable	E

Relapsing Polychondritis

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Clinical Features

Relapsing polychondritis (RP) is a rare autoimmune systemic disease, especially in children, characterized by episodic inflammation of multiple cartilaginous sites. To date there have been less than 100 cases of childhood RP reported in the literature [155]. The typical age of presentation for RP is in the fourth or fifth decade, however the age of onset has been reported as early as 1.7 years of age [155, 156].

Current diagnosis of RP is based upon the presence of chondritis in two of three characteristic anatomical sites (auricular, nasal, or laryngotracheal), or chondritis of one of these sites and two other features, such as ocular inflammation, audiovestibular damage or seronegative inflammatory arthritis.

Auricular chondritis and arthritis are the most common initial manifestation of RP in children and adults. Children, however, appear to experience more severe and frequent respiratory tract involvement requiring tracheostomy, symptomatic costochondritis, and destructive arthritis with epiphyseal plate involvement [155, 156]. Non-specific dermatologic findings including erythema nodosum, maculopapular rash, and purpura have also been associated with RP [156].

Relative to adult RP, childhood RP has also been shown to be more highly associated with family history of autoimmune disease and less likely to present with other concurrent inflammatory and hematologic conditions (15 % compared with estimated 30 % in adults) [155, 156]. Morbidity and mortality from RP most commonly arise from infectious, cardiovascular, pulmonary, and renal complications of associated systemic diseases.

Investigations Recommended

While the exact etiology of RP remains to be elucidated, humoral and cellular specific responses against collagen II, IX, XI, and/or matrilin-1 are thought to play a key role in pathogenesis [157]. Unfortunately, less than 50 % of patients have positive antibodies to these proposed antigens, thus limiting their clinical utility. Inflammatory markers such as ESR and CRP are often obtained to track disease activity, but lack disease specificity. A thorough history and physical examination should be performed to determine need for further workup. Additional studies to consider are listed in Table 22.13.

Management Strategies

Given the rarity of this disease, especially in children, there is no consensus guideline for the treatment of pediatric RP. For mildly affected patients, non-steroidal anti-inflammatory drugs (NSAIDs) may be sufficient in

Table 22.13 Supplemental studies

Audiometry
Pulmonary imaging
Pulmonary function tests
Electrocardiogram
Echocardiogram
Urine analysis

Table 22.14 Surgical therapies

Tracheostomy
Tracheobronchial stents
Cardiac valve replacement
Corneal transplant
Aneurysm resection
Nasal reconstruction
Nephrostomy

controlling disease. For most patients, systemic corticosteroids are the first-line therapy of choice. Second-line therapies consistent mostly of steroid-sparing immunosuppressive alternatives [155, 158]. While biologics are being increasingly trialed in adults, there remain very few cases of biologic use in children [159, 160]. Surgical interventions do not affect the course of RP, but play a role in treating associated complications (Table 22.14) [155, 161].

First Line Therapies

Therapy	Dose	Evidence level
NSAIDs	Ibuprofen: 20–40 mg/kg/day in 3–4 divided doses; max 2.4 g/day (per RA dosing)	D
	Naproxen: 5 mg/kg 2 times a day; max 1 g/day (per RA dosing)	
Corticosteroids	Oral prednisone at 1–2 mg/kg/day (or equivalent) for 2–4 weeks then taper	D
	Intravenous methylprednisolone at 30 mg/kg/day (max 1 g) for 3 days	

Second Line Therapies

Therapy	Dose	Evidence level
Methotrexate	0.5–1 mg/kg per week; range of 5–25 mg once weekly	E
	Folic acid supplementation 1 mg daily	
Dapsone	2 mg/kg/day; range 25–200 mg daily	E
Azathioprine	1–3 mg/kg/day; max of 250 mg daily	E
Mycophenolate mofetil	600 mg/m^2 twice daily	E
	Total dose of 1–2 g/day	
Cyclophosphamide	500 mg/m^2 every 2–3 weeks	E
Cyclosporine	3–6 mg/kg/day	E
Anti-TNF agents	Infliximab: 5–10 mg/kg every 2–8 weeks or etanercept or adalimumab	E
Intravenous immunoglobulin	2 g/kg (maximum 70 g) every 3–6 weeks	E
IL-1 receptor antagonist	100 mg/day subcutaneous injections	E
antiCD20 monoclonal antibody	375 mg/m^2 every 4 weeks	E

Systemic Sclerosis

Kate Khorsand, MD and Heather A. Brandling-Bennett, MD

Clinical Features

Systemic sclerosis (SSc) is a rare chronic connective tissue disorder characterized by fibrosis of multiple organ systems, and less than 5 % of cases start in childhood. Systemic sclerosis has also been called scleroderma, but is distinct from localized scleroderma or morphea, which is more common and has a more favorable prognosis [162]. Juvenile systemic sclerosis (jSSc) has been classified in two forms: (1) diffuse cutaneous SSc, with widespread rapidly progressive skin thickening and early organ involvement; or (2) limited cutaneous SSc, with restricted and non-progressive thickening of the skin of the distal extremities and possible pulmonary, arterial, and absorptive abnormalities [163]. Systemic sclerosis also exists as part of an overlap syndrome, with manifestations of other autoimmune conditions, and overlap disease is more common in children than adults. The median age of onset of jSSc is 8.1 years of age, with a peak in disease activity between 10 and 16 years [162].

In most patients, Raynaud's phenomenon is the most common presenting symptom, followed by proximal skin induration [164]. Other commonly involved organ systems include the lungs, gastrointestinal tract, and heart. Renal and central nervous system involvement are rare in children. There is less frequent visceral involvement in children [165], but higher incidence of arthritis and myositis than in adults [164]. Given the often insidious onset of symptoms, there is, on average, 1.9–2.8 years between onset of symptoms and diagnosis [162]. Diagnosis of jSSc was aided by the development of consensus classification criteria in 2007. Diagnosis is made in patients less than 16 years of age, with proximal skin sclerosis/induration and at least 2 of 20 minor criteria [166].

Prognosis in jSSc has been found in several studies to be better than that of adult-onset SSc [164, 167], with 5-year survival rates of approximately 90 % and 15-year survival rates between 75 and 85 %, depending on the extent and severity of organ involvement.

Management Strategies

In jSSc, management is tailored to the symptoms and organ involvement of a particular patient. The 2007 classification criteria also addressed management, giving recommendations on treatment of the most common and the most concerning aspects of this condition [166].

First Line Therapies

Treatment of SSc is highly dependent on specific organ involvement. The European League Against Rheumatism (EULAR) scleroderma trials and research group (EUSTAR), developed evidence-based and consensus-derived recommendations for treatments, which guides initial therapy today, in additional to several other large studies which supported the use of methotrexate for skin involvement and angiotensin-converting enzyme inhibitors (ACEi) (e.g. captopril) for renal crisis [168–171].

Therapy	Dose	Evidence
Raynaud's phenomenon, digital ulcers		
Nifedipine	Initial dose 0.2–0.5 mg/kg/day	A
	Maximum dose 3 mg/kg/day	
Bosentan	10–20 kg: Initial: 31.25 mg once daily for 4 weeks; increase to maintenance dose of 31.25 mg twice daily	A
	>20–40 kg: Initial: 31.25 mg twice daily for 4 weeks; increase to maintenance dose of 62.5 mg twice daily	
	>40 kg: Initial: 62.5 mg twice daily for 4 weeks; increase to maintenance dose of 125 mg twice daily	
Pulmonary arterial hypertension		
Bosentan	10–20 kg: Initial: 31.25 mg once daily for 4 weeks; increase to maintenance dose of 31.25 mg twice daily	A
	>20–40 kg: Initial: 31.25 mg twice daily for 4 weeks; increase to maintenance dose of 62.5 mg twice daily	
	>40 kg: Initial: 62.5 mg twice daily for 4 weeks; increase to maintenance dose of 125 mg twice daily	
Sildenafil	Infant dosing: 0.3 mg/kg/dose every 6–12 h	A
	Adult dosing: 5–20 mg three times daily, maximum dose 20 mg three times daily	
Interstitial lung disease		
Mycophenylate mofetil	Children ≥5 years and Adolescents: Induction or maintenance: Initial: 250–500 mg twice daily and gradually increased up to 750–1000 mg twice daily	C
Myositis, arthritis, tenosynovitis		
Prednisone (caution for increased risk of scleroderma renal crisis)	0.3–0.5 mg/kg/day	C
Gastrointestinal involvement		
Proton pump inhibitors (e.g. omeprazole)	5 kg to <10 kg: 5 mg once daily	B
	10 kg to <20 kg: 10 mg once daily	
	≥20 kg: 20 mg once daily	
Prokinetic agents (e.g. metoclopramide, erythromycin, domperidone)	Standard dosing	C
Skin involvement		
Methotrexate	7.5–15 mg/week	A
Scleroderma renal crisis		
Angiotension converting enzyme inhibitors (ACEi) (e.g. captopril)	Initial: 0.3–0.5 mg/kg/dose every 8 h; titrate upward to maximum of 6 mg/kg/day in 2–4 divided doses	C
	Maximum daily dose: 450 mg daily	

Second Line Therapies

There are few second line therapies available, however several have been supported with high level evidence. Management is focused on specific symptoms and organ system involvement.

Therapy	Dose	Evidence
Raynaud's phenomenon, digital ulceration		
Rituximab (Rituxan)	BSA ≤1.5 m^2, 575 mg/m^2 at week 0 and week 2	E
	BSA >1.5 m^2, 750 mg/m^2 (up to 1 g/infusion) at weeks 0 and 2	
Pulmonary artery hypertension		
Continuous intravenous epoprostanol	Not applicable	A
Interstitial lung disease		
Cyclophosphamide	0.5–1 g/m^2 every 4 weeks for at least 6 months	A
	Give with mesna and aggressive hydration to prevent bladder damage	
Gastrointestinal		
Rotating antibiotics (to treat malabsorption caused by bacterial overgrowth)	Standard dosing	D

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Inborn Metabolic Disorders and Endocrine Disorders

23

Joseph Lam and Dawn M. Davis

Introduction

Errors of metabolism account for rare but serious diseases in childhood and adolescence. While most are genetically transmitted and can be detected by neonatal screening, this is unavailable in underdeveloped countries. Early detection via genetic testing, or a high index of clinical suspicion, is necessary so clinical interventions and lifestyle modifications can be instituted promptly to halt disease progression.

Nutritional deficiencies are commonplace, and unfortunately reach pandemic proportions in certain third-world countries, reflecting poverty and resource scarcity. In developed nations, nutritional inadequacy is a consequence of fad diets, cultural practices, and malabsorption disorders of the gastrointestinal tract. Most of these conditions are reversible with adequate food obtainment, education of the patient and family unit, and treatment of concomitant medical disease.

Phenylketonuria (PKU)

Phenylketonuria (PKU) is caused by a complete or near-complete deficiency of phenylalanine hydroxylase activity, and results in intolerance to the dietary intake of the essential amino acid phenylalanine (Phe). PAH deficiency is common in Caucasians, in whom the overall incidence is 1 in 10,000 live births. Without dietary restriction of phenylalanine, most children with PKU develop profound and irreversible intellectual disability [1].

Neonates with PKU show no physical signs of the disease. However, when untreated, older children can show the following dermatological manifestations: decreased skin and hair pigmentation, eczema, and a musty body odor. In particular, episodes of protein deficiency can cause alternating light and dark bands of color along individual hair fibers. This finding is known as the "flag sign" (Fig. 23.1). Non-dermatological findings include microcephaly, epilepsy, severe intellectual disability, and behavior problems, as well as structural brain changes visible on MRI.

Specific Investigations

- Newborn screening (tandem mass spectrometry)
- Plasma amino acid analysis
- Molecular genetic testing

PKU can be diagnosed by newborn screening in virtually 100 % of cases using tandem mass spectrometry. Elevated Phe concentrations in blood spots can be quantified as early as 24 h after birth, and tyrosine (Tyr) concentrations can be used to calculate a Phe:Tyr ratio. Plasma amino acid analysis is the standard method for confirming elevated Phe in newborns having a positive newborn screen. PKU is diagnosed in individuals with plasma Phe concentrations higher than 1,000 μmol/L in the untreated state. Molecular genetic testing of PAH is used primarily for genetic counseling purposes to determine carrier status of at-risk relatives and for prenatal testing.

Table 23.1 First-line therapies

Diet (Phe-restricted diet)	B (level of evidence)

A Phe-restricted diet and a Phe-free medical formula should be started as soon as possible after birth under the direction of a nutritionist. Intake of tyrosine and total amino acids must be monitored. Children under age 2 years should maintain a total amino acid intake of at least 3 g/kg/day including 25 mg tyrosine/kg/day. Care must be taken to avoid long periods of low blood Phe concentration, which is also harmful to brain development.

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Fig. 23.1 Alternating bands of *light* and *dark color* along hair fibers indicative of periods of protein deficiency in phenylketonuria (Courtesy of Dr. Maureen Rogers)

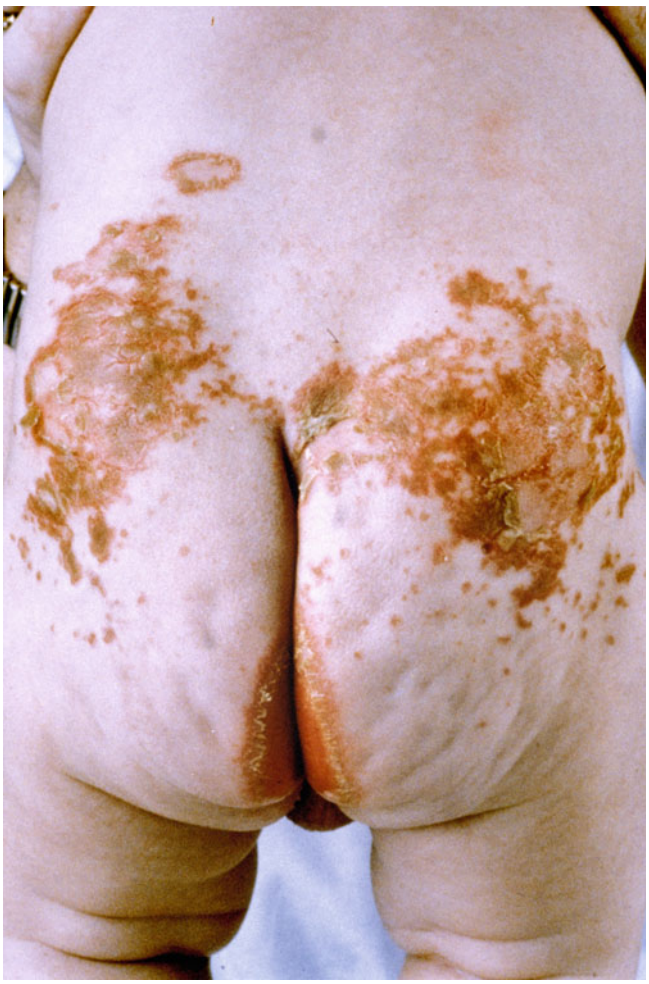

Fig. 23.2 Erythematous erosive scaly plaques over the lower back and perianal skin in a patient with acrodermatitis enteropathica (Courtesy of Dr. Maureen Rogers)

Reduction of phenylalanine levels by dietary restriction can prevent neurocognitive dysfunction, although a mild reduction in IQ (when compared to siblings) and defect in executive function can be present even in optimally treated subjects [1].

Table 23.2 Second-line therapies

Sapropterin dihydrochloride	A (level of evidence)
Large neutral amino acids (LNAA)	A (level of evidence)

Although the treatment of PKU with phenylalanine-restricted diets has been hugely successful, the poor palatability of the diet results in poor compliance in adolescence and adulthood. A number of attempts to find other treatment modalities for PKU are ongoing. Patients with the milder variants are more likely to respond to pharmacological treatment with sapropterin, a synthetic analog of tetrahydrobiopterin [2].

Acrodermatitis Enteropathica

Acrodermatitis enteropathica (AE) is an autosomal recessive disorder caused by a mutation in the SLC39A4 gene, resulting in reduced synthesis of the intestinal zinc transporter, ZIP4. This results in defective absorption of dietary zinc, leading to severe zinc deficiency. AE occurs worldwide, with an estimated incidence of 1 per 500,000 children, and usually presents within days in bottle-fed infants and days to weeks after weaning in breast-fed infants. AE presents with erythematous eczematous scaly plaques over the extremities, anogenital and periorificial skin and can become vesicular, bullous, pustular, desquamative, and erosive (Figs. 23.2 and 23.3). Without treatment, patients can develop generalized alopecia and diarrhea. In later stages, clinical features include growth and developmental delay, poor wound healing, anemia, photophobia, hypogeusia, anorexia, secondary infections, delayed puberty, and hypogonadism in males. Acquired zinc

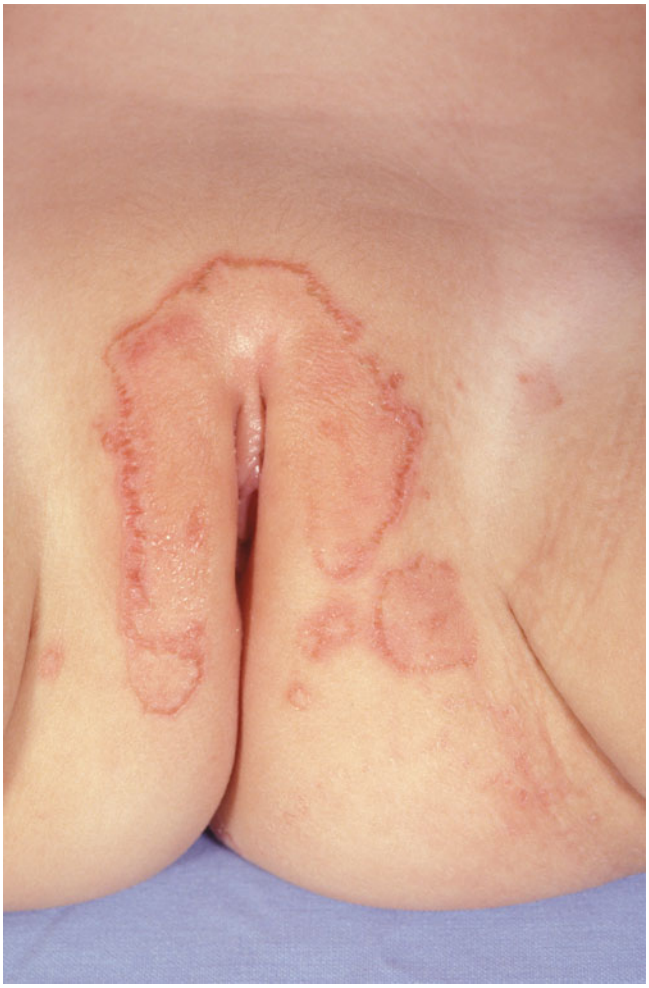

Fig. 23.3 Erythematous erosive scaly plaques over the anogenital skin in a patient with acrodermatitis enteropathica (Courtesy of Dr. Maureen Rogers)

deficiency secondary to insufficient intake, excessive losses, or malabsoption can present with identical clinical features.

Specific Investigations

- Plasma zinc concentration
- Alkaline phosphatase
- Histopathology
- DNA analysis

The diagnosis of AE is made through recognition of the clinical presentation, supported by histopathology and laboratory tests. Zinc levels can be determined by measurement of plasma or serum zinc concentrations, which is ideally drawn before breakfast, in a trace element-free collection tube. Pre-breakfast zinc levels should be greater than 70 ug/dL. Subsequent meals during the day will lower this value. A serum zinc level of less than 50 ug/dL is suggestive of AE [3]. A low serum alkaline phosphatase, a zinc-dependent enzyme, can support the diagnosis of zinc deficiency. The histopathologic features of AE classically show "necrolysis," a term describing cytoplasmic pallor, vacuolization, ballooning degeneration, and confluent necrosis of keratinocytes within the superficial stratum spinosum and stratum granulosum of the epidermis. In resolving or chronic AE lesions, psoriasiform hyperplasia is present, and necrolysis may be minimal to absent.

Table 23.3 First-line therapies

Zinc supplementation	C (level of evidence)

Zinc replacement therapy should be started at 3 mg/kg/day of elemental zinc (there is 50 mg of elemental zinc per 220 mg of zinc sulfate). Typically, clinical improvement is seen very rapidly, within days to weeks, even before a significant change in serum zinc levels. Serum or plasma zinc levels and zinc-dependent enzyme levels should be monitored every 3–6 months and the dose of zinc sulfate should be adjusted appropriately. Acute zinc overdose may cause diarrhea, light-headedness, gait disturbances, lethargy, vomiting, epigastric pain, and abdominal cramps. Chronic overdose may lead to neutropenia, leukopenia, copper and/or iron deficiency, anemia, growth retardation, decreased high-density lipoprotein, and increased low-density lipoprotein.

Biotin Deficiency

Biotin deficiency may be acquired or inherited. The inherited form of biotin deficiency is due to innate errors of biotin metabolism caused by a deficiency in holocarboxylase synthetase (HCS), biotinidase (BTD), or the sodium-dependent multivitamin transporter (SMVT). All three lead to multiple carboxylase deficiency and manifest with metabolic acidosis, neurological abnormalities, and a skin eruption. Acquired biotin deficiency occurs as a result of inadequate intake or excessive losses.

Patients with inherited biotin deficiency typically present within the first weeks to first year of life. The most common symptoms are developmental delay, hypotonia and seizures. The cutaneous findings usually consist of an erythematous and scaly eruption typically localized to moist and periorificial areas. Other skin findings include alopecia and sparse hair, cutaneous grayish pallor and atrophy of the lingual papillae. Other symptoms include conjunctivitis, blepharitis, optic atrophy, metabolic acidosis, vomiting, lethargy, ataxia, and hearing loss.

Biotinidase deficiency should be considered in children with skin eruption or hair loss who also show neurologic

dysfunction, especially infantile seizures, or unexplained breathing problems associated with keto-lactic acidosis, organic aciduria, and hyperammonemia.

Failure to diagnose and treat BTD deficiency at an early stage may cause irreversible neurological damage, leading to developmental delay and autistic behavior.

Specific Investigations

- Serum and urinary biotin levels
- Biotinidase, holocarboxylase synthetase and sodium-dependent multivitamin transporter activity

Laboratory evaluation will show decreased biotin levels. Biotinidase deficiency can be diagnosed by demonstrating decreased or absent enzyme activity in serum, peripheral blood leukocytes, or cultured skin fibroblasts. Prenatal diagnosis is also possible because biotinidase activity can be measured in cultured amniotic fluid cells.

Table 23.4 First-line therapies

Oral biotin	C (level of evidence)

In cases of biotin deficiency, treatment includes oral biotin supplementation with doses of 5–40 mg daily [4]. Skin and neurologic symptoms improve rapidly if biotin therapy is initiated early. However, if treatment is delayed, neurologic dysfunction may be permanent. In inherited forms of biotin deficiency, biotin therapy must be continued throughout life.

Organic Acidemia

Organic acidemias are a diverse set of metabolic conditions which include maple syrup urine disease (MSUD), methylmalonic acidemia (MMA), and propionic acidemia. These congenital branched-chain amino acid metabolism disorders lead to protein intolerance and can unfrequently cause a generalized exfoliative erythroderma or a periorificial and acral eruption similar to acrodermatitis enteropathica [5].

MSUD is caused by a deficiency of the branched-chain keto acid dehydrogenase complex and results in elevated leucine, isoleucine, and valine concentrations in blood, urine, and tissues. Poor feeding, vomiting, respiratory problems, lethargy, hypotonia, and seizures are the main features of MSUD that appear during the neonatal period. Methylmalonic acidemia is caused by a reduction in the activity of methylmalonic coenzyme A (CoA) mutase or its coenzyme adenosylcobalamin. Propionic acidemia is caused by a deficiency of propionyl CoA carboxylase or abnormal metabolism of its coenzyme, biotin. The clinical features of both MMA and propionic acidemia are similar; poor feeding, hypotonia, vomiting, metabolic acidosis, and lethargy, which may result in neonatal death. Cutaneous lesions are uncommon, but can include superficial desquamation, periorificial dermatitis, psoriasiform eruptions, and alopecia.

Specific Investigations

- Urine organic acids
- Specific enzyme activity assay
- Molecular testing

Laboratory findings that point to an organic acidemia include acidosis, ketosis, hyperammonemia, and abnormalities in liver synthetic function. Organic acidemias can be identified though measurement of urine organic acids using gas chromatography with mass spectrometry. When done in times of illness, the diagnostic yield is higher. Confirmatory testing can be done through assay of the activity of the deficient enzyme in lymphocytes or cultured fibroblasts and/or molecular genetic testing.

Table 23.5 First-line therapy

Low protein diet	C (level of evidence)

Table 23.6 Second-line therapy

Oral thiamine (MSUD)	E (level of evidence)
Hydroxocobalamin (MMA)	E (level of evidence)
Oral antibiotics (propionic acidemia)	E (level of evidence)

Table 23.7 Third-line therapy

Liver and kidney transplantation	E (level of evidence)

In the organic acidemias, a low-protein diet with supplementation of essential amino acids is the therapy of choice [6]. The use of specific formulas deficient in the particular precursor amino acids for each disorder is a critical part of management, as it provides the essential amino acids in an otherwise protein-deficient diet. However, if the diet is strictly limited in branched-chain amino acids, the most critical one being isoleucine, cutaneous lesions resembling acrodermatitis enteropathica may also result. In select cases, adjunctive compounds can be used to reduce the burden of toxic metabolites and/or increase activity of deficient enzymes. Examples would be oral thiamine in select cases of MSUD, hydroxocobalamin in MMA, and antibiotics to decrease the production of propionate by gut bacteria in propionic acidemia. Liver and kidney transplantation is uncommonly used to treat cases of MMA and propionic acidemia.

Kwashiorkor

Also known as "protein energy malnutrition," kwashiorkor is a prevalent disease with a high mortality rate of 30–50%. Approximately 30,000 children die each day from kwashiorkor, mostly children ages 0–4 who live in Africa. Death is usually secondary to electrolyte imbalance from uncontrollable diarrhea or infection. Kwashiorkor is defined by 60–80% predicted body weight for age and height, plus edema and/or hypoalbuminemia. Multiple social and economic factors influence its prevalence and distribution, including poverty and resource allocation in third-world countries, and fad diets, food avoidance (for perceived allergies), and food withdrawal (child abuse) in the United States. The disease onset in developing countries coincides with the discontinuation of breastfeeding.

Social chaos and disruptive family dynamics are common in the household of kwashiorkor patients, regardless of the underlying cause of malnutrition. Patients with protein malnutrition who appear to live in a stable home environment with adequate, consistent food sources should be investigated for medical causes for protein malabsorption of the gastrointestinal tract, as cystic fibrosis and Crohn's disease have been documented causes of kwashiorkor.

While insufficient protein intake is the presumed primary etiology of this condition, many other factors may play a role. Several hypotheses support this notion, especially since total caloric deprivation (marasmus) has a lower mortality rate than kwashiorkor. Aflatoxins in food, poor innate protein synthesis, and increased susceptibility to infection are suggested perpetuating factors. The "free radical theory" proposes these processes saturate the serum and tissue with free radicals, depleting the patient's internal antioxidant stores. This theory is supported by increased serum markers of oxidative stress and low antioxidant levels during active disease, and normalization of levels after treatment.

Physical examination will show an apathetic, irritable child with profound delay in developmental milestones. The patient will oftentimes have an overall pallor to the skin, remarkably lighter than other family members. A prominent exam finding is red-brown patches and plaques of inflamed skin with a hyperkeratotic rim, called "flaking paint dermatitis." This dermatitis is most prominent along the trunk, and spares the dorsal hands and feet. Alternating bands of scalp hair pigment, the "flag sign," may be present. Loss of hair pigment signifies times of greater protein restriction.

Specific Investigations

- Serum chemistries for protein deficiency (albumin)
- Serum chemistries for anemia (CBC, iron level, TIBC)
- Serum chemistries for electrolyte imbalance (Na, K, Ca, Cl)
- Serum chemistries of suspected vitamin deficiencies (Zinc, Vitamin B12, Folate, Vitamin B6, etc.)
- Investigation for gastrointestinal malabsorption, if applicable

It is uncommon for kwashiorkor patients to have isolated protein deficiency. Multiple nutritional stores are often depleted, especially zinc and iron. The flaking paint dermatitis of kwashiorkor is commonly mistaken for the desquamative dermatitis of acrodermatitis enteropathica. Both entities may be present in the patient.

First-Line Therapies

- Supplementation of protein
- Supplementation of other deficient nutrients
- Correction of underlying gastrointestinal disease, if present

Introduction of food stuffs to the patient, and his/her GI tract, must be slow and cautious. Overzealous, rapid reintroduction can lead to paradoxical worsening of diarrhea. Care should be in an inpatient setting if at all possible for the initial stages of refeeding, until medical stabilization occurs.

Second-Line Therapies

- Occupational therapy for oral tolerance
- Social work assistance
- Family therapy

Children whose food opportunities are erratic, sparse, or emotionally charged may have oral aversion to refeeding. A solid psychosocial support network for the patient and family are imperative for the child to regain a healthy status and maintain it.

Third-Line Therapies

- Resumption of breastfeeding, if necessary and possible
- Antioxidant supplementation

Some patients may be slow to accept liquids besides breast milk. If breastfeeding is an option for the patient and his/her mother, it may be resumed while food is introduced. This will help correct dehydration if present.

Various antioxidant preparations have been given to kwashiorkor patients, with limited success [7].

Essential Fatty Acid Deficiency

Essential fatty acids (EFA) cannot be synthesized by humans and are required from external sources. The two essential fatty acids, linoleic acid and alpha-linolenic acid, are required for synthesis for arachinoids, eicosanoids, prostaglandins, thromboxanes, and leukotrienes that are important for cell membrane function. In essential fatty acid deficiencies, the abnormal metabolite, eicosatrienoic acid, accumulates and the normal metabolite, arachidonic acid, decreases.

In healthy individuals, for EFA deficiency to develop, dietary intake must be very low. Even small amounts of EFAs can prevent EFA deficiency. However, EFA deficiency can occur in patients on long-term total parenteral nutrition without adequate lipid supplementation, and in patients with conditions such as chronic fat malabsorption, cystic fibrosis, prematurity, and severe malnourishment.

Cutaneous signs of essential fatty acid deficiency include generalized xerosis (which can resemble congenital ichthyosis in infants), alopecia with light-colored hair, and poor wound healing. Non-cutaneous findings include failure to thrive, increased susceptibility to infection, thrombocytopenia, and steatohepatitis.

Specific Investigations

- Plasma eicosatrienoic acid: arachidonic acid ratio
- Serum levels of essential fatty acids

A plasma eicosatrienoic acid:arachidonic acid (triene:tetraene) ratio greater than 0.4 is generally considered indicative of essential fatty acid deficiency. The diagnosis can be confirmed by abnormal serum levels of linoleic, arachidonic, and eicosatrienoic acids.

Table 23.8 First-line therapies

Essential fatty acid supplementation	E (level of evidence)

Treatment consists of supplementation of dietary EFAs, which reverses the deficiency. In some cases, cutaneous application of linoleic acid (safflower/sunflower) oil may be beneficial, although the literature shows mixed results.

Hyperlipidemia

Children who have severe hypercholesterolemia or hypertriglyceridemia are likely to have a clinically identifiable genetic condition. The most common of these is familial hypercholesterolemia (FH). Other primary genetic causes of hyperlipidemia include other autosomal dominant hypercholeterolemias, autosomal recessive hypercholesterolemia, familial defective ApoB-100, familial hypertriglyceridemia, familial hyperchylomicronemia, familial apoprotein CII deficiency, familial combined hyperlipidemia, familial dysbetalipoproteinemia, B-sitosterolemia, and hypoalphalipoproteinemia.

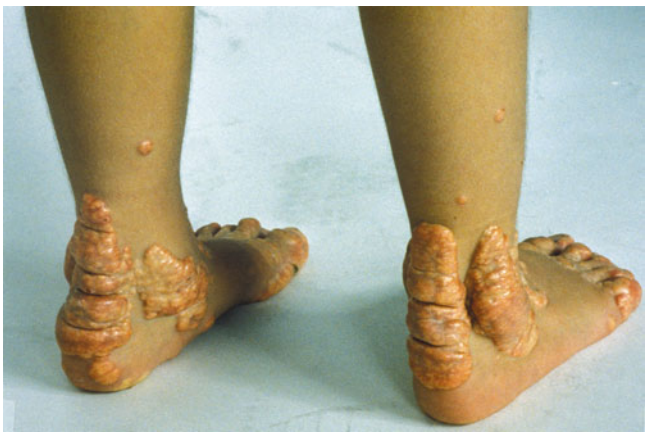

Fig. 23.4 Firm, painless, *red-yellow* nodules overlying the Achilles tendon in a patient with familial hypercholesterolemia (Courtesy of Dr. Maureen Rogers)

Secondary dyslipidemia can also occur due to chronic diseases (diabetes mellitus, chronic renal insufficiency, hypothyroidism, and liver diseases) and drugs (e.g. glucocorticoids, beta-blockers, and anti-retroviral agents).

FH has an autosomal codominant inheritance with a prevalence of approximately one case per one million persons. Heterozygous FH has an estimated incidence of 1 per 500 worldwide. Most mutations affect either the quantity or function of the low-density lipoprotein (LDL) receptor gene, leading to a decreased amount of LDL-receptor function, which results in a doubling of the plasma concentrations of LDL and total cholesterol.

Clinically, patients with homozygous familial hypercholesterolemia (HoFH) present with severe hypercholesterolemia associated with cutaneous and tendon xanthomas (Figs. 23.4 and 23.5), valvular and supravalvular stenosis, and accelerated atherosclerosis in the first two decades of life. Other primary forms of hyperlipidemia that present with cutaneous xanthomas include familial hyperchylomicronemia, familial apoprotein CII deficiency, and familial dysbetalipoproteinemia.

Specific Investigations

- Total cholesterol
- LDL-c (>500 mg/dL or 13 mmol/L)
- ApoB
- Triglycerides

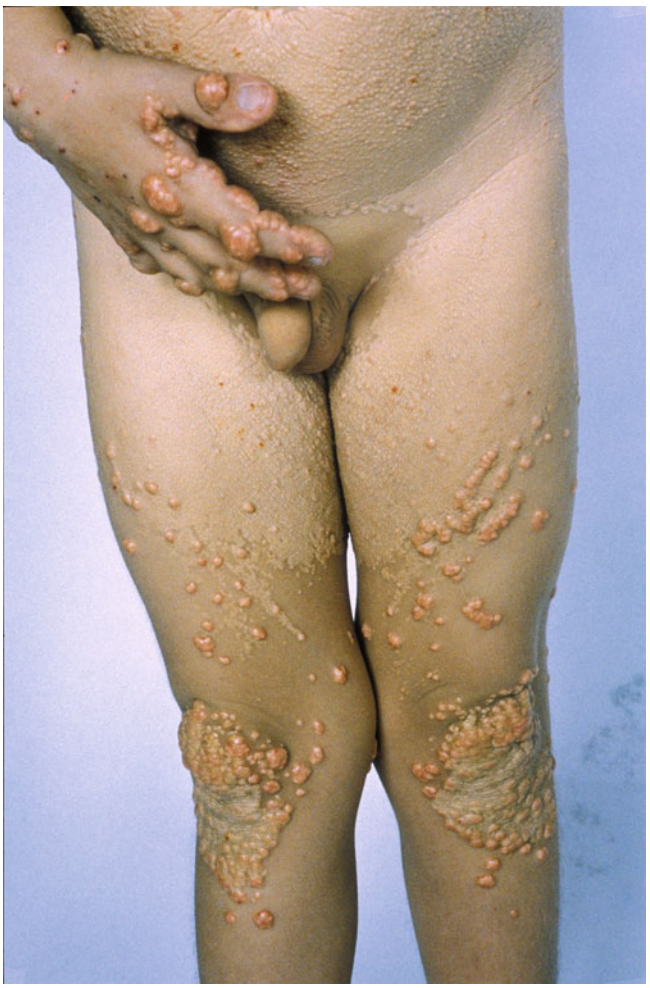

Fig. 23.5 Crops of small, *red-yellow* papules in a patient with familial hypercholesterolemia (Courtesy of Dr. Maureen Rogers)

- HDL-c
- ApoA
- Genetic testing

Although the diagnostic criteria for HoFH are not uniform, clinical diagnosis is typically based on the presence of xanthomas at an early age (<10 years), an untreated LDL-cholesterol concentration of >500 mg/dL (13 mmol/L), a treated LDL-cholesterol concentration of >300 mg/dL (7.76 mmol/L), or a non-high-density lipoprotein (HDL)-cholesterol of >330 mg/dL (8.5 mmol/L) [8]. Interdigital xanthomas, particularly between the thumb and index finger, are pathognomonic for HoFH.

Genetic testing may be helpful for confirmation of HoFH.

Table 23.9 First-line therapies (for HoFH)

Low-fat diet	B (level of evidence)
HMG-CoA reductase inhibitors (for hypercholesterolemia)	A (level of evidence)

In comparison with secondary forms of hyperlipidemia, dietary changes have only a modest lowering effect on LDL-c in primary dyslipidemias.

Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins have greatly advanced treatment of FH, including HoFH. These include simvastatin, atorvastatin, and rosuvastatin [9].

Table 23.10 Second-line therapies (for HoFH)

LDL apheresis (for HoFH)	D (level of evidence)

In patients with HoFH who are inadequately controlled on statins alone, the current practice is to perform LDL apheresis at weekly intervals to achieve the lowest possible LDL cholesterol levels. Apheresis may be the best option for patients who are resistant to, or intolerant of, statin therapy, and is generally recommended only in adults and children older than age 7 years.

Table 23.11 Third-line therapies (for HoFH)

Liver transplantation	E (level of evidence)

Liver transplantation can be curative for HoFH, but is best performed before vascular complications emerge. Its use is limited by the lack of donor organs and the need for ongoing post-operative immunosuppression.

Adjunctive Therapies

Ezetimibe	B (level of evidence)
Niacin	A (level of evidence)
Bile acid sequestrants	B (level of evidence)
Fibrates	A (level of evidence)
Omega-3 fatty acids	B (level of evidence)

Other cholesterol-lowering medications in combination with statins, such as ezetimibe, niacin, bile acid sequestrants, fibrates, and omega-3 fatty acids, may have benefits in addition to statin therapy for the treatment of FH patients.

Mucopolysaccharidosis

The mucopolysaccharidoses (MPSs) are a group of rare genetic disorders of glycosaminoglycan (GAG) catabolism, caused by a deficiency of lysosomal enzymes required for GAG degradation. Incomplete breakdown of glycosaminoglycans leads to progressive accumulation of these substances in many tissues throughout the body. Children who have a MPS disorder are normal at birth. However, if

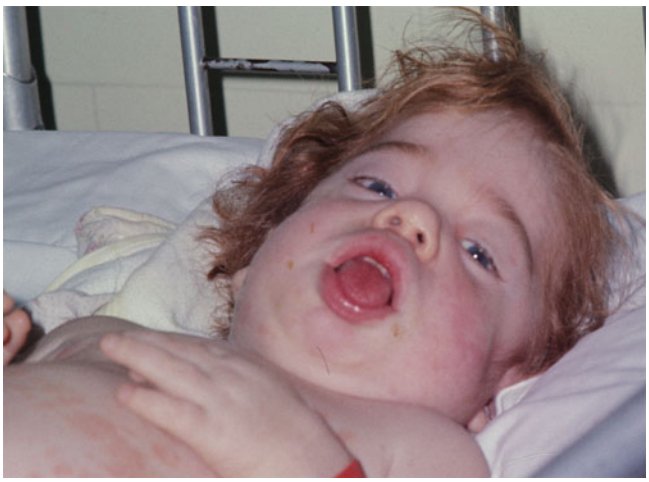

Fig. 23.6 Coarse facial features with low nasal bridge, flat face, and protruding forehead in a patient with mucopolysaccharidosis type I (Hurler syndrome) (Courtesy of Dr. Maureen Rogers)

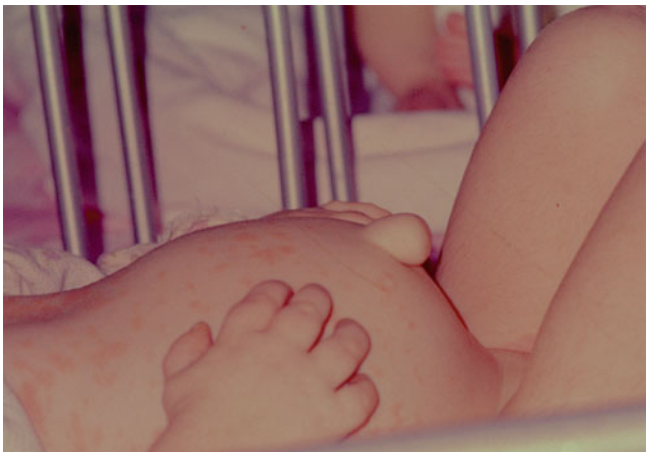

Fig. 23.7 Protuberant abdomen as a result of massive hepatosplenomegaly in a patient with mucopolysaccharidosis type I (Hurler syndrome) (Courtesy of Dr. Maureen Rogers)

untreated, most patients develop neurologic involvement and intellectual disability. Coarsened facial features (Fig. 23.6), hepatosplenomegaly (Fig. 23.7), joint involvement, skeletal dysostosis multiplex, and developmental delay followed by regression are common clinical features in children who have an MPS.

The seven MPS disorders include three that have both central nervous system (CNS) and somatic involvement (MPS I: Hunter/Scheie syndrome; MPS II: Hunter syndrome; and MPS VII: Sly syndrome); one disorder that has somatic involvement but minimal CNS involvement (MPS VI: Maroteaux-Lamy syndrome); one disorder that has CNS involvement and minimal somatic involvement (MPS III: Sanfilippo syndrome); and two disorders that have bone or joint involvement (MPS IV: Morquio syndrome and MPS IX).

Dermatological findings include extensive dermal melanocytosis (Mongolian spots) in MPS II and VI, and a characteristic pebbling of the skin in MPS II.

Specific Investigations

- Urinary GAG levels (screening)
- Enzyme activity assay
- Skeletal radiographs

Measurement of urinary GAG levels is a useful screening test for the MPS disorders. A positive result is very suggestive of an MPS, but false-negative results are common. Radiographs looking for evidence of bony involvement (dysostosis multiplex) often are helpful. Enzyme activity assays based on cultured fibroblasts, leukocytes, plasma, or serum are definitive for a specific MPS, and are regarded as the ideal method of diagnosis.

Therapies

Hematopoietic stem cell transplantation (MPS I, VI and VII)	B (level of evidence)
Enzyme replacement (MPS I, II, VI)	A (level of evidence)

The introduction of hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) has dramatically changed the natural history of MPS I, II, VI and VII.

HSCT with bone marrow or umbilical cord stem cells has been revealed to prevent many clinical features of the severe phenotypes of MPS I, VI, and VII. If performed before developmental deterioration of MPS I patients, successful HSCT can significantly preserve intellectual development for most children who, on the basis of mutational analysis, would have been predicted to develop severe mental impairment. In general, it is recommended that HSCT be performed before age 2 years to maximize benefit [10].

Over the last 10 years, ERT with recombinant human enzyme for MPS I, II, and VI has been approved in the USA, Europe, and many other countries worldwide [11, 12].

Wilson Disease

Hepatolenticular degeneration, or Wilson disease, is an autosomal recessive disorder of copper metabolism. There are over 100 mutations in the ATP7B gene (chromosome 13q) that account for the clinical triad of liver cirrhosis, progressive neurologic dysfunction, and copper deposition on the cornea (Kayser-Fleischer rings). With an incidence of 1:30,000 and carrier rate of 1:90 persons, it is a common

cause of liver disease and liver failure in the pediatric population [13]. Left untreated, it is uniformly fatal via infection or liver failure.

Copper is a common element in the human diet, present in high quantities in nuts, chocolate, shellfish, mushrooms, and broccoli. Ninety-percent of all ingested copper is bound to albumin within the liver. ATP7B proteins transfer the albumin-bound copper to a chaperone protein in the Golgi apparatus. It will be used for important metabolic processes (electron transfer, free-radical scavenging, pigment production, neurotransmission) before being excreted via bile. When the ATP7B protein is defective, copper accumulates primarily in the liver. Upon liver saturation, deposits occur in the brain and kidneys.

While the liver becomes toxic from excess copper first, oftentimes it is the neurologic deposition that leads to the first clinical signs that trigger an investigation. Tremor, dysarthria, and ataxia are frequently more noticeable to the patient and family members than jaundice or ascites. Abrupt personality changes occur in 20 % of Wilson disease patients, along with deteriorating school performance, further encouraging patients to seek medical evaluation. Most proband cases of Wilson disease are diagnosed in adolescence, although clinical signs and symptoms may be evident by age 3.

A high index of suspicion is imperative to allow prompt intervention. Wilson disease should be considered in any pediatric patient or young adult with incidental elevated liver enzymes, liver disease, and psychological disturbances, Coombs-negative hemolytic anemia, or unexplained liver cirrhosis or failure.

Physical examination will reveal various signs based on phenotypic variability and the extent of organ saturation. Patients may be jaundiced and have hepatomegaly and ascites. Spider angiomas may be present, and increased pigmentation along the anterior shins and genitalia may be noted (and may be confused for Addison's disease). Fingernails and toenails may show blue lunulae, or may be diffusely white. Generalized skin xerosis is also common, affecting 45 % of patients. Ocular examination may demonstrate the classic Kayser-Fleischer rings on the cornea, evidenced by a green-brown rim of copper around the iris. These are present in 50 % of liver infiltrated patients, and 98 % of patients with neurologic impairment. While slit-lamp examination is the preferred method of assessment, examination with side lighting may be adequate to visualize them.

Specific Investigations

- Serum copper levels (<100 mg/dL)
- Serum ceruloplasmin levels (<20 mg/dL)
- Urine copper levels (>100 μg; diagnostic if >1,600 μg)
- Liver biopsy (>250 μg per gram dry tissue)
- Genetic testing

There are several ways to test for Wilson disease. The gold standard test is hepatic biopsy and weighing the specimen for copper content. This is complex and may not be readily available. Genetic testing for the ATP7B protein is available. Not all mutations are identified, and testing is currently thought to have a 1–2 % error rate. Serum lab testing will show decreased serum copper and ceruloplasmin with elevated copper in the urine. Abnormal values consistent with Wilson disease are listed in parentheses above.

Table 23.12 First-line therapies

D-penicillamine: 1–2 g/day divided TID, 30 min prior to meals	C (level of evidence)
Pyridoxine: 12.5–25 mg/day, or 50 mg once a week	C (level of evidence)
Low copper diet	E (level of evidence)

The chelating agent D-penicillamine is the gold standard treatment for Wilson disease patients. Most patients who tolerate the medication will get significant improvement, but slowly; some patients will need 12 months of therapy for all symptoms to reverse. Therapy is life-long. D-penicillamine inhibits pyridoxine-dependent enzymes, so pyridoxine supplementation must occur with chelation therapy, either daily or weekly. D-penicillamine side effects can be severe, including hypersensitivity reactions, leukopenia, and thrombocytopenia, necessitating discontinuation.

Patients should be encouraged to avoid foods rich in copper such as nuts, chocolate, shellfish, mushrooms, and broccoli.

Table 23.13 Second-line therapies

Zinc: 25–50 mg TID	C (level of evidence)
Trientine: 1–2 g/day divided TID	E (level of evidence)

Patients who do not tolerate D-penicillamine should be treated with trientine, or trientine plus zinc. Patients on trientine should be monitored for sideroblastic anemia; otherwise, the medication is well tolerated. Zinc can be used as monotherapy in early disease, if patients are diagnosed before symptom onset. Rarely zinc monotherapy is chosen when patients tolerate neither D-penicillamine nor trientine.

Table 23.14 Third-line therapies

Liver transplantation	E (level of evidence)

Transplantation is recommended for all patients with fulminant liver failure or end-stage liver disease. Transplantation

will reverse liver symptomatology but not neurologic sequelae. Transplant patients then require standard-of-care transplant care process models, which is expensive and laborious, with its unique morbidities.

Homocystinuria

The word homocystinuria literally describes the elevation of homocysteine levels in the urine. This definition is limiting, as the term homocystinuria is used to reference a genetically inherited biochemical disorder with numerous deleterious systemic effects.

The unifying variable amongst all forms of homocystinuria is the defective conversion of methionine into cysteine. The most common form of the disorder results from the deficiency or absence of the enzyme cystathionine beta-synthase (CBS; chromosome 21q22) within the liver, causing elevated systemic levels of methionine. This defect is inherited in an autosomal recessive pattern, and has a carrier frequency of 1 in 135 individuals, with an increased prevalence in persons of Northern European heritage. With over 90 mutations in the CBS gene known to date, there is much variably in phenotypic expression and complications.

Patients with homocystinuria suffer embolic, ophthalmologic, and neurologic sequelae, as homocysteine causes increased platelet adhesion and direct destruction of endothelial linings. Vascular complications (myocardial infarction, cerebrovascular accidents, pulmonary embolism) occur in approximately one-fourth of pediatric patients, and increases to one-half of all adults. If left untreated, the mortality rate by age 25 is 50 %, usually from an embolic event. Mental retardation is prominent within this patient population, affecting 80 % of untreated individuals. Other serious sequelae include glaucoma, cataracts, and seizures.

Physical examination signs to aid the practitioner with diagnosis manifest with age. Frequently, patients have sparse, fine blond hair, and progressive livedo-like changes diffusely along the skin. Ectopia lentis is extremely common and develops in most patients by age 10. Homocystinuria patients also display a Marfanoid body habitus, with scoliosis, high-arched palate, and shuffling gate.

Specific Investigations

- Serum and urine amino acid testing of methionine, homocysteine, and cysteine

Newborns do not show any specific signs to alert providers of an enzymatic abnormality, and early intervention to decrease cumulative methionine toxicity is imperative. Since amino acid levels may not reach abnormal levels for the first few days of life, testing is recommended between 5 and 14 days of life. Positive results will show elevated methionine levels (>2 mg/dL serum), elevated homocysteine levels, and reduced cysteine.

Table 23.15 First-line therapies

Pyridoxine (vitamin B6): 250–500 mg/day	C (level of evidence)

Approximately 50 % of patients will respond well to pyridoxine therapy alone. Note that higher doses of pyridoxine (>900 mg/day) can cause neuropathy, so thorough education of the patient and family is warranted.

Table 23.16 Second-line therapies

Methionine-restricted, cystine-supplemented diet	E (level of evidence)
Folic acid supplementation	E (level of evidence)
Cobalamin (vitamin B12) supplementation	E (level of evidence)
Betaine therapy	E (level of evidence)

Patients who do not improve solely with pyridoxine therapy oftentimes respond to a combination of pyridoxine, folic acid, and cobalamin. In addition, counseling with a dietician to obtain a methionine-poor, cystine-rich diet is strongly encouraged. Foods rich in methionine include milk, wheat, rice, meat, fish, nuts, and dried fruit.

Table 23.17 Third-line therapies

Aspirin	E (level of evidence)
Dipyridamole	E (level of evidence)

Patients who have suffered embolic events may be advised to take anti-platelet medications daily as a prevention strategy, or during high risk times. Embolic events are known to increase for homocystinuria patients during surgery and with immobilization.

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Cutaneous Manifestations of Systemic Disease

24

Katherine L. Johnson and Marla N. Jahnke

Primary Immunodeficiency Disorders

Immunoglobulin Deficiencies, Chronic Granulomatous Disease, Leukocyte Adhesion Deficiencies, Severe Combined Immunodeficiencies

Clinical Features

Signs of underlying immunodeficiency in a child can include frequent, abnormally severe, recurring, or unusually long-standing, infections. Additionally, suspicion should heighten if patients have incomplete clearance of an infection despite proper management, or if unusual pathogens are cultured. Other concerning signs include failure to thrive and poor wound healing. Patients with an immunodeficiency can manifest at a young age, coinciding with the natural weaning of maternal immunoglobulins.

The primary immunodeficiency disorders are divided into immunoglobulin deficiencies, chronic granulomatous disease (CGD), leukocyte adhesion deficiencies (LAD), and severe combined immunodeficiency (SCID) (Figs. 24.1 and 24.2). See Table 24.1 for a list of disorders and their associated features [1, 91, 93, 113].

Management Strategies

Patients with primary immunodeficiency disorders require a multidisciplinary approach with collaboration from immunology, infectious disease, dermatology, and others. Appropriate antimicrobial agents, and topical and systemic therapies should be administered for corresponding cutaneous manifestations, depending on the patient's presentation (refer to the corresponding sections in this textbook for treatment of specific diseases). When indicated, surgical treatment of wounds and abscesses may be necessary. The goal of dermatologic care is to treat any active cutaneous

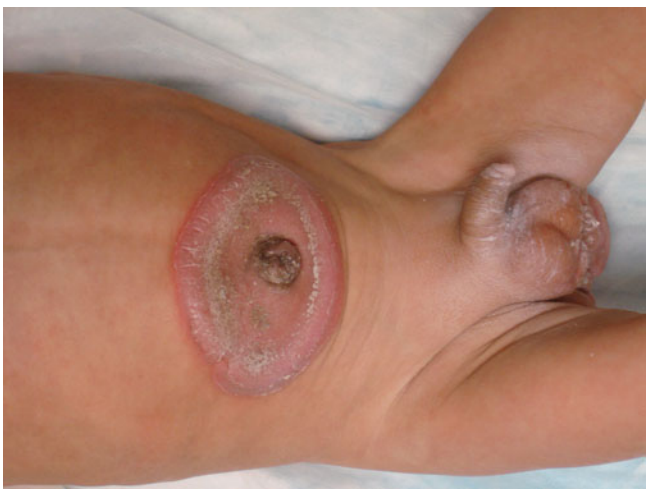

Fig. 24.1 A baby with failure to thrive and poor wound healing after delayed separation of umbilical stump

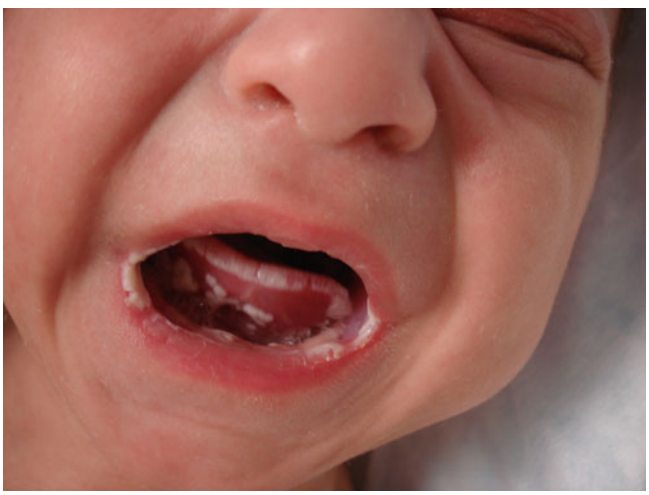

Fig. 24.2 Treatment-resistant thrush in undifferentiated immunodeficiency disorder

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Table 24.1 Clinical cutaneous features of primary immunodeficiency disorders

Disorder	Cutaneous features
Immunoglobulin deficiencies	
IgA deficiency	Autoimmune-like disorders: vitiligo, atopic dermatitis, lupus, recurrent candida infections, purpura, necrotizing vasculitis, lipodystrophy, and visceral granulomas
Combined variable immunodeficiency	Verruca, pyoderma, extensive dermatophyte infections, autoimmune diseases as seen in IgA deficiency, sarcoidal and deep granuloma annulare-like granulomas
X-linked hypogammaglobulinemia	Cutaneous abscesses, furuncles, cellulitis, pyoderma gangrenosum, and dermatomyositis-like disorder
X-linked hypogammaglobulinemia with hyper-IgM syndrome	Pyoderma, extensive verruca, and mucosal ulcerations
Warts, hypogammaglobulinemia, infections and myelokathexis	Extensive verruca, skin infections, and alopecia
Chronic granulomatous disease	Cutaneous granulomas, facial and perianal infections, aphthosis, seborrheic dermatitis, folliculitis, and neutrophilic-like disorders
Leukocyte adhesion deficiencies	Delayed separation of umbilical stump, facial and perianal infections, poor wound healing, wounds become large and similar to pyoderma gangrenosum (Fig. 24.1), and blueberry muffin lesions in LAD Type 3
Severe combined immunodeficiency	Severe seborrheic dermatitis, erythroderma, morbilliform eruption, alopecia, candidal infections (Fig. 24.2), absent reactive lymphadenopathy, perianal rash and thrush

Ig immunoglobulin

issues, maintain the integrity of the skin barrier, and prevent trauma or other insults to the skin surface in order to avoid infection.

Investigations Recommended

For diagnosis	
Test	Purpose of evaluation
Punch biopsy of skin	Differentiate between SCID and GVHD from maternal-cell engraftment
Culture of skin lesions or wounds	Check for bacterial, atypical mycobacterial, and fungal infections
CBC with differential and peripheral smear, ESR	Leukocytosis in CGD and LAD; anemia in CGD and assess level of inflammation in CGD
Flow cytometric dihydrorhodamine assay	Detects CGD (in place of the nitroblue tetrazolium test)
Quantitative immunoglobulins	Check for immunoglobulin deficiencies; hypergammaglobulinemia in CGD
ACE level	Rule out sarcoidosis if granuloma formation
Referrals to: hematology/oncology and infectious disease if clinically appropriate	Evaluate for underlying disease and immunodeficiency

ACE angiotensin converting enzyme, *CBC* complete blood count, *ESR* erythrocyte sedimentation rate, *GVHD* graft-versus-host disease

Recommended Therapies

Antibody replacement for immunoglobulin deficiency	B
Systemic steroids for development of granulomas in skin or visceral organs:	E
Methylprednisolone 1–2 mg/kg/day with gradual taper	
Prophylactic antimicrobial therapy:	A
Trimethoprim and sulfamethoxazole 510 mg/kg/day divided every 12 h, three times a week, on consecutive days	
Itraconazole therapy 5 mg/kg/day in CGD	
Hematopoietic stem cell transplant in severe cases of CGD, LAD, SCID, and combined variable immunodeficiency	B

CGD chronic granulomatous disease, *LAD* leukocyte adhesion deficiencies, *SCID* severe combined immunodeficiency

In general, management of immunoglobulin deficiencies consists of replacing the deficient or absent immunoglobulin, with the exception of IgA deficiency [86]. When a deficiency is not life threatening, systemic steroids are beneficial in conditions that develop cutaneous or visceral granulomas or symptoms similar to sarcoidosis [7]. CGD requires prophylactic therapy to prevent serious bacterial or fungal infections. This is managed with daily administration of itraconazole and trimethoprim-sulfamethoxazole [43, 74, 109].

In SCID, hematopoietic stem cell transplantation is the only chance of survival, and it is most successful if performed within the first 3 months of life. It should also be considered in common variable immunodeficiency although there is a high mortality rate with the procedure [143].

Graft-Versus-Host Disease

Clinical Features

Graft-versus-host disease (GVHD) occurs when transplanted immunocompetent cells, which are introduced into an immunocompromised host, cause an immunologic insult to the host. A complex interaction occurs between the donor's and

recipient's humoral and adaptive immunities, resulting in signs and symptoms similar to those seen in autoimmune diseases. Morbidity and mortality vary depending on the extent of involvement and the host's response to treatment. Hematopoietic stem cell transplant or nonirradiated blood products administered to an immunocompromised patient are common associations with GVHD. Despite preventive and protective measures before, during and after the transplant, GVHD remains a significant cause of morbidity and mortality in transplant patients.

Historically, GVHD has been classified as acute or chronic, with 100 days being the cutoff time between the two. Given changes in transplant medicine and subsequent patient outcomes, the National Institutes of Health Consensus Development Project on the Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease has adapted the GVHD classification to the following: Acute GVHD includes (1) classic acute disease occurring within 100 days after transplantation and (2) persistent, recurrent, late-onset acute GVHD with an appearance of acute GVHD occurring beyond 100 days after transplantation (often seen with tapering or withdrawal of immunosuppressive therapy). Chronic GVHD includes a (1) classic chronic GVHD subtype and (2) an overlap syndrome with features of chronic and acute GVHD [42].

Early in the course of GVHD, findings may be subtle. Some patients may feel fatigue, lethargy, and mild pruritus, or develop slight erythema, all of which appear similar to a viral illness. Non-transplant physicians may help identify drug reactions, infections (especially viral exanthems in children), recurring malignancy or other skin conditions, which must be excluded prior to diagnosing GVHD.

Acute GVHD may present with pruritus, edema, erythema, and dysesthesia. As the process continues, skin involvement may range from erythematous macules to papules, vesicles, bullae, or ulceration (Figs. 24.3 and 24.4). Acute GVHD with generalized erythroderma or resembling Stevens-Johnson syndrome heralds a more severe reaction.

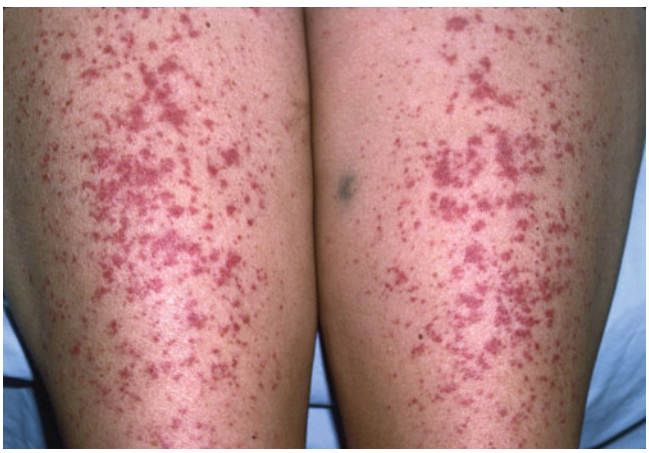

Fig. 24.3 Pupuric macules in graft-versus-host disease (Courtesy of Chauncey McHargue, MD)

Extracutaneous features often include cholestasis, nausea, vomiting, anorexia, diarrhea, or ileus [42]. The severity of the acute reaction is based on the skin findings, bilirubin levels, and gastrointestinal involvement.

Chronic GVHD can affect any organ system, although the skin may be the only organ involved (see Table 24.2).

Management Strategies

Because of the potential severity of GVHD and often suboptimal results with treatment, the main focus is on prevention. Pretreatment of transplant tissue via elimination of immunoreactive T cells and the use of immunosuppressive medications during the first 100–180 days post-transplant

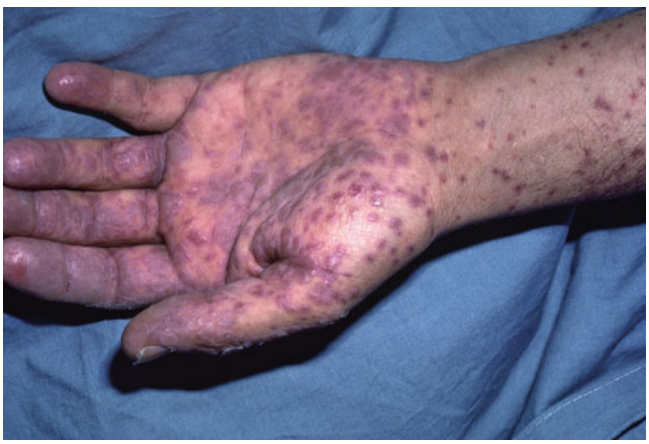

Fig. 24.4 Violaceous macules and papules in graft-versus-host disease (Courtesy of Chauncey McHargue, MD)

Table 24.2 Cutaneous features of acute and chronic GVHD

Acute GVHD	Chronic GVHD
Folliculocentric or morbilliform erythema with confluence	Diagnostic
Edema	Poikiloderma
Dysesthesias	Lichen planus-like
	Sclerodermatous
	Morphea-like
	Lichen sclerosus-like
	Characteristic but not diagnostic
	Keratosis pilaris-like
	Ichthyosiform
	Depigmentation
	Nail dystrophy, onychorrhexis, pterygium, and nail loss
	Alopecia, scarring or non-scarring
Shared features	
Erythema	
Morbilliform rash	
Pruritus	

GVHD graft versus host disease

Table 24.3 Recommended guidelines for non-pharmacologic evaluation and management of GVHD

Routine full-body skin evaluation performed by dermatologist every 3–6 months
Evaluate for skin changes of acute or chronic GVHD
Evaluate for changing skin lesions worrisome for dysplastic nevi, melanoma, and nonmelanoma skin cancers
Evaluate for portals of entry for infection
Evaluate/inquire about genital involvement or other mucosal surface changes
Evaluate for contractures, other sclerodermoid changes, or changes affecting range-of-motion
Encourage routine self skin examinations
Parental education on early warning signs of GVHD
Parental education on photoprotection
Broad-spectrum sunscreen and photoprotective clothing
Skin and nail care
Keep nails trimmed to avoid scratching and inducing skin injury
Daily moisturizing with emollients to maintain skin barrier
Avoid abrasive clothing or ill-fitting shoes to prevent blistering

GVHD graft versus host disease

attempt to prevent GVHD. Prophylactic systemic medications that are most commonly used include tacrolimus, mycophenolate mofetil, methotrexate, cyclosporine, and steroids. Additionally, bowel rest, irradiation of blood products, and prophylaxis for fungal, viral, and bacterial infections also aim to prevent GVHD.

Acute GVHD is a risk factor for developing chronic GVHD, and chronic, progressive GVHD portends a poor prognosis. Therefore, treatment of any type of GVHD is important and depends on disease severity. Topical treatments for mild cutaneous symptoms are adequate [42]. When patients have more moderate to severe disease or multi-organ involvement, systemic immunosuppression is required. Additionally, contractures seen with sclerodermoid-type GVHD may need intervention by occupational and physical therapy [29]. A multidisciplinary approach, regardless of acuity, is prudent.

While the transplant team carefully manages patients, the non-transplant physician plays an important role in disease monitoring and patient education (see Table 24.3).

Investigations Recommended

Test	Purpose of evaluation
For diagnosis	
Punch biopsy of skin	Confirm GVHD vs. other cutaneous eruption
Culture of ulcers or non-healing wounds	Check for bacterial or fungal infection
CBC with differential (attention to eosinophilia), CMP	Check for eosinophilia, lactate dehydrogenase levels and liver function with aminotransferases and bilirubin
For treatment	
Lipid panel, magnesium, and uric acid	Cyclosporine
Blood pressure	Cyclosporine
Referrals to: transplant team, ophthalmology, pulmonology, otolaryngology, and physical therapy/occupational therapy if clinically indicated	Evaluate for GVHD manifestations in other organs and therapy for contractures from sclerodermoid-type of GVHD

CBC complete blood count, *CMP* complete metabolic profile

Recommended Therapies

Table 24.4 First line therapies

Topical therapies	
Topical steroids BID prn	E
Triamcinolone 0.1 % BID for body and hydrocortisone 1 % or 2.5 % for face, folds and groin	
If unresponsive consider wet wraps to enhance penetration or stronger topical steroids	
Tacrolimus BID	C[a]
Pimecrolimus daily	E
Systemic therapies	
Prednisone	B[a]
Prednisone + cyclosporine, alternating each medication every other day	B[a]
Mycophenolate mofetil	B[a]
Methotrexate	B[a]
Systemic tacrolimus + mycophenolate mofetil	B

[a]Denotes adult study

Topical steroids are the mainstay of treatment for localized cutaneous GVHD, although there are no well-designed studies in children or adults with GVHD [32]. Tacrolimus 0.03 % or pimecrolimus 1 % may similarly be considered instead of topical steroids. When topical medicaments fail to control mild disease, patients may benefit from prednisone, although results are often suboptimal [72].

Pediatric studies show that systemic tacrolimus in combination with mycophenolate mofetil is effective in reducing the incidence of acute GVHD [87]. A Cochrane review

Table 24.5 Second line therapies

Topical therapies	
NB-UVB ± topical steroids	C, E
UVA1	C[a]
Bath PUVA (8-methoxy-psoralen in bath soak for 20 min then UVA exposure), 3 times weekly until clinical improvement then taper	E
PUVA	E[a]
Systemic therapies	
Etanercept + topical steroids	B[a]

NB-UVB narrowband ultraviolet B, *PUVA* psoralen combined with ultraviolet A, *UVA1* ultraviolet A1

[a]Denotes adult study

showed that mycophenolate mofetil and methotrexate are equally efficacious, although mycophenolate mofetil had a slightly better tolerability profile [63].

One pediatric study showed NB-UVB to benefit eight out of ten patients who failed first-line therapies. Other isolated pediatric case reports show good results with NB-UVB plus topical steroids for the treatment of eczematous-type GVHD [18, 124].

For both acute and chronic forms of GVHD, UVA1 as adjunctive treatment or first-line treatment may lead to complete or partial responses without concomitant steroids [144]. Bath PUVA may also be effective while avoiding the side effects of oral photosensitizers [15, 54, 144].

Etanercept, in addition to topical steroids, in grade I (skin-only) disease have reduced the incidence of development of grades II-IV GVHD when compared to topical steroids alone [44].

Table 24.6 Third line therapies

Imatinib 100 mg/day increased to 400 mg/day	B[a]
Extracorporeal photopheresis	E

[a]Denotes adult study

Imatinib may serve as a treatment for steroid-refractory chronic GVHD, possibly due to its anti-inflammatory effects as seen with several fibrotic diseases. An additional benefit is that patients do not require hospitalization or long-term venous access [85]. Extracorporeal photopheresis for chronic GVHD in adults and children may improve sclerotic changes in the skin for up to 12 years after the onset of GVHD [137].

Melkersson-Rosenthal Syndrome

Clinical Features

Melkersson-Rosenthal syndrome (MRS) is a rare neuromucocutaneous disease characterized by infiltration of the skin and subcutaneous tissues with noncaseating granulomas. Patients predominately present as females in the third decade of life with an incomplete triad of fissured tongue (lingua plicata), relapsing facial paralysis, and recurrent or persistent facial edema [37] (Fig. 24.5). Children tend to present differently than adults, with unilateral facial nerve palsy as the inciting event. This can precede the edema by several months. Isolated eyelid edema as a solitary presenting sign of MRS has also been reported [100] (Fig. 24.6).

The etiology of MRS is unknown. It is theorized that granulomas lead to lymphatic and vascular congestion, which causes swelling of the lips, cheeks, and/or eyelids [37]. A genetic link is suspected, as up to 30 % of cases have a first- or second-degree relative with a history of "facial palsy [119]." Additionally, autoimmune diseases and infectious etiologies have been associated with MRS in some case reports.

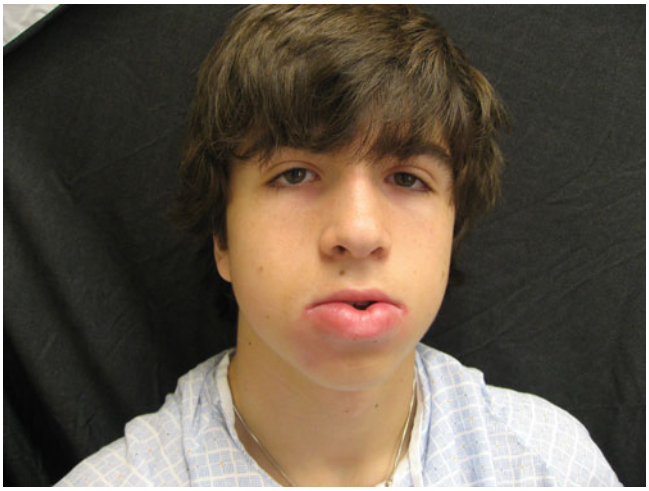

Fig. 24.5 Labial edema in Melkersson-Rosenthal syndrome (Courtesy of Tor Shwayder, MD)

Fig. 24.6 Thirteen-year-old with isolated bilateral upper eyelid edema in Melkersson-Rosenthal syndrome (Courtesy of Tor Shwayder, MD)

Management Strategies

Due to the rarity of the condition and paucity of reported cases of pediatric MRS, treatment relies upon anecdotal evidence in children and studies from the adult literature. Therapeutic

management is determined by the severity of disease. In solitary lip swelling, topical and intralesional therapies should be attempted first. When patients have disfiguring or debilitating symptoms, or if conservative measures are ineffective, oral agents are the next appropriate step. Finally, surgical approaches may be employed if there is permanent aesthetic and functional deformity and all other therapies have failed.

Investigations Recommended

Because of its variable presentation, MRS is a diagnosis of exclusion. It can present in a similar fashion to other disorders such as Bell's palsy, angioedema, contact dermatitis, Crohn's disease (CD) or infection. A skin biopsy can aid in diagnosis, but may only show edema in the early stages. Additional studies may help exclude diseases in the differential diagnosis.

Test	Purpose of evaluation
For diagnosis	
Punch biopsy of skin	Check for foreign body reaction, allergic dermatitis, lymphoma, or other granulomatous diseases
CBC with differential, ESR	Check for infection and assess for inflammation
ANA	Evaluate for underlying autoimmune disease
HSV PCR	HSV as etiologic agent in recurrent episodes and facial palsy
Complement levels (C3, C4); if abnormal, then check C1 esterase inhibitor level and function	Evaluate for angioedema
ACE level	Evaluate for sarcoidosis
Chest X-ray	Evaluate for hilar lymphadenopathy as seen in sarcoidosis
Patch testing	Allergic contact dermatitis to metals, foods, oral care products or other allergens
Referrals to: gastroenterology if clinically indicated	Evaluate for CD and possible endoscopy/colonoscopy
For treatment	
Test	Purpose
G6PD	Dapsone
CMP	Systemic medications (prednisone, methotrexate, and adalimumab)
PPD	Check for latent TB before using immune suppressing medications or biologics

ACE Angiotensin converting enzyme, *ANA* antinuclear antibody, *CBC* complete blood count, *CMP* complete metabolic profile, *ESR* erythrocyte sedimentation rate, *HSV PCR* herpes simplex virus polymerase chain reaction, *G6PD* glucose-6-phosphate dehydrogenase, *PPD* purified protein derivative

Recommended Therapies

Table 24.7 First line therapies

Intralesional triamcinolone 10–40 mg/ml monthly	E[a]
Topical steroid gel (fluocinonide) BID prn	E[a]
Prednisone 0.5–1 mg/kg/day	E
Minocycline 100 mg twice daily or doxycycline 200 mg daily if permanent tooth development is complete	E[a]
Nonsteroidal anti-inflammatory drugs	D[a], E

[a]Denotes adult study

Few published cases of pediatric MRS are available. In the largest series to date on MRS patients with the full triad of disease, only one child was included. She responded to intralesional triamcinolone and dapsone [37]. Intralesional therapy may also help localized swelling and occasional flares [9, 117].

Systemic prednisone can be used alone or in combination with minocycline in children. Prednisone can show rapid resolution of the swelling and dramatic improvement of facial paralysis, however, rebound inflammation may occur upon its discontinuation. Minocycline has shown anti-inflammatory effects as well as inhibition of granuloma formation in other granulomatous disorders, and can be considered as an adjunctive measure with prednisone [88, 117]. After initial improvement of the symptoms, the prednisone can be tapered with gradual weaning of the minocycline, if tolerated.

Table 24.8 Second line therapies

Adalimumab	E[a]
Dapsone 125 mg once daily	E
Methotrexate	E
Sulfapyridine	E
Colchicine	E
Metronidazole 250 mg twice daily	E[a]

[a]Denotes adult study

Tumor necrosis factor (TNF) alpha inhibitors have been used in MRS. Case reports of adults refractory to prednisone, intralesional steroids, oral antibiotics, clofazamine, methotrexate, and azathioprine had complete resolution and subsequent remission on adalimumab [104, 117]. A 10-year-old female had a complete response to dapsone plus intralesional steroids [37].

Adults with the full triad of MRS showed variable responses to dapsone, metronidazole 250 mg twice daily, and nonsteroidal anti-inflammatory drugs. Other combination therapies with reported success in the pediatric literature

include: intralesional steroid injections, oral dapsone and sulfapyridine and intralesional steroid injections, colchicine, and doxycycline [71].

Table 24.9 Third line therapies

Clofazamine 100–200 mg daily; alternate dosing is 100 mg four times weekly	D[a], E[a]
Plastic surgery for cheilitis granulomatosa	E

[a]Denotes adult study

Clofazamine is a well-known treatment of leprosy, as it has antimicrobial properties and is successful in treating granulomatous diseases. Clofazamine may decrease granulomatous infiltration of the lips in MRS, although the possible untoward side effect of skin pigmentation can occur within weeks of initiating treatment [40, 121].

Reduction cheiloplasty and facial liposuction may improve the cosmetic appearance of facial and lip swelling in treatment-resistant patients [123].

Cutaneous Crohn's Disease

Clinical Features

Crohn's disease (CD) is a chronic granulomatous inflammatory bowel disorder that can affect any part of the gastrointestinal (GI) system. Extraintestinal manifestations can affect the skin, joints, eyes, and liver. The etiology of CD is multifactorial and is due to an immune-mediated inflammatory process.

Pediatric patients with underlying CD most commonly present with growth failure. GI signs and symptoms may be subtle, such as mild indigestion after meals or intermittent constipation. More common manifestations of CD include diarrhea, weight loss, fever, and fatigue.

Cutaneous CD falls into one of two categories: "nonspecific" or "specific," which are detailed in Table 24.10. About 20 % of patients with CD present with cutaneous lesions preceding the onset of GI disease by months or years. Of the children with cutaneous CD, up to two-thirds have genital involvement (Figs. 24.7 and 24.8), which may have the mistaken appearance of child abuse or sexually transmitted infections [31, 94, 98, 101]. In general, any pediatric patient with GI complaints and cutaneous lesions should be biopsied for evaluation and referred to gastroenterology. Furthermore, patients with isolated genital swelling and erythema should be evaluated for CD in the appropriate clinical setting.

Table 24.10 Cutaneous manifestation of Crohn's disease

Specific	Nonspecific
Perianal lesions	Reactive conditions
Skin tags	Erythema nodosum
Anal fissures	Pyoderma gangrenosum
Fistulas	Aphthous stomatitis
Abscesses	Erythema multiforme
Perioral lesions	Epidermolysis bullosa acquisita
Cobblestoning of mucosa	Cutaneous vasculitis
Oral ulcerations	Associated conditions
Cheilitis granulomatosa	Vitiligo
Metastatic Crohn's disease	Palmoplantar pustulosis
Swelling/ulceration/erythema/edema of perineum, vulva, scrotum, clitoris, labia or penis	Clubbing
Isolated lymphedema of the genitals	Palmar erythema
Sterile folliculitis	Lesions from nutritional deficiency
Nonspecific papules, pustules, plaques, ulcers, or abscesses on any skin surface	Therapy-related
	Psoriasis (from TNF-α inhibitors)
	Lupus
	Drug hypersensitivities

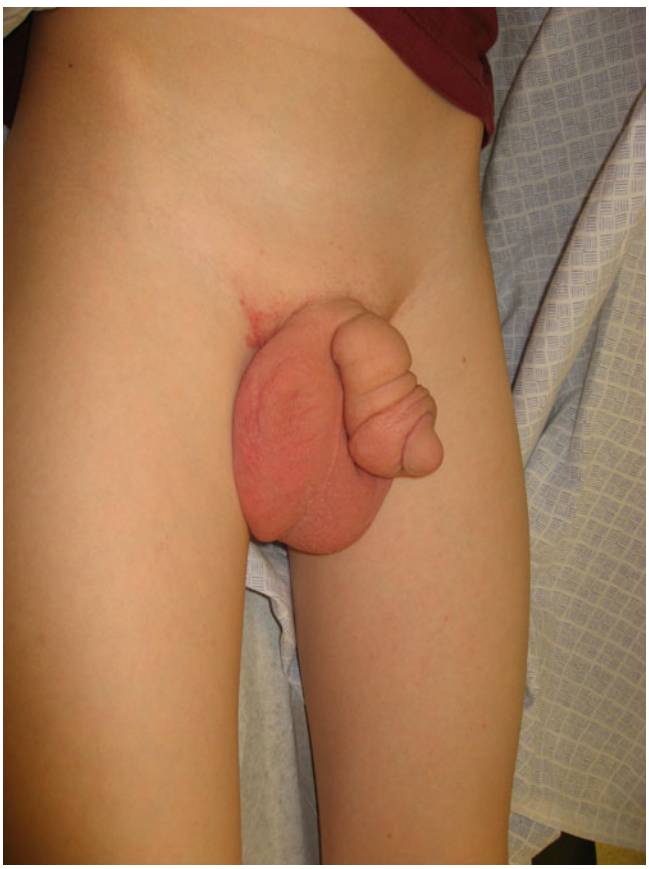

Fig. 24.7 Isolated scrotal edema in cutaneous Crohn's disease (Courtesy of Tor Shwayder, MD)

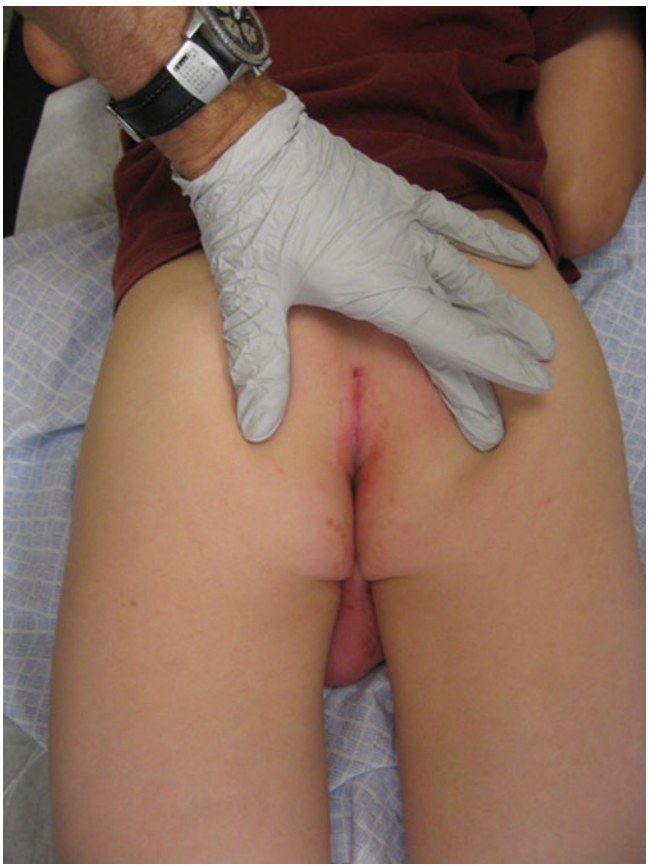

Fig. 24.8 Perianal irritation and erythema in cutaneous Crohn's disease (Courtesy of Tor Shwayder, MD)

Management Strategies

The goal of treatment in pediatric CD is to optimize nourishment for growth and development. Additionally, management of the systemic disease by the gastroenterologist to induce remission and prevent relapse is critical. Localized lesions can be treated with topical steroids and/or intralesional steroids. If lesions are located on the face, low-potency steroids or calcineurin inhibitors should be used. Multiple lesions or complicated lesions such as fistulas or abscesses may require systemic medications [57, 96].

Finally, cutaneous or GI surgery is reserved for patients who do not respond to medications, or in patients with progressive, debilitating complications.

Investigations Recommended

Test	Purpose of evaluation
For diagnosis	
Punch biopsy of skin with special stains (acid fast and PAS) and polarized microscopy	Check for atypical mycobacteria, fungus, other granulomatous diseases or foreign body reaction
Culture of skin lesions	Check for bacterial, atypical mycobacterial, fungal and viral causes; check for sexually transmitted infections
CBC with differential, ESR, CRP, and CMP	Check for underlying disease and assess level of inflammation
Chest x-ray	Evaluate for hilar lymphadenopathy as seen in sarcoidosis; evaluate for tuberculosis
PPD	Check for TB as a cause of granulomatous disease
Referral to: gastroenterology if CD is clinically suspected	Evaluate for CD and possible endoscopy/colonoscopy
For treatment	
TPMT	Azathioprine or mercaptopurine
PPD	Check for latent TB before using immune suppressing medications or biologics

CBC complete blood count, *CD* Crohn's disease, *CMP* complete metabolic profile, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PAS* periodic acid-shiff, *PPD* purified protein derivative, *TB* tuberculosis, *TPMT* thiopurine methyltransferase

Recommended Therapies

Table 24.11 First line therapies

Systemic induction therapy for systemic CD and severe cutaneous disease	
For mild CD	
Aminosalicylates:	B
Mesalamine 50–80 mg/kg/day	
Sulfasalazine	
Thiopurines	B
Azathioprine 2–3 mg/kg/day	
Mercaptopurine 1–1.5 mg/kg/day	
For moderate to severe CD	
Systemic steroids	B
Prednisolone 1–2 mg/kg/day	B
Prednisone 20 mg daily	B
Oral budesonide 3 mg three times a day	
For severe CD	
Infliximab 5 mg/kg at weeks 0, 2, 6, and every 8 weeks	B
Adalimumab	B
Induction dosing at week 0 and 4:	
<40 kg: 160 mg, 80 mg	
≥40 kg: 80 mg, 40 mg	
Systemic maintenance therapy	
For mild CD	
Aminosalicylates:	B
Mesalamine 50–80 mg/kg/day	
Sulfasalazine, max dose 4–6 g/day + folate 1 mg daily	
For moderate to severe CD	
Thiopurines	B
Azathioprine 2–3 mg/kg/day	
Mercaptopurine 1–1.5 mg/kg/day	
Infliximab 5 mg/kg every 8 weeks	B

Table 24.11 (continued)

Methotrexate 15 mg/m^2 weekly	B
Adalimumab	B
Maintenance dosing every other week:	
<40 kg: 10–20 mg	
≥40 kg: 20–40 mg	
Topical and additional systemic therapy for cutaneous CD	
Tacrolimus 0.03 % ointment twice daily	D, E[a]
Intralesional corticosteroid	D
1 ml of 10 mg/ml triamcinolone + 1 ml lidocaine 1 % for pain relief	
Topical steroids	E[a]
Mid-high potency twice daily	

CD Crohn's disease
[a]Denotes adult study

For induction therapy, aminosalicylates, glucocorticoids, biologics, and thiopurines are chosen, depending on the severity of the disease. For moderate to severe disease, glucocorticoids remain the first-line treatment for acute therapy. Corticosteroids are then bridged with an immunomodulator or biologic therapy to avoid side effects in the growing child [69]. Induction therapy with infliximab for moderate to severe CD had lower recurrence rates at 3 years when compared to induction with systemic steroids [68]. Adalimumab is approved for children older than 6 years of age with moderate to severe CD that is unresponsive to conventional therapies.

For the maintenance phase of treatment, many of the aforementioned therapies can be continued for control of the disease, with the exception of corticosteroids. Steroids should be reserved for acute exacerbations and tapered if there is adequate control with steroid-sparing agents. Methotrexate can also be considered a maintenance therapy alone or in combination with other medications. Furthermore, methotrexate should be considered in patients who do not respond to, or cannot tolerate, aminosalicylates and thiopurines [120, 136].

For topical treatment of cutaneous CD, tacrolimus ointment showed promising results in small series of pediatric patients and in adult case reports [28, 110]. Similarly, topical steroids and intralesional triamcinolone can be beneficial [31, 134].

Table 24.12 Second line therapies

Systemic therapy	
Mycophenolate mofetil 15 mg/kg/day + prednisone taper	B[a]
Topical and additional systemic therapy for cutaneous Crohn's disease	
Metronidazole 250 mg three times a day	E

[a]Denotes adult study

Mycophenolate mofetil is becoming more widely utilized in CD. In cases where azathioprine is contraindicated, mycophenolate mofetil in addition to prednisone showed efficacy in inducing remission and sustaining control of the disease [82].

For cutaneous lesions unaccompanied by active gastrointestinal CD, metronidazole can also be used alone or in conjunction with methotrexate, prednisone, and topical therapies [94].

Table 24.13 Third line therapies

Systemic therapy	
Thalidomide 50 mg nightly increased stepwise to 150 mg if needed	D
Surgery	E
Hyperbaric oxygen	E[a]

[a]Denotes adult study

For pediatric patients who fail all of the previous therapies, rescue treatment with thalidomide is considered a potentially effective treatment [41]. For more severe and resistant cases, surgery and hyperbaric oxygen therapy may be beneficial [65, 98].

Sarcoidosis

Clinical Features

Sarcoidosis is a multisystem disorder characterized by non-caseating granuloma formation due to an unknown etiology. Although it most commonly affects adults, there are two observed pediatric forms, early-onset sarcoidosis (EOS) and a later-onset disease. The two groups vary in presentation and systemic involvement (Table 24.14).

EOS is caused by a sporadic mutation in the *NOD2* gene, also known as *CARD15*. Blau syndrome, clinically identical to EOS, is also caused by a *NOD2* mutation, but is due to an autosomal dominant inheritance [27]. The course of EOS is unpredictable, as some lesions can persist for many years while others can occur intermittently with sporadic resolution. Pediatric patients in the older population (ages >5 years) tend to have advanced disease demonstrating constitutional symptoms and pulmonary findings similar to adults [147]. The cutaneous findings of the two variants of pediatric sarcoidosis have overlapping features and a wide range of distinct primary lesions (Fig. 24.9 and Table 24.14).

The prognosis of pediatric sarcoidosis relies upon the degree of organ involvement, as neurosarcoidosis and extensive hilar involvement have shown increased morbidity and mortality [112]. Erythema nodosum portends a favorable prognosis, similar to that seen in adults [114]. Cutaneous sarcoidosis may herald future systemic involvement, which can lag behind the cutaneous presentation by several years. Thus,

Table 24.14 Characteristics of pediatric sarcoidosis

Characteristics	Early-onset	Later-onset
Ages	0–5 years	>5 years
Etiology	NOD2/CARD15	Unknown
Classic presentation	Triad of arthritis, uveitis and dermatitis	Constitutional symptoms and lung involvement
Organ involvement	Polyarticular arthritis	Fever, lethargy, malaise, cough, and dyspnea
	Uveitis (77%) with anterior uveitis being the most common and most serious	Lacrimal glands infiltration
	Liver, kidney, gastrointestinal tract, brain and bone	Anterior uveitis
		Lymphadenopathy
		Arthritis
		Hematologic abnormalities
Pulmonary findings	Pneumonitis	Advanced parenchymal disease
	Bronchial granulomas	Hilar lymphadenopathy
Reported cutaneous findings	Tan or erythematous scaly papules, plaques and/or nodules	Papules, patches, plaques, nodules, ulcerations and necrotic lesions
	Solitary growths mimicking cutaneous histiocytosis	Associated exanthem
	Erythema nodosum	Vasculitides
	Lesions that resolve with pitted scarring	Erythema nodosum
		Keloidal changes to preexisting scars

Data from El Sayed et al. [36], Ohga et al. [83], Singal et al. [114], and Yanardag et al. [147]

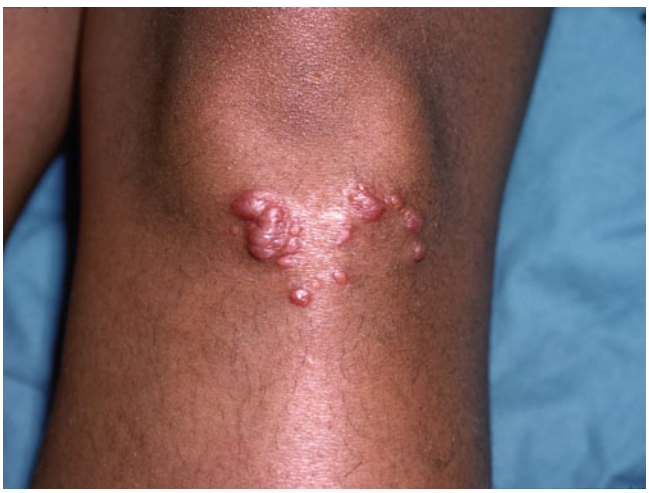

Fig. 24.9 Firm papules on the knee of cutaneous sarcoidosis (Courtesy of Chauncey McHargue, MD)

even with resolution of cutaneous sarcoidosis, patients should be monitored annually for development of extracutaneous involvement [83]. While the majority of pediatric cases resolve spontaneously within 6 years, some have persistent organ damage [79].

Management Strategies

In general, treatment should reflect the activity and symptomology of disease and the type of organ involvement. If the disease is symptomatic, rapidly progressive, scarring, or otherwise affecting quality of life, the provider must address the risks and benefits of choosing a particular therapy. Limited cutaneous disease may only require topical therapy, whereas more aggressive disease often necessitates systemic therapy. Also, combinations of therapies may help control the inflammatory process.

Investigations Recommended

Sarcoidosis is a diagnosis of exclusion. It is important to check inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein. Angiotensin converting enzyme levels are helpful in the older pediatric population due to the involvement of the lung as well as its utility in following disease activity and response to treatment. However, it must be noted that unaffected children can have angiotensin converting enzyme levels greater than two standard deviations of the adult range [103].

Test	Purpose of evaluation
For diagnosis	
Skin punch biopsy with PAS or biopsy of lymph node with PAS if no skin lesions	Check for other granulomatous diseases
Culture of blood, stool, urine, and cerebrospinal fluid	Check for fungal, bacterial or viral causes of granulomatous disease
CBC with differential, CMP, CRP, and ESR	Check for hypercalcemia, organ involvement, and assess level of inflammation
ANA	Evaluate for underlying autoimmune disease

Test	Purpose of evaluation
Rheumatoid factor	Rule out rheumatoid arthritis
Urinalysis	Monitor kidney function and check for proteinuria
1,25-dihydroxy vitamin D	Increased levels can be seen in sarcoidosis causing hypercalcemia
ACE level	Level of disease activity in sarcoidosis
Chest X-ray and joint X-rays	Evaluate for joint deformities/swelling
Referrals to: rheumatology, ophthalmology, pulmonology, nephrology, and cardiology if clinically indicated	Evaluate for multiorgan disease; ophthalmology to evaluate for use of antimalarials; cardiology to evaluate for electrocardiogram for conduction defects due to granulomas
For treatment	
TPMT	Azathioprine
ACE level	Therapeutic monitoring
PPD	Check for latent TB before using immune suppressing medications or biologics

ACE angiotensin converting enzyme, *ANA* antinuclear antibody, *CBC* complete blood count, *CMP* complete metabolic profile, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PAS* periodic acid-shiff, *PPD* purified protein derivative, *TPMT* thiopurine methyltransferase, *TB* tuberculosis

Recommended Therapies

Table 24.15 First line therapies

Topical therapies	
Topical pimecrolimus 1 % twice daily	E[a]
Topical tacrolimus 0.03 %–0.1 % twice daily	E[a]
Topical steroids (mid-high potency) twice daily until resolution, with or without occlusion; consider once weekly application of steroid with hydrocolloid occlusion if possible	E, D[a]
Intralesional steroids 3 mg/mL–20 mg/mL every 4 weeks until resolution	D[a]
Systemic therapies	
Systemic steroids 1–2 mg/kg/day (alone or in addition to methotrexate)	D

[a]Denotes adult study

For localized disease, topical steroids or calcineurin inhibitors can be effective. Topical tacrolimus 0.1 %, pimecrolimus 1 % [48, 122, 138], and topical steroids all can induce complete regression of skin lesions [30, 49, 64, 140]. Intralesional steroids may also be beneficial, alone or in combination with other medications [12, 30, 146]. This therapy should be considered in older, more tolerant children who have small sarcoidal papules and plaques.

Prednisone can hasten remission and alleviate clinical symptoms, with slow tapering after clinical resolution occurs [36, 83]. Angiotensin converting enzyme levels may serve as a guide for tapering [103].

Table 24.16 Second line therapies

Topical therapies	
Topical gel PUVA 8-methoxypsoralen gel 0.005 % once or twice weekly	D[a]
Pulsed dye laser 0.5 ms pulse duration, 7 mm spot size, 7.6–7.8 mj/s^2	E
δ-aminolevulinic acid with intense pulsed light	E[a]
Systemic therapies	
Methotrexate 10–15 mg/m^2 weekly	C, B[a]
Minocycline or doxycycline 100 mg twice daily if permanent tooth development is complete	C[a]
Adalimumab 40 mg once weekly	C[a]
Infliximab 6 mg/kg every 4 weeks	E, C[a]
Azathioprine	B[a]
Hydroxychloroquine 2–3 mg/kg/day	C[a]

PUVA psoralen and ultraviolet A
[a]Denotes adult study

Phototherapy for cutaneous sarcoidosis has demonstrated success in case reports and small case series. Topical gel PUVA and δ-aminolevulinic acid with intense pulsed light can be considered second line cutaneous treatment [47, 51]. Pulsed dye laser has also shown success in lupus pernio and scar sarcoidosis in a child [38, 55].

For systemic treatment, methotrexate or antimalarials can be added when there is inadequate response from oral steroids or as a steroid-sparing maintenance therapy [3]. Azathioprine and methotrexate have demonstrated similar steroid-sparing capacities in adult studies and can be considered in refractory systemic sarcoidosis [45, 66, 83, 141].

Minocycline and doxycycline have shown benefit in adults with cutaneous lesions [10]. Hydroxychloroquine has also shown clinical response and allowed tapering and discontinuation of other medications [59].

Adalimumab and infliximab show promise for cutaneous sarcoidosis [95]. Infliximab in combination with methotrexate and steroids should be considered for EOS and multisystem disease [16, 107].

Table 24.17 Third line therapies

Thalidomide 2 mg/kg/day	E for EOS; see discussion below
Isotretinoin	E[a]
Allopurinol 200 mg/day	E
Leflunomide 20 mg/day	D[a]
Melatonin 20 mg daily at 2000	E[a]
Oral tacrolimus 6 mg/day	E

EOS early-onset sarcoidosis
[a]Denotes adult study

Thalidomide can alleviate fever, optic nerve papillitis, and normalize inflammatory markers in EOS [148]. Its use may

be controversial, however, as a randomized double-blind placebo-controlled study of 39 adult patients with primarily cutaneous sarcoidosis concluded that thalidomide should not be considered a mainstream therapy due to lack of efficacy and side effects [34].

Several other therapies may also be considered, including isotretinoin for single system skin disease and allopurinol [30, 35, 46, 142]. Leflunomide is approved by the U. S. Food and Drug Administration for rheumatoid arthritis in adults and it has been studied in children with no adverse effects. In adults with sarcoidosis of the lung and skin, leflunomide appears to be as effective as methotrexate but with less toxicity. Thus, it can be an alternative therapy in patients who cannot tolerate methotrexate side effects [14, 73]. Interestingly, melatonin has been used in adults affected by pulmonary and cutaneous sarcoidosis who were unresponsive to systemic steroid therapy [22].

Oral tacrolimus has resulted in complete resolution of lichenoid-type cutaneous sarcoidosis in a child [131].

Autoinflammatory Disorders Part I

Hereditary Periodic Fever Syndromes and Cryopyrinopathies

Clinical Features

The classification of "hereditary periodic fever syndromes" encompasses familial Mediterranean fever (FMF), TNF receptor-associated periodic fever syndrome, and periodic fever associated with mevalonate kinase deficiency, known in the past as "hyper-IgD syndrome." The "cryopyrinopathies," also known as cryopyrin associated periodic syndrome (CAPS), include familial cold auto-inflammatory syndrome, Muckle-Wells syndrome, and chronic infantile cutaneous articular syndrome/neonatal-onset multi-systemic inflammatory disease (CINCA/NOMID) syndromes. See Table 24.18 for characteristics associated with these disorders.

Management Strategies

Management of the hereditary periodic fever syndromes and CAPS relies on proper work-up and evaluation to rule out more common etiologies, such as infections and autoimmune diseases. In CINCA/NOMID syndrome, prompt identification of the disease and early initiation of treatment can prevent irreversible organ damage and life-long disability. Treatment of these diseases relies on anecdotal case reports, with the exception of colchicine, which has been well studied in the management of FMF. Overall, TNF-α inhibitors and interleukin-1 inhibitors show the best efficacy when dealing with the system-wide inflammation that is characteristic of these disorders.

Table 24.18 Hereditary periodic fever syndromes and cryopyrinopathies

Disorder (inheritance)	Gene defect/ gene product	Features
FMF (AR)	*MEFV*/pyrin	Recurrent, painful febrile attacks
		Severe abdominal pain, which may mimic serositis
		Arthritis
		Erysipelas-like cutaneous eruption
		Secondary AA amyloidosis that can result in renal failure if untreated
TRAPS (AD)	*TNFRSF1A*/ P55 TNF receptor	1–3 week long fevers
		Serositis
		Arthralgias
		Conjunctivitis
		Abdominal pain
		Serpiginous and urticarial-like rash, often occurring over the areas of myalgia
		Reactive AA amyloidosis that can result in renal failure if untreated
MVK (AR)	*MVK*/ mevalonate kinase	Starts in infancy
		Recurrent fevers every 1–2 months
		Abdominal distress and diarrhea
		Arthritis
		Cervical adenitis
		Aphthosis
		Headaches
		Splenomegaly
		Erythematous lesions with petechiae and purpura
		Macrophage-activation syndrome, which can lead to death if not appropriately treated
FCAS (AD)	*CIAS1*/ cryopyrin	Early onset cold-induced urticarial eruption
		Conjunctivitis
		Recurrent febrile episodes
		Arthralgias
MWS (AD)	*CIAS1*/ cryopyrin	Recurrent fevers
		Urticarial-type eruptions
		Progressive deafness
		Reactive amyloidosis
CINCA/ NOMID	*CIAS1*/ cryopyrin	Appears shortly after birth
		Skin rash
		Arthritis
		Central nervous system disorders that can result in permanent damage if untreated
		Associated with prematurity, oligohydramnios and intrauterine growth retardation

Data from: Bader-Meunier et al. [11], Kanazawa and Furukawa [60], Paccaud et al. [90], and Vitale et al. [139]

AD autosomal dominant, *AR* autosomal recessive, *CINCA/NOMID* chronic infantile cutaneous articular syndrome/neonatal-onset multi-systemic inflammatory disease, *FCAS* familial cold auto-inflammatory syndrome, *FMF* familial Mediterranean fever, *MWS* Muckle-Wells syndrome, *TRAPS* tumor necrosis factor receptor-associated periodic fever syndrome

Investigations Recommended

For diagnosis	
Biopsy of skin lesions	Evaluate for other causes of skin eruption, such as vasculitis, infections, drug sensitivities, etc.
Culture of blood and urine	Check for underlying infection
CBC with differential, CRP, ESR, and CMP	Check for leukocytosis, anemia, inflammation, and organ function
Urinalysis	Proteinuria from renal amyloidosis
IgD plasma levels	Check for MKD
Urinary mevalonic acid	Check for MKD
Serum amyloid A	Secondary amyloidosis
Consider cerebrospinal fluid analysis if neonate/infant	Check for infection and inflammation
For treatment	
PPD	Check for latent TB before using immune suppressing medications or biologics

CBC complete blood count, *CMP* complete metabolic profile, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *MKD* mevalonate kinase deficiency, *PPD* purified protein derivative, *TB* tuberculosis

Recommended Therapies

Table 24.19 First line therapies

Colchicine for FMF	A
Oral steroids for breakthrough attacks	E
Nonsteroidal anti-inflammatory drugs for analgesia during attacks	E
Infliximab 5 mg/kg/dose on week 0, 2, 6 and every 8 weeks	E
Adalimumab 40 mg every other week	E
Etanercept 0.4 mg/kg twice weekly	E
Anakinra 1–2 mg/kg/day or canakinumab 150 mg every 60 days	D, E, E[a]

FMF familial Mediterranean fever
[a]Denotes adult study

Colchicine has been well studied and is effective in the treatment of FMF. When patients are unresponsive to colchicine, anti-TNF-α agents must be considered. Corticosteroids and nonsteroidal anti-inflammatory drugs can be used to treat breakthrough inflammation and pain [127]. In TNF receptor-associated periodic fever syndrome, colchicine is not effective, but patients respond to high-dose oral prednisone, anti-TNF-α agents, and anti-IL-1 therapies.

TNF-α blockade has been shown to induce remission in some patients with hereditary periodic fever syndromes and cryopyrinopathies [11, 127]. Etanercept and infliximab may improve renal function and prevent amyloid deposition in FMF [6, 39]. Adalimumab has also been efficacious in treatment of mevalonate kinase deficiency [11].

Anti-IL-1 medications, such as anakinra and canakinumab, have induced remission with normalization of acute phase reactants in patients suffering from FMF [127]. In Muckle-Wells syndrome, canakinumab has shown rapid improvement in serum amyloid levels, C-reactive protein levels, renal function, and clinical symptoms [108]. Anakinra has helped children as young as 3 weeks old with CINCA/NOMID syndrome [84]. Because of their clinical efficacy, anti-IL-1 agents should be considered when patients are non-responsive to colchicine and anti-TNF-α medications [13].

Autoinflammatory Disorders Part II

PAPA, PFAPA, PAPASH, PASH and PASS Syndromes

Clinical Features

The clinical features of these autoinflammatory disorders are as follows:

- PAPA: pyogenic sterile arthritis, pyoderma gangrenosum (PG) and acne
- PFAPA: periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
- PAPASH: pyogenic arthritis, PG, acne and suppurative hidradenitis
- PASH: PG, acne and suppurative hidradenitis
- PASS: PG, acne, suppurative hidradenitis and seronegative spondyloarthritis

The etiologies of these autoinflammatory diseases are unknown, except in PAPA and PAPASH syndrome, where a mutation in the proline-serine-threonine-phosphatase protein 1 (*PSTPIP1*) gene has been identified. There is incomplete penetrance of this genetic mutation causing variable clinical expressivity, and some children never develop the full manifestations of disease [75]. The timing and presentation vary among all of the autoinflammatory syndromes.

Clinically, PAPA syndrome presents with recurrent, erosive arthritis beginning in childhood, either spontaneously or provoked by trauma. By puberty, the arthritis diminishes, while the skin starts showing signs of inflammation. Children tend to get severe cystic acne as well as recurrent nonhealing sterile ulcers that resemble PG (Fig. 24.10). Pathergy is also a clinical clue, which can characteristically develop at vaccination sites.

PFAPA often occurs in children less than 5 years of age, manifesting with recurring, cyclic fevers lasting days. Pharyngitis, aphthous stomatitis, and cervical adenitis occur, mimicking an acute viral or bacterial infection. PAPASH has the same constellation of findings as PAPA, with the addition of hidradenitis suppurativa. Presentations vary, but acne may not be as severe as that seen in the other diseases [75].

PASH may only present with severe acne lesions in adolescence and develop the full triad later in adulthood [17].

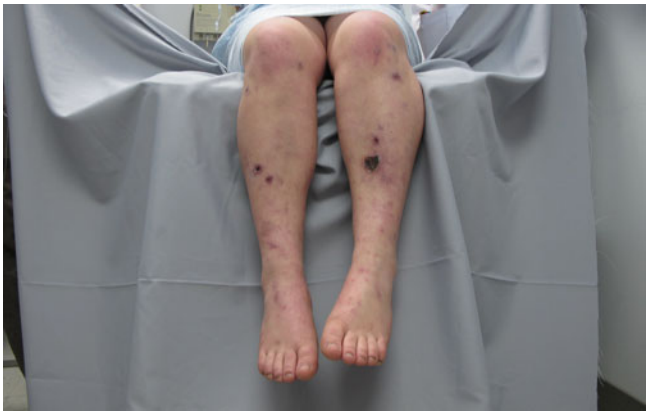

Fig. 24.10 Non-healing ulcerations of pyoderma gangrenosum (Courtesy of Tor Shwayder, MD)

Seronegative spondyloarthritis is a characteristic of PASS syndrome. Only one case has been reported in the literature, and it is considered to be along the same spectrum as the other diseases [20].

Management Strategies

The initial approach to treating these disorders involves conventional therapies aimed at the treatment of acne, hidradenitis suppurativa, and PG (see the corresponding chapter sections for further details on treatment of those diseases). Steroids are often used in the acute inflammatory phase, which is characterized by fever, skin eruptions, and/or arthritis. In more moderate to severe disease, other immunosuppressive agents such as anti-IL-1 and anti-TNF-α agents may be necessary and show promising results. Regardless, this spectrum of diseases proves very challenging to manage, and multiple therapeutic modalities are often necessary.

Investigations Recommended

For diagnosis	
CBC with differential, ESR, CRP, and CMP	Check for underlying disease and assess level of inflammation
Culture of ulcers and abscesses	Check for bacterial, atypical mycobacterial, fungal, and viral infections
Referrals to: orthopaedics, rheumatology, and genetics if clinically indicated	Evaluate for septic joint and possible joint aspiration by orthopaedics
	Radiography of affected joints
	Genetic testing
For treatment	
TPMT	Azathioprine
G6PD	Dapsone
Lipid panel, magnesium, and uric acid	Cyclosporine
Blood pressure	Cyclosporine
PPD	Check for latent TB before using immune suppressing medications or biologics

CBC complete blood count, *CRP* C-reactive protein, *CMP* complete metabolic profile, *ESR* erythrocyte sedimentation rate, *G6PD* glucose 6 phosphate dehydrogenase, *MRSA* methicillin-resistant Staphylococcus aureus, *PPD* purified protein derivative, *TB* tuberculosis, *TPMT* thiopurine methyltransferase

Recommended Therapies

Tonsillectomy in PFAPA	A
Cimetidine 20 mg/kg/day for fevers in PFAPA	E
Prednisolone or prednisone 1–2 mg/kg/day	E
Nonsteroidal anti-inflammatory drugs	E
Adalimumab 20–40 mg every 2 weeks	E
Infliximab 5 mg/kg/dose at week 0, 2, then every 8 weeks	E
Etanercept 50 mg weekly	E[a]
Dapsone 2 mg/kg daily with a max of 100 mg daily	E[a]
Cyclosporine 2.5–5 mg/kg/day	E[a]
Colchicine 0.5 mg daily	E
Azathioprine + systemic steroids	E[a]
Anakinra 1 mg/kg/day for 1 week or more	D[a], E

[a]Denotes adult treatment

Tonsillectomy in patients with PFAPA syndrome has shown immediate improvement, and is associated with complete symptom resolution when compared to no surgical intervention [21]. Cimetidine may also show benefit in PFAPA, as periodic fevers resolved in three reported pediatric cases [97]. Prednisone with or without additional immunomodulators aids in controlling inflammation and promotes healing of ulcerations [17]. TNF-α inhibitors show promise in controlling the inflammation, although there is appreciable difference in efficacy among the different drugs [20, 116, 127]. Infliximab appears to be the most advantageous when other treatments fail [118]. Additionally, many case reports show the best results when combining anti-TNF-α agents with other systemic therapies listed above [116].

Anakinra shows rapid response and complete resolution of symptoms within days of initiation. It may be the only successful therapy in treating chronic PG lesions and arthritic flares that fail to respond to conventional therapies [17, 19].

Pyoderma Gangrenosum (PG)

Clinical Features

PG is a rare ulcerating skin disease that tends to follow a chronic course and results in severe scarring. Usually a small pustule (Fig. 24.11) or nodule develops into a progressively enlarging necrotic ulcer with undermined borders. The ulcer

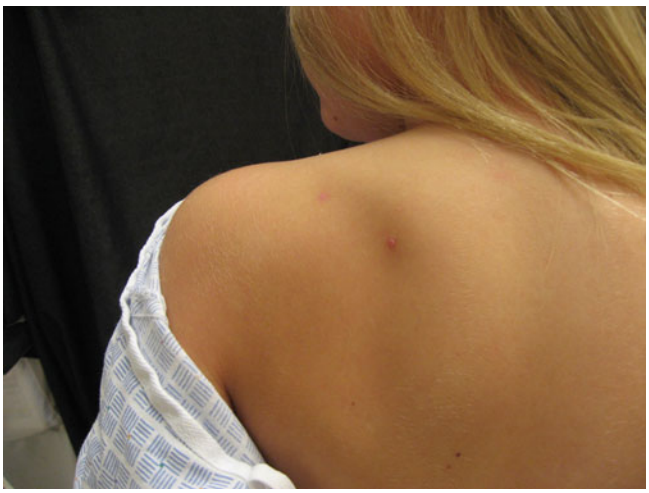

Fig. 24.11 Small papule as an initial stage of pyoderma gangrenosum (Courtesy of Tor Shwayder, MD)

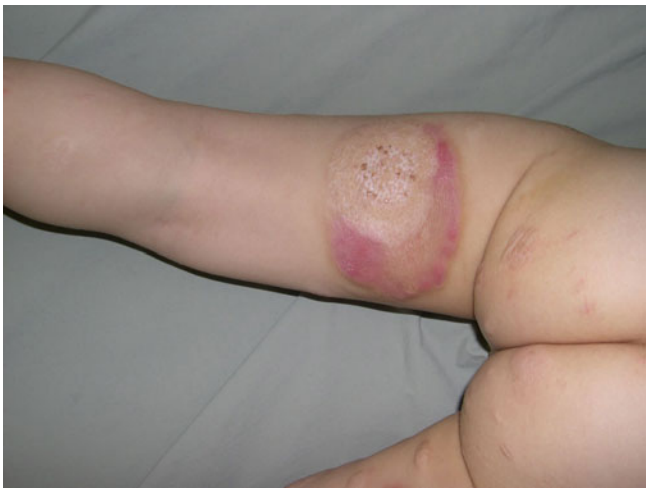

Fig. 24.12 Characteristic cribiform scarring from pyoderma gangrenosum (Courtesy of Tor Shwayder, MD)

can enlarge as quickly as 1–2 cm/day. There are several different forms of PG, including ulcerative (the classic form), pustular, bullous, vegetative, peristomal, genital, infantile/childhood, and extracutaneous [105]. Pediatric cases, which comprise 3–4 % of cases, typically present similarly to the classic "ulcerative" form seen in adults. In infants, the lesions are more commonly found in the facial, genital, and perianal areas. Children tend to have a more favorable outcome compared to adults. However, some patients can suffer from severe, refractory disease with residual scarring [25, 105] (Fig. 24.12).

Pathergy may occur in venipuncture or vaccination sites. The diaper region can be especially concerning due to friction and microtrauma. Additionally, debridement of lesions can cause worsening of the ulceration.

Table 24.20 Associated diseases and conditions of pyoderma gangrenosum

Category	Associated diseases and conditions
Gastrointestinal	Inflammatory bowel diseases (ulcerative colitis and Crohn's disease), and hepatitis
Rheumatologic	Rheumatoid arthritis, lupus, and other types of arthritis
Hematologic	Leukemia, monoclonal gammopathy, multiple myeloma, Hodgkin's disease, myeodysplastic syndrome, and immunodeficiency disorders
Vascular	Takayasu's arteritis, necrotizing vasculitis, and antineutrophil cytoplasmic antibody associated vasculitides
Infectious	HIV and syphilis
Other	Malignancies and diabetes mellitus

Table 24.21 Differential diagnosis of pyoderma gangrenosum

Categories	Diseases and conditions
Vascular	Vascular ulceration, vasculopathy, venous or arterial diseases
Infectious	Syphilis, anthrax, mycobacterial infections, gangrene, or deep fungal infections
Traumatic	Factitious or burn
Autoimmune/inflammatory	Sweet's syndrome, antiphospholipid syndrome, Behçet's disease, Wegener's granulomatosis, rheumatoid arthritis, or panniculitis
Neoplastic	Cutaneous lymphomas or cutaneous malignancies (melanoma and nonmelanoma skin cancers)
Drug/toxins	Brown recluse spider bite
Other	Ulcerated necrobiosis lipoidica, purpura fulminans or delayed wound healing secondary to immunodeficiency

About 50 % of cases are idiopathic, with the remainder of cases associated with underlying systemic diseases due to autoimmune, rheumatologic, and immunodeficiency disorders [105]. Table 24.20 shows diseases and conditions associated with PG.

Management Strategies

Evaluation and management of PG is twofold. First, the physician must rule out other causes of cutaneous ulceration (see Table 24.21). Infection must be excluded as a cause of the ulceration, since treatment for PG relies on immunosuppressive agents. Secondly, if PG is confirmed, evaluation for underlying or contributory systemic diseases must be considered, with referrals to the appropriate

specialists. If an underlying disease is discovered, the focus should shift toward treatment of the primary disease. If no underlying disease is found, or if treatment of the disease does not result in improvement of PG, additional therapies should be sought.

Treatment typically starts with intralesional and systemic steroids. Adjunctive steroid-sparing therapies, such as cyclosporine, dapsone, and topical nitrogen mustard have benefited some patients. Most importantly, avoidance of pathergy is essential. Patients with PG should never receive aggressive surgical debridement or extensive skin grafting.

Treatment is also based on the location of the lesions and extent of involvement. If PG affects sensitive structures, such as acral surfaces or genitalia, more aggressive therapies should be employed. In contrast, if PG is recognized early in the disease and is well localized, topical therapy or intralesional steroids may be the only treatment necessary.

From a strictly dermatological perspective, the treatment of PG revolves around appropriate wound care, treatment of any secondary infections, and local or systemic immunosuppressive therapies.

Investigations Recommended

For diagnosis	
Punch biopsy of skin	Rule out underlying malignancy or an infectious cause
Culture of wound, blood, and urine	Check for bacterial, fungal or viral infections
CBC with differential, CMP, CRP, and ESR	Check organ function, infection, and assess level of inflammation
Rapid plasma reagin	Check for syphilis as a cause of ulceration if clinically warranted
Referrals to: rheumatology, hematology/oncology, and gastroenterology if clinically indicated	Evaluate for underlying rheumatologic disease, malignancy and inflammatory bowel disease
For treatment	
G6PD	Dapsone
TPMT level	Azathioprine
Lipid panel, magnesium and uric acid	Cyclosporine
Measurement of blood pressure	Cyclosporine
PPD	Check for latent TB before using immune suppressing medications or biologics

CBC complete blood count, *CMP* complete metabolic profile, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *G6PD* glucose-6-phosphate dehydrogenase, *PPD* purified protein derivative, *TB* tuberculosis, *TPMT* thiopurine methyltransferase

Recommended Therapies

Table 24.22 First line therapies

Topical tacrolimus 0.03 % twice daily under occlusion	D[a], E
Topical pimecrolimus 1 % twice daily under occlusion with dressing changes	E
Topical steroids (clobetasol, triamcinolone) ± occlusion	E, E[a]
Systemic steroids	E[a], E
Prednisone 0.5–3 mg/kg/day	
Pulsed methylprednisolone cycles separated by 20 days at 10 mg/kg/day × 3 days plus oral methylprednisolone 1 mg/kg/day daily between cycles	
Pulsed dexamethasone	
Intralesional steroids, 10 mg/ml	E[a]
Cyclosporine 2–4 mg/kg/day	E[a], E
In all cases: appropriate wound care from professionals familiar with PG	

[a]Denotes adult study

Topical steroids are successful in treating localized PG [92, 145]. Tacrolimus twice daily as monotherapy, under occlusion, or in addition to prednisone, can achieve remission without disease recurrence [8, 76]. Intralesional steroids placed at the advancing border of lesion can result in healing of the ulceration [58].

Systemic steroids should be first-line therapies in widespread PG or for PG not responding to treatment of underlying disease. Oral prednisone can dramatically improve or resolve lesions in as quickly as 1–2 weeks. For more aggressive disease, pulsed methylprednisolone and pulsed dexamethasone can heal skin lesions and alleviate associated pain [4, 25, 115, 128, 129]. Once the disease improves, slow tapering of steroids over one to 3 months or longer is recommended to avoid rebound flares [4, 132].

For patients who cannot tolerate steroids, or for patients who are refractory to steroid treatment, cyclosporine should be considered. It is best used in aggressive, unremitting PG, and can be given orally or intravenously if necessary.

Table 24.23 Second line therapies

Dapsone	E[a]
Mycophenolate mofetil	E[a]
Infliximab 5 mg/kg, given on week 0, 1, 2, 6 then every 8 weeks; alternative dosing every 1–2 weeks, depending on severity	E, E[a]
Topical cromolyn sodium ± occlusion	E[a]
Minocycline 100 mg, orally, twice daily if permanent tooth development is complete	E[a]

[a]Denotes adult study

Second-line therapies can be used alone or in combination with first-line therapies. Well-controlled studies are lacking, but case reports show some improvement and

complete resolution of PG lesions with dapsone, mycophenolate mofetil, topical cromolyn sodium, and minocycline.

Infliximab, even in infants, may be appropriate [23, 56, 67, 99, 102]. A 4-month-old with laryngeal involvement and extensive cutaneous PG, who was unresponsive to conventional systemic therapies, was administered infliximab every 2 weeks for a total of four treatments, with complete and sustained remission [99]. Infliximab can also be combined with methylprednisolone [4, 145].

Table 24.24 Third line therapies

Etanercept 0.8 mg/kg/weekly	E
Adalimumab 40 mg every 2 weeks	E
Oral tacrolimus (with goal trough levels of 3.0 ng/mL)	E
Intravenous immunoglobulin 2 g/day	E[a]
Topical nitrogen mustard in aqueous solution (20%) once daily	E[a]
Hyperbaric oxygen treatments at 2.0 atm for 90 min twice daily until improvement	E[a]
Cultured keratinocyte autograph	E[a]

[a]Denotes treatment in adults

Treatments with oral tacrolimus, etanercept, adalimumab, and intravenous immunoglobulin have shown improvement and remission of disease [4, 78, 80].

Daily application of topical nitrogen mustard in a patient who was unable to tolerate systemic immunosuppressants completely healed a persistent ulcer after 3 months of treatment [130].

Hyperbaric oxygen treatments may also be employed, especially for the extremities, when large surface areas are involved or when tendons are exposed [145]. Hyperbaric oxygen promotes angiogenesis and triggers a cascade of beneficial auto-inflammatory processes needed for re-epithelialization [133].

Cultured keratinocyte autographs can provide a patient with permanent wound coverage if the PG lesions are large and not responsive to other treatments [70].

Behçet's Disease

Clinical Features

Behçet's disease (BD) is a rare multisystem disease characterized by recurrent oral and genital ulcerations and inflammatory disease of the eye. It may also affect the central nervous system and gastrointestinal system. BD is considered to be an auto-inflammatory disease that affects small and large blood vessels [89]. The etiology is complex, although it is known to be associated with HLA-B51 and the IL-10 and IL23/17 pathways. Genetic inheritance also plays a role in the disease, as some studies show up to 20% of pediatric cases have a family history of BD [62].

The classic diagnostic criteria for BD include recurrent oral ulcerations with two of the following: recurrent genital ulcerations, eye lesions, skin lesions, or positive pathergy. In the pediatric population, BD can have a heterogeneous presentation. The most common initial signs are oral and genital ulceration [62] (Figs. 24.13 and 24.14). Children tend to

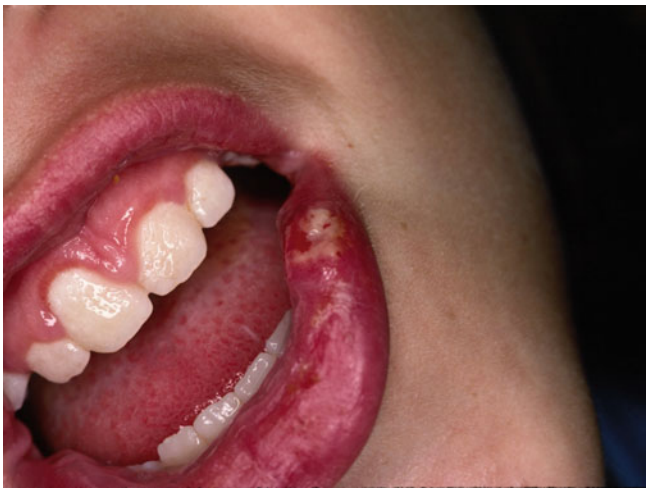

Fig. 24.13 Oral ulcerations as a feature of Behçet's disease (Courtesy of Chauncey McHargue, MD)

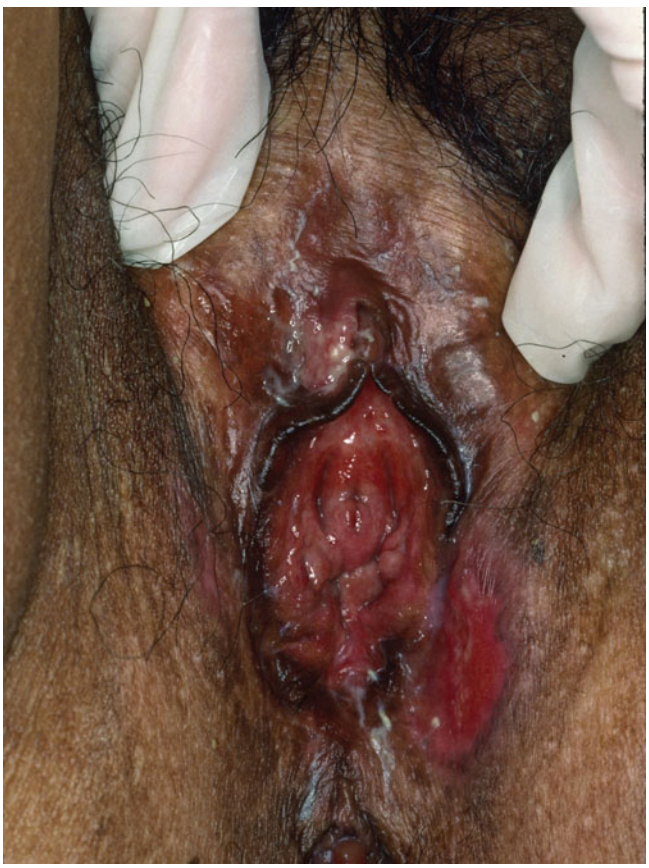

Fig. 24.14 Genital ulcerations as a feature of Behçet's disease (Courtesy of Chauncey McHargue, MD)

Table 24.25 Clinical and systemic associations of Behçet's disease

Organ system	Reported findings
Neurological	Benign intracranial hypertension, multiple sclerosis-like symptoms, pyramidal involvement, psychiatric disturbances, migraines, paresthesias, and urinary retention
Gastrointestinal	Mucosal ulcerations
Musculoskeletal	Non-destructive arthritis
Cutaneous	Folliculitis, acneiform eruption, erythema nodosum, vasculitis, and positive pathergy
Eye	Iritis, posterior uveitis, hypopyon uveitis, optic neuritis, and retinal vessel thrombosis
Mucous membranes	Painful oral aphthae that last 1–2 weeks without scarring; genital ulcerations with scarring
Vascular	Superficial or deep vein thrombosis, superior vena cava obstruction, and pulmonary artery vasculitis

present differently than adults, manifesting gastrointestinal complaints, fevers, and neurologic symptoms [2]. See Table 24.25 for a list of findings associated with BD.

Patients with BD have a normal life expectancy unless they have neurologic complications. Furthermore, eye involvement can result in blindness if not appropriately treated.

Management Strategies

Management of BD relies on a multidisciplinary approach. For localized and self-limited disease, the goal of treatment is to hasten the recovery process and alleviate symptoms. In most patients, topical therapies suffice. For more severe disease affecting the neurologic, ocular, and vascular systems, systemic therapy is needed to quickly suppress inflammation and prevent long-term sequelae.

Investigations Recommended

Test	Purpose of evaluation
For diagnosis	
Punch biopsy of skin	Determine if vasculitis is present; check for other causes of ulceration
Culture of genital and oral ulcerations	Check for bacterial and viral infections, including sexually transmitted infections and HSV
CBC with differential, CMP, ESR and CRP	Check for infection, renal involvement and assess degree of inflammation
ANA	Evaluate for underlying autoimmune disease
Epstein-Barr virus serologies	Rule out Epstein-Barr virus, which can cause genital ulcerations
Physical examination including: measurement of blood pressure, temperature, and deep tendon reflexes	Check for hypertension (vascular involvement), fever, and neurologic involvement
Referrals to: rheumatology, ophthalmology, gastroenterology, and neurology if clinically appropriate	Evaluate for underlying rheumatologic disease, eye disease, gastrointestinal and neurological involvement
For treatment	
TPMT	Azathioprine
G6PD	Dapsone
Lipid panel, magnesium, uric acid	Cyclosporine
Measurement of blood pressure	Cyclosporine
PPD	Check for latent TB before using immune suppressing medications or biologics

ANA anti-nuclear antibody, *CBC* complete blood count, *CMP* complete metabolic profile, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *G6PD* glucose-6-phosphate dehydrogenase, *HSV* herpes simplex virus, *PPD* purified protein derivative, *TB* tuberculosis, *TPMT* thiopurine methyltransferase

Recommended Therapies

Table 24.26 First line therapies

Topical therapy	
Topical steroids for ulcerations:	E
Betamethasone diproprionate 0.05 % ointment twice daily	
Triamcinolone acetonide 0.1 % ointment twice-three times daily	
Topical pimecrolimus 1 %	B[a]
Topical sucralfate suspension for oral ulcers; use as mouthwash for 2–4 min nightly at bedtime and after routine oral care	A[a]
Intralesional steroids; triamcinolone acetonide 3 mg–5 mg/ml	E
Lidocaine gel 2 % for ulcerations	E
Oral rinses for oral pain with elixir of diphenhydramine, Maalox (Novartis), prednisolone, lidocaine; also known as "Magic Mouthwash"	E
Lactobacilli lozenges: 6 lozenges/day every 2–3 h while awake for 7 days [125]	B[a]
Topical hyaluronic acid 0.2 % twice daily	E
Rest and analgesics for arthritis	E
Systemic therapy	
Systemic steroids:	E
Methylprednisolone 30 mg/kg/day IV × 3 days	
Prednisolone 1–2 mg/kg/day	
Colchicine 0.5–1.5 mg once daily	E, A[a]
Azathioprine 2.5 mg/kg/day	A[a]
Cyclosporine 5 mg/kg/day	A[a]
Dapsone 100 mg once daily	A[a]
Pentoxifylline 400 mg twice daily	E[a]

[a]Denotes adult study

Topical treatments, such as mid-high potency steroids in gel or ointment form, will help heal mucosal ulcerations [126]. Other topical treatments such as lidocaine gel, hyaluronic acid gel, topical pimecrolimus, and topical sucralfate can provide pain relief and promote healing in genital and oral ulcerations [77].

Systemic steroids are often used as a first-line therapy for prompt control of the inflammation, with eventual tapering once the disease is improved. Systemic steroids can help inflammation, however, they have not been shown to improve skin ulcerations [77]. If the disease continues to flare, colchicine, biologics, or other immunomodulators should be added. The general consensus in the expert population is that colchicine is most beneficial in mucocutaneous lesions, and is often used as an adjunctive therapy alongside immunosuppressive or immunomodulating medications [33, 149].

Azathioprine, cyclosporine, and dapsone have been studied in adults with double-blind, placebo-controlled trials. Overall, they show favorable results for mucocutaneous manifestations of BD [53, 106, 111].

Pentoxifylline is a good alternative to steroids and immunosuppressants, as it acts as a non-selective phosphodiesterase inhibitor with anti-inflammatory effects. It has led to clearance and sustained remission of ulcerations and anterior uveitis in patients who were unresponsive to prednisone and azathioprine [5, 84].

Table 24.27 Second line therapies

Etanercept 25–50 mg weekly	A[a]
Infliximab 5 mg/kg on week 0, 2, 6 and every 8 weeks	E, A[a]
Adalimumab 40 mg every other week	E
Methotrexate 7.5 mg weekly, increase as necessary	E[a]
Minocycline 100 mg once-twice daily if permanent tooth development is complete	E[a]
Azithromycin 500 mg three times weekly for 4 weeks followed by colchicine 1.5 mg daily × 4 weeks	D[a]

[a]Denotes adult study

The TNF-α inhibitors, including etanercept, infliximab and adalimumab, demonstrate variable efficacy for moderate to severe BD. Sometimes additional immunomodulators are required [53].

Antibiotics such as minocycline and azithromycin have also been studied for their anti-inflammatory properties, showing some success in case reports [61, 81].

Table 24.28 Third line therapies

Cyclophosphamide 750 mg/m^2 IV monthly for vascular involvement only	A[a], E
Thalidomide 100 mg daily	A[a]
Tacrolimus (for goal trough level of 7 ng/ml)	E
Anakinra 100–150 mg/day	E[a]
± prednisone 5 mg/day–25 mg/day	
± colchicine 1 mg/day	
Gevokizumab 0.3 mg/kg	E[a]
Canakinumab 150 mg single dose or every 6–8 weeks	E
Tocalizumab	E[a]
Ustekinumab	E[a]
Rituximab 1 g every 2 weeks for 2 doses	E[a]
+ prednisone 0.5–1 mg/kg/day	
± methotrexate 10–20 mg/week	

[a]Denotes adult study

Third-line medications should be reserved for moderate to severe disease activity that is either not responding to therapy or is complicated by neurological, severe mucosal or vascular involvement. Thalidomide 100 mg daily may simultaneously treat and prevent the development of mucocutaneous ulcerations, but it does not show sustained remission after discontinuation [50].

Interleukin-1 blocking agents have recently been studied in management of BD. Case studies in adults show encouraging efficacy of these agents, as IL-1 seems to play a large role in the development of the disease. Anakinra, gevokizumab, and canakinumab show complete resolution in some cases, occurring in as early as a few days. Some cases required additional medications such as prednisone and colchicine to control the disease [24, 135].

Other biologic medications that have been studied include tocalizumab, ustekinumab, and rituximab. These medications have been used in isolated cases with variable responses [26]. Apremilast is an oral phosphodiesterase four inhibitor that is currently being studied for the treatment of mucocutaneous ulcerations in BD. Phase II randomized, placebo-controlled, double-blind studies have shown promising results, and European studies are underway in children to assess its safety and efficacy [52].

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Cutaneous Manifestations of Psychiatric Disorders and Management

25

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Delusional Infestation

Delusional infestation (DI) is a fixed, false belief that a person or his or her environment is infested with living or inanimate objects, and that belief is held despite medical evidence to the contrary [3]. This disorder has a long history and has alternative names including Ekbom's syndrome and delusional parasitosis. The prevalence of the disorder is estimated at 17 per million, and the disorder presents more frequently in women than in men [4]. While this can be a primary delusional disorder, symptoms may also develop secondary to illicit drug use, medications, and medical disease. Primary DI is extremely rare in children; delusions of infestation are most frequently related to substance abuse in children and adolescents, or due to a false belief shared with family members.

Clinical Manifestations

Patients with delusional infestation present with complaints of pathogens or inanimate objects inhabiting their skin, organs, or environment [5]. Patients may complain of sensations of the pathogens crawling, burrowing, or biting. They may also report having seen the pathogen and may present to clinic with "evidence" of the pathogen in the form of skin debris or objects from the environment [1]. The patient may have taken drastic measures to eliminate the pathogen, such as the use of harsh chemicals on their skin, and often resort to social isolation to prevent further infestation of others. Damage to the skin is produced by chemicals and by excoriations that are meant to extricate the pathogens, and this skin damage further perpetuates the belief of infestation.

DI may be secondary to medical illness, though this is rare in children. Causes of secondary DI include brain tumors, traumatic brain injury, infections, endocrine disorders, malnutrition, and autoimmune disorders [4, 6]. Substances of abuse—including alcohol, stimulants, cocaine, and cannabis—most frequently cause delusional infestation in adolescents [5]. Delusional infestation may also occur as part of schizophrenia or major depressive disorder with psychotic features.

In children presenting with DI, it is particularly important to screen for folie à deux, or a shared belief that may occur between child and caregiver [5]. Delusional infestation by proxy may also present in a child. In this case, the parent or caregiver believes that the child is infested.

Management Strategies

Management of patients presenting with symptoms of DI should first start with ruling out actual infestation or causes of generalized pruritus. If a patient brings in samples of infestation, these should be examined microscopically; taking the patient's complaints seriously will also help to establish rapport. Comprehensive examination of the skin should be performed. General medical conditions can be ruled out by a thorough history, including all medications and travel history, and laboratory examinations. A complete blood count, erythrocyte sedimentation rate, comprehensive metabolic panel, thyroid stimulating hormone, and urine drug screen can help rule out many secondary causes of DI [4]. Determining the onset and progression of symptoms will also improve understanding of the overall clinical picture.

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Table 25.1 Pharmacologic treatment of delusional infestation [2, 4–6]

Medication	Mechanism	Starting dose	Max dose	Weight gain	Sedation	FDA approval in children	Evidence level	Notes
Risperidone (Risperdal)	SGA	0.25 mg	6 mg	++	+	SCZ age 13–17, BP 1 acute manic/mixed age10–17, ASD 5–17	E*	May be associated with gynecomastia and elevated Prolactin
Aripiprazole (Abilify)	SGA	2 mg	30 mg	+	+	SCZ age 13–17, BP 1 manic/mixed age 10–17, ASD age 6–17	None	Least weight gain and sedation
Quetiapine (Seroquel)	SGA	25 mg	800 mg	++	++	SCZ age 13–17, BP 1 acute manic age 10–17	None	Most weight gain and sedation

* anecdotal case reports in adults but none exist in pediatric patients
Due to low prevalence and difficulty engaging this patient population, evidence for pharmacologic treatment is limited
±, mixed data; –, none; +, mild; ++, moderate; +++, severe
SGA second generation antipsychotic, *SCZ* schizophrenia, *BP 1* bipolar 1, ASD autism spectrum disorder

In the case of children, shared psychiatric disorders (folie à deux) or delusional infestation by proxy may pose harm to the child's well-being, as children may be subjected to potentially dangerous means to rid them of the infestation. Harmful medical interventions may also lead to actual skin lesions. If infestation by proxy is suspected, involving Child Protective Services may be warranted.

Treatment should first involve addressing the underlying cause. Cessation of the medication or substance suspected as the cause is imperative. If DI is secondary to an underlying general medical condition, then the primary disease should be first treated [5]. Skin lesions may be treated with conservative wound care and treatment of secondary infections.

Once secondary causes are ruled out, a diagnosis of primary DI or DI secondary to another psychiatric disorder can be made. Consulting psychiatry is recommended in these cases, for both safety assessment and medication management, as these cases are challenging even for experienced pediatric psychiatrists. There is no role for psychotherapy in the management of primary DI; antipsychotics are recommended as first-line treatment. See Table 25.1.

Body Dysmorphic Disorder

Body Dysmorphic Disorder (BDD) is a psychiatric disorder that is characterized by preoccupation with defects in physical appearance, repetitive behaviors or mental acts in response to concern about appearance, and significant distress and impairment as a result of this concern. Prevalence ranges from 0.7 % to 2.4 % in the general community, with higher rates of up to 13 % in nonclinical student populations [4, 6]. Symptoms usually begin in adolescence, a time in which one is establishing an individual identity and in this process may become more self-conscious about physical changes. Patients with BDD are less likely to seek psychiatric care than they are to seek help from dermatologists or plastic surgeons to correct the perceived physical defect [7].

Clinical Manifestations

By definition, the dermatologic manifestations of BDD are minor, if not absent, in comparison to the level of preoccupation and distress related to the perceived defect. Patients with BDD frequently report concerns with the face, but concerns can involve any body area [1]. Skin color dissatisfaction can lead to harmful attempts to lighten or darken skin in all ethnic groups [7]. Patients often spend many hours at tasks intended to correct the perceived defect. Poor insight is characteristic of BDD, with children and adolescents having less insight than their adult counterparts. In addition, adolescents with BDD have higher rates of suicide attempts when compared to adults [8]. There is high co-morbidity with major depressive disorder, obsessive-compulsive disorder, social phobia, and substance use disorders [9]. Adolescence is a developmental period during which peer groups become increasingly important, and negative body image may lead patients with BDD to become socially isolated. Social isolation can lead to further impairment in development of social skills, education, and overall quality of life [1, 7, 10].

Management Strategies

The most critical aspect of management of BDD is establishing rapport with the patient. It is vital to understand the underlying nature of the complaint without invalidating concerns.

Once a patient feels more comfortable, there are many diagnostic instruments that can be used in addition to the structured interview. The Body Dysmorphic Disorder Questionnaire has been validated in dermatologic settings [10]. The Cosmetic

Table 25.2 Pharmacologic treatment of body dysmorphic disorder [2, 4, 8–10]

Medication	Mechanism	Starting dose	Max dose	Weight gain	Sedation	FDA approval in children	Evidence level	Notes
Citalopram (Celexa)	SSRI	10 mg	40 mg	–	±	No	E* (chart review)	Consider ECG first
Escitalopram (Lexapro)	SSRI	2.5–5 mg	20 mg	–	±	Depression age 12–17	E* (chart review)	Few drug interactions
Fluoxetine (Prozac)	SSRI	10 mg	60 mg	–	±	OCD age 7–17 and Depression age 8–17	D	Most activating and longest half life
Sertraline (Zoloft)	SSRI	12.5–25 mg	200 mg	–	±	OCD age 6–17	E	High dose range
Clomipramine (Anafranil)	TCA	25 mg	200 mg	++	+++	OCD age 10–17	E*	Not recommended in children <10

* anecdotal case reports in adults but none exist in pediatric patients
SSRIs and TCAs may cause rare activation of suicidal ideation and behavior in patients under 24.[11]
±, mixed data; –, none; +, mild; ++, moderate; +++, severe
TCA tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor, *TTM* trichotillomania

Procedure Screening Questionnaire can be used to screen for symptoms and to track symptoms over time [4]. The Yale-Brown Obsessive Compulsive Scale Modified for BDD also rates symptom severity [10]. In addition to screening for BDD, it is imperative to screen for comorbidities.

Assessing how the perceived defect has affected a patient's life will help the doctor grasp a more comprehensive view of the problem. Suicide rates are high in this population, so a safety assessment should also be considered [1, 8].

Treatment options should start with referral to a mental health professional for both treatment of BDD as well as further exploration of underlying psychiatric co-morbidities. A multidisciplinary approach to treating patients with BDD is recommended, involving psychiatry and dermatology.

Cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) are well supported, first-line therapies for BDD in adults and are accepted as first line for children and adolescents [8]. CBT including exposure and response prevention (ERP), anxiety management training (AMT), and mindfulness-based cognitive therapy have been shown to be efficacious in case reports. Engaging the family in treatment and maintaining a positive therapeutic alliance with the patient and family are also recommended.

Though some SSRIs are FDA approved for OCD in children and adolescents, evidence for their usefulness in BDD is lacking. Case reports and one case series provide support for SSRIs particularly fluoxetine (Prozac) and sertraline (Zoloft). High doses are generally needed for OCD and are recommended for BDD as well [8–10]. See Table 25.2.

Anorexia Nervosa and Bulimia Nervosa

Eating disorders including anorexia nervosa (AN) and bulimia nervosa (BN) are psychiatric disorders that affect multiple organs, including the skin. Diagnostic criteria for AN include restriction of energy intake relative to requirements, leading to significantly low body weight and intense fear of gaining weight or becoming fat. Diagnostic criteria for BN include recurrent episodes of binge eating and recurrent compensatory behaviors in order to prevent weight gain, with binging and inappropriate compensatory behaviors each taking place at least once weekly for 3 months. Disturbance in body image is a diagnostic criterion in both disorders [3]. The lifetime prevalence of AN and BN are 0.5 % and 1–3 % respectively [12], and these disorders frequently begin in childhood and adolescence. The earlier these disorders are identified and treated, the better the prognosis. As skin signs may be the only detectable signs in hidden anorexia and bulimia, dermatologists have an important role in early identification of these disorders. The pathophysiology of skin signs is related to starvation, purging, and laxative or diuretic abuse.

Clinical Features

Signs secondary to starvation include lanugo-like body hair, asteatosis, carotenoderma, acrocyanosis, acrodermatitis, and changes with hair and nails [12]. Lanugo-like body hair is fine, soft hair that lacks pigment and is present on the arms, back, and abdomen. This type of hair is frequently seen on newborns, but is also seen in patients who are malnourished. Asteatosis (dry, scaly skin) is often seen by the fourth week of starvation, though it may be present earlier. Starvation leads to a decreased production of sebum and an altered composition of sebum, and asteatosis is seen in approximately 70 % of patients with anorexia [12]. Low body mass index (BMI) is a risk factor for acrocyanosis, making this condition more prevalent in patients with AN than in the general population. Low BMI also correlates with reported pruritus, likely due to multiple pathophysiologic mechanisms including endocrine dysfunction and impaired hepatic, renal, and thyroid function. Eczema is more frequent in AN, as are hair and nail fragility, nail pitting, and periungual erythema.

Carotenoderma, or yellowed pigmentation of the palms, soles, and nasolabial folds is common in patients with AN and is thought to be due to a diet rich in carrots and yellow vegetables though it may also be related to changes in lipid metabolism [13]. Vitamin deficiencies of zinc, biotin, and fatty acids can lead to acrodermatitis. An excess of vitamin A can lead to hair loss [12].

Signs secondary to repeated vomiting ("purging") in BN include salivary gland enlargement (though this sign is non-specific and is also seen in other medical conditions). Recurrent purging lowers the pH of saliva, which contributes to loss of tooth enamel [12]. "Russell sign" is a callus found on the dorsal knuckles of the patient's dominant hand, caused by self-induced vomiting.

Signs secondary to laxative or diuretic abuse are associated with the side effects of the specific drug used. Thiazide diuretics are associated with increase in photosensitivity. Urticaria is seen in phenolphthalein laxatives, and clubbing on the fingers is seen in patients using senna [12].

Management Strategies

Treatment of skin signs in AN and BN involves treatment of the underlying disorder, as most signs resolve with weight gain or cessation of harmful behaviors. As eating disorders affect multiple organ systems, a multidisciplinary approach is best, including psychiatric care. Once an eating disorder is suspected, referral to a psychiatrist is recommended, as early intervention including therapy is likely to improve prognosis. If there is concern that the patient's malnourishment is life-threatening, inpatient hospitalization may be required. Criteria for consideration of hospitalization include a heart rate near 40 bpm, orthostatic blood pressure changes, a blood pressure less than 80/50 mmHg, hypokalemia, hypophosphatemia, hypomagnesemia, refusal to eat, a body weight less than 85 % of healthy body weight, or suicidal ideation.

Factitious Disorders

Factitious skin disorders are defined as self-harming behaviors in which patients deliberately produce cutaneous lesions with the intention of assuming the sick role in order to fulfill an unconscious psychological need [1]. Contrary to malingering, any external motive or secondary gain that may be present with this condition is not the primary motivating factor. Factitious skin disorder also differs from self-injurious behavior in which lesions are produced in order to obtain relief from an intolerable emotional state [14].

Factitious skin disorder by proxy occurs when there is deliberate production of cutaneous symptoms in another person who is under an individual's care, in this case to fulfill psychological needs of the caregiver, and is considered a form of child abuse [15].

Malingering is the falsification of symptoms in order to obtain some type of secondary gain including insurance money, hospitalization for housing, or—in the case of children or adolescents—avoidance of school, and is not a true disorder. The motivation for malingering is *external* (and conscious), as opposed to factitious disorder, in which the motivation is *internal* (and unconscious).

Clinical Manifestation

Factitious skin disorder is rare in children; emergence often begins in adolescence or adulthood [16]. The history does not match the physical examination, and is often accompanied by bewilderment from the patient as to how the lesion arose [1, 14]. Lesions are most frequently seen on the side of the body contralateral to the dominant hand and are on the most accessible areas of the body. Lesions vary significantly, based on the method used, and morphology differs from recognizable dermatitis [17]. Methods used include cutting, applying heat, suction, dyes, caustic substances, pressure, and injection of substances including chemicals or bodily secretions [17]. Lesions are often geometric, with well-defined borders surrounded by healthy skin. Purpura may be created by suction, with the size of the lesion corresponding to the shape of the object used [18].

Histopathology from a biopsy of the skin is not specific or diagnostic, though in the case of injection, foreign body giant cells may be seen [16]. Factitious skin disorder in children may be associated with neglect or abuse. Patients who suffer from factitious skin disorder may also suffer from other psychiatric co-morbidities, including body image disorders and personality disorders [14, 16].

Factitious skin disorder by proxy also presents with varied lesions with no specific histopathology. The individual producing the lesions may be highly involved in the patient's care, and may keep close record of the patient's diagnostic studies and procedures, and may have a personal or family connection to the healthcare field [15].

Screening for other signs and symptoms such as reactions caused by medications, metabolic abnormalities, fever, diarrhea, and vomiting should be done, as falsification of symptoms may extend beyond cutaneous manifestations [16].

Malingering presents similarly to factitious disorder in the sense that there are various methods used to produce the lesion. The history presented by the patient may be inconsistent with the dermatologic presentation [14, 16].

Management Strategies

Early recognition of factitious disorders can limit the illness [15]. It is vital to rule out infections, cancer, or other illness that could be causing the lesions, and to discuss these findings with the patient. This may open a discussion of what is

causing the lesion. Accusatory confrontation is rarely helpful, and often leads to patients leaving the office and refusing to return. Instead, clinicians should work to build a strong doctor-patient relationship characterized by empathy for the patient's suffering [7, 17]. Treating the lesion symptomatically with mild ointment and an occlusive dressing will help the lesion heal quickly and protect the skin from further damage [16]. Due to the association of factitious disorder with depression and PTSD, selective serotonin reuptake inhibitors (SSRIs) may help alleviate the unconscious psychological need and may be helpful in alleviating psychiatric symptoms. Supportive therapy or dialectical behavioral therapy may be helpful in this population [16]. Referral to psychiatry and psychology is recommended, though this should be done cautiously and only after doctor-patient rapport has been well established [4].

In the case of a factitious disorder by proxy, a multidisciplinary team should be involved, including a child psychiatrist and Child Protective Services [15, 19].

In the case of malingering, taking a good social history is recommended, as a child may produce symptoms in order to avoid environments where he or she is being mistreated. Screening for bullying and verbal, physical, and sexual abuse is vital. If abuse is suspected, involving Child Protective Services is warranted.

Excoriation (Skin Picking) Disorder

Excoriation Disorder, previously known as neurotic excoriations or dermatotillomania, is an obsessive-compulsive related disorder characterized by conscious, recurrent, repetitive picking of the skin that results in visible cutaneous damage, and is associated with significant distress or impairment in social, academic, or other important areas of functioning [3]. The lifetime prevalence of this disorder in the general population is 1.4 % [3] with a prevalence of up to 2.7–3.8 % in college student populations [20, 21]. Skin picking is also more common in patients with other obsessive-compulsive disorder diagnoses. Skin picking is a common problem in patients with Prader Willi syndrome, occurring in up to 65–97 % of patients [22, 23].

Clinical Features

Patients with excoriation disorder often present with lesions in the most accessible parts of the body, including face, arms, and legs [20]. Lesions on the upper back usually spare the difficult-to-reach areas, displaying what is called the "Butterfly sign." Appearance of the lesions varies, with acute picking resulting in erosions and crusts, while repeated picking may lead to scars and hyperpigmentation [1, 20]. Infections may also develop at the site of picking. Patients may use their fingernails or other objects, such as needles and tweezers, resulting in geometric or irregularly shaped scars (Figs. 25.1 and 25.2) [24].

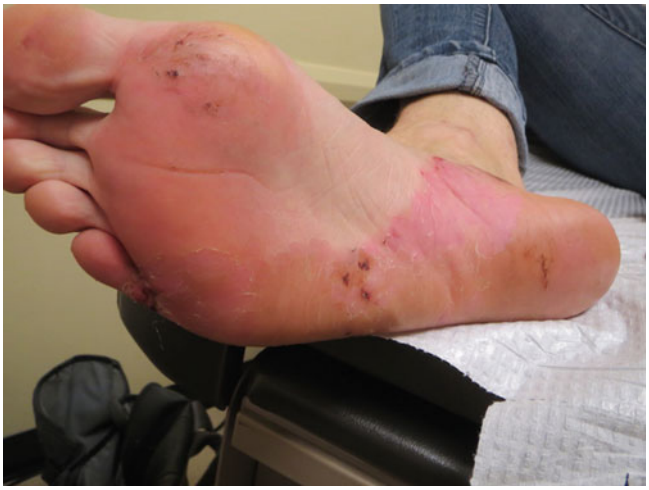

Fig. 25.1 An 18-year-old girl compulsively picked at the skin of her foot

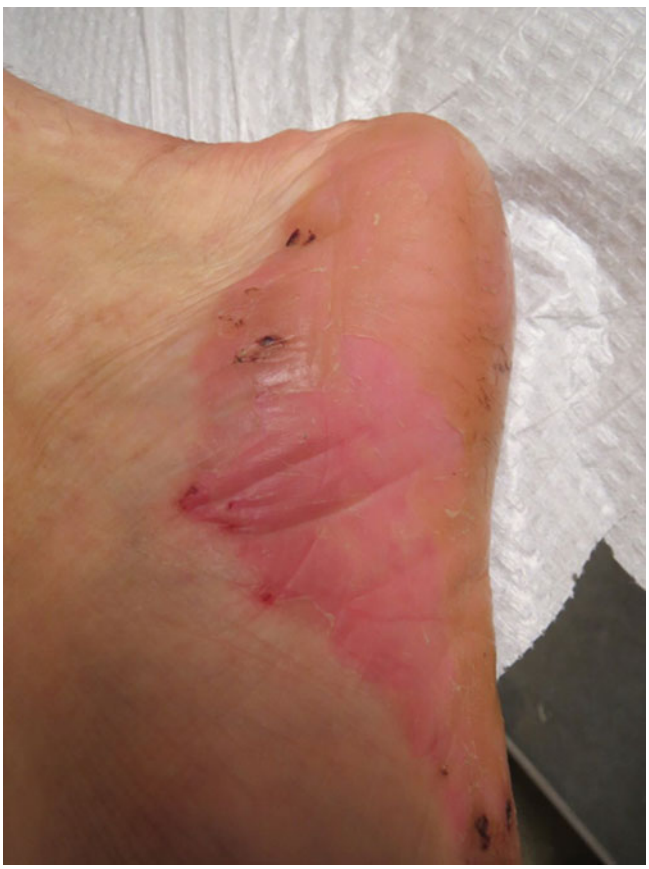

Fig. 25.2 An 18-year-old girl compulsively picked at the skin of her foot

Acne excoriée is another obsessive-compulsive disorder in which lesions begin as an existing blemish that is worsened by the picking behaviors. Acne excoriée is most frequently seen in adolescent girls [16].

Management Strategies

Excoriation disorder is diagnosed through history and clinical exam [24]. Unlike patients with delusional disorders, most patients with skin picking are aware of what they are doing to their skin, and will confirm their behaviors when asked in a non-confrontational manner apart from their family. The clinician should attempt to "normalize" their behavior by explaining that it is common for people to relieve stress by biting their nails or picking at their skin. However, if the skin damage becomes significant enough, for example requiring a visit to a dermatologist, the stress has become overwhelming. In this case, the patient needs additional help in managing the stress, as the symptoms are unlikely to improve without intervention.

Once the patient and practitioner can speak freely about the skin picking, it is important to document the frequency and locations of picking, objects used, triggers, time spent, and whether the behavior is planned or impulsive [4]. Assessing the level of distress related to the disorder also helps to gauge severity, and expressing empathy will help keep patients engaged in treatment. Patients should be screened for psychiatric co-morbidities, and referral to psychiatry made if indicated.

First-line treatments include cognitive behavioral therapy (CBT), with an emphasis on stimulus control and habit reversal training [21, 24]. Environmental modification can also be helpful; removing objects used to pick, or changing the environment where the acts occur (e.g. mirrors), may reduce picking behaviors. Enlisting the help of loved ones, especially in the cases of younger patients, may improve prognosis.

Evidence demonstrating effectiveness of pharmacotherapy in the pediatric population is limited. A case report in a 16-year-old female has shown topiramate (Topamax) to be helpful in reducing the intensity and frequency of the skin picking behavior [11]. There is some evidence in adults that selective serotonin reuptake inhibitors (SSRIs) and olanzapine (Zyprexa) (a second-generation antipsychotic) may have some efficacy, though they were not shown to be as effective as CBT [4]. Case reports in adults have shown clomipramine (Anafranil) and doxepin (Sinequan), both TCAs, to be helpful in reducing the severity of excoriations [16]. Doxepin may be used to reduce pruritus associated with excoriations; the antipruritic effect can be noticed right away secondary to histamine blockade [2, 17, 20]. Evidence supporting the efficacy of naltrexone (ReVia) is limited to case reports [24]. See Table 25.3.

In addition to pharmacotherapy to treat picking behaviors, treating acne will be helpful for patients with acne excoriée. Some literature suggests the use of isotretinoin (Accutane, Sotret, and others) for even mild acne lesions in this population, due to the amount of emotional distress seen in patients with acne excoriée [20]. This should be done with caution, as the use of isotretinoin has been reported as having exacerbated psychiatric symptoms, including depression. Until the relationship between isotretinoin and psychiatric effects is made clear, it is important that the practitioner monitor the patient for psychiatric changes if treating with isotretinoin [25].

Table 25.3 Pharmacologic treatment of excoriation (skin picking) disorder [2, 4, 6, 11, 16, 17, 20]

Medication	Mechanism	Starting dose	Max dose	Weight gain	Sedation	FDA approval in children	Evidence level	Notes
Citalopram (Celexa)	SSRI	10 mg	40 mg	–	±	No	E*	Consider ECG first
Escitalopram (Lexapro)	SSRI	2.5–5 mg	20 mg	–	±	Depression age 12–17	E*	Few drug interactions
Fluoxetine (Prozac)	SSRI	10 mg	60 mg	–	±	OCD age 7–17 and Depression age 8–17	E*	Most activating and longest half life
Sertraline (Zoloft)	SSRI	12.5–25 mg	200 mg	–	±	OCD age 6–17	E*	High dose range
Clomipramine (Anafranil)	TCA	25 mg	200 mg	++	+++	OCD age 10–17	E*	Not recommended in children <10
Doxepin (Sinequan)	TCA	25 mg	300 mg	++	+++	No	E*	Not recommended in children <12
Topiramate (Topamax)	Blocks Voltage Dependent Sodium Channels	100 mg (starting dose in case report)	200 mg (maximum dose in case report)	–	+++	Approved for seizure disorder age 2 and above	E	Dosing given based on case report. Cognitive side effects
Naltrexone (Revia)	Antagonizes various opioid receptors	25 mg (adult dosing)	50 mg (adult dosing)	–	–	No	E*	Consider in teens with comorbid opioid or alcohol use

* anecdotal case reports in adults but none exist in pediatric patients
SSRIs and TCAs may cause rare activation of suicidal ideation and behavior in patients under 24.[11]
±, mixed data; –, none; +, mild; ++, moderate; +++, severe
TCA tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor

Trichotillomania

Trichotillomania (TTM) is an obsessive-compulsive related disorder that involves recurrent pulling out of one's hair, resulting in noticeable hair loss. Patients note an increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior, and pleasure, gratification, or relief when pulling out the hair [3]. Lifetime prevalence is 0.6–3.5 %, with an estimated prevalence of 1–3 % in college-aged individuals [4, 6, 26, 27], and the disorder is more common in females than in males [26–28]. Onset is usually in early adolescence [29].

Clinical Manifestation

Trichotillomania presents with patchy areas of hair loss between zones of normal hair growth. Within each area of hair loss one can see hair of varying lengths, corresponding to hairs that have not been pulled, those that have been recently pulled with absent hairs within the follicles, and regrowing hairs that are too short to pull. This "triple zone" appearance differentiates TTM from other types of non-scarring alopecia, including tinea capitis, alopecia areata, androgenetic alopecia, and connective tissue disorders. While most hair pulling occurs on the scalp, other sites include eyebrows, eyelashes (upper more commonly pulled than lower), pubic hair, and body hair [30]. Hair on the temple is usually spared, as it is most painful to pluck. See Fig. 25.3.

Two types of hair-pulling behaviors have been described, "automatic" (unconscious) and "focused" (conscious and often associated with triggers or urges.) [27–29] Evidence supports an association between TTM with mood and anxiety disorders, and hair-pulling behaviors may increase in times of stress. Some patients with TTM will swallow their hair, resulting in a trichobezoar, which may have gastrointestinal complications [26].

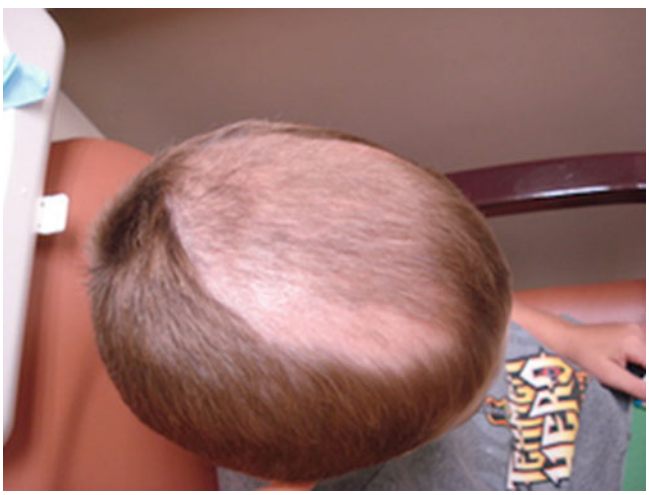

Fig. 25.3 A young boy with TTM, originally thought to be alopecia areata that did respond to medications used for that condition

Management Strategies

The diagnosis of trichotillomania is made clinically, based on history and physical examination. Both the patient and his or her guardians should assist in providing history. In the case of adolescents, interviewing the patient first and assessing how much he or she wants parents involved may help establish rapport and make patients feel more comfortable.

For those patients who may be manipulating their hair unconsciously, journaling can be helpful in developing patient insight. As with skin-picking disorder, it is often helpful to normalize the condition to the patient to decrease feelings of embarrassment. When diagnosis is in question, a scalp biopsy can be performed to demonstrate the characteristic "pigment casts" on histopathology [16, 30]. Another technique is to shave a small patch of hair on the head of the patient and see them back in a few weeks to assess regrowth. While many hair-loss conditions will regrow slowly or imperfectly, those with TTM will often have uniform hair growth in this area, as the hairs are too short to pluck. Due to association with other psychiatric disorders, it is beneficial to screen for depression, anxiety, eating disorders, and substance abuse.

Treatment should involve a multidisciplinary approach, and referral to psychology and psychiatry is recommended. First-line therapy in adults is cognitive behavioral therapy, with special emphasis on habit reversal therapy (HRT), and may be effective in children as well [26, 29]. For example, behaviors such as fist clenching are incompatible with pulling hair [16]. Older children are more inclined to engage in "focused" hair-pulling related to triggers, and therapy targeting emotional management, such as dialectal behavioral therapy, may be more beneficial in this population [28]. Sometimes a clear stressor can be identified, such as divorce, new school, birth of a new sibling, etc. that may have precipitated the behavior, in which case brief therapy or counseling may prove to be helpful.

While selective serotonin reuptake inhibitors may be helpful in treating co-morbid depression and anxiety, several randomized, controlled trials in adults have shown a lack of effectiveness in treating the primary symptom of hair pulling [29]. One study in adults showed some effectiveness of clomipramine (Anafranil), a tricyclic antidepressant (TCA); however, utility in children may be limited secondary to poor tolerability [29]. Support for antipsychotics and naltrexone is limited to case reports and uncontrolled trials [29]. A trial of N-acetylcysteine (Mucomyst)

Table 25.4 Pharmacologic treatment of trichotillomania [2, 4, 6, 16, 26, 29]

Medication	Mechanism	Starting dose	Max dose	Weight gain	Sedation	FDA approval in children	Evidence level	Notes
Citalopram (Celexa)	SSRI	10 mg	40 mg	–	±	No	(–)[a]	Consider ECG first
Escitalopram (Lexapro)	SSRI	2.5–5 mg	20 mg	–	±	Depression age 12–17	(–)[a]	Few drug interactions
Fluoxetine (Prozac)	SSRI	10 mg	60 mg	–	±	OCD age 7–17 and Depression age 8–17	(–)[a]	Most activating and longest half life
Sertraline (Zoloft)	SSRI	12.5–25 mg	200 mg	–	±	OCD age 6–17	(–)[a]	High dose range
Clomipramine (Anafranil)	TCA	25 mg	200 mg	++	+++	OCD age 10–17	E*	Not recommended in children <10
Naltrexone (Revia)	Antagonizes various opioid receptors	25 mg (adult dosing)	50 mg (adult dosing)	–	rare	No	E*	Consider in teens with comorbid opioid or alcohol use
N-Acetylcysteine (Mucomyst)	Glutamate modulator	1200 mg	2400 mg	–	–	No	E*	Evidence in Adults only

* anecdotal case reports in adults but none exist in pediatric patients
SSRIs and TCAs may cause rare activation of suicidal ideation and behavior in patients under 24.[11]
±, mixed data; –, none; +, mild; ++, moderate; +++, severe
TCA tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor
(–)[a]Randomized Controlled Trials have shown lack of effectiveness in adults for primary symptom of hair pulling

in adults showed efficacy for TTM, though no trials have been reported in children [6, 26, 29]. See Table 25.4.

Prognosis in young children is generally good compared to adults, and with appropriate treatment, many patients can regrow their hair normally. Hair-pulling behaviors that have lasted longer than 6 months may be more treatment-resistant [16].

Psychogenic Purpura (Gardner-Diamond Syndrome)

Psychogenic purpura is a rare condition that is also known as Gardner-Diamond syndrome or autoerythrocyte sensitization syndrome. It is usually seen in adult women with psychiatric co-morbidities. Some literature describes the syndrome as a type of factitious disorder [14], yet other literature supports that it is considered an autoimmune vasculopathy [6] that has a strong association with severe stress, trauma, or psychiatric disorder which is separate from factitious purpura [16]. Pathophysiology is poorly understood, though autosensitization to phosphatidylserine may have an important role in pathogenesis [6].

Clinical Manifestations

Psychogenic purpura is characterized by a prodromal phase with fatigue, malaise, headache, and arthralgia. Lesions begin with pruritus or burning pain, followed by development of edematous erythema and ecchymotic skin lesions. Ecchymoses are blue in color with a yellow shade [6]. Lesions regress and heal typically within 1–2 weeks. Patients report association with gastrointestinal symptoms, weight loss, headache, hematuria, epistaxis, and menorrhagia [14]. Associations with fluctuation in estrogen have also been reported [6].

Management Strategies

Diagnosis is made when intradermal injection of the patient's own washed erythrocytes result in reproduction of clinical lesions [16], however, a negative test does not rule out diagnosis [6]. It is of pivotal importance to inquire about stress or trauma preceding development of the lesion, due to the association with psychological factors; therefore a careful psychiatric history is recommended. Histopathology may assist with diagnosis, demonstrating extravascular erythrocytes in the dermis, edema and non-specific lymphocytic infiltration around blood vessels, and pigment deposition in macrophages [6]. Hematological parameters are within normal limits, though laboratory testing may be done to rule out other causes such as idiopathic thrombocytopenic purpura.

In the case of children, child abuse must be considered in the differential, and it may be beneficial to interview the child without the parents. Purpura in the pattern of a handprint or encirclements should be concerning. If child abuse is suspected, Child Protective Services must be contacted. There are case reports of factitious purpura in children [18], and this diagnosis should be considered, especially in the setting of a vague or inconsistent history.

There is no specific treatment for psychogenic purpura. Individual and family oriented psychotherapy may be helpful to address psychological factors. Selective serotonin reuptake inhibitors and other antidepressants may help treat comorbid mood and anxiety disorders. There is some evidence to support the use of antihistamines, corticosteroids, and vitamins [6] to alleviate symptoms of the disease. Referral to a mental health provider is recommended to address associated psychological issues.

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Pearls for Pediatric Dermatologic Procedures

26

Latanya T. Benjamin

Evidence Level
A: Double blind study
B: Clinical trial ≥20 subjects
C: Clinical trial <20 subjects
D: Series ≥5 subjects
E: Anecdotal case reports

Scissor Excision with Electrocautery

Scissor-snip excisions are very useful for removal of small pedunculated lesions in the office setting. These benign growths often have a tendency for recurrence. Electrocautery provides the added benefit of minimizing the chance for recurrence, along with the ease of controlling intra- and post-op bleeding. Additional benefits include fast healing, no suture needed, and minimal post-op care. Post-care recommendation includes keeping the wound moist until the resulting eschar heals completely. Considerations for the pediatric population are that this is a fast, simple, relatively pain-free procedure that produces excellent cosmetic results on the face and other body regions.

Pearl
Apply ethyl chloride vapocoolant spray to the area of skin just prior to skin tag removal. (B) [1]
Procedure technique
Apply topical anesthetic and/or local anesthetic to the skin
Snip at the base of the lesion using a curved iris scissor
Gently cauterize the base
Dress with vaseline and/or spot bandage

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Common Applications

Skin tags/acrochordons
Filiform warts
Pyogenic granulomas

Intralesional (IL) Injections

Intralesional injections deliver small aliquots of medication concentrated to a particular area of skin. For examples, medications such as corticosteroid, candida antigen, and botulinum toxin are frequently used in a pediatric dermatology practice. The recommended dose for IL Kenalog injections of the scalp for alopecia areata is 5–10 mg/mL (max 20 mg per session) and eyebrows 2.5–4 mg/mL [2]. Keloids and hypertrophic scars typically require higher doses of 20–40 mg/mL with injections spaced at 4- to 6-week intervals. The recommended total dose for Candida injections to treat recalcitrant warts is 0.3 mL. Botulinum toxin type A is 50 U per body part (total 200 U). Consideration for the pediatric population includes the associated pain of having serial and often multiple injections at a time. It is recommended to apply a topical anesthetic or other numbing technique prior to injections.

Pearl
Create a mixture by adding a small amount of 1 % lidocaine in combination with Kenalog for steroid injections.[a]
Numb the skin locally with a frozen ice pack just prior to each botulinum toxin injection
Procedure technique
Wipe area of skin clean with a rubbing alcohol pad
Gather any adjacent loose skin between the thumb and pointer finger
Insert 30 ½ gauge needle at 90°
Slowly infiltrate desired amount of medication
Massage medication under the skin

[a]Be aware that intra-articular injection with combination local anesthetic and corticosteroid can lead to chondrotoxicity [3]

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Common Applications

Alopecia areata	B [4]
Infantile hemangioma, focal type	B [5, 6]
Keloid/hypertrophic scar	A [7]
Warts, recalcitrant	A [8]
Hyperhidrosis, focal	A [9]

Minor Office Procedures, Including Cryotherapy, Laser and Skin Biopsies

Many pediatric dermatologic minor procedures can be carried out in the office setting. Set-up is the key. This includes having informed consent and all parent/child questions addressed beforehand. Everyone in the room should be positioned, parents seated, and the procedural work area clear. The child should have used the restroom if needed and be positioned facing a TV screen or supportive parent. It is imperative to have the surgical tray with needles and other sharp instrumentation out of the view of the child. Safety equipment should be on and available for everyone in the room prior to the start of the procedure.

Pearl
Restrain the child *last*- only when ready to begin the procedure
Avoid the need for general anesthesia in the pediatric population when possible
Use one or more of the following forms of anesthesia for minor office procedures

Available Therapies or Techniques

Distraction anesthesia	E [10]
Parent-child tent	E [11]
LMX/EMLA	A [12]
Oral sucrose (24 %)	E [13]
Ethyl chloride or pain ease spray	B [14, 15]
Lidocaine (IL, ophthalmic solution, topical, viscous)	C [16]
Peripheral nerve block	E [17]
Intranasal versed	A [18]

Procedures Performed Under General Anesthesia

Full patient cooperation may not always be possible in the office setting. Therefore, sedation in children may be required at times to successfully perform more complex surgical and laser cases safely. For example, a nail matrix biopsy, due to the painful nature and long procedure time, is best accomplished in a controlled setting using general anesthesia, where better results can be achieved. There is increasing support in the literature on the safe use of general anesthesia in healthy children undergoing elective dermatologic surgery along with an experienced pediatric-trained anesthesiologist [19]. Many dermatologic surgeries and laser procedures can be accomplished within 1 h, and therefore shorter-acting anesthetics can be employed.

Pearl
Utilize the services of a certified child life specialist whenever possible in preparation for elective day surgery
Laser protocol
Place protective corneal eye shield (s) for laser treatment of vascular stains around the eye
Outline the vascular stain with a white eyeliner prior to induction with general anesthesia (E) [20]

Available Therapies or Techniques

Child life specialist	A [21]
Fentanyl lollipop (premedication)	A [22]
Combination propofol and fentanyl	B [23, 24]
Other general anesthetics	D [25]

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Light-Based Procedures in Pediatric Dermatology

27

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Evidence Level
A: Double blind study
B: Clinical Trial ≥20 subjects
C: Clinical trial <20 subjects
D: Series ≥5 subjects
E: Anecdotal case reports

Neonatal Nursery Phototherapy

The preferred phototherapy light to treat neonatal jaundice is blue light. Blue light falls within the spectral range of 420–480 nm (peak 458 nm). It is used primarily to prevent bilirubin encephalopathy (kernicterus) in the neonatal period by decreasing systemic bilirubin to safe levels [1, 2]. This is not an ultraviolet light therapy, and is an important consideration for the pediatric population.

Therapy
Blue light
Green light
Turquoise light
Therapy protocol
Protective eyewear
Daily until safe bilirubin levels are established

Table 27.1 First line

Neonatal hyperbilirubinemia	B

Light-Emitting Diode (LED)

LED is considered a single-color light therapy. The distinctive feature of LED is that it is a broad-spectrum continuous wave of visible light. Blue light is within the spectral range of 407–425 nm (peak 420 nm) and red light 550–700 nm (660 nm). Blue or red light phototherapy can also be considered as second-line acne treatment in pregnant or lactating females [3].

Therapy
Blue-light (B) [4]
Red-light
Blue-red light (A) [5]
Therapy protocol
Twice daily × 4 weeks

Table 27.2 Second line

Acne, mild to moderate inflammatory	B [4]

Intense Pulsed Light (IPL)

IPL uses broad spectrum, pulse-delivered polychromatic light. Considerations for the use of IPL in the pediatric population include pain, edema, erythema, crusting and blistering.

Therapy
IPL
IPL + PDT (photodynamic therapy) [6]
Therapy protocol
Not established (typically three sessions with 3- to 4-week intervals in between)

Table 27.3 Third line

Acne, non-inflammatory and inflammatory	C

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Photodynamic Therapy (PDT)

PDT utilizes a photosensitizing agent, commonly 5-aminolevulinic acid (ALA), to increase the effect of an ensuing light- (or laser-) based therapy [7]. Considerations for the use of PDT in the pediatric population include pain, burning, swelling, redness, transient hyperpigmentation, and superficial exfoliation. PDT can be considered as an alternative treatment of extensive viral warts in immunosuppressed individuals.

Therapy ALA-PDT
ALA+ Red-light (B)
ALA + Blue-light (C)
ALA + IPL (C) [8]
Therapy protocol
20 % ALA moisturizing cream
0.5 % ALA liposomal spray
Short (15–30 min) or longer (3 h) incubation time

Table 27.4 Third line

Acne, moderate to severe inflammatory	B [6, 9]
Hidradenitis suppurativa	C [10]
Viral warts, recalcitrant	A [11–14]
Facial flat warts	C [15, 16]

Phototherapy

Phototherapy is utilized to treat a variety of photodermatoses, including photoresponsive inflammatory and autoimmune conditions.

UVA Phototherapy

UVA utilizes ultraviolet light in the 320–400 nm wavelength (UVA_1 340–400 nm). This long-wave ultraviolet light is often combined with the oral drug psoralen (PUVA). Considerations for the use of PUVA in the pediatric population include the ability of the child to comply with safety procedure and to hold still in a closed booth, ingesting a systemic psoralen and tolerating any associated nausea, and the cumulative risk for the potential development of skin cancer.

Therapy
UVA
UVA_1 (B) [17]
UVA + psoralen (**PUVA**)
Therapy protocol
Requires strict 24 h of protective eyewear
Once to twice weekly treatment sessions; at least 48–72 h apart
Psoralens can be delivered topically, given as a bath, or orally
Psoralen is taken 45–60 min prior to UVA exposure

Table 27.5 First line

Morphea (generalized)	[18–21]
GVHD	D [22]
Granuloma annulare (generalized)	E

Table 27.6 Second line

Psoriasis	A [23]
Morphea	B
Atopic dermatitis	B [24]
Pityriasis lichenoides	C [25–27]
Alopecia areata	B [28, 29]
Solar urticaria	E [30, 31]
Mastocytosis	E [32, 33]
Vitiligo	B [34–36]
CTCL/Mycosis fungoides	B [37–39]

UVB Phototherapy

UVB is ultraviolet light that falls in the 280–320 nm wavelength spectrum of light. UVB has been found to be an effective, safe, well-tolerated, and practical alternative treatment modality in the pediatric population, and has surpassed PUVA as the phototherapy of choice in some immune mediated skin diseases.

Therapy
UVA/UVB
Broadband UVB (bUVB)
Excimer laser (308 nm)
Narrowband UVB (311–312 nm)
Therapy protocol
Two to three times weekly protocol

Table 27.7 Second line

Atopic dermatitis	B [40, 41]
Psoriasis	A [23, 42]
Vitiligo	A [43]
Pityriasis lichenoides	B [44]
Morphea	E [45]
Alopecia areata	D [46]
Mycosis fungoides	B [47]
Pruritus (generalized)	B [48]
Nodular prurigo	D [49]
Hydroa vacciniforme	E [50, 51]
Granuloma annulare	E [52, 53]
Lichen planus	B [54]
Pityriasis rosea	B [55]

Photopatch Testing

Photopatch testing is used to further investigate patients with a history of photosensitivity. Ultraviolet radiation is

employed while undergoing patch testing with various allergens. Before undergoing photopatch testing, it is prudent to rule out the possibility of the patient having another endogenous photosensitivity, such as polymorphous light eruption (PLE).

Therapy
UVA
Therapy protocol
Back is exposed to UV light following patch take down on day 2 (after 24–48 h)

Table 27.8 First line

Photoallergic contact dermatitis	[56]
Photoallergic drug eruption	[56]

Extracorporeal Photochemotherapy

Extracorporeal photopheresis (ECP) is used mainly to treat autoimmune diseases by removing abnormal cells from the bloodstream via lymphocyte activation and cell death. The blood is first separated and treated with a photosensitizing agent, and then irradiated with UV light. Following this photodynamic therapy, the blood is then returned to the patient.

Therapy
8-MOP + UVA
Therapy protocol
4 h per day on two consecutive days, each month

Table 27.9 First line

Mycosis fungoides (erythrodermic) Sezary's syndrome	D

Table 27.10 Second line

SLE	C [57]
Lichen planus (erosive)	D [58]
Chronic GVHD	E [59]
CTCL	D [60, 61]
Pemphigus vulgaris	E
Scleroderma/systemic sclerosis	C [59, 62]
Epidermolysis bullosa acquisita	E [63–65]

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