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Buka's Emergencies in Dermatology

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Preface

"A thick skin is a gift from God."

—Konrad Adenauer (1876–1976), German statesman

As dermatology residents, long before we are asked to discern papulosquamous from eczematous, mentors ask the much simpler question, "dangerous" or "benign?" It seemed so rudimentary at the time, but the response to this basic query dictates every other aspect of the patient encounter to follow. How quickly to act? How varied is the differential diagnosis? What treatments to offer and which would present an acceptable risk:benefit analysis? When must we swiftly enjoin additional subspecialists? The entire algorithm of care stems from this first, most critical element: "Is this a crisis?"

Buka's Emergencies in Dermatology is designed to address this pivotal question for medical students, residents, emergency personnel, and community and attending physicians alike. We begin with an overview of critical care—how to manage patients with a severely compromised skin structure and function. Next, we focus on the pediatric population and special considerations for emergency care therein. Our remaining 14 chapters serve as a reference resource, each devoted to urgent care for the 14 classes of specific dermatologic emergency. We hope to equip readers with a more complete appreciation for the early recognition and treatment for those skin disorders that offer a grave risk of morbidity or mortality.

Thankfully, the field of dermatology offers very few critical presentations; this is precisely the reason we must endeavor to recognize these early and respond thoroughly.

New York, NY, USA

Robert L. Buka

Bobby Buka, MD JD

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To Mom, whose support turned every challenge into an opportunity for greatness.

To Uncles Steve and Dave and their spirit of mischief.

To Bari who showed me how to be a doctor first and a physician second.

To Bogi who taught me the periscope has two ends.

and

To Matt, my older and dearest friend.

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Neonatal and Pediatric Dermatologic Emergencies

1

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1.1 Introduction

A wide variety of neonatal and childhood dermatologic conditions can be emergencies. These may arise from genetic disorders, including those causing skin structural protein and keratin dysfunction, vascular birthmarks with systemic associations, autoimmune disorders, and infections. If left untreated, these conditions can lead to systemic effects or may increase the risk of developing secondary complications, potentially resulting in death. It is therefore important that these entities be rapidly identified and addressed. The following pages present a limited collection of some of the most important emergency situations.

1.2 Neonatal Emergencies

There are broad sets of neonatal dermatologic conditions that are true emergencies. Vesicles, pustules, and denuded skin at birth or in the neonatal period may be localized lesions without consequence, such as sucking blisters, or signs of a life-threatening genetic mechanobullous disorder such as epidermolysis bullosa. Herpes simplex virus (HSV) and opportunistic infections can be dermatologic emergencies, requiring prompt recognition, diagnosis, and initiation of therapy. Vascular tumors, including port-wine stains (PWS) and hemangiomas, may require urgent management including diagnostic workup, referral for specialty evaluation, and/or early introduction of therapy. The conditions discussed below are only a select subset of neonatal dermatologic issues that may be considered emergencies. Other resources more extensively discuss other neonatal dermatologic conditions (e.g., *Neonatal Dermatology*, 2nd Edition. Eichenfield, Frieden and Esterly, Saunders/Elsevier).

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1.3 Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a group of congenital disorders characterized by the profound susceptibility of skin and mucosa to separate from underlying tissues following mechanical trauma. EB generally presents at birth or in the first few weeks of life with denuded skin, vesicles, or bullae. Milder forms may present later in life. EB is caused by mutations in structural proteins in the skin, and is generally categorized by the level of blistering and the target proteins: EB simplex (EBS) (epidermolytic), junctional EB (JEB) (lysis in the lamina lucida, or "lucidolytic"), dystrophic (dermolytic), and Kindler syndrome (mixed blistering levels) [1].

EB has an incidence of 1 in every 50,000 births, consisting mostly of the milder EBS type [2]. Of the three types of EB, EBS and JEB generally heal without scarring. In contrast, healing with milia suggests Dystrophic EB (DEB), but has been reported in other types. Some children exhibit a congenital localized absence of skin (Bart syndrome) at birth, which is characterized by large ulcers usually in the lower extremities [3]. Oral erosions are most commonly found in JEB and DEB, and are rarely found in EBS. Extensive blistering can lead to fluid and electrolyte abnormalities, temperature dysregulation, as well as sepsis; supportive measures are essential in the treatment plan.

The differential diagnosis of erosions, blisters, or denuded skin includes infections (e.g., HSV) and other blistering diseases. To diagnose EB, a biopsy should be taken from unaffected skin. The area to be biopsied may be rubbed for 1 min, generally with a pencil eraser, to induce cutaneous blistering; after a 5–10-min wait, a shave, or punch biopsy is taken [2]. Evaluation can include light microscopy, immunofluorescence antigen mapping for absent or attenuated antigens diagnostic for the EB subtype, or transmission electron microscopy, which may visualize the ultrastructural level exhibiting the plane of separation. Specific genetic testing may be utilized as well.

1.3.1 Epidermolysis Bullosa Simplex

EBS, the mildest and most common type of EB, is characterized by the lysis of basal keratinocytes above the basement membrane zone [1]. Most subtypes of EBS are autosomal dominant mutations in Keratin 5 or 14 (such as Weber–Cockayne, Koebner, and Dowling–Meara); however, autosomal recessive mutations and mutations in other genes have been reported. Keratin 5 and 14 function in the adhesion of cells to the hemidesmosome through plectin, another EBS-associated protein [2]. Most EBS children experience an increased tendency to blister as temperature increases; however, their overall prognosis is excellent with normal life expectancy and decreased tendency to blister with time. The Weber–Cockayne (WC) EBS subtype is the mildest, most common subtype of EBS where the bullae, though temperature sensitive, are confined predominantly to the hands and feet. In Koebner (K) EBS, patients experience generalized blistering with little to no mucosal involvement. 20% of patients experience nail involvement; however, all symptoms improve with advancing age. Dowling-Meara (DM) EBS is most severe in the neonate and infant, and can be fatal in the neonatal period. Large generalized blistering predominates; however, blisters do decrease with age. DM children experience profound mucosal involvement, as well as nail involvement and mild acral blistering. Unlike other major EBS disorders, EBS with muscular dystrophy is characterized by an autosomal recessive mutation in the gene coding plectin. These patients experience early-onset generalized blistering with laryngeal and mucosal involvement, as well as progressive muscular dystrophy. Finally, EBS with mottled pigmentation is a rare autosomal dominant subtype characterized by mechanically induced blistering, unaffected mucosa, and a mixture of hyper- and hypopigmented macules [4].

1.3.2 Junctional Epidermolysis Bullosa

JEB (Fig. 1.1), characterized by mechanically induced blistering occurring within the basement membrane at the lamina lucida [1], is the least common form of EB, showing poor outcome in infancy. JEB is caused by autosomal recessive mutations in genes coding components of the hemidesmosome-anchoring complex critical for dermal–epidermal adhesion. The Herlitz and non-Herlitz subtypes of JEB are characterized by mutations in laminin 5, which is essential for the adhesion of keratin intermediate filaments to the basement membrane. In the most common form, the Herlitz subtype, there is significant mortality (approximately 50%) by 2 years of age [2]. This subtype is characterized by exuberant granulation tissue within ulcers especially in the ocular and perioral region with sparing of the lips. Affected individuals experience dental enamel dysplasia, severe blistering of the periungual and finger pad regions, and erosions of the laryngeal and respiratory epithelium, resulting in hoarseness. Blisters heal with atrophy but not milia. The amount of blistering is often not predictive of prognosis. Common complications include anemia of chronic disease and growth retardation. In severe cases, death may be due to severe sepsis and failure to thrive. In contrast, the non-Herlitz subtypes are characterized by less severe but similar manifestations to the Herlitz type including dental, nail, and laryngeal involvement; however, patients experience less mucosal involvement and improved prognosis. Finally, JEB with pyloric atresia is a rare subtype characterized by a mutation in α6β4 integrin and sometimes a mutation in the plectin gene. Patients present at birth with upper gastrointestinal obstruction, most often affecting the pyloric region. There is variable skin involvement; however, the ocular, respiratory, and urogenital epithelium are almost always affected. Prenatal signs include polyhydramnios and abdominal masses. Corrective surgery is necessary. The prognosis is often poor due to failure to thrive, fluid and electrolyte imbalances, and sepsis [3].

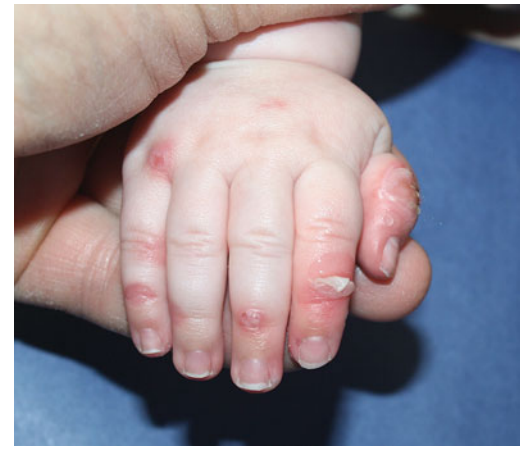

Fig. 1.1 Junctional epidermolysis bullosa. Erosions, blisters, and denudation on the hands

1.3.3 Dystrophic Epidermolysis Bullosa

DEB is characterized by blistering below the lamina densa of the basement membrane zone, causing lysis of the dermis [1]. DEB is caused by autosomal dominant and recessive mutations in type VII collagen, a major component of anchoring fibrils, thus resulting in defective attachment of the basement membrane to the underlying dermis [2]. There exists a profound variation in the prognosis of DEB patients due to the spectrum of presenting symptoms. Dominant DEB is a much milder subtype with an onset from birth to early infancy. Blistering predominates on elbows, knees, lower legs, and the dorsum of hands; 80% of children experience nail dystrophy [3]. Milia are associated with scarring, which was once thought to be pathognomonic for DEB, and some patients develop scar-like lesions on the trunk. In contrast, Recessive DEB is present at birth and characterized by widespread blistering, scarring, and milia. Patients experience deformities due to scarring such as digital fusion and joint contractions. There may be severe involvement of the nails and mucous membranes of the gastrointestinal tract, ocular mucosa, and genitourinary system. In severe cases, failure to thrive may result from chronic wound healing, poor nutrition, infection, and blood loss from erosions. Children and

adolescents often experience growth retardation and are greatly predisposed later in life to squamous cell carcinoma in heavily scarred areas [4].

Emergent evaluation of a neonate with possible EB includes skin biopsy and institution of aggressive supportive measures, including excellent skin care. Fluids and electrolytes must be closely monitored, and the temperature must be kept moderate since heat can induce blistering. Care must be taken to minimize new blisters and erosions through gentle handling and the use of nonadhesive bandages especially for the first layer of bandaging. The skin care regimen must promote wound healing through daily bathing and vigilant inspection of blisters. A topical or systemic antimicrobial can be used to prevent infection, though use must be balanced by the potential for selection of resistant microbes. Topical antibiotics may be rotated and the use of such products should be discontinued when the wound is clean [2]. Nonsteroidal anti-inflammatory drugs or opiates can be administered to decrease pain during bandaging and other procedures. Intact blisters must be incised on the dependent side using a sterile needle to prevent lesion extension. It is important to properly diagnose the EB type and subtype, as well as counsel and educate parents on prognosis and future therapy. Referral for genetic counseling is appropriate. In-hospital care may be appropriate until the infant is feeding well and gaining weight with stable skin involvement, and the family has adequate training in skin care management.

1.4 Disorders of Keratinization (Ichthyosis)

There are several ichthyotic conditions that manifest during the neonatal period as either collodion baby or scaling erythroderma. These disorders encompass a wide range of genetic conditions with molecular defects affecting the epidermis [3]. At birth and up to the first day of life, desquamation of the skin is abnormal and the differential diagnosis includes congenital ichthyosis, intrauterine stress, and postmaturity [5]. For most ichthyotic conditions, early recognition, therapy, and monitoring will be required to prevent infection or fluid and electrolyte imbalance.

1.4.1 Collodion Baby

The collodion infant presents at birth encased in a shiny, thickened, variably erythematous, cellophane-like membrane [5]. This presentation is associated with several disorders, including nonbullous congenital ichthyosiform erythroderma (NCIE), lamellar ichthyosis, and self-healing collodion baby. Less commonly encountered conditions that may present with collodion membranes include Sjögren–Larsson syndrome, Conradi–Hünermann syndrome, trichothiodystrophy, and neonatal Gaucher's disease [3].

Despite the markedly thickened stratum corneum in collodion infants, the membrane acts as a poor barrier due to cracking and fissuring. This results in increased water and electrolyte loss leading to a hypovolemic hypernatremic state, heat loss, and an increased risk of developing cutaneous infections and sepsis. Infants are also at risk for developing pneumonia from aspiration of squamous material in utero, and have difficulty closing their eyes due to the thickened skin and ectropion [3].

Treatment of an infant with a collodion membrane is primarily supportive. The babies should be placed in a high-humidity, neutrally thermal environment with the application of bland emollients such as petrolatum ointment to prevent dehydration. Serum electrolytes and fluids should be monitored. Surgical debridement is contraindicated and the use of keratolytics in the neonatal period through the first 6 months of life is not recommended due to the increased risk of toxicity from excessive absorption through permeable skin [5].

The management of these infants should include a dermatological consultation to help identify the ichthyotic disorder and tailor their treatment. A skin biopsy evaluating the histologic appearance of lesional skin and the use of electron microscopy and/or specific genetic testing may confirm the etiologic diagnosis. Because

involvement of the face may result in ectropion formation, ophthalmologic consultation is appropriate [5].

1.5 Herpes Simplex Virus

HSV is a DNA virus that can cause acute skin infections and serious illness in neonates and infants, ranking as one of the most significant dermatologic emergencies in the first year of life. HSV-2 causes 70–85% of neonatal HSV infections, with HSV-1 associated with the remainder of cases. The rate of neonatal HSV disease in the United States is approximately 1 per 10,000 births [6], roughly 1,500 cases per year.

HSV infection of the neonate can occur during the intrauterine (5%), peripartum (85%), or postpartum (10%) periods [7]. Most neonatal HSV infections are acquired by contact with asymptomatic primary or recurrent genital HSV infection during delivery [8]; the risk of transmission is substantially reduced by caesarean section. Transmission risk is increased by prolonged rupture of the membranes, as well as vacuum or forceps delivery and placement of fetal scalp monitors, which breach the integrity of the mucocutaneous barrier and may serve as an inoculation site for HSV.

HSV infections occur with three distinct clinical presentations: (1) disease limited to the skin, eyes, and/or mouth (SEM disease), (2) central nervous system (CNS) disease, with or without skin lesions, and (3) disseminated disease involving multiple visceral organs, including the lungs, liver, adrenal glands, skin, eyes, and brain [8].

SEM disease accounts for 45% of neonatal HSV cases. Skin is involved in 80–85% of cases [8]. Isolated or grouped vesicles on an erythematous base appear 1–2 weeks following inoculation. Within 1–3 days, vesicles progress to coalescing crusted papules and plaques. The lesions may erode or ulcerate [9]. Systemic therapy is required; otherwise, dissemination of the infection may occur. With treatment, the long-term developmental outcome of SEM disease is good. Neonates with SEM disease often have recurrent cutaneous herpes during early childhood [10].

CNS disease, which represents 30% of neonatal HSV cases, generally presents in full-term infants after 16–19 days of life [10]. Skin lesions are only present in 60% of infants. Encephalitis can result from retrograde neuronal spread of mucosal lesions [8]. HSV encephalitis or meningoencephalitis can cause irritability, lethargy, poor feeding, seizures, coma, and death. Prompt initiation of acyclovir therapy substantially improves outcome; prolonged therapy has been associated with better outcomes. A significant number of neonates with HSV-2 CNS infections may have neurologic problems at 1 year, including developmental delay, epilepsy, blindness, and cognitive disabilities [10].

Disseminated disease occurs in 25% of neonates, and is the most common presentation of HSV in premature infants. Clinical manifestations appear after 1–2 weeks of life. Skin or mucosal lesions are present in 60% of cases [8]. Disseminated disease commonly involves the lung, liver, and brain, resulting in shock, disseminated intravascular coagulation, and multiple organ system failure [10]. Mortality is 75% in untreated neonates and can be as high as 30% despite treatment.

The presence of a vesicular rash in a febrile neonate, with or without lethargy, seizures, or systemic findings should raise suspicion for HSV disease [9]. Early consideration and diagnosis of HSV infection allow initiation of therapy, thus minimizing significant viral replication and dissemination [10]. HSV infection in neonates may present as eroded or denuded skin. However, since vesicular rashes and erosions may be absent in HSV infection, neonates with CNS infection or sepsis should prompt consideration of HSV. A complete workup should include cultures of the CSF, blood, mouth, nasopharynx, conjunctivae, rectum, and skin vesicles. Histologic examination of scrapings from the base of a vesicle or mucosal ulceration, for the presence of multinucleated giant cells and eosinophilic intranuclear inclusions typical of HSV (i.e., with Tzanck test), has low sensitivity. Direct fluorescence antibody staining of vesicle scrapings allows for rapid diagnosis. Polymerase chain reaction (PCR) assay of CSF to detect HSV DNA is currently the diagnostic method of choice for CNS disease. A complete

blood count and comprehensive metabolic panel, including liver transaminases, should be performed to assess systemic involvement [8].

High-dose parenteral acyclovir is the treatment of choice for neonatal HSV infections. Acyclovir (generally given as 60 mg/kg/day given in three divided doses over 21 days) improves both mortality and morbidity from neonatal disseminated and CNS HSV. Similar dosing for a shorter duration is recommended for SEM disease, and for asymptomatic infants born to women acquiring HSV infection near term [8, 10]. A recent multicenter observational study of neonates with HSV infection determined that delayed initiation of acyclovir therapy is associated with a higher rate of in-hospital death [11]. Thus, it is reasonable to consider empiric acyclovir therapy in ill neonates where HSV is being considered in the differential diagnosis while awaiting diagnostic testing results. Pediatric infectious disease consultation is reasonable in established cases of CNS or disseminated infection [10]. Transient neutropenia may occur in up to 20% of neonates treated with high-dose acyclovir, but may not result in clinically significant adverse outcomes.

1.6 Vascular Birthmarks

1.6.1 Hemangiomas

Infantile hemangiomas (IHs) are the most common vascular tumor, affecting 4–10% of all infants born in the United States. IHs are benign tumors that may not be present at birth, but present within the first few weeks of life. Precursor lesions are common but often subtle; early signs include pallor, telangiectases, a bruise-like appearance, or, rarely, skin ulceration. IHs typically proliferate, with rapid growth of the tumor in the first several months of life. This phase is followed by an involution stage, with slow, spontaneous diminishment of the lesion over several years. Following involution of the vascular component, there is sometimes a residual fibro-fatty mass.

Occasionally, IHs may require emergent attention and therapy [12]. IHs that are near vital structures may be dangerous and even life-threatening. Of particular concern are IHs in the periorbital, perioral, deep subcutaneous, and perineal regions. Facial and perineal hemangiomas should raise consideration of associated structural anomalies such as the PHACES and PELVIS/SACRAL syndromes, as these may be associated with significant medical risks.

IHs found periocularly may permanently affect vision; unless the lesion is both superficial and small in size, an ophthalmologist should be consulted. For lesions that may partially or fully obstruct vision, systemic therapy is usually indicated. The contralateral eye may be patched for several hours each day to promote opening of the affected eye. Systemic therapy, such as propranolol or prednisone, should be instituted early by a specialist with expertise in treating IHs. Occasionally, intralesional corticosteroids are utilized for periocular lesions, although there have been rare reports of ipsilateral and even contralateral blindness after such procedures.

Perioral IHs not only risk deformation of the lip cosmetically but may be also associated with pharyngeal or tracheal lesions, potentially causing airway obstruction and stridor. In patients with large mandibular IHs, especially involving multiple areas of the perioral, chin, and bilateral jawline segments, imaging of the airway by direct visualization, CT, or MRI should be considered. Systemic therapy should also be instituted in cases involving airway obstruction. In more severe cases, an otolaryngologist may utilize laser or other surgically destructive techniques.

Deep IHs are more difficult to monitor, as the exact size is less clinically discernible. CT or MRI imaging can aid in determining the extent of involvement as well as elucidate proximity to organs and vascular structures, such as the carotid artery and vein, which are at risk for compression during the proliferative stage. Deep IHs that are in close proximity to vascular structures need to be monitored very closely during the proliferative stage; systemic therapy should also be initiated to minimize functional impact and potential deformation.

IHs in the perineal region need special consideration, since these lesions can affect genitouri-

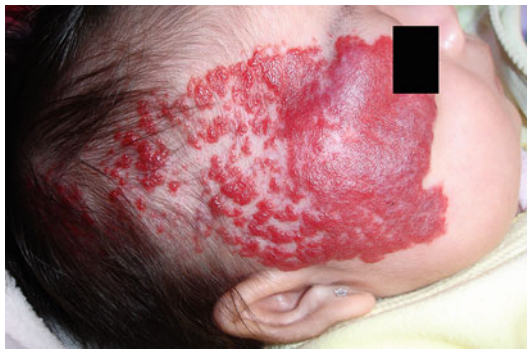

Fig. 1.2 PHACES. Infant with large segmental hemangioma of the face, one of the diagnostic criteria for PHACE syndrome

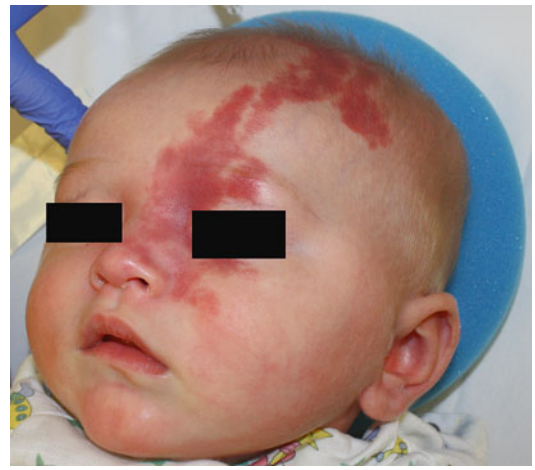

Fig. 1.3 Port Wine Stain. Infant with port wine stain involving the ophthalmic branch (V1) of the trigeminal nerve

nary and gastrointestinal functions. CT or MRI imaging may be helpful in delineating the extent of involvement, and systemic therapy may also be required.

PHACE syndrome (Fig. 1.2), a constellation of clinical findings associated with IHs, refers to Posterior fossa brain abnormalities, Hemangiomas, Arterial malformations, Coarctation of the aorta and other cardiac defects, and Eye abnormalities. Diagnostic criteria for PHACE syndrome and possible PHACE syndrome include major and minor findings such as cerebrovascular, cardiovascular, ocular, brain, and ventral or midline defects [13]. An IH of at least 5 cm in size found on the head and neck region should undergo a workup to rule out underlying abnormalities that may be life-threatening. An MRI and MRA of the soft tissues of the head and neck, as well as of the brain, should be performed. An ECHO and EKG may identify cardiac anomalies, and an eye exam should be performed. Despite their benign appearance, facial IHs may portend serious underlying malformations.

Large, segmental hemangiomas in the anogenital region have also been found to be associated with underlying anomalies. The acronyms PELVIS syndrome (Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag), LUMBAR syndrome (Lower body hemangioma and other cutaneous defects, Urogenital anomalies, ulceration, Myelopathy, Bony deformities, Anorectal malformations, arterial anomalies, and Renal anomalies), and SACRAL syndrome are all used to refer to the similar findings associated with larger IHs in the anogenital region. There are no published guidelines regarding the appropriate threshold for performing imaging and workup to look for associated anomalies. Further studies are needed to establish both the size and location of perineal IHs of concern. Functionally significant or potentially deforming hemangiomas warrant early referral to specialists with expertise in workup and management.

1.6.2 Port-Wine Stains

PWS (Fig. 1.3) are non-palpable vascular malformations composed of capillary venules present at birth, which may be isolated cutaneous findings or associated with syndromic features. PWS on the face, primarily involving the ophthalmic branch of the trigeminal nerve (V1), may be associated with Sturge–Weber Syndrome (SWS) [14]. SWS may manifest with seizures and developmental delay, and/or glaucoma. PWS may also be associated with more complex vascular malformations.

Management in the neonatal period should include consideration of the differential diagnosis (PWS, hemangioma, complex malformation) and evaluation for possible syndromic features that may require emergent measures. Facial PWS

overlying the V1 distribution require urgent evaluation for possible glaucoma [14]. Evaluations for CNS manifestations may be considered, but need not be performed as a part of emergency management.

1.7 Opportunistic Fungal Infections

Due to their immature skin barrier, premature neonates are at risk for cutaneous fungal infections. These infections can manifest as pustules, vesicles, plaques, indurations, ecchymoses, crusts, erosions, and necrotic lesions often initially appearing at sites of skin trauma [15]. Opportunistic fungi can easily disseminate, and even with treatment are associated with high mortality rates.

An aggressive workup is necessary given the very broad differential diagnosis (intrauterine epidermal necrosis, HSV, Behçet's disease, lupus, etc.) [15]. The infant's maternal, family, perinatal, and neonatal histories should be evaluated. A CBC with differential, coagulation studies, and antibody studies, if cutaneous lupus is being considered (anti-SSA/Ro, SSB/La, U_1RNP, ANA) are recommended. Tissue cultures, blood cultures, biopsies, and appropriate rapid diagnostic testing (e.g., HSV direct fluorescent antibodies, PCR) should be performed and are critical for identifying causative organisms.

Treatment consists of excision or debridement along with systemic antifungals [15]. The antifungal therapy of choice is dependent on the identity of the organism, and infectious disease specialists should advise its selection.

1.8 Childhood Emergencies

Emergency dermatologic conditions in children are extensive in number and scope. While many conditions are discussed elsewhere in this book, this section emphasizes several conditions that may commonly be considered in the differential diagnosis of emergent conditions in childhood, including urticarial eruptions, drug eruptions, Stevens–Johnson Syndrome (SJS) and toxic epidermolysis, acute infectious complications of atopic dermatitis, and some primary infections due to bacteria, viruses, and fungi.

1.9 Drug Eruptions and Drug Hypersensitivity

1.9.1 Urticaria

Urticaria is characterized by pruritic, well-circumscribed, pink, edematous papules or plaques (wheals) usually associated with allergic responses or infections. The lesions may be localized or generalized, and usually last less than 24 h; however, associated angioedema can last hours to days. Systemic symptoms may include diarrhea, breathing difficulties, fever, fatigue, or arthralgias.

Acute urticaria is caused by viral infection in 80% of children as well as by foods and drugs in most teenagers. Penicillins, sulfonamides, cephalosporins, aspirin, NSAIDs, anticonvulsants, tetracyclines, opiates, and radiocontrast are common causes of urticaria [16]. Milk, eggs, nuts, shellfish, and wheat are examples of food triggers. Contact, pressure, aquagenic, cholinergic, and cold urticaria are further considerations. The differential diagnosis includes arthropod bites, contact dermatitis, erythema multiforme, mastocytosis, dermatographism, serum sickness-like reaction (SSLR), and urticarial vasculitis.

The diagnosis is made clinically. In contrast to erythema multiforme, lesions of annular urticaria usually lack a dusky center. However, in younger children, bruising may occur secondary to urticaria that can be confused with erythema multiforme. For atypical lesions with purpura or those lasting longer than 24 h, a biopsy should be performed to rule out urticarial vasculitis.

Urticaria is usually self-limited once the inciting agent is removed, and lesions usually disappear in a few days. If urticarial lesions persist for more than 6 weeks, an infectious workup may be warranted, although without specific signs or symptoms it may be difficult to make a causative diagnosis. Approximately 80% of patients respond

to oral therapy with twice-daily dosing of second-generation antihistamines such as cetirizine, loratadine, levocetirizine, or fexofenadine [16]. These agents should be tapered over several weeks after the urticaria resolves. Severe outbreaks or pruritus can be treated with first-generation antihistamines such as hydroxyzine or diphenhydramine, doxepin, or even H2 blockers such as ranitidine or cimetidine. Oral corticosteroids should be reserved for nonresponsive cases in order to avoid potential side effects and rebound. Epinephrine can be used for anaphylaxis and an epinephrine pen should be considered in patients at risk for severe allergic responses.

1.9.2 Exanthematous Reaction

Exanthematous or morbilliform drug reactions are the most common type of drug eruptions. Classic findings are pruritic, pink macules, or papules coalescing into patches or plaques beginning at 1–2 weeks after starting a medication. The eruption is symmetric and usually appears on the trunk before generalized dissemination. A coexisting viral infection can increase the incidence and severity of a morbilliform reaction as seen when amoxicillin is prescribed during an Epstein–Barr Virus infection.

Penicillins, sulfonamides, cephalosporins, and anticonvulsants are common causes of exanthematous reactions [16]. The differential diagnosis includes viral exanthems, pityriasis rosea, acute graft versus host disease, allergic contact dermatitis, scarlet fever, and eczema. In contrast to viral exanthems, a drug exanthem is more likely to be pruritic.

Usually, the diagnosis is made on clinical grounds. Occasionally, a skin biopsy may be helpful, especially in differentiating from other conditions, such as graft versus host disease. It is important to assess if drug reactions are isolated to the skin, or affect other organ systems, as occurs with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, which affects hematologic, lymphatic, hepatic, renal, and pulmonary systems. The offending drug should be discontinued if not completely necessary. Oral antihistamines such as diphenhydramine, cetirizine, or hydroxyzine, bland emollients, or topical corticosteroids may be administered for pruritus [16]. After 1–2 weeks, the eruption usually desquamates leaving a temporary hyperpigmentation.

1.9.3 Serum Sickness-Like Reaction

SSLR is characterized by fever, an urticaria-like eruption, and arthralgias that occur 1–3 weeks after a drug exposure. The eruption can be fixed and may become purpuric. Unlike true serum sickness, this type of eruption is not associated with immune complexes, vasculitis, hypocomplementemia, or renal involvement.

Cephalosporins, penicillins, minocycline, sulfonamides, and bupropion are the main causes, with cefaclor being the most common [15]. The differential diagnosis includes viral or drug exanthems, rheumatoid arthritis, urticarial vasculitis, urticaria, drug vasculitis, and post-viral synovitis.

Management includes discontinuing the offending medication; antihistamines and topical corticosteroids can be administered for pruritus. If fever or arthralgias are severe, a short course of oral corticosteroids (1–2 mg/kg/day) may be prescribed. Since cefaclor rarely cross-reacts with other beta-lactam antibiotics, other cephalosporins are usually tolerated.

1.9.4 Fixed Drug Eruption

A fixed drug eruption is characterized by a few well-circumscribed, oval, erythematous, or hyperpigmented plaques that recur at the same sites with repeat drug administration. Lesions favor the lips, extremities, upper trunk, and genitalia. The eruption occurs 1–2 weeks after drug exposure and tends to be asymptomatic. Barbiturates, sulfonamides, acetaminophen, ibuprofen, aspirin, tetracyclines, pseudoephedrine, lamotrigine, and phenolphthalein are the typical triggers [16]. The differential diagnosis includes arthropod bites, contact dermatitis, eczema, cellulitis, urticaria, and erythema multiforme.

To confirm the diagnosis, a skin biopsy or drug rechallenge may be performed. Histologically, a fixed drug eruption resembles erythema multiforme with additional evidence of chronicity. Identifying and removing the offending drug are essential. Other treatments are usually not necessary, but topical corticosteroids may be used for pruritus.

1.9.5 Erythema Multiforme

Erythema multiforme (EM) is a type of hypersensitivity that occurs in response to infections, medications, or other illnesses. The eruption consists of symmetric, targetoid, erythematous plaques on the skin and sometimes in the oral cavity (Fig. 1.4). Epidermal detachment is not a hallmark finding. Lesions may appear anywhere, with a preference for the palms and soles, extensor extremities, and the backs of hands and feet. Local symptoms include pruritus or burning. Fever, fatigue, arthralgias, or other viral-like symptoms may be present. The majority of EM cases in children are caused by infections, mostly from an HSV, followed by mycoplasma. Less commonly, NSAIDs, sulfonamides, penicillins, allopurinol, or anticonvulsants may cause this eruption [16]. The differential diagnosis includes bullous diseases, fixed drug eruption, subacute lupus erythematosus, polymorphous light eruption, vasculitis, urticaria, and tinea corporis.

The diagnosis of EM is mainly clinical, but a biopsy should be considered if lupus erythematosus, vasculitis, or another condition is suspected. Herpes or mycoplasma cultures and antibody titers may be performed if appropriate. Most cases of EM resolve within 2–3 weeks. Symptomatic treatment with oral antihistamines, emollients, and topical corticosteroids may be administered for pruritus [16]. For recurrent episodes associated with HSV, prophylactic acyclovir should be considered; however, treatment with acyclovir during each EM episode is usually not effective. In most cases, oral corticosteroids can result in longer and more frequent recurrences, but are sometimes prescribed for severe symptoms.

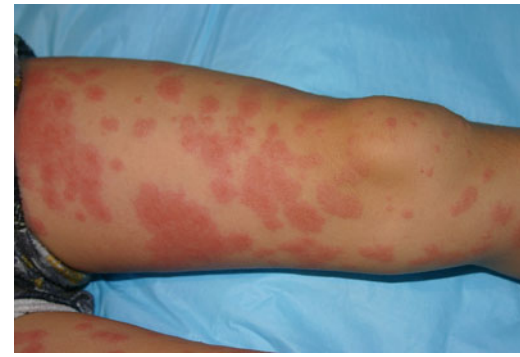

Fig. 1.4 Erythema multiforme. Targetoid plaques with central crusting on the leg

1.9.6 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and toxic epidermal necrolysis (TEN) are life-threatening skin conditions defined by the percentage of epidermal detachment. Epidermal detachment of less than 10% of the total body surface is considered to be SJS, while 10–30% is SJS/TEN overlap, and >30% is TEN. These eruptions are immune-mediated hypersensitivity reactions involving the skin and membranes, which may include eyes, nose, mouth, respiratory tract, and gastrointestinal, genital, and urethral mucosa. Prior to the rash, patients have prodromal symptoms such as malaise, fever, cough, headache, and anorexia. SJS and TEN are characterized by confluent targetoid lesions, erythroderma, or bullae, requiring involvement of at least 2 mucous membranes, with patients demonstrating the Nikolsky sign. Lesions usually start on the face and upper trunk, but can spread to other areas, often involving the palms and soles.

In contrast to EM, SJS or TEN is most commonly caused by drugs, mainly sulfonamides, NSAIDs, allopurinol, penicillins, and anticonvulsants [17]. Infections have also been associated with SJS and TEN. The differential diagnosis includes erythema multiforme, Kawasaki disease, Staphylococcal scalded skin syndrome (SSSS), pemphigus, and bullous lupus erythematosus. SSSS presents with a more superficial exfoliation pattern with crusting, and primarily affects periorificial and flexural areas.

Mortality estimates for SJS and TEN are as high as 1–5% and 25–35%, respectively [17]. Withdrawing the offending drug is essential. If epidermal detachment is extensive, patients should be transferred to an ICU or burn unit to optimize wound care, prevent infections, and attend to hydration and nutrition. Ophthalmology should be consulted for ocular involvement. The administration of systemic corticosteroids is controversial and is advocated by some for treatment during the first few days of the eruption. A longer course may increase morbidity due to increased risk of infections. Furthermore, IVIG (2.5–3 mg/kg/day) over 3–5 days has been advocated as another treatment option. Additionally, there have been reports of improvement with cyclosporine, plasmapheresis, and cyclophosphamide. Of importance, aromatic anticonvulsants (phenobarbital, phenytoin, and carbamazepine) may cross-react and should not be substituted for one another.

1.9.7 Drug Rash with Eosinophilia and Systemic Symptoms

DRESS is a life-threatening condition that develops 1–8 weeks after drug exposure. Patients usually present with a morbilliform eruption, as well as edema, cervical lymphadenopathy, fever, and internal organ involvement (hepatitis, pneumonitis, interstitial nephritis, encephalitis, myocarditis, and thyroiditis). Drugs implicated in DRESS include aromatic anticonvulsants, dapsone, allopurinol, minocycline, sulfonamides, lamotrigine, and terbinafine. Furthermore, the differential diagnosis consists of bacterial or viral infections, lymphoma, and idiopathic hypereosinophilic syndrome. A new rash associated with unexplained eosinophilia, atypical lymphocytosis, and elevated transaminases may be indicative of DRESS. Hepatic transaminases, a CBC, urinalysis, serum creatinine, and thyroid testing should be ordered at baseline and followed. A skin biopsy is usually nonspecific.

Management includes immediate removal of the offending drug. In cases of visceral involvement, systemic corticosteroids (1–2 mg/kg/day) may be useful. Topical corticosteroids and antihistamines can be prescribed for pruritus. Symptoms and labs may initially improve and then flare after a few weeks. Thyroid testing should be repeated 2–3 months after treatment to test for autoimmune thyroiditis, even if the results are normal at baseline.

1.10 Selected Pediatric Systemic Diseases

1.10.1 Juvenile Dermatomyositis

Juvenile Dermatomyositis (JD), a humoral and cellular immune-mediated chronic inflammatory condition characterized by generalized capillary vasculopathy, results in a pronounced erythematous rash of the face or extremities and symmetrical muscle weakness. JD has an incidence of 3 per million children per year [2]. Specific HLA and cytokine polymorphisms, as well as environmental triggers such as group A hemolytic streptococci and other microbial infections have been implicated in disease pathogenesis. JD should be considered when a child presents with characteristic rashes (a violaceous rash of the periocular area, pink-red papules of the dorsal fingers, photosensitive dermatitis) and two or more of the following: progressive symmetrical proximal muscle weakness, inflammatory and atrophic muscle histopathology, elevated muscle-derived enzymes, and EMG changes or MRI appearance of inflammatory myopathy. Fifty percent of patients report a progressive onset characterized by weakness, anorexia, malaise, abdominal pain, and a violaceous rash that precedes or follows muscle weakness. Thirty percent have fulminant onset of fever, weakness, and multisystem involvement [3].

Cutaneous signs include photosensitive skin changes of the hands and knuckles, “Gottron’s sign,” cutaneous ulceration at pressure points, heliotrope rash of the face, periungal changes (telangiectasia, cuticular overgrowth), and less commonly calcinosis. Nondestructive, nondeforming arthritis of the knee can occur in parallel with proximal muscle weakness, resulting in an

inability to rise from the floor. Currently, there has been no association with malignancy in children; however, myositis and muscle weakness can result in decreased esophageal motility, reflux with ulceration or aspiration pneumonia, and decreased respiratory capacity. Vasculitis of mesenteric vessels, the retina and eyelid, and renal ischemia leading to renal failure are further complications that must be considered [4].

Prompt evaluation by a specialist is warranted, as earlier diagnosis and initiation of therapy may improve overall prognosis. Workup may include CBC, CPK, LDH, Aldolase, antibody screens, and MRI.

First-line treatment includes high-dose oral corticosteroid therapy (1–2 mg/kg/day) or intravenous methylprednisone (3-day pulses of 30 mg/kg) when there is multisystem involvement. Methotrexate can be administered as second-line therapy, and has been shown to improve muscular strength as well as other signs of disease activity; evolving use of biologics should be considered. Patients should be counseled in sun protection and referred to physiotherapy following resolution of the acute phase of the disease.

1.10.2 Henoch–Schönlein Purpura

Henoch–Schönlein Purpura (HSP), an acute nongranulomatous vasculitis of small blood vessels, is the most common childhood vasculitis [2]. HSP affects predominantly male children aged two and older, and is characterized by the differential regulation of pro- and anti-inflammatory cytokines in response to IgA immune complex deposition. Although several HLA alleles have been linked to this disease, in more than half the cases, HSP is preceded by upper respiratory tract infections of viral or bacterial nature. Noninfectious triggers include antibiotics, nonsteroidal anti-inflammatory drugs, vaccinations, immune response modifiers, and insect bites.

HSP usually presents with characteristic nonblanching palpable purpura or petechiae due to edema and extravasation of erythrocytes, with lower leg predominance. Organ involvement other than skin usually involves joints, the gastrointestinal tract, and/or kidneys. Skin lesions can begin as urticarial macules or papules that may become purpuric, bullous, or necrotic. Although 80% of cases have joint and skin involvement, in 25% of cases, non-migratory oligoarthritis may be the only presenting sign [3]. Gastrointestinal symptoms range from colicky abdominal pain and positive fecal occult blood to serious complications such as intussusception, acute pancreatitis, bowel perforation, and protein-losing enteropathy. Renal complications include transient microscopic hematuria, proteinuria, gross hematuria, nephrotic syndrome, acute nephritis, and, in the long-term, end-stage renal disease; however, most renal cases have excellent prognosis with complete resolution. In rare cases, neurological symptoms such as headache, intracerebral bleeds, and seizures have been reported.

Often the diagnosis is straightforward in children presenting with purpura of the buttocks and lower extremities, and with other associated systemic findings [4]. A differential diagnosis of hypersensitivity vasculitis can be excluded by a careful diagnostic workup including patient history detailing recent infections and medications, and relevant laboratory investigations, including metabolic panels, blood cell counts, coagulation studies, radiographic studies, stool guaiac testing, urinalysis, abdominal ultrasonography for GI symptoms, and kidney biopsy with IgA immunofluorescence. A skin biopsy with IgA immunofluorescence is unnecessary unless the child presents with atypical symptoms such as hemorrhagic bullous purpura. Treatment includes supportive hydration, bed rest, and symptomatic pain relief such as nonsteroidal anti-inflammatory drugs for joint pain. Systematic corticosteroids may be administered for severe GI, joint, and renal complications, as well as hemorrhagic bullous purpura, but may not prevent long-term renal impairment. Most cases of HSP resolve spontaneously within 4 weeks; however, patients must be educated regarding recurrent attacks. Furthermore, patients with renal abnormalities require laboratory monitoring and subsequent follow-up.

1.10.3 Kawasaki Disease

Kawasaki disease (KD, mucocutaneous lymph node syndrome) is an acute febrile systemic inflammatory illness with vasculitis primarily occurring in young children. It has a proclivity to involve the coronary arteries, and is therefore a leading cause of acquired heart disease in the pediatric population [2].

The disease typically manifests as a fever lasting at least 5 days that is unresponsive to antipyretics, with at least four of the five following findings: (1) non-exudative bilateral conjunctival injection (Fig. 1.5); (2) peripheral extremity changes including erythema, edema, and periungual desquamation; (3) oropharyngeal changes including erythematous or fissured lips, strawberry tongue, and pharyngeal injection; (4) polymorphous rash; and (5) acute non-purulent cervical adenopathy. Other findings can include cardiac manifestations (arrhythmia, myocarditis, pericardial effusion), CNS manifestations (aseptic meningitis, mononuclear CSF pleocytosis, facial palsy, hearing loss), gastrointestinal manifestations (diarrhea, abdominal pain, jaundice, enlarged gallbladder, enlarged liver), musculoskeletal manifestations (arthritis, arthralgia), irritability or lethargy, urethritis and sterile pyuria, and anterior uveitis [2, 4].

KD should be considered in the differential diagnosis of children with prolonged fever and rash. Management of KD is focused on the reduction of systemic and coronary artery inflammation [18]. Treatment during the early, acute stage is usually IVIG plus high doses of aspirin until the fever is controlled or until day 14 of the disease, followed by low doses of aspirin until blood counts and echocardiograms normalize (usually 2–3 months after onset). If symptoms persist (often signaled by a rising or elevated CRP), a second course of IVIG is often effective [2, 4]. Other therapies for refractory KD include corticosteroids, pentoxifylline, methotrexate, TNF inhibitors, cyclophosphamide, ulinastatin, plasmapheresis, and cyclosporine.

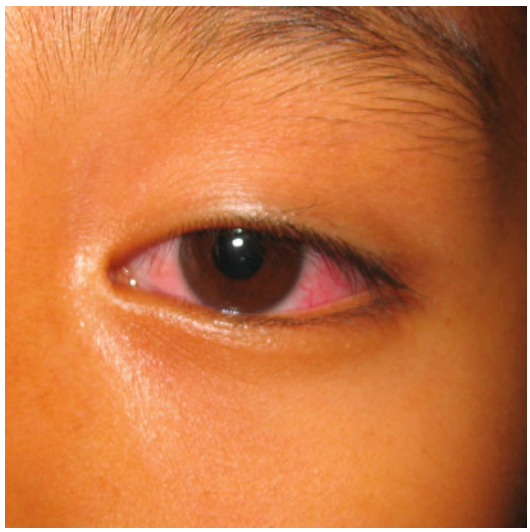

Fig. 1.5 Kawasaki's Disease. Non-exudative conjunctival injection with limbal sparing

1.11 Atopic Dermatitis

Atopic Dermatitis is the most common eczematous eruption. It presents as a chronic pruritic eruption, commonly in the first few years of life. Severe atopic dermatitis may be considered a medical emergency if associated with significant infection and/or erythroderma.

1.11.1 Eczema Herpeticum

Eczema Herpeticum (EH, Kaposi's varicelliform eruption) is a cutaneous HSV infection in patients with atopic dermatitis. The herpes virus can disseminate, leading to further complications. Patients usually present with clustered vesicles, pustules, crusts, and punched-out lesions often in areas of active dermatitis (Fig. 1.6). Direct fluorescent assay, viral culture, Tzanck tests, or HSV genomic probes can verify the diagnosis, although these techniques are not standardized for skin use [4]. Antiviral treatment should be initiated with acyclovir or similar antivirals intravenously or orally depending on disease severity. Additional supportive treatments include antipyretics, analgesics, topical corticosteroids, skin care, and antibiotics. The consideration of con-

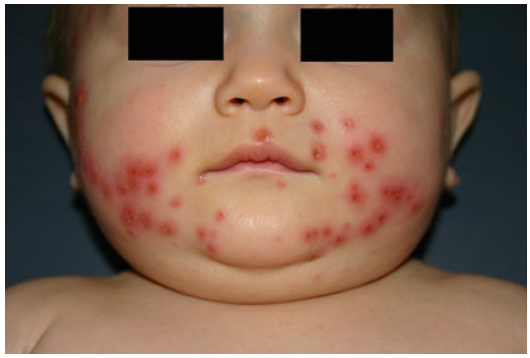

Fig. 1.6 Eczema Herpeticum. Clustered "punched-out" vesicles and erosions in areas of dermatitis indicative of eczema herpeticum

current bacterial infection with staphylococcus or streptococcus species is appropriate.

1.11.2 Bacterial Superinfection

Staphylococcus aureus superinfections are very common in patients with atopic dermatitis. They can manifest as honey-colored crusted lesions, impetigo, pustules, abscesses, and cellulitis. Active superinfected atopic dermatitis may be associated with systemic findings and can therefore be considered a dermatologic emergency. Management should include antibiotic therapy with coverage for methicillin-sensitive *S. aureus* [4]. In the case of a more significant or life-threatening infection, broader antibiotic coverage including methicillin-resistant *S. aureus* (MRSA) antibiotics is appropriate.

1.11.3 Erythroderma

Erythroderma is a generalized erythema of essentially all skin surfaces (Fig. 1.7) with inflammation and scaling, most commonly secondary to atopic dermatitis and psoriasis. The differential diagnosis includes other conditions such as cutaneous lymphoma, malignancy, drug hypersensitivity, and metabolic diseases. Erythroderma in children is generally an emergency that warrants evaluation for underlying diagnosis as well as acute skin management, and may be complicated by

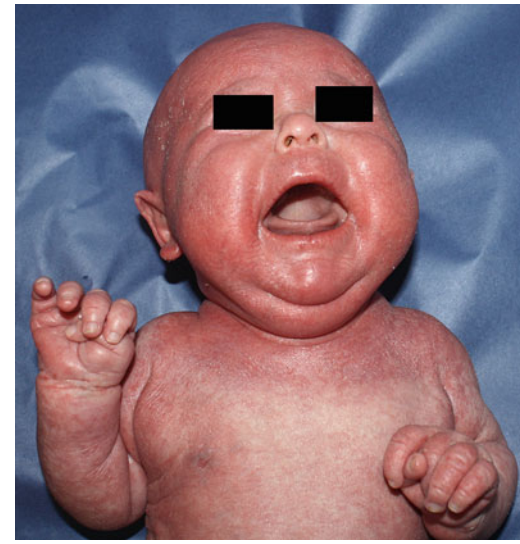

Fig. 1.7 Erythroderma. Infant with generalized erythema and scaling

sepsis. Treatment for systemic infection and intensive skin care are appropriate.

1.12 Primary Infections

1.12.1 Staphylococcal Scalded Skin Syndrome

SSSS is a superficial desquamative condition that usually presents with fever and tender skin. The exfoliative toxin-producing *S. aureus* phage group II, with hematogenous transport of the exotoxin to the skin, causes characteristic erythema and widespread sloughing of the superficial epidermis. SSSS predominately affects children less than 5 years old, who have not yet developed protective antibodies against the staphylococcal toxins and have reduced renal clearance of exfoliatins, leading to their accumulation in the body. Transmission occurs by asymptomatic carriers, such as nursery attendants and parents [19].

SSSS begins as fever, malaise, and generalized, tender, macular erythema that rapidly evolves into a scarlatiniform eruption. Over 2–5 days, flaky desquamation of the entire skin occurs [3]. In severe cases, after the erythrodermic phase, diffuse, sterile, flaccid blisters develop

with bullous desquamation of large sheets of skin. At this stage, the epidermis may separate upon gentle shear force (Nikolsky's sign) resulting in a scalded appearance. Mucous membranes are spared, distinguishing SSSS from toxic epidermal necrolysis.

Cultures of blood, cerebrospinal fluid, urine, nasopharynx, umbilicus, etc. should be obtained to identify the primary infection site [3]. However, skin cultures are classically negative, since cutaneous findings are due to a systemic toxin, not local infection. Histopathological examination of a biopsy of the roof of a blister demonstrating intraepidermal acantholysis within the stratum granulosum confirms the diagnosis.

In older literature, childhood mortality was cited as approximately 11% and usually occurred in conjunction with extensive exfoliation, overwhelming sepsis and the resulting electrolyte imbalance [20]. Improved recognition and diagnosis have markedly decreased mortality. Treatment with intravenous antibiotics, such as a beta-lactamase-resistant anti-staphylococcal antibiotics or, if MRSA is suspected, vancomycin, is appropriate. Alternatively, clindamycin may be prescribed if the Staphylococcus aureus strain is found to be susceptible to this agent. Management also consists of analgesia, sterile dressings, temperature regulation, and fluid replacement. The skin usually heals without scarring.

1.12.2 Necrotizing Fasciitis

Necrotizing fasciitis is a bacterial infection of the superficial fascia and subcutaneous cellular tissue, and is considered an acute emergency with high morbidity and mortality. Type 1 infections are polymicrobial, commonly with streptococcus, staphylococcus, bacteroides, and gram-negative enterobacteriaceae. Type 2 are monomicrobial infections, classically caused by group A Streptococcus (GAS) either alone or in association with Staphylococcus aureus. Recently, community-acquired MRSA has been identified as a cause of necrotizing fasciitis in up to 39% of cases, with 93% of these cases monomicrobial in nature [21]. GAS is reportedly the most commonly isolated organism in children with necrotizing fasciitis [22]. Pediatric risk factors include chronic illness, trauma, surgery, and recent infection with varicella [23].

Necrotizing fasciitis commonly presents with localized pain and erythema [22]. Within hours to days the infection can progress to a large area of necrosis, ulceration, and bullae, as well as septic shock [3]. Imaging studies may aid in the diagnosis of necrotizing fasciitis. However, imaging should not delay surgical inspection to identify and debride deep soft tissue infection, as well as to obtain surgical specimens for Gram culture and stain. Delay in surgical debridement is a significant modifiable contributor to increased mortality. Currently, pediatric mortality rates are as high as 5.4% [22].

If necrotizing fasciitis is suspected, immediate management should be in an intensive care setting involving surgical consultation, antibiotic coverage, and fluid resuscitation. The priority is early surgical debridement to remove all affected, necrotic tissue. GAS infections should be treated with intravenous penicillin and clindamycin while treatment for non-GAS infections should include intravenous broad spectrum antibiotics with aerobic, anaerobic, and MRSA coverage.

1.12.3 Herpes Simplex Virus

Gingivostomatitis is the most common clinical manifestation of primary HSV infection in childhood [8]. HSV-1 causes 90% of the cases. Gingivostomatitis is characterized by multiple crops of vesicles on any oral mucosal surface. An intensely erythematous, edematous, and ulcerated gingiva may be accompanied by fever, malaise, headache, dysphagia, salivation, regional lymphadenitis, and even life-threatening encephalitis. Treatment includes adequate hydration, nutrition, analgesia, and antipyretics. While there is insufficient evidence that oral acyclovir is effective in decreasing symptoms, many experts treat severe cases [9, 24].

A less common presentation of HSV is herpetic whitlow (herpetic paronychia). In children, this may be the result of digital/oral contact; in

adolescents, digital/genital contact is more common, making HSV-2 the principal infectious agent. Herpetic whitlow usually manifests with local swelling, erythema, and one or more small, tender, ulcerated vesicles on the pulp of the distal phalanx of the hand. Fever and malaise may be present, especially in infants. Oral antiviral medications may be used in extensive disease [9].

1.12.4 Fungal Infections

Cutaneous fungal infections, which include dermatophyte infections of hair, skin, and nails, are not generally pediatric emergencies. However, there are some fungal infections that are associated with a more severe clinical picture, and these may be life-threatening in immune-compromised patients. Risk factors for cutaneous fungal infections include immunosuppression, long-term hospital stays, prolonged broad-spectrum antibiotic use, parenteral feeding, and long-term intravascular catheters [25]. Some of the most important and/or dangerous of these life-threatening cutaneous fungal infections are systemic candidiasis, Paracoccidioidomycosis, sporotrichosis, zygomycosis, and histoplasmosis and should be included in the differential diagnosis of atypical cutaneous rashes and viral drug reactions.

Candida and *Aspergillus* species are the leading causes of invasive fungal infections in pediatric patients [26]. Dermatologic manifestations of systemic candidiasis affect 13–36% of patients. Cutaneous findings in systemic candidiasis are typically erythematous or purpuric plaques, macules, or nodules, sometimes with central pale vesicular or pustular centers. The rash may be generalized or localized to the extremities. Pediatric invasive *Aspergillus* (Fig. 1.8) cases have cutaneous involvement in 14–41%. In a large multicenter pediatric study, 53% of children with cutaneous manifestations presented with disease strictly localized to the skin [27]. Cutaneous findings are typically tender, erythematous macules, or vesicles, which frequently progress to necrotic eschars.

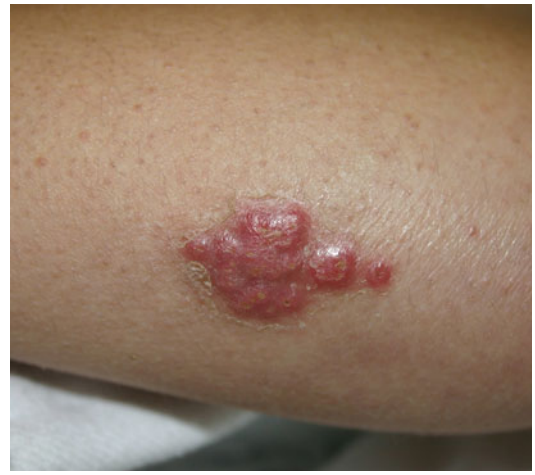

Fig. 1.8 Aspergillosis. Erythematous plaque with superficial scale

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Infectious Emergencies in Dermatology

2

Emily Stamell and Karthik Krishnamurthy

2.1 Introduction

While most infections with dermatological manifestations are self-limited, there are clinical scenarios when infectious cutaneous diseases are associated with life-threatening systemic symptoms. These diseases may be difficult to diagnose, but a dermatologist can use visual cues to create a differential. The majority of infectious emergencies in dermatology are due to a bacterial pathogen; however, select viruses, fungi, and parasites can also cause severe disease. This chapter focuses on cutaneous infections where prompt diagnosis and initiation of treatment are paramount. We highlight the main cutaneous patterns, individuals at risk, diagnostic modalities applicable to the dermatologist, and treatment options for each infectious emergency in dermatology.

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2.2 Bacterial Infections

2.2.1 Necrotizing Fasciitis

Necrotizing fasciitis is characterized by rapidly progressive necrosis of subcutaneous fat and fascia. In many cases, no identifiable cause is found; however, patients often have a history of trauma [1]. Most patients have preexisting conditions increasing their susceptibility to infection, including immunosuppression, diabetes, chronic disease, drugs (e.g., steroids), malnutrition, age greater than 60, intravenous drug misuse, peripheral vascular disease, renal failure, underlying malignancy, or obesity [2].

Necrotizing fasciitis can be divided into three categories based on etiologic agent. Type I is polymicrobial and can include Group A β-hemolytic Streptococcus *Streptococcus pyogenes* or GAS), *Staphylococcus aureus, Klebsiella* species, *Enterococci*, *Escherichia coli*, as well as *Clostridium* and *Bacteroides* species. Type II is caused by GAS only and Type III is associated with *Vibrio vulnificus*, which is introduced into the subcutaneous tissue by puncture wounds from fish or marine creatures [3].

The initial clinical features may be nonspecific, often leading to misdiagnosis. Early findings include pain, cellulitis, fever, tachycardia, swelling, induration, and skin anesthesia. As the infection progresses, severe pain out of proportion with the skin examination, purple or black skin discoloration, blistering, hemorrhagic bullae, crepitus, discharge

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Table 2.1 Antimicrobial regimens for necrotizing fasciitis [3]

Organism	First-line therapy
Mixed Infections	Ampicllin–sulbactam intravenous 1.5–3 g every 6 h or Piperacillin–tazobactam intravenous (dose based on creatinine clearance) + Clindamycin intravenous 450–900 mg every 8 h + Ciprofloxacin intravenous 400 mg every 12 h or Meropenem 500 mg every 8 h/cefotaxime 1–2 g every 8–12 h + Metronidazole 500 mg every 8 h/Clindamycin intravenous 450–900 mg every 8 h
GAS	Penicillin intravenous 1–2 million units every 6 h + Clindamycin intravenous 450–900 mg every 8 h
S. aureus	Nafcillin intravenous 1–2 g every 4–6 h or Oxacillin intravenous 1–1.5 g every 4–6 h or Cefazolin intravenous 1–2 g every 6–8 h or Clindamycin intravenous 450–900 mg every 8 h
MRSA	Vancomycin intravenous 1 g every 12 h (doses adjusted based on creatinine clearance and vancomycin troughs)
Clostridium	Penicillin intravenous 1–2 million units every 6 h + Clindamycin intravenous 450–900 mg every 8 h
P. aeruginosa	Ceftazidime intravenous 2 g every 8 h

of "dishwater," or murky, grayish, fluid, severe sepsis, systemic inflammatory response syndrome, or multiorgan failure can develop [2]. The infection rapidly evolves over hours or days.

The pathognomonic finding of crepitus and soft tissue air on plain radiograph is only seen in 37% and 57% of patients, respectively. Crepitus results from anaerobic tissue metabolism, which produces hydrogen and nitrogen, insoluble gases, that accumulate in the subcutaneous tissues. Other common laboratory findings include elevated white cell count, increased concentrations of serum glucose, urea, and creatinine, hypoalbuminemia, acidosis, and altered coagulation profile [4]. However, given the nonspecific nature of these studies, the diagnosis is clinical. Clinical signs that favor necrotizing fasciitis over cellulitis include presence of cutaneous anesthesia as it suggests a deeper component to the infection affecting sensory nerves, severe pain, rapidly spreading tense edema, hemorrhagic bullae formation, gray-blue discoloration, and foul-smelling discharge [5].

The mainstay of effective treatment is extensive surgical debridement in conjunction with broad-spectrum antibiotics. Gram stain can guide appropriate antimicrobial therapy, but should not be delayed while awaiting results. Initial therapy should include a β-lactam/β-lactamase inhibitor combined with broad-spectrum coverage against Gram-negative bacilli, *Staphylococci, Streptococci*, and anaerobes. Antibiotics can be tailored depending on the isolated organism(s). Table 2.1 outlines the antimicrobial algorithm for necrotizing fasciitis [3]. Hyperbaric oxygen has been postulated to decrease the number of debridements and mortality; however, no large study has confirmed this theory [6]. Intravenous immunoglobulin (IVIG) has been used as an adjuvant therapy primarily in patients with GAS necrotizing

fasciitis. Studies have showed varying success, and it should not replace the gold standard of debridement and antimicrobial therapy [7, 8].

Mortality rates range from 20 to 40% [5]. One retrospective study identified eight independent predictors of mortality for necrotizing fasciitis: liver cirrhosis, soft tissue air, *Aeromonas* infection, a gram-negative facultative anaerobic rod, age over 60 years, band polymorphonuclear neutrophils greater than 10%, activated partial thromoplastin time of greater than 60 s, and serum creatinine greater than 2 mg/dL [9].

2.2.2 Preseptal and Orbital Cellulitis

Bacterial infections involving the orbit potentially cause severe damage to the eye, cavernous sinus thrombosis, and death. Preseptal cellulitis is an infection of the eyelids and surrounding skin anterior to the orbital septum whereas orbital cellulitis is an infection posterior to the septum. Preseptal cellulitis is usually secondary to trauma or bacteremia and the average age of patients is 21 months of age. On the other hand, orbital (also known as post-septal) cellulitis is a complication of sinusitis, with average incident age of 12 years [10]. It is imperative to distinguish orbital cellulitis from preseptal cellulitis as the former is a more severe infection, threatening permanent vision damage, requiring hospitalization, and intravenous antibiotics [3].

Clinical signs can be useful in characterizing preseptal and orbital cellulitis. Patients with either form of cellulitis complain of pain, conjunctivitis, epiphora (insufficient tear film drainage from the eyes), and blurred vision. Physical exam will reveal periorbital erythema and edema. However, patients with orbital cellulitis may also display ophthalmoplegia, pain on eye motion, proptosis, vision loss, abnormal papillary reflexes, and/or disk edema [10]. If clinical evaluation is unequivocal, computed tomography (CT) with intravenous contrast can distinguish the two conditions [11].

The pathogenesis of the infection usually dictates the causative organism. The pathogen in preseptal cellulitis due to trauma is most likely *S. aureus* or GAS, whereas preseptal cellulitis due to primary bacteremia is usually due to *Streptococcus pneumoniae*. Orbital cellulitis may be polymicrobial and is caused by pathogens responsible for sinusitis, including *S. pneumoniae*, non-typable *Haemophilus influenzae*, *Moraxella catarrhalis*, GAS, *S. aureus*, and/or anaerobes [10].

Consultation with ophthalmology and otolaryngology should be obtained immediately with concomitant initiation of antimicrobials against the common pathogens. Preseptal cellulitis is managed with oral antibiotics whereas orbital cellulitis requires intravenous antimicrobials. Surgical intervention, such as abscess drainage, has a role in the management of patients with orbital cellulitis. A recent national perspective study found that older patients, those with diplopia, and hospital admission via the emergency room were predictors of surgery [12]. With prompt initiation of antimicrobials, prognosis is very good. When treatment is inadequate or delayed, however, complications include blindness, cranial nerve palsies, brain abscesses, and death [13].

2.2.3 Malignant Otitis Externa

Malignant otitis externa is a severe form of otitis externa most commonly seen in elderly diabetic patients. Patients often report failure of local therapy. Clinically, they have severe tenderness around the auricle, persistent drainage, and granulation tissue at the junction of the osseous and cartilaginous portions of the external ear canal. Almost all cases are due to *P. aeruginosa* and antimicrobial treatment should be directed against this pathogen. While the treatment of choice was previously oral ciprofloxacin 750 mg twice daily with or without rifampin, as mentioned previously, increasing pseudomonal resistance to fluoroquinolones now necessitates hospitalization and intravenous antibiotics with a third-generation cephalosporin, such as ceftazidime 2 g every 8 h. Complications include osteomyelitis of the skull, nerve palsies, mastoiditis, sepsis, sigmoid sinus thrombosis, and a mortality rate of around 20% [5, 14].

2.2.4 Meningococcemia

Meningococcemia is a serious medical emergency that is frequently diagnosed by dermatologists due to the presence of a classic petechial eruption seen in one-third to one-half of patients. The causative pathogen is *Neisseria meningitidis*, an aerobic Gram-negative diplococcus, and primarily affects young children and young adults with a male predominance [15]. The incidence of endemic disease is up to 5 cases per 100,000 population per year worldwide [16]. Epidemic rates of disease are seen in sub-Saharan Africa [17]. The most common serogroups are A, B, C, Y, and W-135. Worldwide, the majority of cases are due to serogroups A and C; however, in the United States, serogroups B and C predominate [15].

Transmission is via respiratory droplets and there is an average incubation period of 3–4 days [18]. Although not all *N. meningitidis* infections result in septicemia, when they do, a petechial eruption precedes the development of ecchymoses and ischemic necrosis (Fig. 2.1). Other occasional skin findings include bullous hemorrhagic lesions and a transient blanchable morbilliform eruption. The rash of meningococcemia can be accompanied by systemic symptoms including fever, chills, hypotension, meningitis, meningoencephalitis, pneumonia, arthritis, periarditits, myocarditits, and disseminated intravascular coagulation (DIC) [5].

Prompt diagnosis and initiation of treatment with intravenous antibiotics are paramount. Diagnosis is confirmed through detection of *N. meningitidis* in blood or cerebral spinal fluid cultures. Polymerase chain reaction analysis has been developed for rapid detection of specific serogroups of *N. meningitidis*, but is not commercially available in many countries [18]. Appropriate antibiotics include penicillin G 500,000 U/kg/day in six divided doses, ceftriaxone 100 mg/kg/day in one or two divided doses, or cefotaxime 200 mg/kg/day in three divided doses. Close contacts should receive prophylactic antibiotic treatment with rifampin [16, 19]. Hearing loss, limb amputation, and a mortality rate of 10% are among the complications of meningococcemia [20]. A quadrivalent polysaccharide vaccine has been available in the United States since 1982. This vaccine is effective against serogroups A, C, Y, and W-135 and induces serotype-specific antibodies in older children and adults, but is not immunogenic in young children. While this vaccine was approved for individuals older than 2 years of age, it was only recommended to control outbreaks, to protect immunocompromised individuals, for people traveling to epidemic areas, or for individuals living in close quarters. Recommendations have more recently changed with the development of a quadrivalent A, C, Y, and W-135 conjugate vaccine. This vaccine provides long-term protection as it induces immunologic memory [20]. Current vaccination recommendations released by the Centers for Disease Control and Prevention (CDC) include routine vaccination of adolescents at age 11–12 years, unvaccinated adolescents at entry to high school or age 15 (whichever comes first), all college freshman residing in dormitories, military personnel, and high-risk groups [16]. It is important to note that neither vaccine protects against serogroup B, one of the most commonly isolated types in the United States.

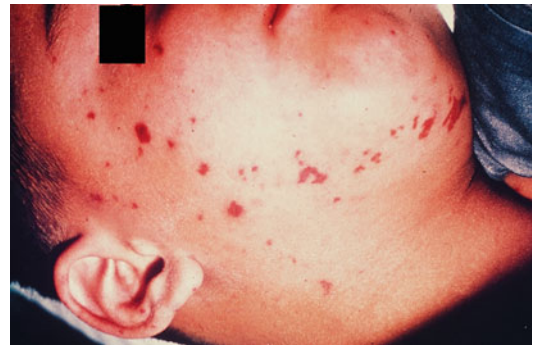

Fig. 2.1 Meningococcemia

2.2.5 Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is the most common rickettsial disease in the United States and is characterized by the history of a tick bite, fever, and rash [21]. *Rickettsia rickettsii*, a small gram-negative bacteria, is transmitted into the dermis by a tick bite and replicates in the

endothelial cells, subsequently causing vasculitis, hypoperfusion, and end-organ damage. In the United States, the vector is the American dog tick, *Dermacentor variabilis*, and the Rocky Mountain wood tick, *Dermacentor andersoni* [22]. RMSF has been reported in the United States, Western Canada, Western and Central Mexico, Panama, Costa Rica, Northwestern Argentina, Brazil, and Colombia. In the United States, RMSF has occurred in every state except for Vermont and Maine, with half the cases found in Oklahoma, Tennessee, Arkansas, Maryland, Virginia, and the Carolinas [23]. Up to 1,200 cases annually have been reported in the United States, but there are likely a number of unreported cases each year [24]. The highest incidence of disease has been seen in children less than 10 years of age and adults between 40 and 64 years old as well as men and Caucasians [23].

The diagnosis is primarily clinical. The triad of fever, headache, and rash in an individual with the history of a tick bite or exposure to ticks should raise suspicion for RMSF; however, this is only seen in 3% of patients with RMSF [25]. Fever often accompanied by headache and myalgia precedes the rash by 3–6 days. Other early symptoms include nausea, vomiting, and abdominal pain. The patient may eventually develop hypotension, thrombocytopenia, and acute renal failure followed by hypotensive shock and acute respiratory failure. The rash begins as small macules around the wrists and ankles, eventually involving the majority of the body, but spares the face. Red-pink macules and papules are seen on the palms and soles later in the course of disease. Petechiae develop within the macules or papules due to severe vascular injury. The petechiae eventually evolve to cutaneous necrosis [5, 19, 21].

Definitive diagnosis can be made by immunofluorescence or immunohistochemistry in a biopsy specimen of an eschar, macule, papule, or petechial lesion. Serologic diagnosis cannot be utilized at the time of diagnosis as antibodies do not develop until at least 7 days after the onset of the illness. Acute and convalescent-phase serum samples can be used for indirect immunofluorescence, latex agglutination, and enzyme immunoassay to detect anti-rickettsial antibodies. Often a clinical diagnosis is rendered as treatment with doxycycline 100 mg twice daily for adults or 2.2 mg/kg twice daily for children under 45 kg for 7–14 days should not be delayed for diagnostic confirmation [21]. Chloramphenicol 50 mg/kg is an alternative treatment for patients younger than 9 years of age or pregnant women [18]. Of 100 individuals infected, 5–10 of those will die and many others will suffer amputation, deafness, or permanent learning disability from hypoperfusion [22]. As there are no current vaccines to prevent rickettsial diseases, preventative measures have been emphasized. General recommendations for prevention of RMSF include avoidance of tick habitats, implementation of personal protective measures to limit possibility of tick exposure, frequent examination of oneself to identify any attached ticks, and proper removal of attached ticks to reduce transmission [23, 26]. A minimum of 4–6-h period of attachment is required for transmission of *R. rickettsii*. Therefore, early and proper removal techniques are emphasized to decrease the risk of transmission. These include wearing protective gloves, grasping the tick with fine forceps close to the point of attachment and pulling straight outward, avoiding jerking, twisting, or squeezing the tick, and disinfecting the bite wound after tick removal [27]. Both the use of Tick repellent (*N*,*N*-diethyl-*meta*-toluamide, DEET) on exposed skin and application of an acaricide (e.g.,disease is caused permethrin) on clothing can be helpful [23, 28].

2.2.6 Lyme Disease

Lyme disease, also known as Lyme borreliosis, is the most common tick-borne infectious disease in North America [29]. The disease is caused by the spirochete *Borrelia burgdorferi* sensu lato complex and is transmitted by Ixodes ticks. In the United States, Lyme borreliosis is caused specifically by *B. burgdorferi* sensu stricto and *Ixodes scapularis* serves as the primary vector. Small mammals, such as white-footed mouse, white-tailed deer, and raccoons, and are the reservoir for the disease. Lyme disease is transmitted through the saliva of the *Ixodes* ticks, and a

feeding period of more than 36 h is usually required for transmission [30]. Disease transmission is most common between June and August [29].

Erythema migrans is the most common clinical manifestation of localized disease and has been seen in as many as 89% of patients in one case series [31]. Clinically, an expanding red annular patch with or without central clearing is appreciated at the site of the tick bite. Borrelial lymphocytoma, a painless bluish-red nodule or plaque usually on the ear lobe, ear helix, nipple, or scrotum, is a rare cutaneous lesion that also occurs at the site of a tick bite during the early disseminated stage of Lyme disease. Early disseminated disease is characterized by one of the following: two or more erythema migrans lesions, Lyme neuroborreliosis (meningo-radiculitis, meningitis, or peripheral facial palsy), or Lyme carditis (acute onset of atrioventricular conduction delays, rhythm disturbances, myocarditis, or pericarditis). Late Lyme disease manifests as arthritis, which is characterized by recurrent attacks or persistent swelling in one or more large joints, or acrodermatitis chronica atrophicans (chronic erythematous plaques on the extensor surfaces of the extremities, which eventually become atrophic) [32]. Late Lyme neuroborreliosis is uncommon and presents as slowly progressing encephalomyelitis [33].

Diagnosis of Lyme disease can be made clinically by the presence of erythema migrans as serologic studies early in the disease are generally negative [29]. Serologic evaluation is pursued in patients without erythema migrans. Samples are first screened with an enzyme-linked immunosorbent assay (ELISA). IgM antibodies appear 2–6 weeks after exposure and IgG titers can be detected 3–4 weeks thereafter [34]. The utility of the ELISA varies depending on disease prevalence. The positive predictive value is much lower, ranging from 8 to 28% depending on the sensitivity and specificity, in a region with low prevalence of disease whereas the positive predictive value is as high as 83% in a region with a high prevalence of disease. The false negative rate is low for the ELISA with the negative predictive value of the test ranging from 95 to 99% [35]. If the ELISA is positive or equivocal, then IgM and IgG immunoblots are performed. Of note, IgG levels are positive after at least 4 weeks of symptoms [36].

Treatment is required to prevent disseminated disease and the development of delayed complications. A single dose of doxycycline 200 mg orally can be administered within 72 h of removal of an Ixodes scapularis as a chemoprophylactic measure except to children less than 8 years of age and pregnant women [39]. Doxycycline 100 mg twice daily and amoxicillin 500 mg twice daily are both indicated in the treatment of Lyme disease. Cefuroxime axetil 500 mg twice daily is considered second line due to cost and intravenous penicillin is now limited to cases with neurologic involvement. The length of treatment varies based on the clinical manifestations of the disease. A 14-day course of antibiotics is indicated in patients with neurologic involvement or borrelial lymphocytoma. A 28-day course of antibiotics, on the other hand, is required in patients with late neuroborreliosis, recurrent arthritis after one course of oral treatment, and acrodermatitis chronica atrophicans [29, 37].

Prevention of infection is vital in decreasing the incidence of infections and the development of late complications. Repellents are the most effective modality to prevent tick attachment, and the most frequent agent used is DEET [38]. Repellents combined with protective clothing have been shown to reduce the incidence of Lyme disease infections [40]. Permethrin can be applied to clothing, shoes, bed nets, or other outdoor equipment, but has limited utility as a topical agent [38]. If a tick is found attached to an individual, care should be taken to remove the tick appropriately. Both the World Health Organization and the CDC recommend using fine-tipped forceps to grasp the tick closest to the point of entry to the skin, and the body of the tick should not be compressed [34].

2.2.7 Anthrax

Anthrax is caused by *Bacillus anthracis*, an aerobic Gram-positive rod, and results in three different clinical syndromes depending on the mode of

transmission: cutaneous anthrax via inoculation, pulmonary anthrax via inhalation, and gastrointestinal anthrax via ingestion. *B. anthracis* produces three polypeptides that comprise anthrax toxin: protective antigen (PA), lethal factor (LF, a protease), and edema factor (EF, an adenyl cyclase). The PA binds to cellular receptors, is cleaved by cellular furin, oligomerizes, and transports LF and EF into cells. Edema toxin (ET, the combination of PA and EF) is a calcium- and calmodulin-dependent adenylate cyclase that increases the intracellular level of cyclic AMP (cAMP), and ultimately leads to impaired water homeostasis and cellular edema. Lethal toxin (LT, the combination of PA and LF) is a zinc-dependent endoprotease. It cleaves the N-terminus of mitogen-activated protein kinase kinases (MAPKK) and thus inhibits the MAPKKs. As such, lethal toxin promotes macrophage apoptosis and release of tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) [41]. ET and LT are responsible for the clinical symptoms of anthrax infection.

In cutaneous anthrax, the most common form, spores gain access to the skin via trauma and germinate within macrophages locally. The result is edema and necrosis from toxins and a hyperinflammatory response. Although the majority of cases remain localized, up to 10% of untreated cutaneous anthrax may disseminate. In this situation, macrophages carry the spores to regional lymph nodes where they germinate and the bacteria rapidly multiply. It subsequently disseminates through the blood, causing hemorrhagic lymphadenitis and possible death from septicemia and toxemia [42].

Cutaneous anthrax starts as a painless pruritic papule approximately 1–12 days after inoculation. The papule enlarges and develops a central vesicle or bulla with surrounding edema within 48 h. The vesicle becomes hemorrhagic with the subsequent development of necrosis and ulceration. The classic black eschar (thick crust) develops over the ulcer with edema and erythema remaining a prominent feature [43]. Associated symptoms include fever, headache, malaise, and regional lymphadenopathy [44]. In 90% of cases, the eschar disengages and heals without scarring over 1–2 weeks without systemic complications. However, in the other 10% of cases, edema of the head and neck resulting in respiratory compromise or toxic shock from overwhelming septicemia can occur [45].

Diagnosis of anthrax must be confirmed with serology or polymerase chain reaction assay via the CDC; however, these tests can take several days. Treatment should not be delayed for confirmation. In uncomplicated cases of cutaneous anthrax, oral ciprofloxacin 500 mg twice daily or doxycycline 100 mg twice daily is indicated for adults. For children, oral ciprofloxacin 10–15 mg/kg twice daily, not to exceed 1 g/d, or doxycycline 100 mg twice daily should be used. The CDC currently advocates for a 60-day course of antibiotics given increased likelihood of reexposure. Intravenous ciprofloxacin 400 mg every 12 h or doxycycline 100 mg every 12 h are indicated for complicated cases of cutaneous anthrax [3]. The mortality rate in untreated cutaneous anthrax is as high as 20%. However, with appropriate treatment, the mortality rate is less than 1% [46].

2.2.8 Tularemia

Tularemia, a bacterial infection caused by *Francisella tularenis*, a Gram-negative, nonmotile coccobacillus, can present as six distinct syndromes according to the mode of transmission and clinical presentation: ulceroglandular, glandular, oculoglandular, oropharyngeal/gastrointestinal, typhoidal/septicemic, and pneumonic [5]. Tularemia is an arthropod-borne disease and is transmitted by the ticks, *Amblyomma americanum* (lone-start tick), *Dermacenter andersoni* (Rocky Mountain wood tick), and *Dermacenter variabilis* (American dog tick) as well as the deerfly, *Chrysops discalis*. *F. tularensis* can also be transmitted by handling infected mammals, such as rabbits, muskrats, prairie dogs, and other rodents, or by contaminated food or water [47].

Ulceroglandular tularemia is the most common type and accounts for 80% of cases of tularemia. A painful erythematous papule develops at the inoculation site and can be solitary or multiple depending on the mode of transmission. The papule(s) develop first into a pustule and then a punched-out ulcer with raised ragged edges and a

gray-to-red necrotic base [48]. A necrotic eschar is seen at the site of the ulcer and tender regional lymphadenopathy follows. In contrast to cutaneous anthrax, the eschar heals with scarring after several weeks to months [48]. Sudden onset of flu-like symptoms develops on average 4–5 days after inoculation. Hematogenous spread to the spleen, liver, lungs, kidneys, intestine, central nervous system, and skeletal muscles can occur [47]. Tularemids, or secondary eruptions, may occur following hematogenous dissemination and presents as macular, morbilliform, nodular, acneiform, papulovesicular, or plaque-like eruptions [48].

Oculoglandular tularemia occurs in less than 1% of cases of tularemia and can present with conjunctivitis, periorbital edema and erythema, lymphadenopathy, and lymphadenitis [49]. The other forms of tularemia do not present with cutaneous findings.

Diagnosis is made by fluorescent antibody testing. First-line treatment is streptomycin 1 g intramuscularly every 12 h for 10 days, but intravenous gentamicin 1.5–2 mg/kg loading dose followed by 1–1.7 mg/kg every 8 h or 5–7 mg/kg every 24 h, ciprofloxacin 500–750 mg twice a day for 10 days, or levofloxacin 500 mg daily for 14 days have also proven efficacious in the treatment of tularemia. Doxycycline 100 mg oral or intravenous for 14–21 days has also demonstrated efficacy, but is associated with higher risk of relapse [5, 50].

2.2.9 Staphyloccocal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS), also known as Ritter's disease or pemphigus neonatorum, is caused by *S. aureus* exfoliative (also known as epidermolytic) toxins (ETs), primarily A and B. The toxins are directed against desmoglein-1, a desmosomal adhesion molecule, which causes an intraepidermal split through the granular layer [51]. As a toxin-mediated disease, the bacterial infection usually lies at a distant focus, most commonly the conjunctiva, nasopharynx, ear, urinary tract, or skin, and no organism is recovered from lesional skin, yielding negative tissue cultures [18]. SSSS primarily affects children and rarely adults with renal disease, as the exfoliative toxins are excreted by the kidneys, or immunocompromise [19, 52, 53].

The initial signs of SSSS are abrupt onset of fever, skin tenderness, and toxic erythema. The erythema first appears on the head and generalizes in 48 h, but sparing the palms, sole, and mucous membranes. Flaccid bullae may develop, and the Nikolsky sign is positive [19]. Within 1–2 days, the skin sloughs, usually starting in the flexural areas. Scaling and desquamation occur for the next 3–5 days, and re-epithelialization is seen 10–14 days after the initial signs [5] (Fig. 2.2). Of note, the absence of mucosal involvement is helpful in clinical differentiation of SSSS from Stevens–Johnson Syndrome and

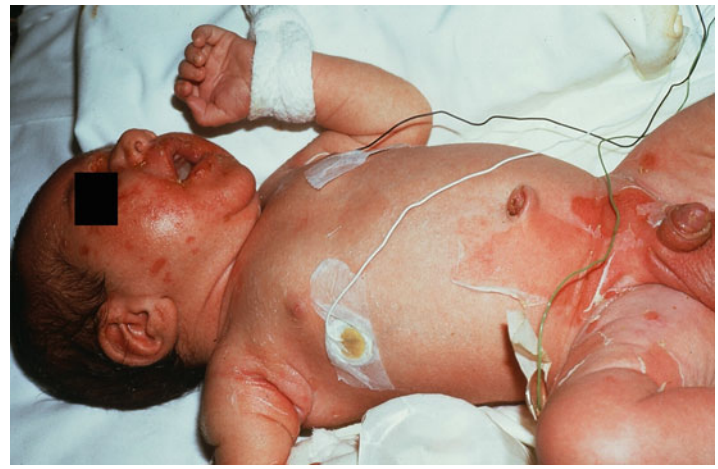

Fig. 2.2 Ritter's disease

toxic epidermal necrolysis (TEN), as desmoglein-1 is not expressed in mucosal epithelium. In addition, the diagnosis can be distinguished from TEN by histologic examination of the roof of a blister, as TEN shows full thickness epidermal necrosis, whereas SSSS only affects the upper layers of the epidermis.

Both immediate initiation of appropriate antimicrobials and supportive care are crucial [19]. Antimicrobial regimens for SSSS include dicloxacillin 2 g every 6 h or cefazolin 1 g every 8 h. If MRSA is suspected, then vancomycin 1 g every 12 h, with doses adjusted based on creatinine clearance and vancomycin troughs, is indicated [54]. Prognosis is good in children, but mortality in adults approaches 50%. In adults with underlying disease, mortality is almost 100% [55].

2.2.10 Toxic Shock Syndrome

Toxic shock syndrome (TSS) results from the release of bacterial antigens, known as superantigens, from *S. aureus*, GAS, and group C streptococcus. The superantigen causes leaking capillaries, which clinically results in fever, exanthem, mucositis, "strawberry" tongue, hypotension, multiorgan dysfunction, and convalescent desquamation [56]. Superantigens have the ability to bypass MHC-limited antigen processing, and instead bind unprocessed directly to MHC class II molecules and activate T-cells [57].

TSS can be divided into two categories: menstrual and non-menstrual. Menstrual TSS is secondary to strains of *S. aureus* that produce toxic shock syndrome toxin-1 (TSST-1) and historically has been linked to superabsorbent tampons [58]. Non-menstrual TSS is associated with any staphylococcal infection that produces TSST-1, staphylococcal enterotoxin (SE) serotype B, and SE serotype C in addition to 11 different streptococcal superantigens [59, 60].

Staphylococcal TSS has an abrupt onset with flu-like symptoms followed by confusion, lethargy, and agitation. Rash is common early in the illness; however, the characteristic desquamation does not occur until 10–21 days after the onset of disease [54]. In contrast, the desquamation in TEN is full thickness and occurs hours to days from the first signs of the disease [5]. The source of infection in *staphylococcal* TSS is not always clear and is not identified in a large number of patients. *S. aureus* is rarely cultured from the blood, but instead is found in the focus of infection if one is identified. In contrast to staphylococcal TSS, which occurs in the setting of menstruation or nosocomial infections, streptococcal TSS usually arises from deep invasive soft-tissue infections [57]. The illness is similar, although more than 60% of cases have positive blood cultures and the source of infection is usually easy to identify [57, 61]. In addition, mortality rate is much higher in streptococcal TSS [62].

Supportive management, source control, and appropriate antimicrobial coverage are the most important immediate steps in treatment. However, it is important to recognize that treatment must both reduce organism load and exotoxin production [57]. Antimicrobial regimens are tailored to the specific organisms responsible for TSS. Table 2.2 outlines first- and second-line therapies for GAS, MSSA, and MRSA infections (Table 2.2). It is important to mention that the role of clindamycin or linezolid in the antimicrobial regimen is to inhibit toxin production by both *S. aureus* and GAS [57].

IVIG has been used as an adjuvant therapy in the treatment of TSS as it has been shown to block T-cell activation by staphylococcal and streptococcal superantigens [63]. A Canadian comparative observational study found that there was an improved 30-day survival in 21 patients who received IVIG compared to the 32 patents who did not [7]. Subsequently, a multicenter randomized placebo control trial attempted to examine the efficacy of IVIG in streptococcal TSS; however, the trial only enrolled 21 patients and was terminated due to low recruitment. The study did analyze the 21 patients and found that there was a higher mortality rate in the placebo group at 28 days, although it did not meet statistical significance [8].

Table 2.2 Antimicrobial regimens for TSS [3, 57]

Organism	First-line therapy	Second-line therapy
GAS	Penicillin G 3–4 million units every 4 h + Clindamycin 600–900 mg every 8 h	Macrolide or fluorquinolone + Clindamycin 600–900 mg every 8 h
S. aureus (MSSA)	Cloxacillin 500 mg PO every 6 h or Nafcillin 1–2 g IV every 4–6 h or Cefazolin 500–1,000 mg every 6–8 h + Clindamycin 600–900 mg every 8 h	Clarithromycin 250–500 mg PO + Clindamycin 600–900 mg every 8 h
S. aureas (MRSA)	Vancomycin 1 g every 12 h (adjusted for creatinine clearance) + Clindamycin 600–900 mg every 8 h or Linezolid 600 mg IV/PO every 12 h	

2.2.11 Purpura Fulminans

Purpura fulminans is seen in three clinical settings: hereditary deficiency of protein C or S; acute infectious purpura fulminans; and idiopathic purpura fulminans [64]. The acute infectious purpura fulminans is the most common form and is discussed in this section [19]. A number of infections induce this syndrome, but the two most common are *Neisseria meningitidis* and streptococcal infections [65].

Infectious purpura fulminans begins with dermal discomfort that progresses within hours to petechiae that then coalesce to form purple ecchymoses [66] (Fig. 2.3). The ecchymoses evolve into hemorrhagic bullae with subsequent necrosis and gangrene [67]. The affected areas are initially sterile, but can develop secondary infections. The pathology in purpura fulminans is not limited to the skin, and as a result, there can be multiorgan failure [68]. Other associated findings include fever, DIC, and flu-like symptoms [67].

If recognized at the initial stage prior to development of necrosis, the syndrome may be completely reversed [67]. The primary treatment is supportive in conjunction with appropriate antimicrobials to treat the underlying infection. Vasopressors may actually contribute to poor peripheral circulation and peripheral tissue damage and should be avoided [19, 67].

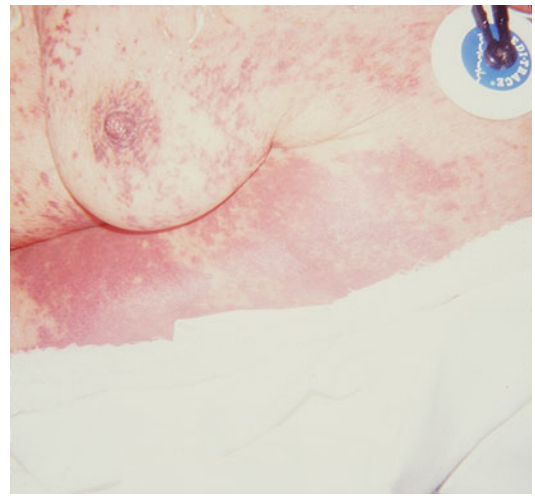

Fig. 2.3 Purpura fulminans

2.2.12 Ecthyma Gangrenosum

Ecthyma gangrenosum is an uncommon cutaneous variant of impetigo most commonly associated with *P. aeruginosa* septicemia, but may occur without bacteremia. It occurs in up to 2.8% of patients with *P. aeruginosa* bacteremia. The mortality rate in individuals with ecthyma gangrenosum due to *Pseudomonas* septicemia can approach 77% compared to the 15% mortality rate in those without bacteremia [69]. The most common risk factor is neutropenia usually due to underlying

malignancy or immunosuppressive therapy. Ecthyma gangrenosum may occur more frequently in infections associated with primary immunodeficiencies, including hypogammaglobulinemia, dysfunctional neutrophils, and chronic granulomatous disease [69, 70]. Occasionally, ecthyma gangrenosum may occur in healthy individuals without any predisposing factors; however, underlying risk factors should be sought out [69, 71].

Ecthyma is a vasculitis affecting the media and adventitia of blood vessels due to hematogenous spread of a pathogen or direct inoculation via the skin [69]. The eruption begins as erythematous or purpuric macules usually in the anogenital area or on an extremity. The lesions evolve into hemorrhagic vesicles or bullae which rupture to form a gangrenous ulcer with a central gray-black eschar [72]. The lesions develop over 12 h and may exist in different stages on the same individual [69]. On histology, lesions show necrotizing hemorrhagic vasculitis, and Gram-negative rods may be visible in the medial and adventitial walls of deeper vessels [72].

In addition to blood and urine cultures, biopsy of a lesion for tissue culture should be performed with immediate administration of antipseudomonal antimicrobials [73]. Due to pseudomonal resistance, intravenous antibiotics with a third-generation cephalosporin with antipseudomonas activity, such as ceftazidime 2 g every 8 h, are indicated.

2.3 Viral Infections

2.3.1 Herpes Simplex Virus

Herpes simplex virus (HSV) is generally associated with self-limiting infections. However, there are a few circumstances where HSV is a dermatological emergency and those clinical scenarios are covered in this section: neonatal HSV, in the setting of immunosuppression, and eczema herpeticum. The mainstay of treatment of HSV in emergency situations is intravenous acyclovir.

Neonatal HSV occurs in approximately 1 in 3,200 deliveries [74]. HSV may be transmitted to the neonate during the intrauterine (5%), intrapartum (85%), or postpartum (10%) periods [3]. In comparison with primary genital herpes, recurrent genital herpes is more common during pregnancy. However, women with primary genital HSV disease are at the highest risk of transmitting HSV to the baby [75]. Approximately two-thirds of women who acquire genital herpes during pregnancy are asymptomatic, and in accordance with this number, 60–80% of women who deliver an HSV-infected infant have no evidence of genital HSV at delivery [76, 77]. Infants who acquire HSV in utero typically have a triad of cutaneous manifestations, ophthalmologic findings, and neurologic involvement. Cutaneous manifestations include scarring, active vesicular lesions, hypo- and hyperpigmentation, aplasia cutis, and an erythematous macular exanthem [75]. HSV can manifest as three different types of infections in neonates: involvement limited to the skin, eyes, or mouth, central nervous system, and disseminated multiorgan infections [3]. Disseminated disease occurs in approximately 25% of neonatal HSV infections with approximately 80% of these cases presenting with a vesicular eruption [78]. Complications include encephalitis in 60–75% of cases, severe coagulopathy, liver dysfunction, pulmonary involvement, and a high mortality rate [75, 79]. Neonatal HSV infection should be treated with intravenous acyclovir 10–20 mg/kg every 8 h for 10–21 days.

Immunosuppressed patients are at risk of developing fulminant herpes infections. Vesicles enlarge to form hemorrhagic blisters and deep ulcers [80] (Fig. 2.4). Death is often secondary to visceral involvement and despite early treatment with intravenous acyclovir 10 mg/kg ideal body weight every 8 h for 7–14 days, herpes encephalitis carries significant morbidity and mortality [81].

Eczema herpeticum (also known as Kaposi's varicelliform eruption) is a herpetic superinfection of a preexisting skin disease, such as atopic dermatitis, cutaneous burns, or skin compromise sustained during cosmetic procedures. Clinically, there is an acute onset of monomorphic vesicles and pustules that coalesce into large superficial erosions that are susceptible to superinfection

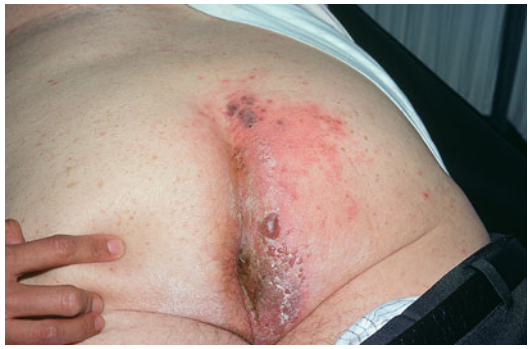

Fig. 2.4 Herpes simplex virus

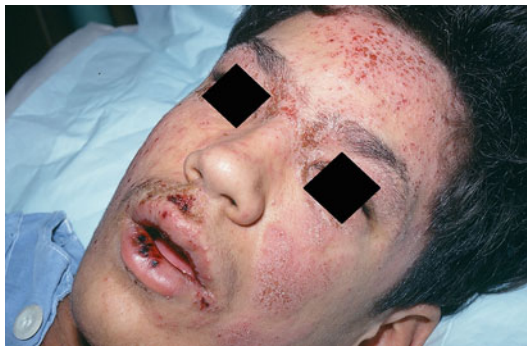

Fig. 2.5 Kaposi varicelliform eruption

[82] (Fig. 2.5). Patients may experience constitutional symptoms. In eczema herpeticum, herpetic lesions bypass the nerve endings and ganglions and directly spread to a diseased cutaneous region [83]. Rapid initiation of intravenous acyclovir 5–10 mg/kg ideal body weight every 8 h for 5–7 days is crucial as HSV may completely disseminate and lead to possible death [84].

2.3.2 Varicella Zoster Virus

2.4 Varicella

Varicella zoster virus (VZV) presents as varicella (chickenpox) as a primary infection and herpes zoster (shingles) when the virus is reactivated. Clinically, varicella lesions start as small erythematous papules, which evolve into vesicles on

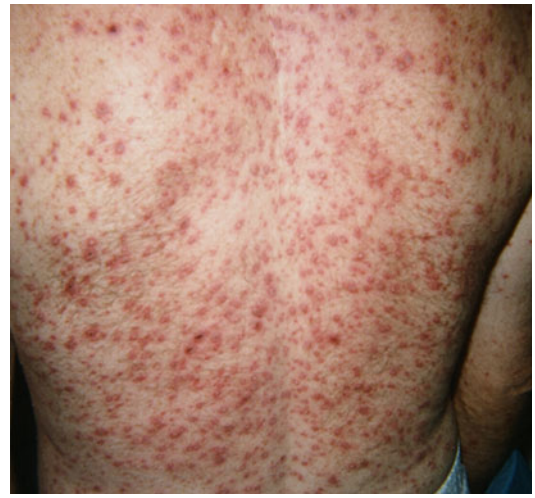

Fig. 2.6 Varicella virus

an erythematous base resembling "dew drops on a rose petal" (Fig. 2.6). The vesicles quickly evolve into pustules that form a crust. The lesions may occur in crops, and the presence of lesions in various stages of development is a characteristic of this condition. Mucosal surfaces may develop aphthous-like ulcers [80]. Both varicella and herpes zoster are usually self-limited diseases, but similar to HSV infection, there are specific circumstances where VZV infections are dermatological emergencies.

Neonatal varicella is seen in two clinical settings: primary VZV infection during pregnancy that is transmitted across the placenta or primary VZV infection during the perinatal period. The former can occur at any point during gestation and results in either congenital varicella syndrome and/or fetal death. It is worth mentioning that not all primary VZV infections during pregnancy result in transplacental infection. Congenital varicella syndrome most commonly occurs with transplacental VZV infection between 13 and 20 weeks of gestation [85]. Affected babies develop cicatricial skin lesions that may be depressed and hyper- or hypopigmented in a dermatomal distribution. Other affected organ systems include ocular (chorioretinitis, microphthalmia, nystagmus, and Horner's syndrome, which is the triad of miosis, ptosis, and anhidrosis), musculoskeletal (hypoplasia

of bones and muscles and malformed digits), central nervous system (cortical atrophy, seizures, mental retardation, and microcephaly), and autonomic nervous system (neurogenic bladder, hydroureter, esophageal dilation, and reflux). Prognosis is poor and death during infancy results from gastroesophageal reflux, aspiration pneumonia, or respiratory failure [86].

The second form of neonatal varicella is perinatal varicella, which occurs when there is maternal disease 5 days before delivery to 2 days after delivery. Infants develop the classic skin vesicles on an erythematous base; however, dissemination may result in pneumonia, hepatitis, encephalitis, and severe coagulopathy [86]. Infants exposed to maternal infection should be given VZIG if available or IVIG at birth or as soon as maternal symptoms develop [87]. Despite VZIG or IVIG, varicella can still develop and acyclovir should be administered if there are any signs of illness [86].

Varicella infections can be life-threatening in a few other circumstances. Immunocompromised individuals with varicella or herpes zoster have an increased risk for systemic complications including pneumonitis, central nervous system involvement, pneumonia, thrombocytopenia, and liver function impairment [80]. Although less than 5% of varicella cases occur in immunocompetent adults, 55% of deaths due to varicella occur in adults. Adults with varicella infection are at increased risk of pneumonitis and most commonly expire secondary to pneumonia with respiratory failure [88].

A live attenuated varicella vaccine was approved for use in children in the United States in 1995 [89]. The vaccine is indicated for children 12 months to 12 years of age in addition to individuals greater than 13 years old who have no evidence of immunity. Finally, the vaccine should be offered to high-risk adults without immunity, including health care providers, household contacts of immunocompromised individuals, nonpregnant women of childbearing age, individuals who work in places where chickenpox transmission may occur, and international travelers [90]. It is noteworthy that the varicella vaccine may reduce the incidence and severity of herpes zoster [5].

2.5 Herpes Zoster

Herpes zoster, the latent reactivation of previous VZV, is rarely life-threatening; however, disseminated disease can be associated with increased morbidity and mortality [80]. Herpes zoster infection is heralded by paresthesias or stabbing pain. Shortly thereafter, an eruption of small vesicles in the same distribution as the pain appears and crusts over during the next 15 days [80] (Fig. 2.7). Generally, herpes zoster appears in a dermatomal distribution; however, in immunosuppressed patients, disseminated disease may occur, defined as more than 20 vesicles outside the area of the primary or adjacent dermatome [5]. Common complications of disseminated disease include pneumonia, encephalitis, and hepatitis. The mortality rate has been reduced due to antiviral therapy.

Herpes zoster often begins with a prodrome of intense pain associated with pruritus, tingling, or hyperesthesia. If severe enough, the pain can be misdiagnosed as an acute abdomen or myocardial infarction, depending on the dermatome involved. Patients usually present with tingling and paresthesia in the dermatome where cutaneous lesions eventually develop. Diagnosis is often delayed as the cutaneous lesions are not present at the onset of disease and mortality rate remains high despite initiation of antiviral therapy [91].

Immunocompromised patients are at an increased risk not only for uncomplicated herpes zoster infections but also for complications of

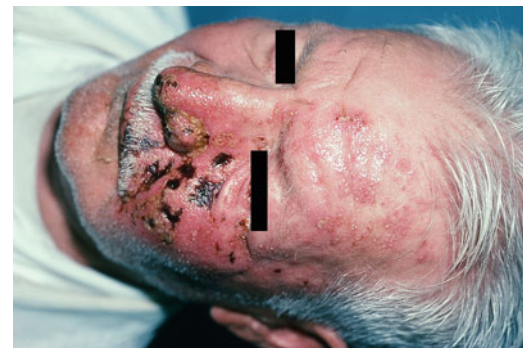

Fig. 2.7 Zoster virus

zoster. Patients with AIDS or other conditions with depressed cellular immunity are at risk for chronic VZV encephalitis which may occur months after an episode of herpes zoster. Patients have a subacute clinical presentation with headache, fever, mental status changes, seizures, and focal neurologic defects [91]. Cerebrospinal fluid analysis reveals VZV DNA by polymerase chain reaction [92]. Death often results, although case reports have shown that high-dose intravenous acyclovir therapy may be efficacious [91].

Ramsay Hunt syndrome, also known as herpes zoster oticus, is a herpetic infection of the inner, middle, and external ear. It is a reactivation of latent VZV virus in the geniculate ganglion, the sensory ganglion of the facial nerve; however, reactivation affects both the facial nerve (cranial nerve VII) and the vestibulocochlear nerve (cranial nerve VIII) due to their close proximity [93]. The incidence is about 5 cases per 100,000 of the US population annually and occurs more frequently in individuals over the age of 60 years [94]. Patients present with severe ear pain, small vesicles on the pinna or oral mucosa, and facial palsy [95]. Prompt diagnosis is paramount as initiation of antiviral therapy within 72 h of the onset of symptoms leads to resolution of the facial palsy in as many as 75% of cases [94].

Herpes zoster ophthalmicus, the second most common presentation of herpes zoster, involves the ophthalmic division of the trigeminal nerve and occurs in up to 20% of patients with herpes zoster [96, 97]. The ophthalmic division divides into the nasociliary, frontal, and lacrimal branches. The nasociliary nerve innervates the anterior and posterior ethmoidal sinuses, conjunctiva, sclera, cornea, iris, choroid, and the skin of the eyelids and tip of the nose [96]. Hutchinson's sign, first described in 1864, is the appearance of a herpes zoster lesion on the tip or side of the nose and serves as a useful prognostic factor in the ensuing ocular inflammation [98]. Uveitis followed by keratitis are the most common forms of ocular involvement [19]. Clinically, patients develop lesions on the margin of the eyelid occasionally associated with periorbital edema and ptosis. Chronic disease due to neurologic damage occurs in up to 30% of patients with this form of herpes zoster [99]. Early complications include residual ptosis, lid scarring, deep scalp pitting, entropion, ectropion, pigmentary changes, and lid necrosis [97]. Glaucoma, optic neuritis, encephalitis, hemiplegia, and acute retinal necrosis are more severe long-term complications, the risk of which may be reduced by half with prompt initiation of antiviral therapy [19]. If herpes zoster ophthalmicus is suspected, ophthalmology should be consulted immediately.

While uncomplicated zoster may be adequately treated with oral antivirals, such as valacyclovir 1 g every 8 h for 7 days, disseminated and severe infections require intravenous acyclovir 10 mg/kg ideal body weight every 8 h for 7–14 days. Although corticosteroids may be added as an adjuvant therapy in herpes zoster infections due to their anti-inflammatory properties, studies have failed to show a beneficial effect on acute pain and in some instances had adverse effects, including gastrointestinal symptoms, edema, and granulocytosis. However, in Ramsay Hunt syndrome, steroids may be added to antiviral therapy if there are no contraindications [100].

Zostavax is a live attenuated vaccine indicated for the prevention of herpes zoster and post-herpetic neuralgia in individuals greater than 50 years of age [101]. The vaccine has been shown to reduce the incidence of herpes zoster by 51%, reduce the incidence of post-herpetic neuralgia by 67%, and reduce the herpes zoster-related burden of illness by 61% [102]. Gabapentin has been approved since 2002 by the US Food and Drug Administration (FDA) for the treatment of post-herpetic neuralgia [103].

2.5.1 Cytomegalovirus

Cytomegalovirus (CMV) or human herpesvirus-5 (HHV-5), a large double-stranded DNA virus of the viral family herpesviruses, is acquired by exposure to infected children, sexual transmission, and transfusion of CMV-infected blood products. Up to 80% of adults are infected with CMV [19]. CMV causes a mild form of infectious mononucleosis in most affected immunocompetent individuals; however, in rare cases, fatal massive

hepatic necrosis can occur. Immunocompromised individuals, including those with HIV, malignancy, or post-organ transplant patients, may have severe, complicated CMV infections [3].

CMV infection in immunocompromised individuals can either directly induce death or disable the patient's immune system, making them even more susceptible to secondary infections [104]. CMV can be a fatal disease in newborns. When a primary CMV infection is sustained during pregnancy, transplacental transmission may occur and severely affect the fetus [80]. Nonimmune pregnant women, especially those working in healthcare settings or daycare facilities, should take precautions, primarily proper hand washing. Cutaneous manifestations of congenital CMV include jaundice, petechiae, and purpura, referred to as "blueberry muffin" lesions and complications include hearing loss and mental retardation [3].

Antiviral therapy should be given to affected immunocompromised patients in addition to passive immunization of CMV with hyperimmune globulin (HIG). Women who develop primary CMV infections during pregnancy may prevent transmission to the fetus with CMV HIG. Ganciclovir is not approved for pregnant women, but is safe for newborns [3].

2.5.2 Measles (Rubeola)

Measles, due to the morbillivirus, an RNA virus in the *Paramyxoviridae* family, has markedly decreased in incidence since the development of vaccination against the virus. However, it remains an active disease in both developed and developing countries [105]. Generally, affected individuals are unvaccinated children less than 5 years of age or vaccinated school-age children who failed to develop immunity to the vaccine [106].

The virus is transmitted via respiratory secretions. Following an asymptomatic incubation of 10–11 days, a high fever develops with subsequent rapid defervescence. Coryza, conjunctivitis, and a barking cough are characteristic. Additionally, an eruption begins on the head with erythematous macules and papules that coalesce and spread distally involving the palms and soles. One to two days prior to the exanthem, Herman's spots, bluish gray areas on the tonsils, and Koplik's spots, punctate blue-white lesions surrounded by an erythematous ring on the buccal mucosa, appear [80]. Complications of measles include encephalitis, subacute sclerosing panencephalitis, and fetal death if infection occurs during pregnancy [107].

Vaccination is the gold standard for preventing infection. The measles, mumps, rubella (MMR) or MMR plus varicella (MMRV) is a live attenuated vaccine and as a result cannot be used in immuncompromised patients [3]. Although no antivirals have been effective in treating measles infection, vitamin A supplementation may reduce deaths from measles by 50% as vitamin A deficiency has been shown to increase morbidity and mortality [108].

2.5.3 German Measles (Rubella)

Rubella is a viral infection caused by the rubella virus, an RNA virus in the *Togaviridae* family. It is associated with mild constitutional symptoms that are more severe in adults compared to children. Following a 2-week incubation period, a pale erythematous eruption appears on the head and spreads to the feet, lasting approximately 3 days. Forchheimer's spots, macular petechiae, can be identified on the soft palate. Often there is coexistent tender lymphadenopathy, especially of the occipital, posterior auricular, and cervical chains. Rubella is generally self-limiting, but severe complications may occur. Children are more susceptible to thrombocytopenia, vasculitis, orchitis, neuronitis, and progressive panencephalitis [80]. Neonatal infections in the first trimester can result in congenital defects, fetal death, spontaneous abortion, or premature delivery.

Prevention is via vaccination, and, as previously stated, is contraindicated in immunocompromised patients. Treatment of infection is supportive [3].

2.5.4 Parvovirus B19

Parvovirus B19 is a small, single-stranded DNA-containing virus causing a wide range of diseases varying from asymptomatic infections to fetal

demise. The most common form of infection is erythema infectiosum, or "fifth disease." In general, regardless of the clinical presentation, the virus is self-limited with the exception of a few circumstances [80]. The peak incidence of infection occurs in the winter and spring. It is transmitted through respiratory secretions, blood products, or vertically during pregnancy. Although parvovirus B19 is more common in children, infection does occur in adults with varying clinical presentation. The seroprevalance of parvovirus B19 antibodies increases with age—up to 15% of children 1–5 years of age are affected versus up to 80% of adults [5].

Erythema infectiosum occurs after a 4–14-day incubation period. Individuals develop the classic "slapped-cheek" facial erythema that spares the nasal bridge and circumoral regions. One to four days later, erythematous macules and papules appear which progress to form a lacy, reticulate pattern most commonly observed on the extremities, lasting 1–3 weeks. Once cutaneous signs appear, the individual is no longer contagious [5, 80]. Arthralgia or arthritis, seen in up to 10% of patients with erythema infectiosum, is more common in female adults and may occur in up to 60% of those infected [109].

Both children and adults may develop a distinct syndrome known as papular purpuric glove and socks syndrome which is also secondary to parvovirus B19. Clinically, patients have edema and erythema of the palms and soles with petechiae and purpura associated with burning and pruritus [5].

Parvovirus B19 can cause complications in three situations: immunosuppression, pregnancy, and underlying hematologic disease. Patients with hematologic disease, such as sickle cell anemia or hereditary spherocytosis, who become infected with parvovirus B19 are at risk of developing severe transient aplastic anemia. In general, recovery is usually spontaneous, but heart failure and death may occur. Thrombocytopenia is another less common complication. Fetal infection with parvovirus B19 can result in miscarriage or nonimmune hydrops fetalis [80]. The greatest risk to the fetus is when infection is acquired before 20 weeks gestation. Most fetal losses occur between 20 and 28 weeks gestation [110].

The mainstay of treatment is supportive. However, there are treatment modalities that have been used. High-dose IVIG have been shown to eliminate parvovirus B19 from the bone marrow. Intrauterine transfusions can reverse fetal anemia and reduce fetal demise. Prevention and measures to avoid susceptible people are often difficult as once the rash appears and is recognized as parvovirus B19, patients are no longer contagious [3, 111].

2.6 Fungal Infections

2.6.1 Systemic Candidiasis

Candida species are the most common cause of fungal infections. While *Candida albicans* is the most common pathogen in oropharyngeal and cutaneous candidiasis, other species of *Candida* have been isolated in a rising number of infections in both invasive and vaginal candidiasis [112]. Systemic candidiasis is a fatal infection that is increasing in incidence, especially in immunocompromised patients. Risk factors include chemotherapy, hematological diseases, and prolonged use of broad-spectrum antibiotics [113, 114].

Cutaneous lesions occur in a minority of patients, but when present can aid in early diagnosis and rapid initiation of appropriate treatment, especially since there is no specific diagnostic tool for systemic candidiasis [113]. Clinically, cutaneous lesions in systemic candidiasis begin as macules that develop into papules, pustules, or nodules with a surrounding erythematous halo. The lesions are common on the trunk and extremities. Purpura can be seen in patients with or without thrombocytopenia [113]. Tissue culture may isolate the fungi.

Antifungal medications should be started once systemic candidiasis is suspected. Fluconazole is the treatment of choice for *C. albicans*; however, other species of *Candida* require amphotericin B deoxycholate [113, 115]. The mortality rate associated with systemic candidiasis ranges from 46 to 75% [116].

2.6.2 Mucormycosis

Mucormycosis, previously encompassed by the now obsolete term zygomycosis, is a potentially life-threatening fungal infection [117]. Mucormycosis is caused by fungi in the order Mucorales and the family Mucoraceae. The genus contains over 3,000 species; however, not all cause disease in humans. The most commonly isolated genera include *Rhizopus, Mucor, Rhizomucor*, and *Absidia* [118]. Disease can be classified as rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, or disseminated forms, and the host influences which form of disease develops. Immunocompromised individuals are most susceptible to mucormycosis. Diabetics commonly present with the rhino-orbital-cerebral form. Those individuals receiving deferoxamine are more susceptible to pulmonary, followed by rhinocerebral, and finally disseminated disease. Ferric complex of deferoxamine stimulates iron uptake and growth of *Rhizopus*. [119, 120]. Cerebral disease is most commonly seen in intravenous drug users, and solid-organ transplant patients may develop pulmonary or rhino-orbital-cerebral disease [119, 121]. Recently *Apophysomyces elegans*, a pathogen causing mucormycosis, has led to primary cutaneous and rhino-orbital-cerebral disease in immunocompetent patients [122]. This section covers the rhino-orbital-cerebral, cutaneous, and disseminated forms of disease.

Rhino-orbital-cerebral disease can present as rhinosinusitis, sinusitis, rhino-orbital, or rhinocerebral disease. Clinically, rapid development of tissue necrosis is seen in invasive mucormycosis due to vascular invasion and thrombosis [117]. Progressive disease is seen with necrosis or eschar formation in the nasal cavity or on the palate. Patients can also develop trigeminal and facial cranial nerve palsy, ophthalmoplegia, epidural or subdural abscesses, and cavernous or sagittal sinus thrombosis [117].

Cutaneous mucormycosis develops after direct spore inoculation in a wound. Initially, patients develop erythema and induration of the skin, which progresses to necrosis with a black eschar [117]. Disseminated disease develops in patients with cerebral, cutaneous, or pulmonary mucormycosis [119].

Diagnosis of cutaneous lesions can be confirmed by histopathologic examination, revealing wide-angled branching fungal hyphae. Potassium hydroxide preparations can be used to identify the hyphae from bronchoalveolar lavage samples. Blood cultures are often negative, even when the diagnosis is confirmed with hyphae on histology [3].

It is important to be aware of risk factors for the development of mucormycosis as treatment includes reversal of these underlying risk factors if present. Risk factors include long-term neutropenia, high-dose glucocorticoid therapy, hyperglycemia, diabetes with or without ketoacidosis, iron overload, and use of defoxamine treatment [117]. Early diagnosis is required for successful treatment of mucormycosis with prompt administration of antifungal therapy and surgical debridement in select patients [123]. One study found that a greater than 6-day delay in treatment with intravenous amphotericin-B 0.5–1 mg/kg/day after diagnosis led to a doubled mortality rate at 12 weeks [124].

2.6.3 Histoplasmosis

Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum var. capsulatum*, is a common infection in Southeastern and Central United States. Birds and bats serve as reservoirs for histoplasmosis, and their feces contain the organism. Individuals acquire the disease either through inhalation or, less commonly, by direct cutaneous inoculation of the fungus. While immunocompromised individuals are at a higher risk for disseminated histoplasmosis, immunocompetent hosts can become infected if the exposure is significant [3].

Clinical presentations range from primary cutaneous to pulmonary to disseminated histoplasmosis. The latter is covered in this section as it is the only clinical presentation of histoplasmosis that would constitute a dermatologic emergency. Most patients infected with histoplasmosis experience asymptomatic hematogenous dissemination through macrophages infected with the parasite [125]. Risk

factors for developing disseminated disease include young age, AIDS, hematologic malignancies, solid organ transplant, hematopoietic stem cell transplant, immunosuppressive agents, and congenital T-cell deficiencies [126]. Patients often have fever, malaise, anorexia, and weight loss. Cutaneous findings in disseminated histoplasmosis are nonspecific. They vary from mucocutaneous oral ulcers or erosions to erythematous or molluscum-like papules or nodules [3, 127]. The most common extracutaneous sites for disseminated involvement are the lung, spleen, lymph nodes, bone marrow, and liver; however, any organ system can be involved. Severe disseminated disease can present as sepsis with hypotension, disseminated intravascular coagulation, renal failure, and acute respiratory distress [126]. Uncommonly, patients can develop endocarditis, central nervous system infection, or Addison's disease when there is destruction of bilateral adrenal glands by the fungus [126, 128].

Laboratory abnormalities are nonspecific, but will often include elevated alkaline phosphatase levels, pancytopenia, an increased sedimentation rate, elevated C-reactive protein levels, high lactate dehydrogenase levels, hypercalcemia, and increased ferritin expression [125, 126]. The fungi can be cultured in the blood, but the diagnosis of disseminated histoplasmosis can be obtained by tissue biopsy of any involved site, revealing intracellular yeast forms surrounded by a rim of clearing [3, 129].

Treatment is not indicated in self-limited infections. However, disseminated histoplasmosis requires systemic antifungal therapy (amphotericin B 0.7–1 mg/kg/day or itraconazole 200–400 mg daily) [3].

2.7 Parasitic Infections

2.7.1 American Trypanosomiasis (Chagas Disease)

Chagas disease, also known as American trypanosomiasis, is caused by the parasite *Trypanosoma cruzi*, which is found in tropical zones of the Americas. The parasite is transmitted by the reduviid bug, which constitutes three main species: T*riatoma infestans, Rhodnius prolixus*, and *Panstronglus megistus* [130]. Transmission occurs when a prior wound or an intact mucous membrane is inoculated with the feces of an infected bug [131].

Chagas disease occurs in two main phases: the acute and chronic phases [132]. Acute Chagas disease develops after a 1–2-week incubation period and begins with a macular or papulonodular, erythematous to violet, hard, painless lesion at the inoculation site [3]. Inoculation through the conjunctiva results in nonpainful, unilateral edema of the upper and lower eyelid for several weeks, known as Romaña's sign [131]. The lesion may ulcerate, but usually regresses in 3 weeks. A maculopapular, morbilliform, or urticarial eruption may also be seen. Associated signs of acute infection include satellite lymphadenitis, fever, myalgia, and hepatosplenomegaly [3]. The acute phase lasts for 4–8 weeks [131].

Without successful treatment, the patient can go on to develop chronic Chagas disease [131]. The chronic form is characterized by cardiac and gastrointestinal manifestations. Early cardiac findings include conduction-system abnormalities and ventricular wall-motion abnormalities [130]. After time, patients progress to high-degree heart block, sustained and nonsustained ventricular tachycardia, sinus-node dysfunction, apical aneurysm, embolic phenomena, and progressive dilated cardiomyopathy [133]. With these findings, there is a high risk of sudden death [134]. Gastrointestinal Chagas disease involves the esophagus, colon, or both. Uncommon findings are megaesophagus and megacolon [135].

Diagnosis during the acute phase is made by direct examination of Giemsa-stained blood smears, touch preps, or lymph-node biopsy. In the chronic phase, direct immunofluorescence and PCR for anti-*T. cruzi* immunoglobulin M antibodies can be diagnostic [132].

Treatment with benznidazole 5 mg/kg/day or nifurtimox 8–10 mg/kg/day in 3–4 doses has been shown to reduce the severity of symptom and shorten the clinical course during the acute infection. The cure rate during the acute phase is between 60 and 85% [130]. The efficacy of treatment for chronic infection is unclear [136].

2.7.2 Mucocutaneous Leishmaniasis

Leishmaniasis, caused by protozoa in the genus *Leishmania*, encompasses three clinical forms: cutaneous, mucocutaneous, and visceral leishmaniasis. Although leishmaniasis is endemic in Southern Europe, Central and South America, Africa, the Middle East, and South Asia, it is increasingly seen in non-endemic regions in the setting of travel to endemic countries [137]. *Leishmania*, an intracellular parasite that targets macrophages, dendritic cells, and neutrophils, is transmitted via the bite of an infected female sand fly, primarily *Phlebotomus* (Old World) and *Lutzomyia* (New World) [138, 139].

While cutaneous leishmaniasis is generally benign and self-limiting, mucocutaneous leishmaniasis is a potentially life-threatening infection that requires treatment [138]. The progression to mucosal disease depends on the virulence of the parasite as well as the individual cell-mediated immunity. Only 1–10% of infected patients will develop mucosal involvement [140]. Immunodeficiency is not necessarily a predisposing factor [141].

Patients with mucocutaneous leishmaniasis will often have a history of cutaneous leishmaniasis starting 1–5 years prior to the mucosal involvement. The primary cutaneous lesion is generally ulcerative and can be solitary or multiple [140]. Persistent nasal congestion is the most common presenting symptom [141]. As the disease progresses, patients develop erythema, erosions, and ulcers around the nares and lips followed by lesions on the oropharynx, and occasionally widespread cutaneous disease [137] (Fig. 2.8). Later in the disease course, patients can have nasal septal perforation and palatal ulceration with eventual destruction of the oronasopharyngeal mucosa and cartilaginous facial and upper airway structures [137, 138]. Other findings include lymphadenopathy, fever, and hepatomegaly [137].

Histopathology and touch preparations are diagnostic in cutaneous leishmaniasis; however, biopsy is necessary in mucocutaneous disease as there are very few parasites in the nasal mucosa. Diagnosis is confirmed by the presence of intracellular amastigotes, but often specimens will show granulomas [141]. When suspicion is high and biopsy only shows granulomas, PCR may be used to isolate *Leishmania* DNA [142].

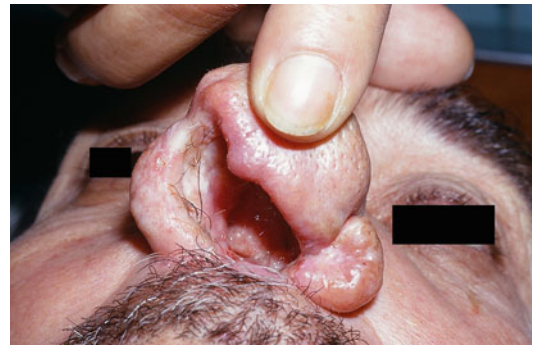

Fig. 2.8 Mucocutaneous leishmaniasis

Pentavalent antimony is first-line therapy followed by amphotericin B 0.5–1 mg/kg/day [143].

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Drug Eruptions

3

Rita V. Patel and Gary Goldenberg

3.1 Introduction

Cutaneous reactions are the most frequently occurring adverse reactions to drugs. These reactions can range from mild (two-thirds of cases) to life-threatening (one-third of cases) in the hospital setting [1, 2]. Distinguishing a mild versus a life-threatening reaction is challenging, yet critical, in the management of drug allergies. Cutaneous manifestations are frequently the earliest signs of a systemic drug allergy and can provide information on the severity and prognosis of an allergic reaction [3]. Numerous risk factors predispose patients to severe cutaneous drug reactions, including immunosuppression (especially infection with human immunodeficiency virus [4] or mononucleosis) [5], female gender [6], number of drugs being taken, and elderly age [7].

Cutaneous reactions are considered severe when they result in serious skin compromise or involve multiple organs. Severe cutaneous adverse reactions (SCARs) include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS). Recently, the SCARs definition was reclassified to include acute generalized exanthematous pustulosis (AGEP). Due to the evolving definition, the true incidence of SCARs is difficult to ascertain. However, in one study conducted in Singapore in 2002, analysis of an inpatient network-based electronic drug allergy notification system showed that in over 90,000 admissions, 210 drug allergy cases were verified by an allergist. Cutaneous manifestations were the most common clinical presentation (96%) with SCARs occurring in 5% of patients. The most common causative drugs were antimicrobials and antiepileptic drugs [8].

3.2 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN are severe reactions commonly triggered by medications. They are chiefly distinguished by the severity and percentage of body surface involvement. Blistering and skin loss between 1 and 10% of the body surface area (BSA) is known as SJS, whereas skin detachment greater than 30% is known as TEN (Table 3.1). SJS/TEN overlap syndrome describes patients with involvement of greater than 10% but less than 30% BSA [9]. SJS was first described in the 1920s as an acute mucocutaneous syndrome characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and purpuric macules and was thought to have an infectious etiology at the time. First reported in the 1950s,TEN was believed to be triggered by drugs as reports accumulated.

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Table 3.1 Clinical features distinguishing SJS, SJS/TEN overlap, and TEN [9]

Clinical entity	SJS	SJS/TEN overlap	TEN
Primary Lesions	Dusky red lesions Flat atypical targets	Dusky red lesions Flat atypical targets	Poorly delineated erythematous plaques with desquamation Dusky red lesions Flat atypical targets
Distribution	Isolated lesions Confluence (+) of face and trunk	Isolated lesions Confluence (++) of face and trunk	Isolated lesions (rare) Confluence (+++) of face and trunk
Mucosal Involvement	Yes	Yes	Yes
Systemic Symptoms	Usually	Always	Always
% BSA Detachment	<10	10–30	>30

In absolute numbers, SJS and TEN are rare diseases with the incidence of severe exfoliative skin reactions estimated at 1–7 cases per million person-years for SJS and 0.4–1.5 cases per million person-years for TEN [10–13]. In children, TEN affects both genders equally. In adults, women are more frequently affected by a ratio of 3:2. Additionally, the elderly seem to be at increased risk of developing TEN [14]. Patients with HIV infection have been reported to be at three times increased risk for SJS/TEN. The reasons for this susceptibility are not fully understood, although exposure to multiple medications (including sulfonamide antibiotics), "slow acetylation" status, immune dysregulation, and presence of concomitant infections may contribute. There is support for genetic susceptibility as well, for instance, an increased incidence of HLA-B12 has been seen in pathogenesis studies of TEN. Certain drugs show a genetic predisposition to cause SJS or TEN in association with certain alleles. Allopurinol and HLA-B*580 in the Han Chinese population as well as HLA-B*150 and carbamazepine have been reported in the same population [15]. In patients with HIV, the annual incidence of TEN is 1,000-fold higher than in the general population, with approximately 1 case per 1,000 patient years. The estimated mortality from SJS is 10%, SJS/TEN overlap 30%, and TEN is almost 50%.

There are differing opinions about the degree to which SJS and TEN overlap with severe erythema multiforme (EM), a condition with similar presentation that is commonly associated with infections, particularly herpes simplex virus and mycoplasma pneumonia [16, 17]. EM, the least severe of the disorders, is characterized by targetoid, edematous papules, and/or plaques. In EM, less than 10% of cases are drug induced and patients typically present with a prodrome of flu-like symptoms prior to the skin eruption which classically affects the hands, feet, and limbs. Characteristic EM lesions can be erythematous macules or wheals and are usually 1–2 cm in diameter (Fig. 3.1). They are usually darker in the center and paler peripherally; sometimes larger lesions exhibit concentric rings, or the so-called

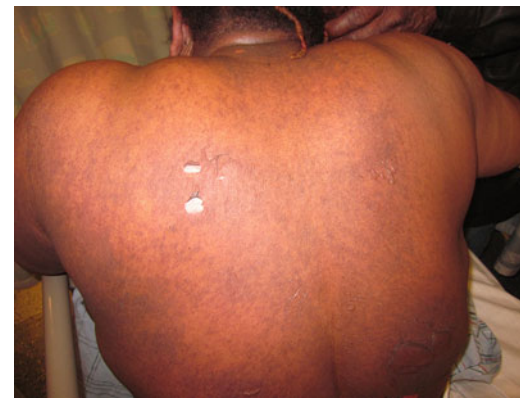

Fig. 3.1 Toxic Epidermal Necrolysis (Courtesy of Jason Emer, MD). Widespread patchy erythema with confluence and darkening at sites of epidermal detachment (flaccid blisters) of the posterior chest

Table 3.2 Commonly associated culprit drugs

SJS/TEN	Allopurinol, sulfonamides>>penicillins>cephalosporins, carbamazepine, dilantin, lamotrigine, and phenobarbital, piroxicam, acetaminophen
DRESS	Aromatic anticonvulsants, lamotrigine, valproic acid, NSAIDs, allopurinol, dapsone, sulfonamides, minocycline, abacavir, nevirapine
AGEP	Penicillins, macrolides, quinolones, hydroxychloroquine, terbinafine, and diltiazem
Serum Sickness	Antithymocyte globulin, infliximab, and rituximab

target lesions. There is often some systemic disturbance including fever, malaise, and organ dysfunction. It has been hypothesized that SJS and TEN are varying degrees of the same process, different in the extent of involvement. However, unifying this concept has not been universally accepted as some cite subtle histologic differences between EM and SJS or TEN [1, 18].

The pathogenesis of SJS and TEN is not completely understood, but the etiology is hypothesized to be immune mediated. Various groups contend that the ligand FasL and the cognate receptor, Fas, permit signaling that triggers the apoptosis of keratinocytes [19]. Gene expression analysis of blister fluid from patients with SJS and TEN has also recently identified secretory granulysin protein, a key molecule responsible for the induction of keratinocyte death [20].

The majority of SJS and TEN cases are caused by drug exposure (Table 3.2). Anti-gout agents (allopurinol), antibiotics (sulfonamides>>penicillins>cephalosporins), antipsychotics and antieplileptics (carbamazepine, dilantin, lamotrigine, and phenobarbital), and analgesics or NSAIDs (piroxicam) [21–24]. A survey of TEN in children identified similar drugs to those in adults, additionally implicating acetaminophen [25]. However, pediatric infections with Mycoplasma pneumonia and herpes virus, rather than drug ingestion, represent a greater proportion of pediatric cases of SJS [26].

SJS/TEN typically presents 1–3 weeks after the administration of the responsible drug. Clinically, both SJS and TEN present similarly.

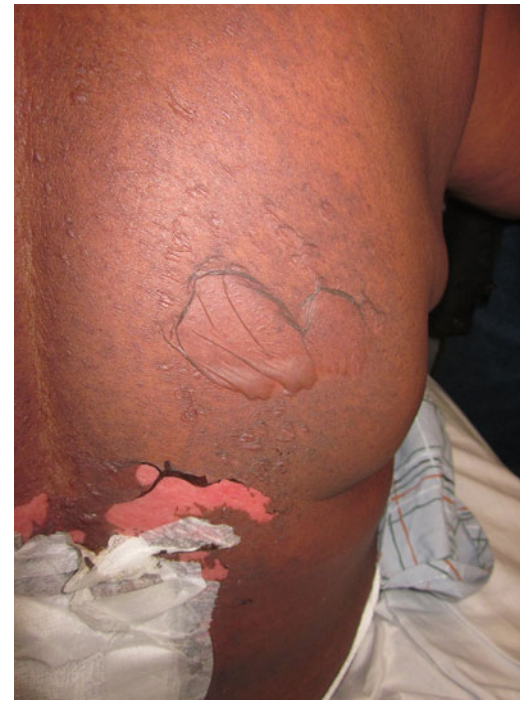

Fig. 3.2 Stevens-Johnson syndrome (Courtesy of Jason Emer, MD). Large flaccid blister on the back of a patient with epidermal detachment

The initial prodromic symptoms can be nonspecific; however, symptoms can include fever, stinging eyes, and discomfort when swallowing. TEN often displays temperatures that are higher than SJS, often exceeding 39°C. Within days, early sites of cutaneous involvement typically occur on the presternal trunk, face, and palms and soles. Skin lesions manifest as generalized macules with purpuric centers which progress to large confluent blisters with subsequent epidermal detachment (Figs. 3.1 and 3.2). A positive Nikolsky sign may be elicited in which light lateral pressure applied with the index finger results in the detachment of the full-thickness epidermis. Erythema and erosions of the buccal, genital, or ocular mucosa occur in greater than 90% of patients, and occasionally the respiratory or gastrointestinal tracts are affected at the same time. In the following 3–5 days, separation of the epidermis advances leading to large denuded areas associated with extreme pain, bleeding, massive fluid loss, hypothermia, and infection [27–29].

Table 3.3 SCORETEN assessment of the severity of TEN [32]

SCORETEN parameter	Individual score	SCORETEN (sum of individual scores)	Predicted mortality (%)
Age >40 years	Yes = 1, No = 0	0–1	3.2
Malignancy	Yes = 1, No = 0	2	12.1
Tachycardia (>120/min)	Yes = 1, No = 0	3	35.8
Initial surface of epidermal detachment >10%	Yes = 1, No = 0	4	58.3
Serum urea >10 mmol/l	Yes = 1, No = 0	>5	90
Serum glucose >14 mmol/l	Yes = 1, No = 0		
Bicarbonate >20 mmol/l	Yes = 1, No = 0		

SJS, TEN, and SJS/TEN overlap syndrome are clinical diagnoses supported by compatible histologic findings. Currently, there are no universally accepted diagnostic criteria and histologic findings are neither specific nor diagnostic. Despite these limitations, the diagnosis of SJS or TEN would be appropriate in a patient with a history of antecedent drug exposure or illness, a prodrome of acute-onset febrile illness with malaise, diffuse erythema which progresses to vesicles or bullae, or necrosis with sloughing of the epidermis. Rapid supportive evidence of SJS or TEN should be obtained by submitting a frozen section of the already peeling layer of skin, which can help the clinician institute treatment as soon as possible. The histology of skin lesions commonly reveals a subepidermal bullae with full-thickness necrosis of the epidermis. Histopathologic analysis of the skin biopsy is critical in ruling out other diagnoses such as autoimmune blistering diseases, bullous fixed drug eruptions, AGEP, and, although uncommon in adults, staphylococcal scalded skin syndrome [30]. Extent of skin involvement is a major prognostic factor and when evaluating BSA coverage, only necrotic skin which is already detached should be included in the evaluation [31]. Various appropriate cultures should be performed on blood, wounds, and mucosal lesions to evaluate for the presence of staphylococcal species, in particular. In children, serologies for Mycoplasma pneumoniae infection should also be sought out.

As soon as the diagnosis of SJS or TEN has been established, the severity, prognosis, and management plan can be determined via the severity-of-illness score for TEN (SCORTEN [Table 3.3]) [32]. Experts advocate admission to an intensive care unit, when the score is 2. Once the SCORTEN reaches 3 the predicted mortality is 35% [1].

Garcia-Doval and colleagues demonstrated better prognosis with early withdrawal of the causative agent, and exposure to agents with long half-lives carried higher mortality [33]. Oplatek et al. [34] showed that early referral to a specialized ICU, along with supportive care, correlated with increased survival rates.

Patients with SJS or TEN are at high risk of infection which can enter through the compromised skin barrier. Sepsis remains a prominent cause of mortality; however, prophylactic systemic antibiotics are not employed by the majority of burn units. Topical antibiotics are commonly used such as silver nitrate and newer silver-imbued nanocrystalline gauze materials [35]. Supportive care is comparable to that in those with severe burns, focusing on correcting hypovolemia, electrolyte imbalance, renal insufficiency, and sepsis. Daily wound care and nutritional/hydrational support most commonly take place in an intensive care setting. A dermatologic consult is warranted for cutaneous care. For the face and sera, isotonic sterile sodium chloride solution should be used to wash sites, an antibiotic ointment should be applied to orifices, and silicone dressings are used to cover denuded areas. An ocular examination by an opthamologist should be carried out regularly as well [15].

The use of systemic corticosteroids in SJS/TEN remainscontroversial.Theoretically,glucocorticoids

increase the risk of sepsis, increase protein catabolism, and decrease the rate of epithelialization. Studies have found that administration of systemic glucocorticoids was associated with increased morbidity and mortality, particularly if patients had TEN and received glucocorticoids for prolonged periods of time [36]. As a consequence of the discovery of the anti-Fas potential of pooled human intravenous immunoglobulins (IVIG) in vitro, IVIG (1 g/kg/day for 3 consecutive days) has been tested for the treatment of TEN. To date the majority of studies confirm the mortality benefit, excellent tolerability, and low toxic potential of IVIG. However, caution should be exercised in those with renal or cardiac insufficiency and thromboembolic risk. Use of IVIG is contraindicated in those with IgA antibodies or IgA deficiency [37–41]. In one phase II trial, although not statistically significant, cyclosporine was administered orally (3 mg/kg/day for 10days) and resulted in no deaths, whereas the prognostic score predicted 2.75 deaths amongst the 29 patients with SJS, SJS/TEN, or TEN included in the trial [42]. Other anti-inflammatory therapies, like tumor necrosis factor-alpha (TNF-α) antagonists, have been published in case reports; however the published data is insufficient to draw a conclusion on the therapeutic potential of TNF-α antagonists in TEN [43].

Rechallenge with culprit drugs is not recommended in the patient with SJS/TEN; however, the current focus of allergy testing lies more on ex vivo/in vitro tests such as the lymphocyte transformation test (LTT) which measures the proliferation of T cells to a drug in vitro by generating T-lymphocyte cell lines and clones. Pichler and Tilch report a sensitivity of 60–70% for those allergic to beta-lactam antibiotics in the classic exanthematic drug rash [44]. However, the sensitivity of LTT is still very low in SJS/TEN. To improve the sensitivity in SJS and TEN, LTT should be done within 1 week after onset of the disease to get the highest sensitivity [45].

Studies have shown TEN to commonly produce sequelae including hypo- and hyperpigmentation (63%), nail dystrophies (38%), and ocular complications [46]. Chronic ophthalmic complications occur more frequently in patients with initial ocular involvement, but loss of vision secondary to corneal inflammation also occurs in those without initial infection of the eye and is considered to be the most severe long-term complication in SJS/TEN survivors [47, 48]. Long-term mucosal complications including xerostomia or keratoconjunctivitis have also been reported in small clinical studies [49].

Hematologic abnormalities, particularly anemia and lymphopenia, are common in TEN. Eosinophilia is unusual despite the strong association of TEN with drug ingestion. Neutropenia is noted in approximately one-third of patients and correlates with poor prognosis. Glucocorticoids can cause demarginalization and mobilization of neutrophils in the circulation, giving a falsely elevated white blood count. This must be considered in patients who received these agents prior to testing, as this may obscure neutropenia [13, 50].

The time course of SJS/TEN from prodrome to hospital discharge in the absence of significant complications is typically 2–4 weeks. Reepithelialization may begin after several days and typically requires 2–3 weeks.

3.3 Drug Rash with Eosinophilia and Systemic Symptoms

DRESS is a severe and potentially fatal adverse drug reaction characterized by fever, skin eruption, hematologic abnormalities (prominent eosinophilia or atypical lymphoctytes), and multi-organ involvement which may affect the liver, kidneys, heart, and/or lungs [51, 52]. Also known as the drug-induced hypersensitivity syndrome, DRESS has other noteworthy features including a delayed onset, usually 2–6 weeks after initiation of drug therapy, and the possible persistence or aggravation of symptoms despite the discontinuation of the culprit drug [17].

The estimated incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures [53]. The incidence may be higher in African Americans and patients from the Caribbean. DRESS is considered to be a Gell and Coombs type IV reaction (Table 3.4). Type IV drug reactions involve the activation of T cells and in some cases other cell types (macrophages, eosinophils,

Table 3.4 Gell and Coombs classification of immunologic reactions [54]

Type	Description	Mechanism	Clinical features
I (Immediate reaction, within 1 h)	IgE-mediated immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances such as histamine, prostaglandins, and leukotrienes	Anaphylaxis Angioedema Bronchospasm Urticaria
II	Antibody-dependent cytotoxicity	Antigen or hapten that is intimately associated with a cell binds to antibody, leading to cell or tissue injury	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage is caused by formation and deposition of antigen–antibody complexes in vessels/tissue. Deposition of immune complexes causes complement activation and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors	Serum sickness
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (i.e., Types IVa–IVd)	SJS/TEN AGEP DRESS Contact dermatitis Some morbilliform reactions

or neutrophils). Clinically, those reactions involving T cells have prominent cutaneous findings, because the skin is a repository for T cells. Many cutaneous T cells are primed memory-effector cells, which react rapidly if immunogenic agents penetrate the skin barrier or diffuse into the skin from the circulation [54, 55].

In Type IV reactions, onset of clinical presentation is usually delayed by at least 48–72 h and sometimes by days to weeks following exposure to culprit drug. Upon rechallenge with the suspect drug, symptoms can appear within 24 h. Onset of symptoms depends partly upon the number of T cells activated by the drug. These responses are polyclonal in nature, and symptoms appear rapidly if the drug stimulates a large number of different T cell clones. In contrast, a drug that activates just a few clones may not cause clinical symptoms until these T cells have proliferated for a longer period of time, such as weeks. In DRESS, patients may suddenly develop signs and symptoms of a fulminant immune reaction. This reaction results from uncontrolled expansion of oligoclonal T cells that have been massively stimulated by the culprit drug, reminiscent of superantigen-like stimulation [56].

Detection of herpes viruses has been recently proposed as a diagnostic marker of DRESS [57]. Herpes viruses have been shown to reactivate in a certain order with the cascade of reactivation initiated by Epstein–Barr virus (EBV), human herpes virus-6 (HHV-6), HHV-7, and then cytomegalovirus (CMV) [58]. In one study, HHV-6 was detected via PCR in six of seven patients with DRESS [58]. It has been hypothesized that certain drugs have intrinsic properties to induce an immunosuppression that reactivates herpes viruses. Subsequent antiviral T cell activation leads to a cross-reaction with drug antigens, and, as a consequence, DRESS develops. Although this could suggest a key role for the viral infection in the development of an immunologic reaction, it could just represent nonspecific activation of a ubiquitous virus [59].

Clinically, this hypersensitivity syndrome develops 2–6 weeks after the culprit drug is initiated, which is of later onset compared to most other immunologically mediated skin reactions. Fever and a morbilliform eruption are the most common symptoms seen in 85 and 75% of cases, respectively. The face, upper trunk, and extremities are usual sites of involvement (Fig. 3.3). Vesicles, tense bullae, pustules, erythroderma, and purpuric lesions can also be seen. In one study by Chen et al. [60] involving DRESS subjects close to half of all patients were reported to

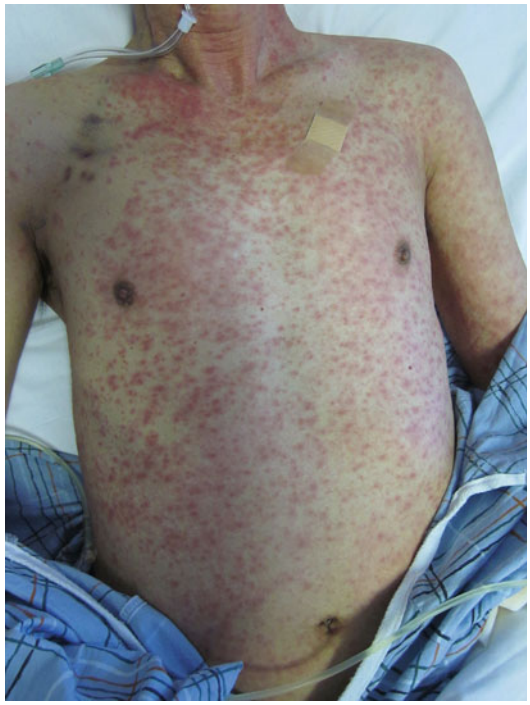

Fig. 3.3 (Courtesy of Jason Emer, MD). Drug rash with eosinophilia and systemic symptoms. Diffuse erythematous patches of the chest

have lesions involving at least one mucosal area, always affecting the oral mucosa. The liver is the most common visceral organ involved with a fulminant hepatitis being the major cause of death in this syndrome. Myocarditis, interstitial pneumonitis, interstitial nephritis, thyroiditis, and infiltration of the brain may be observed. Cutaneous and visceral symptoms can last for weeks even after drug withdrawal. For this reason, liver function tests should be conducted periodically after drug withdrawal. On skin biopsy, specimens showed various degrees of basal vacuolization, dyskeratosis, lymphocyte exocytosis, dermal edema, and superficial perivascular inflammation, resulting in a pathologic diagnosis of EM [60]. Because thyroiditis has been reported to develop in a small subset of patients, thyroid-stimulating hormone levels should also be measured and repeated after 2–3 months [61].

Anticonvulsants (phenytoin, phenobarbital, carbamazepine) are the most common causes of DRESS. Other drugs such as lamotrigine, valproic acid, allopurinol, NSAIDs, and minocycline have also been associated with this clinical entity (Table 3.2) [36]. Certain medications may cause inflammation affecting a specific organ. For example, anticonvulsant-induced DRESS frequently involves hepatitis, allopurinol can cause nephritis, and abacavir can cause pneumonitis [62]. Some DRESS reactions occur more frequently in those with certain HLA types, a phenomenon also seen in SJS/TEN [63]. For instance, DRESS secondary to allopurinol is associated with HLA-B*5801.

Table 3.5 Inclusion criteria for potential cases of DRESS published by RegiSCAR [64]

Hospitalization
Reaction suspected to be drug related
Acute rash
Fever >38 C
Enlarged lymph nodes at a minimum of two sites
Involvement of at least one internal organ
Blood count abnormalities
Lymphocytes above or below normal limits
Eosinophils above the laboratory limits
Platelets below laboratory limits

*Three of these four criteria are required for diagnosis

DRESS can be difficult to distinguish from serum sickness or vasculitis on clinical grounds. The diverse presentations and varied organ involvement highlight the need for a set of diagnostic criteria that are easily applicable in the clinical setting. The RegiSCAR group (Table 3.5) has suggested a series of criteria in which hospitalized patients with a drug rash must have at least three of four systemic features (fever, lymphadenopathy, internal organ involvement, hematological abnormalities). To qualify for a diagnosis of DRESS, abnormalities must include either eosinophilia or atypical lymphocytes as well as changes reflective of hepatic or renal dysfunction [64].

Systemic steroid therapy is the first line for DRESS, starting with a moderate dose followed by a gradual taper. Topical steroids can be utilized for skin manifestations. It is not uncommon for the reaction to flare up again with abrupt discontinuation of steroid therapy [65]. Cross-sensitivity among phenytoin, cabamazepine, and

phenobarbital has been reported in 40–80% of patients with anticonvulsant hypersensitivity syndrome. Therefore, afflicted patients should not be treated with any aromatic anticonvulsants and should inform family members that they too may be at a higher risk for severe adverse reactions to these medications, since susceptibility is believed to be partially genetic [66].

3.4 Acute Generalized Exanthematous Pustulosis

AGEP is characterized by fever above 38°C and a cutaneous eruption with nonfollicular sterile pustules on an edematous erythematous background. The interval between drug administration and onset of eruption can vary from 24 h to 3 weeks. A long interval probably indicates primary sensitization and the shorter interval may be related to an unintentional reexposure [67]. Neutrophil counts are elevated and there is usually no visceral involvement. Spontaneous healing typically occurs in 10–15 days. Similarly to TEN/SJS and DRESS, AGEP is considered to be a type IV drug reaction involving the activation of T cells (Table 3.4).

The eruption begins on the face or intertriginous area and disseminates within a few hours. Subcorneal aseptic pustules are characteristic and easily recognized. Edema of the face also may occur along with targetoid skin lesions, purpura, and vesicles (Fig. 3.4). Mild, non-erosive lesions occur in the mouth and tongue in about 20% of cases [68]. Occasionally the pustules coalesce to produce extensive superficial detachment and a positive Nikolsky sign which may be confused with TEN [69]. The syndrome is generally self-limited, resolving spontaneously in approximately 2 weeks, although fatalities are reported in about 5% of cases [70].

The clinical presentation of AGEP is very similar to that of acute pustular psoriasis (PP). However, in PP, the initial stage is less acute, the fever is lower, and the duration of eruption is usually longer than 3 weeks. A history of plaque psoriasis on the palms and soles is frequent in those with disseminated PP. AGEP also occurs in those with

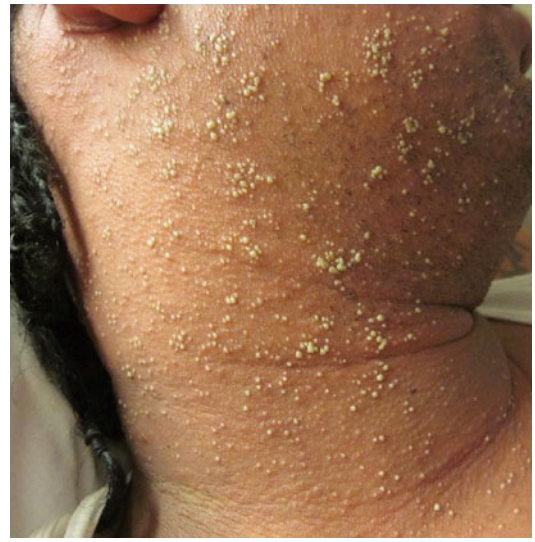

Fig. 3.4 (Courtesy of Jason Emer, MD). Acute generalized erythematous pustulosis Edematous, erythematous plaques of the face and neck dotted with pustules

psoriasis, perhaps more frequently than expected by chance. Nevertheless, skin pathology can help to differentiate the two pustular eruptions. While both entities are characterized by subcorneal spongiform pustules, AGEP is characterized by edema in the superficial dermis, vasculitis, exocytosis of eosinophils, and single-cell necrosis of keratinocytes, while psoriasiform hyperplasia is suggestive of PP. The acute onset of AGEP in association with a recent intake of pharmaceuticals is the cornerstone of its identification [69].

Antibiotics are thought to play a role in 80% of AGEP cases with penicillins and macrolides being the most common offenders (Table 3.2). A large, multinational case–control study also found quinolones, hydroxychloroquine, terbinafine, and diltiazem to be highly associated with AGEP. Additional drugs with weaker associations include glucocorticoids, NSAIDs, and antiepileptics [71]. Infection is a less common cause of AGEP. However, reports of viruses such as enterovirus, parvovirus B19, adenovirus, EBV, CMV, and hepatitis B have been implicated in causing AGEP. AGEP usually spontaneously regresses upon removal of the culprit drug. Topical steroids, antipyretics, and emollients are usually required to assist with the healing process [68].

3.5 Serum Sickness and Serum Sickness-Like Reactions

While not an official part of the SCAR definition, serum sickness and serum sickness-like reactions (SSLRs) are integral members of the family of emergent drug eruptions as afflicted patients can appear severely ill during this self-limited disease. In 1905, von Pirquet and Schick provided the first detailed description of serum sickness in humans. Eight to twelve days after subcutaneous injections of horse serum was injected in children who were being treated with serum containing diphtheria antitoxin, a clinical syndrome characterized by fever, lymphadenopathy, cutaneous eruptions, and arthralgias was reported to occur. Proteinuria without evidence of glomerulonepthritis was also observed. A delay was noted between the administration of the horse serum and the development of symptoms. The delay was shortened if the serum was re-administered [72].

Serum sickness is the prototypic example of Gell and Coombs type III or immune complex-mediated hypersensitivity reaction (Table 3.4). The reaction requires the presence of antibodies directed against an antigen which subsequently form immune complexes. These complexes are normally cleared by the mononuclear phagocyte system; however, if this system is not functioning well or becomes saturated, excess immune complexes deposit in tissues or directly develop within involved tissues. Immune complexes react with the Fc IgG receptors on neutrophils, mast cells, and phagocytes and trigger an inflammatory response releasing cytokines, histamine, and other inflammatory mediators (activating the complement cascade) [73, 74]. Resolution of illness occurs when the antigen is completely cleared from the serum. Recurrence can develop more rapidly if a previously immunized patient becomes reexposed to the culprit antigen. The subsequent amnestic IgG response to a recall antigen initiates a more acute, severe response within 12–36 h [75, 76].

In contrast, SSLRs are defined by the presence of fever, urticaria, and arthralgias occurring 1 to 3 weeks after drug initiation [77]. Other findings such as lymphadenopathy and eosinophilia may also be present; however, immune complexes, hypocomplementemia, vasculitis, and renal involvement are absent [78]. Drugs, particularly antibiotics, are the leading cause of SSLRs. Penicillin, amoxicillin, cefaclor, and trimethoprim-sulfamethoxazole are most commonly implicated, although many drugs have been associated with these reactions. In children, SSLRs are about 15-fold more likely with cefaclor than with other cephalosporins or amoxicillin [79]. In one study of children under the age of five, cefaclor-associated SSLRs were reported to occur in 0.2% with about 50% of these patients requiring hospitalization [80]. SSLRs also occur following infections (especially streptococcal and some viral infections) and a variety of vaccines [79].

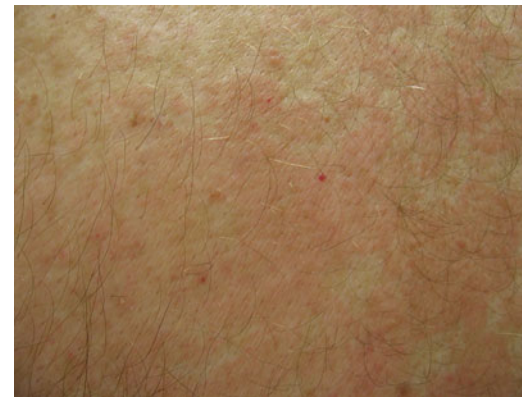

Fig. 3.5 Urticarial reaction. Small erythematous papules

Historically, serum sickness has been described following the administration of antitoxin or antivenom. More recently, serum sickness has been reported in patients receiving biologic immunotherapy with agents such as antithymocyte globulin, infliximab, and rituximab (Table 3.2) [81–85]. Risk factors for serum sickness include increasing dose and duration, nature of the heterologous protein, and age less than 16 years old.

The cutaneous manifestations of serum sickness are variable. Almost all develop a pruritic rash, which is often the earliest clinical feature (Fig. 3.5). The rash often starts in the region

around the injection site if a drug was administered locally by intramuscular or subcutaneous injection. Skin changes may be prominent at the lateral aspect of the feet and the hands, at the junction of the sole and side of the foot, or at the border between the palm and dorsal skin of the fingers or hands. Mucus membranes are spared. Virtually all patients develop fever which usually peaks 38.5°C, and arthralgias appear in approximately two-thirds of patients with metacarpophalangeal joints, knees, wrists, and ankles most commonly involved [73, 74].

Neutropenia, mild thrombocytopenia, and eosinophlia can be present, and mild proteinuria occurs in about 50% of patients. During severe episodes, complement measurements including C3, C4, and total hemolytic complement are depressed reflecting complement consumption. Histologically, mild perivascular infiltrates consisting of lymphocytes and histiocytes in the absence of vessel necrosis are observed in skin biopsies of those who develop serum sickness from equine antithymocyte globulin [86].

Diagnosis of serum sickness and SSLRs is made clinically after exposure to a potential offending agent. Complete blood count with differential, urinalysis, serum chemistries, and complement studies often aid in diagnosis. Skin biopsies are rarely used in confirmation of diagnosis as findings are variable. The differential diagnosis in patients of any age includes viral exanthems, urticarial vasculitis, acute rheumatic fever, and disseminated gonococcemia or meningococcemia.

Randomized controlled trial data concerning the treatment of serum sickness or SSLRs is lacking; however, one published retrospective chart review of the management of children with SSLRs caused by cefaclor showed that discontinuation of the culprit drug in combination with antihistamines and glucocorticoids provides the most symptomatic relief [87].

3.6 Conclusion

All patients who experience a drug eruption should be instructed to avoid the culprit drug and any other closely related drugs with suspicion of cross-reactivity. In the future as the laboratory technology for drug allergy testing develops, there may be an additional means to confirm the clinical diagnosis of a drug eruption. Considering the diagnostic similarities and overlapping morphological features of the various forms of drug eruptions, biopsies should always be used to help make a definitive diagnosis (Table 3.6). Additionally, physicians should always err on the side of caution when dealing with any subject with a possible drug eruption.

Table 3.6 Clinical features of drug eruptions

	SJS/TEN	DRESS	AGEP	Serum sickness
Symptoms	Fever, cough, malaise, macular exanthema, mucosal involvement	Fever, cutaneous eruption, multi-organ failure	Fever, cutaneous eruption, facial edema	Fever, lymphadenopathy, arthralgias, cutaneous eruptions
Laboratory Abnormalities	Anemia, lymphopenia, neutropenia	Atypical lymphocytosis (CD8+) w/prominent eosinophilia; lab abnormalities dependent on the organ involved	Leukocytosis with elevated neutrophil count and esoinophilia	Neutropenia, mild thrombocytopenia, eosinophilia, complement depletion, proteinuria
Onset of Symptoms	2–8 weeks	2–8 weeks	24 h to 3 weeks	1–2 weeks

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Histamine-Mediated Emergencies

4

Alyx Rosen, Sarit Itenberg, and Adam Friedman

4.1 Introduction

The wheel and flare of urticaria is the pathognomonic feature of histamine-mediated cutaneous lesions. In fact, urticaria is one of the most common chief complaints encountered by dermatologists. Fortunately, their life-threatening sequelae, namely, anaphylaxis and shock, are exceedingly rare. Understanding the mechanisms through which histamine release occurs and its subsequent physiologic and potentially pathologic impact is vital to our ability to triage and treat appropriately. All dermatologists should be proficient at recognizing and diagnosing both common and unusual histamine-mediated emergencies in order to implement timely and directed therapy that could be potentially lifesaving.

In this chapter, we review the pathophysiology of histamine-mediated disease, the clinical manifestations, and targeted therapies. Subjects that are discussed in detail include urticaria, angioedema, anaphylaxis and their many etiologies including foods, medications, blood products, latex, arthropod assaults, as well as the many physical urticarias and their triggers. We conclude with a brief review of cutaneous and systemic mastocytosis and their potential to be life-threatening.

4.2 Histamine

Histamine is an organic nitrogen compound that has potent physiologic activity. Several life-threatening emergencies are mediated by histamine, most of which have associated dermatologic manifestations.

Histamine was first discovered in 1910 as a critical mediator of hypersensitivity. About 20 years later, it was identified as a mediator of life-threatening anaphylactic reactions. Histamine belongs to a group of biogenic amines and is synthesized from the amino acid histidine [1]. This process occurs most notably in mast cells and basophils, but also in platelets, histaminergic neurons, and enterochromaffin cells. Histamine is stored intracellularly within vesicles and released upon stimulation. Histamine has a rapid onset of action, able to achieve its maximum

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Table 4.1 Histamine receptors

Receptor	Location	Function
H_1	Smooth muscle, vascular endothelium, heart, CNS	Constriction of bronchial smooth muscle, systemic vasodilation pruritus, symptoms of allergic rhinitis
H_2	Gastric parietal cells, vascular smooth muscle, heart, CNS	Vasodilation gastric acid secretion
H3	CNS > PNS	Autoreceptor in presynaptic histaminergic neurons; Decreases release of histamine, acetylcholine, norepinephrine, serotonin
H4	Bone marrow, WBCs, thymus, small intestine, spleen, colon, liver, lung, testes, tonsils, trachea	Mediates cellular chemotaxis.

CNS central nervous system, *PNS* peripheral nervous system, *WBCs* white blood cells

productivity quite efficiently. Notably, once released into circulation, histamine is elevated for only 30–60 min, making it a poor marker for mast cell and basophil activation [2]. However, a metabolite of histamine, methylhistamine, is present in the urine for up to 24 h after peak plasma histamine levels [2], and may be used as a diagnostic tool.

Histamine exerts specific actions by binding to one of four known human histamine receptors designated H_1–H4 (Table 4.1). Its effects, however, are potentiated mainly through the H_1 and H_2 receptors and include vasodilation (seen as erythema, flushing, and hypotension), increased vascular permeability by separation of endothelial cells (seen as angioedema), smooth muscle contraction (seen as stomach cramps and diarrhea), increased cardiac contraction (leading to tachycardia and arrhythmias), and increased glandular secretion (allergic rhinitis, dyspnea, and bronchoconstriction) [1, 2]. Finally, histamine stimulates the release of cyclic adenine monophosphate (cAMP), leading to increased production of mast cells in the bone marrow. Activation of the H3 receptor in the peripheral and central nervous system leads to increased neurotransmitter release causing vertigo, nausea, and vomiting (Fig. 4.1). The numerous effects of histamine explain why the clinical signs and symptoms of urticaria, angioedema, bronchospasm, hypotension, and gastrointestinal symptoms can occur rapidly after mast cell and basophil activation [2].

Though histamine is the principle mediator of hypersensitivity reactions and anaphylaxis, it is not the only one. Research has shown that other granule-associated preformed mediators (tryptase, chymase, and heparin), newly formed mediators (prostaglandins, leukotrienes, and platelet activating factor), and numerous cytokines and chemokines are released during the degranulation cascade (Fig. 4.2).

Release of mediators can occur within several minutes of the inciting event. The release of inflammatory cytokines, however, can take several hours, thereby mainly contributing to late phase reactions [2]. Late phase reactions occur within 2–24 h of exposure to the inciting event and are due to the migration of leukocytes to the skin, respiratory tract, or gastrointestinal tract. Cytokines may also contribute to protracted reactions that can last hours to days without a clear resolution of symptoms. This is not to be confused with biphasic reactions. Biphasic reactions are characterized by initial symptoms of a uniphasic anaphylactic response that resolve spontaneously or with treatment, followed by an asymptomatic period (1–72 h), and then a recurrence of symptoms without further exposure to antigen [3–5]. The second response in biphasic reactions may be less severe, similar to, or more severe than the original episode, and can be fatal. Biphasic reactions can occur in patients of any age. The mechanism of biphasic reactions is not completely understood. There are also no consistently reported risk factors, which creates a clinical dilemma for clinicians treating patients for anaphylaxis [4].

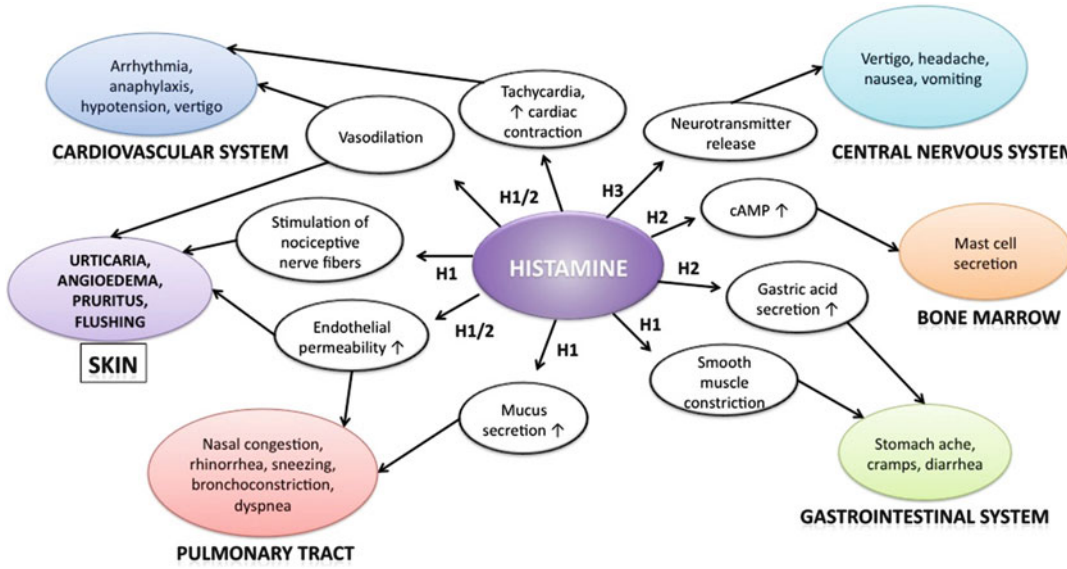

Fig. 4.1 Systemic effects of histamine. Adapted from: Maintz L et al. Dtsch Artzebl 2006;103:A3477–83

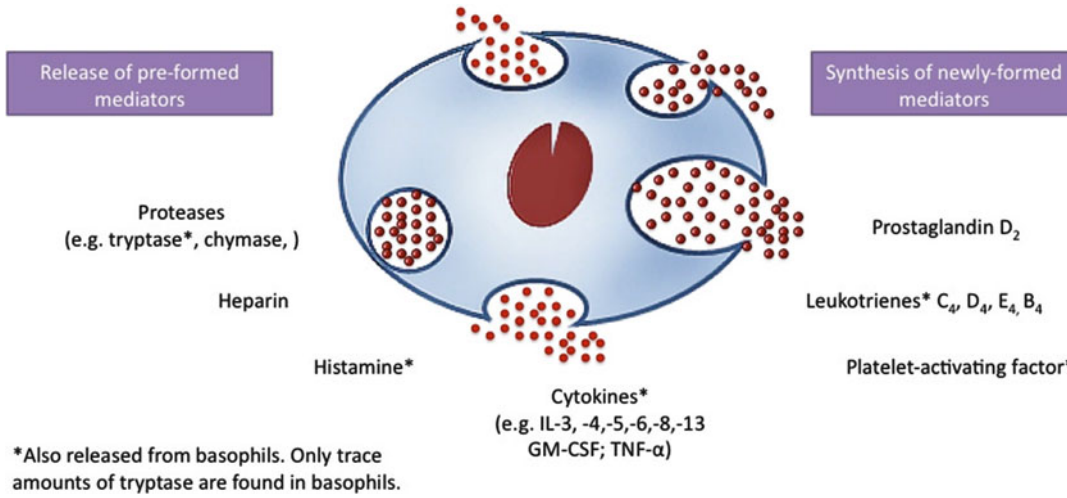

Fig. 4.2 Mediators released by dermal mast cell degranulation. Adapated from Bolognia, Jean, Joseph L. Jorizzo, and Ronald P. Rapini. "Dermatology." 2nd ed. St. Louis, Mo.: Mosby/Elsevier, 2008. Figure 19.4

4.3 Hypersensitivity Reactions

Hypersensitivity, or allergic, reactions are "over-reactions" of the immune system to innocuous environmental antigens in susceptible, pre-sensitized individuals. These reactions can range from localized tissue injury to death. The most common classification of hypersensitivity reactions is that of Gel and Coombs (Table 4.2). Histamine release from mast cell and basophil activation occurs mainly through immunogolublin E (IgE)-mediated immune reactions, which are type I hypersensitivity reactions. In brief, soluble antigen and IgE activation of mast cells and basophils causes degranulation and release of

Table 4.2 Hypersensitivity reactions

Reaction type	Immune mechanism	Examples	Pathologic lesions
Type I (immediate) hypersensitivity	Soluble antigen/IgE activation of mast cells causing vasodilation, vascular leakage, smooth muscle spasm (immediate reaction) and recruitment of inflammatory cells (late phase)	Angioedema, systemic anaphylaxis, allergic rhinitis, asthma, urticaria	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation
Type II (antibody-mediated) hypersensitivity	IgG/IgM bind to antigen on target cell or tissue resulting in phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Autoimmune hemolytic anemia, Goodpasture syndrome, certain drug reactions and reactions to incompatible blood transfusions	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury
Type III (immune complex-mediated) hypersensitivity	Antigen–antibody complexes deposit in tissues → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Systemic lupus erythematosus, some forms of glomerulonephritis, serum sickness, subacute bacterial endocarditis, arthus reaction	Inflammation, vasculitis
Type IV (T-cell-mediated) hypersensitivity	Soluble antigen activates CD4+ T-cells causing the release of cytokines and thus inflammation and macrophage and eosinophil activation Cell-associated antigen activates CD8+ T-cells causing direct T-cell-mediated cytotoxicity	Contact dermatitis, multiple sclerosis, type I diabetes, rheumatoid arthritis, inflammatory bowel disease, tuberculosis Contact dermatitis (e.g., poison ivy), reactions to certain virus-infected cells, some instances of graft rejection	Perivascular cellular infiltrates, edema, granuloma formation, cell destruction

mediators leading to vasodilation, vascular leakage, smooth muscle spasm, and the recruitment of inflammatory cells. These physiological mechanisms result clinically in urticaria, asthma, allergic rhinitis, angioedema, and anaphylaxis.

4.4 Urticaria, Angioedema, and Anaphylaxis

4.4.1 Definitions

Urticaria has been recognized since the beginning of medicine during the times of Hippocrates. The name dates back to the 18th century, when the burning and swelling of skin was likened to that caused by contact with nettles (*Urtica dioica*). Urticaria, or "hives," is a vascular inflammatory reaction of the papillary dermis [6]. The lesions appear as superficial wheals typically surrounded by an erythematous, often pruritic, ring, or flare with central clearing. Mast cells and basophils are the primary effectors of urticarial reactions. They release inflammatory mediators that cause an increase in capillary permeability, the most important of which is histamine [6].

Acute urticaria, by definition, occurs over a period of less than 6 weeks. It typically involves isolated, self-limited lesions that rarely last longer than 24 h, are often migratory, and can recur for indefinite periods of time. Rarely, postinflammatory pigment alteration is noted following resolution. Contact urticaria is defined as the development of acute urticarial lesions at the site where an external agent contacts the skin or mucosa; these lesions are not migratory [7]. In contrast, chronic urticaria requires episodes at least 2 days per week lasting more than 6 weeks duration [8]. While patients with chronic urticaria are observed for IgE-mediated causes, only 10–20% of patients with chronic urticaria have an identifiable trigger.

Angioedema is caused by the same pathophysiologic mechanism as urticaria but occurs deeper, typically in the subcutaneous, and submucosal tissues. Thus, although swelling is appreciated in angioedema, erythema is typically absent.

Anaphylaxis is commonly defined as a life-threatening IgE-mediated type I hypersensitivity reaction that is rapid in onset and involves multiple organ systems [9, 10]. It occurs when an immunologic reaction to an allergen in a sensitized individual causes a life-threatening event [11]. Anaphylactic reactions usually occur within 30 min of exposure to the antigen and rarely last beyond 2 h. Delayed presentations as well as biphasic anaphylactic reactions have been described in patients up to 72 h after exposure [12]. Histamine is the principal mediator of allergic hypersensitivity reactions, including anaphylaxis. Manifestations of anaphylaxis include diffuse erythema, urticaria, and angioedema initially, followed by bronchospasm, laryngeal edema, increased gastrointestinal motility, increased mucosal secretions, hypotension, and cardiac arrhythmias [6].

4.4.2 Epidemiology

Approximately 15–25% of individuals will experience at least one episode of urticaria at some point during their lives. Many people suffer from mild symptoms and fail to recognize it as urticaria. This leads to tremendous under reporting. The majority of these cases are acute urticarial episodes that do not recur; however, up to 30% of cases can advance to chronic urticaria. Urticaria is present in higher proportions in patients with atopic dermatitis. One study found that of patients with acute urticaria, half also suffered from hay fever, allergic asthma, or atopic dermatitis [13]. Acute urticaria is also more common in children and adolescents, while chronic urticaria is seen more frequently in adults.

The epidemiology of anaphylaxis is difficult to quantify, but it is estimated that there are around 84,000 cases of anaphylaxis each year in the USA. Anywhere from 500 to 1000 of these cases are fatal [14]. Based on reports by the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group in 2006, the estimated lifetime prevalence is approximately 0.05–2.0% with the

largest number of incident cases among children and adolescents [15]. However, accurate reporting is complicated by factors such as under diagnosis, under reporting, and a prior lack of a universal definition for anaphylaxis, making a true estimate of exact cases difficult to measure [16].

4.4.3 Pathophysiology

Acute urticaria and angioedema are caused by allergic IgE-mediated, non-IgE-mediated, and nonimmunologic mechanisms. In allergic IgE-mediated urticaria, the body views an antigen and produces specific IgE antibodies against this antigen [17]. The Fc portion of IgE has a strong affinity for the Fcε receptor-1 ($Fc\varepsilon R_1$) proteins on the surface of mast cells and basophils. Once the IgE binds to these receptors, a person is considered "sensitized" to the IgE-specific antigen. As many as half a million molecules of IgE can fix to a single mast cell or basophil [18]. The body can be exposed to an antigen through the skin, mucous membranes, respiratory tract, or the gastrointestinal tract.

Upon reintroduction, the antigen binds to several IgE antibodies already bound to mast cells or basophils, causing cross-linking of the IgE antibodies, thus activating the inflammatory cascade that clinically presents as urticaria and/or angioedema (Fig. 4.3). Cross-linkage of IgE antibodies may also occur from anti-IgE antibodies or other capable allergens. While up to 50% of chronic urticaria cases are thought to be idiopathic, recent studies show that approximately 35–45% of patients with idiopathic chronic urticaria in fact have an IgG autoantibody directed against mast cell or basophil surface-bound IgE. Thus, an autoimmune process may actually cause many cases of chronic urticaria.

Mast cells reside in the skin and in connective tissue near blood vessels in the lower respiratory tract, bronchial lumen, central nervous system, bone marrow, and gastrointestinal tract mucosa [14, 18]. Basophils are polymorphonuclear leukocytes found circulating in the blood. They constitute 0.1–2.0% of peripheral blood leukocytes and are rarely found in tissues [18]. When these cells are activated, preformed and newly formed mediators are released; the most important is histamine.

Similar to urticaria and angioedema described above, anaphylaxis is caused by allergic IgE-mediated, non-IgE-mediated, and nonimmunologic mechanisms. It too is a result of mast cell and basophil activation and subsequent release of histamine and other small molecules. The wide and variable distribution of mast cells and basophils throughout the body may explain why systemic features seen in anaphylaxis are not present during the activation of cutaneous mast cells in patients who present with urticaria or angioedema. The effects of the released chemical mediators include smooth muscle contraction,

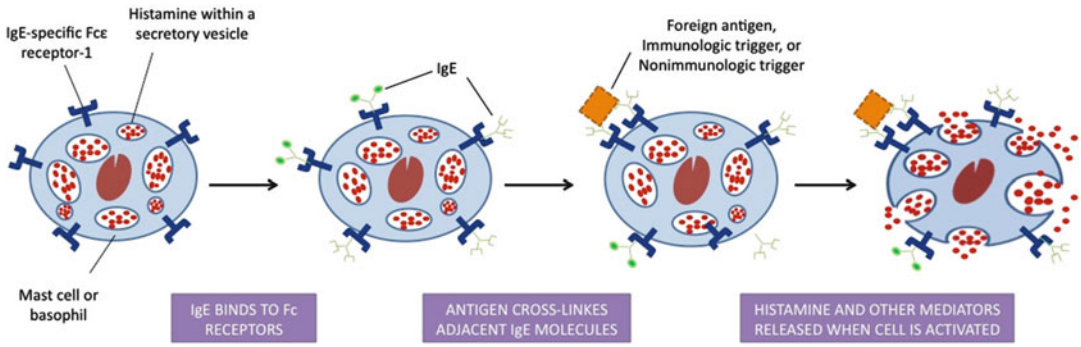

Fig. 4.3 Mast cell/basophil degranulation. Adapted from Alberts, Bruce. *Molecular Biology of the Cell*. 4th ed. 1 vols. New York: Garland Science, 2002. Print. Figure 24–27

especially in the pulmonary and gastrointestinal systems, coronary artery vasoconstriction, increased vascular permeability and capillary leakage. Extravasation of fluid and protein from blood vessels leads to a decrease in plasma volume, reduction in venous return, and circulatory collapse [11, 18].

Anaphylactic shock is reserved for cases of circulatory collapse that occur during anaphylactic reactions. There are four broad classifications of shock (hypovolemic, cardiogenic, distributive, and obstructive). Anaphylactic shock may be a combination of hypovolemic shock due to capillary leakage, distributive shock secondary to vasodilation, and cardiogenic shock because of decreased cardiac contractility [19]. Half of all deaths due to anaphylaxis result from circulatory collapse and shock. The other half are from airway obstruction [20].

Aside from the classic immunologic IgE-mediated hypersensitivity reactions, clinically identical presentations can occur via immunologic non-IgE mediated or nonimmunologic mechanisms. Immunologic non-IgE mediated reactions occur through activation of the complement system via immune complexes, and generation of kallikrein and bradykinin. Certain byproducts of the complement cascade, including plasma-activated complement 3 (C3a), plasma-activated complement 4 (C4a), and plasma-activated complement 5 (C5a), are called anaphylotoxins and can cause mast cell or basophil activation without IgE involvement [21]. Nonimmunologic reactions are a result of physical factors or antigens acting directly on mast cells and basophils to cause degranulation and histamine release, and not via an antigen–antibody interaction [14]. With regards to immunologic contact urticaria, the pathophysiology is similar to what was described above for allergic IgE-mediated urticaria. In contrast, nonimmunologic contact urticaria is thought to occur independent of histamine and rather through prostaglandin release from the epidermis. This is based on the beneficial response in such cases to acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) versus antihistamines [22, 23].

Thus, IgE-dependent reactions occur only after the patient has been previously exposed at least once to the antigen and is sensitized. Conversely, non-IgE mediated reactions can occur following a single, first time exposure to certain agents in non-sensitized individuals. Because immunologic reactions produce the same clinical manifestations, regardless of the method of histamine release, treatment is uniform [24]. Nonimmunologic triggers induce mast cell and basophil activation without evidence of involvement of IgE, IgG, or immune complexes, and are elaborated on later in this chapter.

4.4.4 Clinical Features

The lesions of acute urticaria appear as erythematous wheals (Fig. 4.4). They are pruritic and blanchable and generally resolve within 12–24 h without

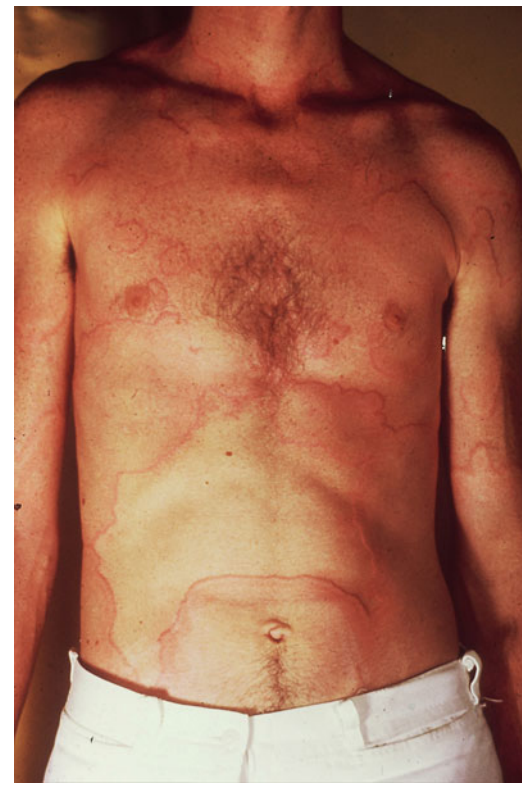

Fig. 4.4 Urticaria. Photo courtesy of Dr. Douglas I. Rosen, Assistant Clinical Professor of Medicine, Division of Dermatology, Montefiore Medical Center

complication or residual skin findings. Wheals may be small or large, single or multiple. In the case of physical urticaria, the distribution pattern and morphology can be helpful in separating the different clinical types. Allergens that are only locally absorbed, as in contact urticaria, usually result in confined symptoms of burning, itching, tingling, and wheals developing at the site of exposure [25]. Angioedema is also often present. In cases of immunologic contact urticaria, however, skin or mucosal contact with an inciting antigen in a sensitized patient can also lead to extracutaneous symptoms such as rhinoconjunctivitis, orolaryngeal and gastrointestinal dysfunction, or even progress to anaphylaxis [22]. Allergens that disseminate systemically through ingestants or inhalants can result in diffuse urticaria.

In contrast to the erythematous pruritic lesions of urticaria, angioedema typically has no corresponding visible erythema, rather patients complain of pain at the involved site. Angioedema typically involves the extremities, head, neck, face, and, in men, and the genitalia in men, and may last for several days. Most importantly, if it occurs in the soft tissues of the larynx and upper airway it can lead to life-threatening airway compromise and death [26]. Urticaria and angioedema may occur in any location together or separately. Urticaria occurs in association with angioedema in up to 50% of patients [27]. Approximately 10% of cases will exhibit angioedema in the absence of urticaria and 40% involve urticaria alone [25].

The classic clinical picture of anaphylaxis begins with scalp pruritus, urticaria, and angioedema, and ends with bronchospasm, hypotension, and gastrointestinal symptoms. Urticaria and angioedema are the most common symptoms in anaphylaxis and are seen in 88% of patients [2]. In nonlethal cases, hypotension often causes symptoms of nausea, vomiting, dyspnea, dizziness, and diaphoresis [19]. However, systemic hypotension and profound shock are clinical emergencies and may rapidly lead to cardiopulmonary arrest within 5–15 min after reaction onset [17, 20]. Patients who experience severe anaphylaxis should be observed for an extended timeframe of up to 72 h to eliminate the risk of a severe biphasic reaction occurring without medical attention. Finally, it is important to remember that anaphylactic reactions can occur without any dermatologic manifestations.

4.4.5 Risk Factors for Severe Hypersensitivity Reactions

Several important factors can increase the likelihood of a severe hypersensitivity reaction. These include very young or old age, pregnancy, comorbidities (e.g., asthma, atopy, or cardiovascular or respiratory disease), and use of certain concurrent medications like angiotensin converting enzyme (ACE) inhibitors or β-blockers, which sometimes hinder the treatment of anaphylaxis [28].

Small retrospective case series and large patient databases have demonstrated that an underlying history of asthma is a major risk factor for fatal or near fatal anaphylactic reactions to food with up to a 3.3 relative risk of anaphylaxis in patients with severe asthma [12, 29]. In addition, severe allergic rhinitis and severe eczema increase the risk of life-threatening anaphylaxis [21]. Atopy also appears to be a risk factor. However, it is not as specific for food-induced anaphylaxis, as patients with atopy may also have an increased incidence of anaphylactic reactions to latex, exercise, and radiocontrast media [14].

More severe and immediate reactions to medications occur when drugs are delivered parenterally versus orally. In patients with allergies to hymenoptera stings, elevated baseline tryptase levels demonstrate a higher risk for severe systemic reactions. Therefore baseline tryptase levels in patients with systemic reactions should be measured [30].

Finally, patients with subclinical or clinical mastocytosis who have a history of a serious hypersensitivity reaction to a known allergen, have a significantly increased risk for future life-threatening reactions [14, 31].

4.4.6 Etiologies

Many of the same causes of urticaria and angioedema can lead to anaphylaxis. Triggers can function via three different mechanisms: immunologic

Table 4.3 Common causes of type I hypersensitivity reactions

Immunologic IgE-mediated	Immunologic non-IgE-mediated	Nonimmunologically mediated
Food	IVIg	Medications causing direct mast cell degranulation (e.g., opioids, tartrazine, polymyxin B, benzoate, vancomycin, NSAIDs)
Medications (Acetylsalicylic acid, NSAIDS)	Animal antiserum	Complement factors (i.e., C3a and C5a)
Insect bites/stings	Autoimmune	Cytokines
Parasitic infections	Febrile illness (viral, bacterial, fungal)	Radiocontrast material
Contact allergens (latex)		Acetylsalicylic acid
		Physical stimuli
Exercise		
Biologic agents (vaccines, mAbs, hormones)		
Radiocontrast material		

IgE-mediated, immunologic non-IgE-mediated, and nonimmunologic (Table 4.3). This section focuses on life-threatening causes of hypersensitivity reactions.

4.4.6 A Food

Food allergy is still considered the most common cause of anaphylaxis. It is also one of the most common causes of immunologic IgE-mediated contact urticaria. Up to 2% of the US population may be affected by food allergies with 4–8% of children and 1–3% of adults with food allergy confirmed by skin prick testing [32]. The contribution of foods differ by age with children most often affected by peanuts, tree nuts, milk, and eggs, and adults with increased rates of allergy to shellfish, fish, and peanuts. Food additives (e.g., spices, vegetable gums, colorants (e.g., carmine), sodium benzoate, nitrates, and papain), food contaminants, and food parasites (e.g., Anisakis simplex) have also rarely been associated with anaphylaxis [14, 28].

Cow's milk protein is often the first allergen to which infants react, with symptoms presenting in the first week that formula feeds are introduced into the diet. The majority of children will outgrow their allergy. This reaction can be either IgE- or non-IgE-mediated with slightly better recovery rates for children with non-IgE-mediated allergies. While fewer studies have been conducted in children with allergies to egg and wheat, a significant percentage of these allergies are also lost by school age [32].

Shellfish allergy is typically an IgE-mediated process with shrimp, crab, and lobster responsible for the majority of reported allergic reactions [33]. Allergy in these patients is typically thought to be lifelong.

Scombroid poisoning or histamine fish poisoning can mimic food-induced anaphylaxis, but results from the consumption of mishandled scombridae fish including tuna, mackerel, and bonito as well as other (non-scombroid) fish species such as mahi mahi or sardines [34]. Bacteria in spoiled fish produces enzymes capable of decarboxylating histadine to produce biogenic amines like histamine and cis-urocanic acid, which are also capable of mast cell degranulation and further histamine release. While there are numerous other proposed mechanisms of toxicity, scombroid poisoning caused by elevated histamine levels in seafood is the most widely understood [34]. Common symptoms are similar to those seen in patients with food allergies. Rarely are serious cardiac and respiratory complications reported and even more infrequently

do patients require hospitalization. One way to help differentiate between fish poisoning and a seafood allergy is that most people eating the same meal will demonstrate a response to scombrotoxic fish versus only those with a specific fish allergy are expected to experience symptoms [35]. Regardless of the mechanism of toxicity, scombroid poisoning is treated in a similar manner to food allergy.

Peanut allergy remains the most common cause of food-induced anaphylaxis. It typically starts in early childhood but a late-onset cohort of patients can also be seen. The incidence of childhood peanut allergy is increasing and exceeds a prevalence of 1% in the US [36]. In contrast to children with milk, egg, and wheat allergies, only a small proportion outgrow peanut allergy [37], and vigilant lifelong avoidance is necessary.

Signs and symptoms of anaphylaxis typically develop within 30 min of food ingestion but can also occur within 5 min and rarely up to 2 h later. The skin and respiratory systems are involved in up to 76% and 80% of patients, respectively, and gastrointestinal symptoms are seen frequently in cases of food-induced anaphylaxis [38, 39]. Respiratory collapse is the cause of death in most fatal cases of food-induced anaphylaxis. Shock is a rare physiologic component and almost never seen without respiratory compromise [32].

Several recent studies have assessed the efficacy, safety, and feasibility of oral immunotherapy (OIT) for high-risk patients with severe peanut allergies. One study was conducted in 23 children, ages 3–14 years, with confirmed IgE-mediated peanut allergies. They received OIT following a rush protocol with roasted peanut for 7 days or, if protective doses of 0.5 g (0.16 teaspoons) of peanut were not achieved during the rush protocol, long-term buildup with biweekly dose increases up to 0.5 g of peanut was performed. Twenty-two of 23 patients continued with the long-term protocol and 14 reached the 0.5 g protective dose after a median of 7 months. Subsequently, these patients were able to tolerate a median of 1 g of peanut, in comparison to 0.19 g of peanut before OIT. Therefore, it was determined that for long-term buildup, but not rush, OIT was safe and effective in reaching clinically relevant protective doses, which may protect many high-risk patients against accidental ingestion reactions [40]. However, until larger randomized trials are conducted to further evaluate the benefit-risk ratio of OIT versus avoidance, which is the current mainstay of management, OIT cannot be considered for routine clinical practice [40, 41].

4.4.6 B Medications and Blood Products

Drug allergy is considered a type of adverse drug reaction and there is tremendous overlap between drugs that lead to urticaria, angioedema, and life-threatening anaphylaxis. Medications can trigger anaphylaxis through immunologic IgE-dependent, immunologic non-IgE-mediated, or nonimmunologic mechanisms. Several medications can also act through multiple different mechanisms. Antibiotics are the most common cause of IgE-dependent reactions, especially beta-lactams such as penicillins and cephalosporins, and less frequently, sulfonamides and tetracyclines [42]. Biologic agents including vaccines and hormones, as well as radiocontrast dye and certain monoclonal antibodies, also act through IgE-dependent pathways; however, the majority of hypersensitivity reactions to radiocontrast media are nonimmunologic. Radiocontrast media may also act via complement activation that subsequently leads to mast cell activation [28]. As the use of monoclonal antibodies in various clinical settings continues to increase, there is also a rise in incidence of hypersensitivity reactions. Many of these reactions are seen with the first dose of therapy, implicating a nonimmunologic mechanism of action. However, many patients also experience IgE-dependent reactions or even delayed reactions, with symptoms developing after several future doses [5]. Systemic infusion reactions related to the rate of monoclonal antibody drug infusion also occur.

Opioids cause mainly nonimmunologic hypersensitivity reactions while ASA classically acts via a non-IgE-mediated immunologic pathway. NSAIDs produce mainly nonimmunologic and rarely IgE-dependent immunologic reactions [28] and are responsible for up to 25% of all adverse drug reactions. After taking ASA

or other NSAIDs, one-third of patients with controlled underlying chronic urticaria and up to two-thirds of patients with active chronic urticaria will have exacerbations of urticaria or angioedema [43, 44].

Vancomycin, a glycopeptide antibiotic, can cause two different hypersensitivity reactions: (1) nonimmunologic mast cell and basophil degranulation causing "Red Man Syndrome" and (2) IgE-mediated anaphylaxis. "Red Man Syndrome" is far more common and is caused by a rapid infusion of vancomycin [45]. It typically presents with flushing, erythema, and pruritus of the face and upper torso but can also progress to angioedema, hypotension, and, rarely, cardiovascular depression [46]. While there is a correlation with the peak plasma histamine concentration during infusion and severity of the reaction, elevated histamine levels may also be seen in patients treated with slower infusion rates who do not experience "Red Man Syndrome" [47]. Other antibiotics have rarely been associated with "Red Man Syndrome."

Urticaria and angioedema can occur together or independent of each other. In the case of angioedema without urticaria, it is important to consider an underlying complement system enzyme deficiency, such as hereditary or acquired C1-esterase inhibitor deficiency. On the other hand, all patients treated with ACE inhibitors, a type of antihypertensive, can experience side effects related to increased bradykinin, including angioedema without urticaria. Therefore, special consideration should be taken when prescribing ACE inhibitors in patients who may have an underlying enzyme deficiency due to their predisposition for angioedema. Furthermore, it should be noted that symptoms of angioedema secondary to an underlying enzyme deficiency may be delayed up to a year after beginning treatment with ACE inhibitors and may be mistaken as a side effect of the drug only.

Life-threatening reactions to the administration of human IgG are rare in clinical practice. The most common blood transfusion related anaphylactic reaction occurs in patients with IgA deficiency. Up to 40% of patients with IgA deficiency produce IgG or IgE anti-IgA antibodies. During blood transfusions, the IgG or IgE anti-IgA antibodies attack the IgA proteins in the donor blood. Two ways to prevent or minimize a serious anaphylactic reaction could be to use washed red blood cells or blood from another IgA deficient individual. In cases when IgA levels are not readily available, patients may be pretreated with antihistamines prior to emergent therapy.

The most severe cases of drug allergies can occur immediately or hours to days following drug administration. Factors including prior sensitization, route of administration, drug metabolism, drug interactions and concomitant food intake play a modifying role [48] and affect the rate of symptom development. Anaphylaxis secondary to cutaneous injections or topical applications has only rarely been reported.

4.4.6 C Latex

Food and latex (natural rubber) are two of the most common causes of immunologic IgE-mediated contact urticaria. In the 1980s, when universal precautions were implemented and the use of latex gloves increased, so too did the incidence of type-I hypersensitivity reactions predominantly in healthcare settings. Typically, reactions from a latex allergy occur within 30 min of exposure and include the development of pruritus and urticaria to the localized area of contact [49]. Generalized urticaria can occur and often results from dissemination of the allergen (antigen) after direct contact with mucosal surfaces. Serious, life-threatening latex induced anaphylactic reactions can also occur.

Latex allergy may be a source of morbidity for patients in their work place, in particular medical workers and people in occupations where they are regularly exposed to or use latex gloves. Individuals can also be exposed in their homes with common latex items including balloons, latex contraceptives, rubber bands, and much more. The latex-fruit syndrome refers to the cross-reaction of latex allergens with many plant-derived food allergens, which results from structural similarities between several latex and plant

antigenic proteins. The most commonly involved fruits include kiwi, banana, avocado, passion fruit, and chestnut. In this situation, it is difficult to determine if the patients were first sensitized to latex or to fruit, which would help provide more evidence-based prophylaxis [49]. It is highly advised that when visiting a doctor patients make their latex allergy known in order to help prevent life-threatening reactions.

4.4.6 D Hymenoptera Stings

Venom from insects of the order Hymenoptera, which includes ants, bees, hornets, wasps, and yellow jackets, or saliva from biting insects such as flies, mosquitoes, ticks, kissing bugs, and caterpillars, can cause severe anaphylactic reactions [50]. Insect stings as a cause of anaphylaxis can be seen all around the world with varying geographic areas affected more commonly by different families of Hymenoptera. Similarly, occupational hazards lend to increased risks of specific allergies. An obvious example is seen with the bee venom allergy, which is found in higher proportions in beekeepers [30]. Population-based studies have difficulty calculating the overall prevalence of Hymenoptera sting allergies, which may be responsible for up to 34.1% of all-cause anaphylaxis [31]. Severe systemic reactions are seen more frequently in adults and may present with all the same features of anaphylaxis with hypotension being the most dominant feature [30]. Baseline serum tryptase levels are the best predictor of the severity of anaphylaxis in insect sting-allergic patients [51, 52]. Understanding the classification of the various insect stings and bites that can lead to life-threatening hypersensitivity reactions is helpful in patient management and future preventive therapy [50]. Specific venom immunotherapy (VIT) can prevent morbidity and mortality in patients with severe hymenoptera sting allergies. A 3–5 year course of subcutaneous injections significantly reduces the risk of anaphylaxis in up to 98% of children and is even effective and safe in high-risk patients with mastocytosis. Indications and recommendations for VIT differ by country and are based on clinical history of systemic reactions, positive skin test, and knowledge of the history and risk factors for a severe reaction to treatment [21, 31].

4.4.6 E Idiopathic

Idiopathic reactions are responsible for up to one-third of all type I hypersensitivity reactions. The diagnosis is one of exclusion after a complete medical history, skin prick testing, serum specific IgE levels, radioallergosorbent test (RAST), and other lab testing reveal no recognizable external trigger. Similarly, any other diseases that could mimic the anaphylactic hypersensitivity reaction picture should be ruled out. Patients should also be evaluated for mastocytosis or clonal mast cell disorders [28]. Serum tryptase can be very useful in differentiating anaphylaxis from many conditions that can masquerade as anaphylaxis [53]. The attack rate is variable and fatalities can occur. Patients typically present with symptoms identical to those of other type I hypersensitivity reactions and individual patients tend to have the same physical manifestations on repeated episodes.

4.4.6 F Less Common Etiologies

Physical urticaria is an eruption in response to physical stimuli. Several defined subtypes of this phenomenon include dermatographic (Fig. 4.5), cold, heat, adrenergic, cholinergic, aquagenic,

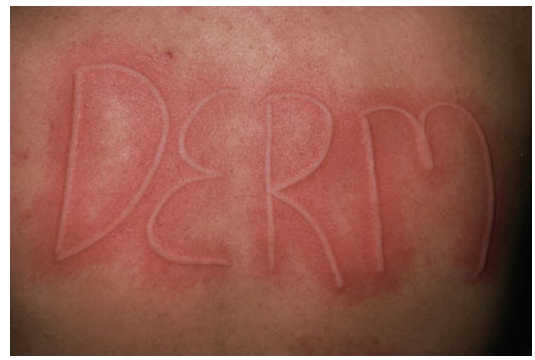

Fig. 4.5 Physical urticaria: dermatographism. Photo courtesy of Dr. Douglas I. Rosen, Assistant Clinical Professor of Medicine, Division of Dermatology, Montefiore Medical Center

solar, pressure, vibratory, and exercise-induced/food and exercise-induced (Table 4.4) [54]. Severe life-threatening responses to physical stimuli are exceedingly rare. Of all the physical urticarias, exercise-induced and food-exercise-induced urticaria/anaphylaxis, and primary cold urticaria have the highest incidence of associated anaphylaxis.

Viral infections, while not a primary cause of urticaria, have also been known to exacerbate urticarial reactions. It is thought that the up regulation of cytokines during acute phases of illness may lead to an enhanced state of mediator release from mast cells.

4.4.7 Differential Diagnosis

The differential diagnosis of histamine-mediated emergencies in dermatology is extensive. Because cutaneous signs such as urticaria are frequently the earliest signs of life-threatening events, conditions with an urticarial component must be ruled out. These include insect bite reactions, Sweets' syndrome (acute febrile neutrophilic dermatosis), the urticarial stage of bullous pemphigoid, acute contact dermatitis of the face, urticarial drug reactions, and urtication caused by rubbing of the lesions of urticaria pigmentosa. The prolonged duration of the individual urticarial lesions in these conditions helps to differentiate them from true urticaria, lesions of which typically last for less than 24 h.

4.4.8 Diagnosis

4.4.8 A Urticaria and Angioedema

A comprehensive history and physical examination are essential in the diagnosis of a suspected histamine-mediated emergency. The sequential exposure to an agent with the development of signs and symptoms, along with details of disease duration, known allergens, occupation, history and frequency of similar episodes, duration of previous episodes, and any previously successful or unsuccessful therapies should be reviewed. A thorough physical exam assessing morphology, location, and duration of cutaneous signs of histamine release, in particular urticaria and angioedema, should also be undertaken. Specific testing should be based on information provided in the history and physical and may include blood tests, skin biopsies of notable lesions in patients with lesions lasting more than 24 h, food challenges, skin testing for allergens, and tests designed to look for functional autoantibodies against IgE or the high-affinity receptor ($Fc\varepsilon R_1$) of dermal mast cells and basophils.

A measurement of serum and urine histamine and histamine metabolites and serum tryptase can be done to demonstrate mast cell or basophil activation. Serum histamine levels remain elevated for only 30–60 min after the onset of symptoms; therefore normal serum histamine levels cannot rule out a serious histamine-mediated reaction. A 24-h urine study of methylhistamine is more accurate and should be initiated as soon as possible after symptoms begin. Tryptase is a proteinase specific to mast cells and levels remain elevated for up to 5 h after mast cell activation. In cases of anaphylaxis, levels are expected to exceed 10 ng/mL and can increase greater than 100 ng/mL in anaphylaxis from hymenoptera stings or medications [12].

Allergen-specific skin testing or radioallergosorbent (RAST) testing can be used to identify certain causes of immunologic IgE-mediated reactions to food, latex, stinging insects, and other environmental allergens. These reactions can manifest as acute urticaria, angioedema, contact urticaria, or anaphylaxis. The recent National Institute for Health and Clinical Excellence guidelines recommend that all children with a clinically suspected immediate-type hypersensitivity reaction, based on an allergy focused clinical history, undergo skin prick testing or specific IgE blood tests, in order to confirm the diagnosis. Additionally, these tests should only be performed where facilities are available to quickly manage and treat an anaphylactic reaction [55]. Patients with severe chronic urticaria should be tested for thyroid autoantibodies as well as have thyroid function tests performed if clinically relevant. Patients with chronic urticaria have a higher incidence of thyroid autoantibodies, which

Table 4.4 Physical urticarias: characteristics, diagnostic features, and treatment

Physical urticaria	Features	Eliciting stimulus	Treatment
Symptomatic dermatographism	Linear wheals at sites of scratching or friction (Most common physical urticaria); Can be delayed by more than 30 min	Stroking or rubbing	Non-sedating H_1 blocker
Cholinergic urticaria	Multiple small (1–5 mm) pruritic wheals surrounded by a flare, "fried-egg" appearance; Symmetric, initially most prominent on upper half of the body but can become generalized; Angioedema can be present	Rise in core temperature and sweating (exercise, hot baths, spicy food, and stress)	Non-sedating H_1 blocker
Cold urticaria (primary)	Urticarial eruption and edema localized to areas of cold exposures, usually the face and hands; Rarely respiratory and cardiovascular compromise occur; Can be fatal if a person goes swimming or showers in cold water; Begins in adulthood	Ice-cube test-positive; Rewarming of skin after cooling can worsen symptoms (localized or systemic)	Non-sedating H_1 blocker; Doxepin 25 mg at bedtime up to 50 mg bid
Delayed pressure urticaria	Superficial and deep erythematous swellings at sites of sustained pressure to the skin; swellings can be painful or pruritic or both; Can have systemic features such as malaise or arthralgias; Diagnosis can be difficult if swelling is over joints	Sustained perpendicular pressure	Non-sedating H_1 blocker
Solar urticaria	Eruption from exposure to ultraviolet light; Key finding is the limitation of physical findings to areas of body exposed to direct sunlight; Prolonged exposure leads to wheals; Anaphylaxis is possible if exposed body surface area is large enough, >80%	Ultraviolet or visible solar radiation	Non-sedating H_1 blocker; Avoidance of trigger
Localized heat urticaria	Formation of wheals when a warm stimulus comes into direct contact with the skin	Local heat contact	Non-sedating H_1 blocker; Tolerance induction; Hydroxychloroquine
Adrenergic urticaria	Small (1–5 mm) red macules and papules with surrounding pallor	Emotional stress	Beta-adrenoreceptor-blocker (e.g., propranolol)
Aquagenic urticaria	Multiple small (1–5 mm) pruritic wheals surrounded by a flare, "fried-egg" appearance	Local water contact at any temperature	Non-sedating H_1 blocker; Avoidance of trigger

Exercise-induced anaphylaxis (EIA)	Wheals tend to be larger than cholinergic wheals and EIA can also occur without wheals; Additional manifestations of mast cell degranulation can occur including bronchospasm or cardiovascular collapse and anaphylaxis	Exercise, not secondary to rise in core temperature like in hot baths	Non-sedating H_1 and H_2 blocker prior to exercise; Self-injectable epinephrine kits in patients with a history of anaphylactic episodes and respiratory symptoms
Food and EIA	Angioedema or anaphylaxis occur within minutes of exercise in patients who have ingested specific foods up to several hours prior to exercising; Some patients may experience food-dependent, EIA with the consumption of any solid food or large meals prior to exercising	Exercise following a heavy food load or eating specific foods	Non-sedating H_1 blocker prior to exercise and avoidance of certain foods or large meals prior to exercise; Self-injectable epinephrine kits in patients with a history of anaphylactic episodes and respiratory symptoms
Vibratory angioedema	Erythema and swelling in response to vibratory stimuli; Familial form is autosomal dominant; Acquired form is milder	Vibration (jogging, using a lawnmower, or riding a motorcycle)	Avoidance of vibratory stimuli

may indicate an autoimmune etiology of the patient's urticaria. Limitations exist in confirming the presence of functional serum autoantibodies. Immunoassays for anti-FcεR_I and anti-IgE may not be completely accurate as patients may have nonfunctional as well as functional autoantibodies. Autologous serum skin tests (ASSTs) can be a helpful screening tool. They involve intradermal injections of autologous serum versus saline controls with positive results demonstrated by a pink wheal response at 30 min that is 1.5 mm greater in diameter than the control. Further research is necessary to find accurate means to diagnose patients with functional autoantibodies and an autoimmune etiology of anaphylaxis.

4.4.8 B Physical Urticaria

Several different standards have been proposed to aid in the diagnosis of the numerous physical urticarias. Table 4 provides a basic elicitation strategy for each physical urticaria. Eliciting for a physical urticaria along with antihistamine-responsive symptoms may be all that is required for diagnosis. However, some patients may prove more difficult to accurately diagnose. Important to remember is that patients may have severe reactions upon eliciting a physical urticaria and testing must be performed in a safe, controlled setting.

4.4.8 C Anaphylaxis

Although anaphylaxis was first described over 100 years ago, and is broadly understood as described above (see Urticaria, Angioedema, and Anaphylaxis: Definitions), there is still no universally accepted definition. In 2006, the second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium on the definition and management of anaphylaxis was held to determine the necessary clinical criteria for diagnosing anaphylaxis. Anaphylaxis is considered highly likely when there is acute onset of illness (within minutes to hours) with involvement of the skin, mucosal tissue, or both AND either respiratory compromise or evidence of end organ dysfunction (i.e., decreased blood pressure, incontinence, syncope). After exposure to a likely allergen, anaphylaxis is also highly likely if at least two of the following signs and symptoms are present: involvement of the skin or mucosa; respiratory compromise; hypotension; or persistent gastrointestinal symptoms. Finally, criteria for diagnosing anaphylaxis can be completely based on a patient's reduced blood pressure after exposure to a known allergen. In adults, a systolic blood pressure of less than 90 mm Hg or a 30% or greater decrease from baseline is considered significant [10].

4.4.9 Treatment

4.4.9 A Urticaria and Angioedema

Urticaria is often idiopathic, infrequently associated with a known allergen, and rarely results in life-threatening conditions. The treatment is not a clear-cut science and often requires a patient specific regimen. All patients who suffer from urticaria should be given information on common precipitants. Antihistamines, topical antipruritic preparations, and the avoidance of known triggers are often a successful initial approach. Some patients, however, will need additional interventions, including systemic steroids.

First line therapy for treatment of urticaria is accomplished with antihistamines, which are most effective when taken on a daily basis rather than as-needed symptomatic relief. Classic sedating H_1-antihistamines include chlorpheniramine, hydroxyzine, and diphenhydramine. While effective in controlling symptoms of urticaria, their potent sedative effects are a drawback, and they are not more efficient than the modern, non-sedating H_1-antihistamines. Additionally, newer H_1-antihistamines and their derivatives have less anticholinergic effects; therefore, patients experience less dry mouth, visual disturbances, tachycardia, or urinary retention. Examples include loratadine, desloratadine, cetirizine, levocetirizine, terfenadine, fexofenadine, and mizolastine (Table 4.5). H_2-antihistamines, such as cimetidine and ranitidine, have no beneficial effect on histamine-induced pruritus, and should therefore not be used as monotherapy for urticaria.

If symptoms are not improved after 2 weeks of treatment with a non-sedating H_1-antihistamine,

Table 4.5 Treatment algorithm for urticaria and angioedema modified from international treatment recommendations

Treatment level	Intervention	Examples
First level	Non-sedating H_1-antihistamine Newer non-sedating H_1-antihistamine	Cetirizine Loratadine Terfenadine Mizolastine Levocetirizine Desloratadine Fexofenadine
Second level	Increase dose of non-sedating H_1-antihistamine up to 4 times	
Third level	Continue non-sedating H_1-antihistamine and add a leukotriene antagonist **Or**, try changing H_1-antihistamine **Or**, continue non-sedating H_1-antihistamine and add Doxepin **Corticosteroids**[a] for severe exacerbations of acute urticaria or resistant cases of chronic urticaria. Short course (3–7 days)	Zafrilukast Montelukast Prednisone Prednisolone
Fourth level	Add one of the following to H_1-antihistamine Cyclosporine H_2-antihistamine Dapsone Omalizumab	 Cimetidine Ranitidine

[a]Pediatric prescribing manuals should be referenced for details on doses on children
Adapted from: Zuberbier, T. et al. *Allergy* 2009: 64: 1427–1443

increasing the dosage up to 4 times may provide relief. Patients with chronic urticaria have demonstrated increased symptomatic relief from doses of antihistamines up to 4 times higher than conventional doses without a compromise in safety [56]. Patients with frequent episodes of idiopathic anaphylaxis may also benefit from the use of daily prophylactic H_1-antihistamine. Patients should wait between 1 and 4 weeks before considering switching to alternative therapies to allow for the full effectiveness of antihistamine therapy. Patients should also try switching to a different H_1-antihistamine before adding on additional medications [57].

Second line therapies should be initiated if symptomatic relief is not accomplished with antihistamines alone. The addition of a leukotriene antagonist, such as zafirlukast or montelukast, may provide some patients relief from symptoms, especially patients with symptoms aggravated by NSAIDs and food additives [58, 59]. While evidence is limited for the use of lipoxygenase (zileuton) and cyclooxygenase (rofecoxib) inhibitors, these medications may also be effective for chronic urticaria [60, 61]. Doxepin, a tricyclic antidepressant with potent H_1- and H_2-antihistamine acitivity, may also be beneficial for patients unresponsive to antihistamine therapy. Dosing begins at 10–25 mg at night, and can be increased to up to 75 mg nightly [62]. Side effects may include sedation and weight gain.

A short course (3–7 days) of high-dose corticosteroids (prednisone or prednisolone 30–60 mg/day) may be effective in antihistamine resistant cases of chronic urticaria or severe episodes of acute urticaria when a rapid clinical response is needed [63]. Longer treatments with steroids beyond 7–14 days are not recommended, but if necessary, should be carried out under the care of a specialty clinic. Long-term use of systemic corticosteroids is associated with substantial adverse effects. Patients may be at increased risk for developing diabetes mellitus, hypertension, osteoporosis, adrenal insufficiency, or gastrointestinal bleeding [64]. Patients who suffer from chronic urticaria or known severe allergies to certain foods, medications, or insect bites should carry a self-injectable epinephrine pen (e.g., EpiPen) and be adequately trained in its use and administration.

If symptomatic relief is still not achieved, the addition of cyclosporine, H_2-antihistamines,

dapsone, or omalizumab are recommended as fourth level treatment by the current international guidelines for management of urticaria (Table 4.5) [57]. Low-dose cyclosporine has shown in several randomized and non-randomized trials to be safe and effective in decreasing urticarial symptoms in patients with chronic idiopathic urticaria [65–67]. Additionally, cyclosporine inhibits the release of preformed histamine and de novo mediators from human skin mast cells and basophils [68]. The combined use of H_1- and H_2-antihistamines may improve symptoms in some patients with difficult chronic urticaria [69]. Dapsone has been shown to achieve better long-term complete resolution of urticaria when used in combination with antihistamines as compared to treatment with antihistamines alone [70, 71]. However, the efficacy of dapsone longer than 3 months after withdrawal has not been well studied.

Omalizumab is a recombinant humanized monoclonal antibody (mAb) that binds to the C3 domain of the IgE antibody, the site where IgE binds to the $Fc\varepsilon R_1$, thereby blocking the binding of IgE to the $Fc\varepsilon R_1$ on the surface of mast cells and basophils. Therefore, it can reduce levels of circulating IgE autoantibodies and inhibit binding of IgE to high-affinity $Fc\varepsilon R_1$ resulting in $Fc\varepsilon R_1$ down regulation [72, 73]. Studies have demonstrated that a fixed subcutaneous dose of omalizumab added to a stable dose of H_1-antihistamine may be effective in patients with refractory chronic idiopathic urticaria or a small subpopulation of chronic urticaria patients who exhibit IgE autoantibodies against thyroperoxidase [73, 74].

Since the recognition that some patients with chronic urticaria may have an autoimmune component to their disease, research is ongoing in the use of other immunomodulatory therapies. These include low-dose methotrexate, rituximab, mycophenolate mofetil, cyclosporine, cyclophosphamide, plasmapheresis, intravenous immunoglobulin therapy, azathioprine, and oral tacrolimus. Methotrexate is an antimetabolite that has demonstrated efficacy in patients with chronic urticaria nonresponsive to conventional therapies. The mechanism of methotrexate in treating chronic urticaria, however, remains unknown [75]. Rituximab is a chimeric murine/human recombinant mAb that binds to CD20, which is found on B-cells. This binding leads to B-cell depletion and possibly decreased production of IgG autoantibodies. Rituximab is being investigated for the treatment of non-IgE autoantibody-mediated forms of chronic autoimmune urticaria, but further research is needed in this patient population [72].

In summary, the treatment of urticaria and angioedema first requires the avoidance of known allergens such as food, drugs, latex, or other contact allergens. Symptomatic relief is often achieved with oral antihistamines. A short course of oral corticosteroids may be necessary for severe protracted episodes and to prevent a late-phase response, though it takes up to 4 hours for the effects of oral corticosteroids to be seen. Finally, epinephrine should be considered only in the acute intervention of severe and life-threatening attacks.

4.4.9 B Anaphylaxis

Despite efforts to avoid known or common triggers of anaphylaxis, there is still no way to absolutely prevent exposures. Therefore, it is crucial that at-risk patients and caregivers be able to recognize early signs and symptoms of anaphylaxis and have knowledge of emergent, life-saving measures. The treatment of anaphylaxis requires implementing standard principles for emergency resuscitation, including an initial assessment of the patient's airway, breathing, circulation, and vital signs, before proceeding with any further management.

Epinephrine is considered an essential component of anaphylaxis treatment by the World Health Organization and World Allergy Organization [76]. Epinephrine should be administered at the first sign of anaphylaxis since delayed administration of epinephrine, especially in the pediatric population, leads to an increased risk of biphasic reactions, hypoxic-ischemic encephalopathy, and mortality. The most important life-saving effects of epinephrine occur through the alpha-1 adrenergic receptors. These include vasoconstriction of small arterioles and precapillary sphincters

with resultant decreased mucosal edema, reduction in angioedema and hives, and relief of upper airway obstruction, hypotension, and shock. Additional benefit from epinephrine follows from the effects on alpha-2 (decreased insulin release), beta-1 (increased heart rate and force of cardiac contractions), and beta-2 (bronchodilation and decreased release of mediators from mast cells and basophils) adrenergic receptors [76].

In an emergency, epinephrine administered intramuscularly or subcutaneously is the treatment of choice; however, intramuscular injections have been shown to reach peak plasma epinephrine levels more rapidly than subcutaneous injections with an auto-injector in children at risk of anaphylaxis [77]. The first-aid dose of epinephrine is 0.5 mg for adults and 0.3 mg for children [78]. Auto-injector formulations of epinephrine include the EpiPen (Dey LP, Napa, California, USA), Adrenaclick and Twinject (Sciele, Division of Shionogi, Japan), and the Anapen (Lincoln Medical, Salisbury, Wiltshire, UK; not available in the USA), and in most countries they are available in two fixed epinephrine doses per injection, 0.3 mg (e.g., EpiPen) and 0.15 mg (e.g., EpiPen Jr.). The Twinject and the Adrenaclick are similar devices but the Twinject contains two doses of epinephrine where the Adrenaclick contains only one. In some countries, the Anapen is also available in a 0.5 mg fixed epinephrine dose. The injections should be administered intramuscularly in the lateral thigh to control symptoms and maintain normal blood pressures. The 0.3 mg and the 0.15 mg injectable doses are appropriate for pediatric patients over 30 kg and between 15 and 30 kg, respectively. However, allergy specialists should be involved in the treatment of children below 15 kg requiring first-aid treatment with epinephrine for anaphylaxis for which the 0.15 mg dose may be too high [79].

With increasing rates of obesity in the USA [80], physicians must be aware that auto-injector needles might not achieve appropriate depths for intramuscular injection, even in pediatric patients [81, 82]. It has been proposed that in such patients, injection into the postero-lateral calf muscle (gastrocnemius/soleus), with little overlying subcutaneous fat and no endangered superficial arteries or nerves, may provide an effective alternative [79]. Otherwise, varying length needles on preloaded syringes provide another option, although with reduced shelf life of the epinephrine.

Up to 20% of patients require a second or multiple injections due to persistent symptoms or a biphasic reaction. Maximum doses may be repeated every 5–15 min as needed in the absence of a response to epinephrine [21]. Posture may also affect mortality in anaphylaxis and thus patients should be kept lying down with raised legs to maintain the vena cava as the lowest part of the body. This helps blood flow return to the right side of the heart and ensures adequate myocardial perfusion [83]. Patients and caretakers must be properly instructed on the importance of and how to use emergency epinephrine auto-injectors so as to avoid injury from unintentional injections and to make sure epinephrine is delivered to the individual experiencing an anaphylactic episode.

Epinephrine auto-injectors, or any self-injectable devices when auto-injectors are unavailable, should be prescribed for individuals who have already experienced anaphylaxis involving respiratory symptoms, hypotension, or shock, patients with known triggers that are commonly encountered in the community, including foods, insect stings, or physical urticarias, and patients with a history of idiopathic anaphylaxis [84]. Clinical judgment should be used when prescribing an epinephrine auto-injector for patients with a history of moderate to severe urticarial reactions after exposure to a known inciting allergen but no history of anaphylaxis. There are no contraindications to using epinephrine in anaphylaxis and thus the threshold for prescribing should be low [78]. When multiple repeat intramuscular doses of epinephrine are required, patients may benefit from intravenous epinephrine in the form of bolus epinephrine or a continuous infusion. However, intravenous administration of epinephrine should only be performed by a trained and experienced specialist [85].

Side effects of epinephrine include tachycardia, anxiety, and headache, and caution should be applied for use in patients with hypertension, ischemic heart disease, cerebrovascular disease, and diabetes mellitus. Additionally, side effects of epinephrine may mimic signs of anaphylaxis and care must be taken not to administer extraneous doses. Oxygen therapy and placing the patient in the supine position with lower extremity elevation should also be maintained. Additional therapies depend on the severity of the anaphylactic episode and include intravenous fluids, antihistamines, vasopressors, corticosteroids, glucagon, atropine, and nebulized albuterol. Monitoring patients for several hours after an anaphylactic episode is extremely important, as is providing instructions on how best to avoid future reactions based on the inciting antigen. The arrhythmogenicity of epinephrine may be augmented by certain medications, including tricyclic antidepressants, drugs such as cocaine, or underlying cardiac arrhythmias [79]. Therefore, the benefits must be weighed against the potential side effects when prescribing epinephrine auto-injectors for patients. Finally, efforts should be made to treat any underlying medical conditions since certain diseases, such as asthma or cardiovascular disease, can increase a patient's risk for a severe anaphylactic episode [78, 86].

4.5 Mastocytosis

4.5.1 Definition and Epidemiology

Mastocytosis represents a collection of heterogeneous disorders characterized by the abnormal growth and accumulation of mast cells and the aberrant release of mast cell mediators, predominantly histamine, in various organ systems. Mastocytosis can be broadly divided into cutaneous mastocytosis, characterized by the presence of one or more lesions limited to the skin; and systemic mastocytosis, defined by lesions affecting various internal organs, commonly the bone marrow, gastrointestinal tract, liver, and spleen. Systemic mastocytosis may or may not involve the skin. Cutaneous involvement is more common in indolent forms and often absent in more advanced forms of systemic disease [87]. Cutaneous mastocytosis is more common in children than in adults, with 55% of patients noted to have onset before 2 years of age and an additional 10% of patients with disease onset before the age of 15 [88]. In childhood disease, the skin is almost exclusively involved and skin lesions typically improve or resolve by late adolescence [89]. In contrast, adult-onset disease occurs between the ages of 20 and 40 years, [89, 90] is more frequently systemic, and disease persists throughout a patient's lifetime. Although cutaneous mastocytosis is less commonly seen in the adult population, patients with systemic mastocytosis and skin involvement are frequently diagnosed based on their cutaneous lesions.

4.5.2 WHO Categorization

The WHO classification of mastocytosis is an accepted clinical approach to help distinguish cutaneous mastocytosis, systemic mastocytosis, and their subvariants [91]. The major types of cutaneous mastocytosis include urticaria pigmentosa, diffuse cutaneous mastocytosis, solitary mastocytoma, and telangiectasia macularis eruptiva perstans. The majority of pediatric cases of cutaneous mastocytosis show a good prognosis with gradual resolution of both symptoms and skin lesions [92].

In children, systemic involvement is rare and disease may regress spontaneously in puberty or early adolescence. In adults, disease does not regress but rather has an indolent clinical course [87]. Survival in patients with indolent systemic mastocytosis is not statistically different from the general population. Prognoses for aggressive systemic mastocytosis and mast cell leukemia, however, are poor, and median survival is around 41 months and 2 months, respectively [93].

4.5.3 Pathophysiology

In most patients with mastocytosis disease is caused by a gain of function mutation in KIT, the mast/stem cell growth factor receptor that is

responsible for the differentiation and growth of mast cells. Mutation results in activation with subsequent accumulation and increased survival of mast cells, although a second "hit" is necessary in the pathogenesis, as the same mutations have been found independent of mastocytosis. Specifically, the D816V point mutation is found in 95% of adult patients with systemic mastocytosis [51]. As the pathogenesis of mastocytosis has become better understood it is known that the mechanisms of disease in the pediatric and adult populations may differ, and the frequency and significance of mutations in pediatric cases of mastocytosis is controversial [51, 87].

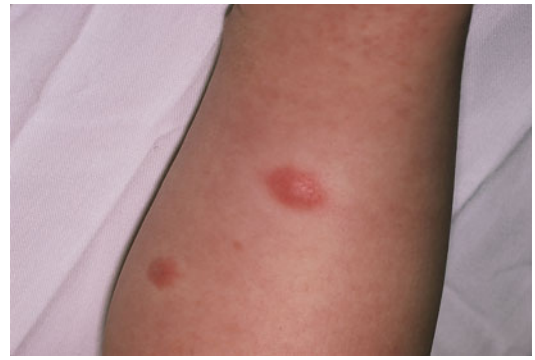

Fig. 4.6 Nodular mastocytoma. Photo courtesy of Dr. Douglas I. Rosen, Assistant Clinical Professor of Medicine, Division of Dermatology, Montefiore Medical Center

4.5.4 Clinical Features

For some patients, the cosmesis of urticaria pigmentosa lesions is the only complaint and the majority of patients with mastocytosis are completely asymptomatic. When present, cutaneous and systemic symptoms are caused by IgE-dependent and non-IgE-mediated degranulation of mast cells and release of histamine and other mediators, including tryptase, from the pathogenic mast cells. The pathophysiology of symptom development in mastocytosis is identical to that described for urticaria, angioedema, and anaphylaxis, and can be precipitated by the same mast cell stimulators as detailed above and outlined in Table 4.3. Symptoms of mastocytosis may be exacerbated by physical stimuli (Table 4.4), alcohol, narcotics, salicylates and other NSAIDs, polymyxin B, or anticholinergic medications.

Childhood cutaneous mastocytosis often presents with a solitary tan or pink to brown plaque or nodule (mastocytoma) (Fig. 4.6) or anywhere from 10 to 1,000 tan to brown macules or papules (urticaria pigmentosa) (Fig. 4.7). Erythema, swelling, and blister formation can occur after stroking or rubbing the lesions [94]. Darier's sign, the development of urticaria after stroking the lesions of mastocytosis, is not always present and correlates with the concentration of mast cells in the lesion. The trunk and extremities are the most common sites involved,

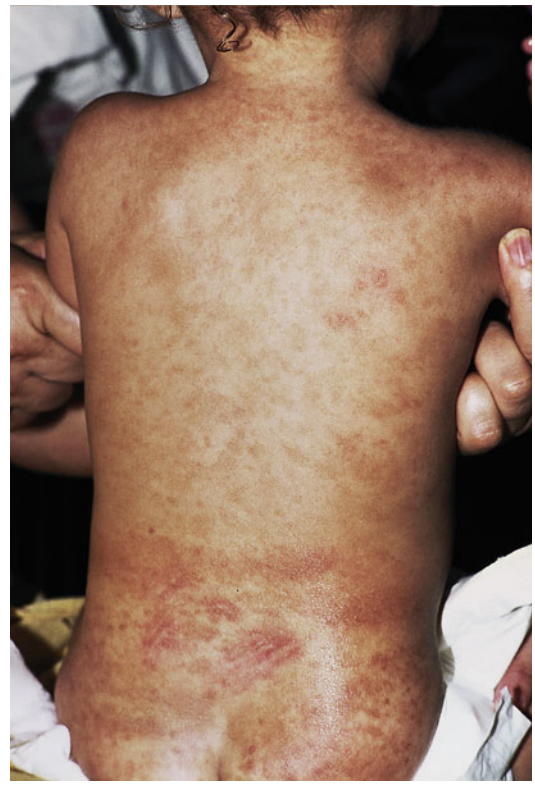

Fig. 4.7 Urticaria pigmentosa. Photo courtesy of Dr. Douglas I. Rosen, Assistant Clinical Professor of Medicine, Division of Dermatology, Montefiore Medical Center

but lesions can also occur on the face, palms, soles, and scalp. Of note, the extent of cutaneous involvement is not directly associated with

symptoms and is also not predictive of systemic disease [89]. Diffuse cutaneous mastocytosis (DCM) is a rare severe form seen predominantly in infants. The skin is infiltrated by mast cells in a generalized and diffuse pattern. The skin is thickened and appears doughy with a yellow discoloration and accentuated folds. In areas of increased mast cell accumulation, nodules or plaques are present. Additionally, edema may result from the mast cell infiltration and degranulation in the skin [92]. Life-threatening hypotensive episodes are common complications of DCM and occur due to the extent of lesions, which can involve the entire skin, and the large amount of mast cell mediator release locally and systemically during severe episodes [94]. Bullous eruptions with hemorrhage is a subvariant of DCM seen predominantly in neonates with blisters erupting spontaneously or from a stimulus. Patients may present at birth (congenital) or in early infancy, but blistering typically resolves by 3–5 years of age [92]. Mild symptoms such as cutaneous flushing, blistering, or pruritus, or more severe symptoms such as shortness of breath, asthma exacerbations, hypotension, and gastrointestinal symptoms, occur more commonly in patients with systemic disease, but may also be seen in patients with severe cutaneous disease, in particular DCM, due to the higher concentrations of mast cells [89].

When cutaneous lesions are present in adults they appear different from the typical lesions seen in children. They are 2–5 mm brown-reddish macules or papules. Telangiectasia macularis eruptiva perstans is seen in <1% of patients and exclusively in adults. The lesions appear as tan-to-brown macules with patchy erythema and telangiectasias.

Evolution of a childhood cutaneous form of mastocytosis to a systemic form is seen infrequently. The signs and symptoms of systemic mastocytosis reflect the infiltration of mast cells into the involved tissues. Patients may present with constitutional signs, skin lesions, mediator-related findings (flushing, syncope, diarrhea, hypotension, headache, and/or abdominal pain), and musculoskeletal disease, with an increased risk of severe osteoporosis [95].

The cumulative prevalence of anaphylaxis in children with mastocytosis is between 6% and 9% and in adults is between 22% and 49%. Patients with systemic disease are at increased risk of anaphylaxis compared to patients with solely cutaneous disease [51]. Severe anaphylactic reactions with shock or cardiopulmonary arrest are more common in patients with systemic mastocytosis, especially individuals with hymenoptera allergies. Deaths associated with extensive mast cell mediator release are rare but have been documented in both the pediatric and adult populations. Overall, the spectrum of cutaneous subtypes of mastocytosis has a good prognosis in comparison to systemic disease.

4.5.5 Diagnosis

The diagnosis of cutaneous mastocytosis requires a high index of suspicion in patients with skin lesions with or without mast cell mediator-related symptoms. These include flushing spells, pruritus, redness, swelling, respiratory symptoms, including asthma exacerbations and shortness of breath, and gastrointestinal symptoms, including peptic ulcer disease and diarrhea. The lesions of childhood and adult mastocytosis are very characteristic and may rarely be confused with other skin disorders. Demonstration of a positive Darier's sign, seen most commonly in patients with mastocytomas, is helpful in the diagnosis. A negative sign, however, does not rule out mastocytosis. Most diagnoses are based on clinical findings and results of skin biopsies. Demonstration of increased mast cells in either the blister fluid or skin biopsy of the mastocytosis patient may establish the correct diagnosis. Special stains that recognize tryptase and KIT (CD117) aid in the identification of tissue mast cells [96]. Analysis of KIT-receptor mutations, specifically the D816V mutation, within skin mast cells is recommended. Serum tryptase levels can also be an indicator of mast cell load, but are more likely to be increased in patients with systemic mastocytosis.

Systemic mastocytosis often requires more invasive diagnostic measures. A workup should

be performed in children when there is suspicion of progression to a systemic adult form, severe recurrent systemic mast cell mediator-related symptoms, organomegaly, or skin lesions that fail to resolve. In adults, a careful workup is necessary to accurately diagnose and stage patients with systemic disease. Initial laboratory testing includes a complete blood count with differentials, a chemistry panel, liver enzymes, and tryptase levels [92]. Bone marrow examination with biopsies is also often indicated in adult patients.

In most patients, histologic evaluation of bone marrow biopsies and mast cell identification allow for the most efficient diagnosis of systemic mastocytosis, as the bone marrow is almost always involved. Just as molecular detection of KIT mutations are performed in skin biopsies, they can be performed on fresh bone marrow aspirate, clot sections, bone marrow biopsy sections, and even peripheral blood if there are circulating mast cells. An immunohistochemistry panel consisting of CD117, tryptase, and CD25, with the latter not present in normal or reactive mast cells, can also detect neoplastic mast cells [95].

Additional laboratory and radiographic studies may be indicated for patients with additional signs of systemic involvement. Patients with complaints of bone pain should have an X-ray evaluation to look for skeletal involvement. However, in children with cutaneous mastocytosis and no evidence of systemic disease, positive X-ray findings may falsely convey signs of systemic disease [97]. The liver, spleen, lymph nodes, gastrointestinal tract, and any other organ may also be involved, and require further imaging or workup for diagnosis.

Ultimately, the diagnosis of systemic mastocytosis is based on World Health Organization criteria, with one major and one minor, or three minor criteria required. The major criterion is the presence of multifocal dense infiltrates of mast cells in bone marrow and/or other extracutaneous tissues. The minor criteria include: (1) More than 25% of the mast cells in bone marrow smears or tissue biopsy sections are spindle shaped or display atypical morphology; (2) Detection of a c-kit mutation in codon 816 in blood, bone marrow, or other lesional tissue; (3) Mast cells in the bone marrow, blood, or other lesional tissue express CD25 or CD2; (4) Baseline total tryptase level is persistently >20 mg/mL [51]. Further criteria are used to subcategorize patients based on the severity of their disease.

4.5.6 Treatment

There are no definitive effective treatments for patients with cutaneous mastocytosis or indolent systemic mastocytosis, and aggressive forms of therapy in these patients are not indicated. In general, treatment of patients with mastocytosis is directed towards alleviating symptoms. Patients should be advised to avoid triggers and medications that induce mast cell degranulation, as well as heat and friction, which can induce local or systemic symptoms. Local and systemic therapies should target symptoms related to mast cell mediator release and symptomatic skin lesions. Patients with more severe disease, and especially those with underlying asthma, respiratory conditions, or known severe allergies (i.e., hymenoptera allergy), who are at increased risk of anaphylaxis, should be directed to carry an emergency kit with self-injectable epinephrine, antihistamines, and corticosteroids at all times. Similar treatments as those described for urticaria, angioedema, and anaphylaxis are also utilized in the treatment of mastocytosis. First-line therapy is non-sedating H_1-anithistamines. For patients with recurrent episodes of anaphylaxis or persistent pruritus, prophylaxis with daily antihistamines is recommended. Additionally, management of pruritus and gastric hypersecretion may be accomplished with proton pump inhibitors, anticholinergics, cromolyn sodium (which inhibits mast cell degranulation), or leukotriene antagonists. Omalizumab (anti-IgE mAb) has also been successful in mastocytosis patients with multiple episodes of anaphylaxis. Topical corticosteroids are effective for localized treatment, such as mastocytomas, and lifelong allergen-specific venom immunotherapy (VIT) is recommended for patients with mastocytosis and hymenoptera

venom allergy [51]. Finally, emergency management of anaphylaxis begins with an initial assessment of the patient's airway, breathing, circulation, and vital signs, and then rapid administration of epinephrine.

4.6 Conclusion

Emergencies in dermatology are infrequent, and histamine-mediated emergencies are even more rare. As a very powerful mediator of hypersensitivity reactions, histamine can result in classic clinical signs and symptoms that should not be overlooked as they could very quickly evolve into life-threatening entities. Immediate diagnosis and appropriate intervention could be lifesaving. Urticaria, angioedema, and mastocytosis are the most important histamine-mediated entities carrying the risk of anaphylaxis, shock, and possibly death. It is of paramount importance to perform a complete history (including possible triggers, individual risk factors, and medications) and a thorough physical examination. Any case of urticaria should prompt a vigilant interaction between clinician and patient.

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Cutaneous Emergencies in the HIV-Positive Patient

5

Markus Boos, Karolyn Wanat, and James Treat

5.1 Overview

The Human Immunodeficiency Virus (HIV) is a member of the retrovirus family of enveloped RNA viruses. Retroviruses rely on an RNA-dependent DNA polymerase (reverse transcriptase) for their replication [1]. HIV is the causative organism in the development of acquired immune deficiency syndrome (AIDS). Although a complete review of the pathogenesis of HIV is beyond the scope of this text, a basic comprehension of the mechanism of HIV infection is helpful in understanding its resultant clinical manifestations. Briefly, HIV initiates infection of cells bearing the CD4 receptor through the interaction of the gp120 envelope glycoprotein present on the surface of HIV particles [2, 3]. Binding of gp120 to CD4 on the surface of T helper (T_H) lymphocytes, monocyte-derived macrophages (including tissue-specific macrophages such as brain microglia), and dendritic cells (including Langerhans cells of the skin) results in a conformational change in gp120 that facilitates binding to the chemokine co-receptors CCR5 and CXCR4 and exposes the HIV gp41 envelope protein, allowing membrane fusion and viral entry into a given cell [3]. Once it has entered a host cell, HIV initiates the synthesis of a double-stranded DNA molecule from its original RNA genome via reverse transcriptase activity; this may result in direct cellular lysis or altered activity of host cells, causing immune dysregulation and subsequent release of HIV virions into the bloodstream [4]. Alternatively, viral DNA may be integrated into the host genome, where it can remain latent in cellular reservoirs (most commonly macrophages). When a host cell infected with latent virus receives subsequent signals to proliferate, this concomitantly activates transcription of the original RNA virus, allowing for continued viral dissemination [4]. Of note, following primary infection there is a rapid rise in HIV viral counts that typically precedes the production of HIV-specific antibodies between 1 and 3 months post infection; it is these antibodies that are detected by HIV screening tests [2, 5, 6]. As a result of their viremia, individuals newly infected with HIV are more infectious and are at increased risk of transmitting the virus to others before being identified as seropositive [5, 7].

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The worldwide morbidity and mortality associated with the AIDS epidemic are substantial, and as such, a significant public health effort has been initiated to control both the spread of HIV and the progression of disease within infected individuals. HIV is transmitted through contact with blood, vaginal secretions, or semen of an infected individual. Transmission most often occurs through sexual intercourse (including oral sex), IV drug use, or via vertical mother-to-child transmission in the womb or during the perinatal period [2, 8]. HIV can also be transmitted via blood transfusion, though improved screening measures make this mode of transmission increasingly rare.

5.2 Primary HIV Infection

The acute manifestations of primary HIV infection are nonspecific, and a high degree of suspicion is required to establish the proper diagnosis. Since early diagnosis and treatment of HIV can help prevent serious sequelae in the source patient and further dissemination of HIV to sexual contacts, it is considered here as an emergency. Symptomatic primary HIV infection has been described as "mononucleosis-like" and most often presents with fever, fatigue, and rash between 2 and 4 weeks after exposure [9–11]. Additionally, symptoms such as sore throat, lymphadenopathy, headache, arthralgias, myalgias, night sweats, nausea, vomiting, and diarrhea are not uncommon [2, 9–11]. Hematologic abnormalities including lymphopenia and thrombocytopenia are frequently seen on laboratory evaluation (Table 5.1) [2, 5, 12]. Any patient who presents with this constellation of signs and symptoms therefore warrants a detailed sexual and drug use history, as well as a thorough physical exam to assist in the early diagnosis of new HIV infection.

The most common cutaneous manifestation of primary HIV infection (estimated to occur in up to 80% of new infections) is a macular or morbilliform eruption that is localized primarily on the upper trunk, but may also include the neck, face, extremities, scalp, palms, and soles [2, 8, 10, 13, 14].

Table 5.1 Constellation of symptoms associated with acute HIV infection

Constitutional	Fever, fatigue, headache, night sweats
Dermatologic	Morbilliform eruption of upper trunk composed of pink-red macules
	Mucocutaneous change: Anal, gential, oropharyngeal ulcers
Gastrointestinal	Sore throat, nausea, vomiting, diarrhea
Musculoskeletal	Arthralgias, myalgias
Hematologic	Lymphadenopathy, lymphopenia, thrombocytopenia

Additionally, patients should have a history of probable antecedent exposure in the preceding 2–4 weeks: either risky sexual behavior or IV drug use

The eruption may resemble a primary roseola exanthema. The macules that compose this rash are typically non-confluent, range in size from 4 to 10 mm, and are pink or red in color [10, 13]. Notably, the exanthem is not painful, rarely pruritic, and usually disappears within 1–2 weeks, occasionally inducing a fine desquamation as it resolves [5, 10, 12, 13]. The histologic features of the rash are also nonspecific and mimic various viral and drug reactions; an absence of epidermal change and a sparse dermal perivascular infiltrate composed mainly of lymphocytes and histiocytes is seen. Other skin findings that have been reported in association with primary HIV infection include a papulopustular and vesicular exanthem, urticaria, and desquamation of the palms and soles [7, 11, 15].

In addition to its characteristic rash, the dermatologic findings common to primary HIV infection include mucocutaneous change. Specifically, anal and genital ulcers, as well as ulceration of the esophagus, buccal mucosa, palate, and gingiva, have been reported in the absence of any other infectious causes [10, 12]. These characteristic ulcers have been described as 5–10 mm, round to oval in shape, with a white base surrounded by a red rim [10]. Enanthema of the soft and hard palates have also been noted [10, 12, 14]. Lymphadenopathy is another visible early manifestation of acute HIV infection; it appears most prominently during resolution of the acute syndrome [2, 9].

5.2.1 Diagnosis

Early diagnosis of HIV infection is of paramount importance, as recognition of new infections helps to prevent inadvertent transmission. Traditionally, the diagnosis of HIV infection is made via a screening enzyme-linked immunosorbent assay (ELISA) followed by a confirmatory Western blot for antibodies against the p24 nucleocapsid antigen, and the gp120 and gp41 envelope proteins. For populations of patients in remote locations or who infrequently or reluctantly visit healthcare practitioners, however, a rapid antibody test may be preferred because, although it can be more user dependent (the presence or absence of a line must be interpreted and proper controls must be used), at least the answer can be given immediately without having to worry that the patient will not be able to be located. One limitation of the traditional ELISA is that it is unable to identify a new HIV infection when the immune system has yet to mount an appreciable antibody response (the so-called window of infectivity) [5, 6]. As a result, alternate tests are needed to establish a diagnosis of HIV when it is suspected in the acute phase before a screening ELISA becomes positive. Two tests are currently used to diagnosis acute HIV infection: the p24 antigen test and a quantitative HIV RNA test. Of these two, evaluation of HIV RNA appears to have greater sensitivity but also has a lower specificity and is more expensive; p24 antigen detection may therefore be a more practical test in a setting of limited resources [5, 16]. Whether p24 or HIV RNA assay is performed, an ELISA should be performed simultaneously to establish the chronicity of infection. These tests should all be performed in consultation with an infectious disease specialist.

5.2.2 Treatment

The rationale for using highly active antiretroviral therapy (HAART) for HIV is not to cure the patient, but rather to reduce the incidence of AIDS defining illnesses and their associated morbidity and mortality. This is achieved by restoring normal immune function via a reduction of viral load and a concomitant increase in CD4 T cell count. The most recent recommendations of the International AIDS Society—USA Panel include beginning HAART at a CD4 cell count of less than or equal to 500/μL; patients who wait until they have a CD4 count below 350 or become symptomatic typically have worse outcomes. Other indications to initiate HAART include a high viral load (>100,000) or a rapid decrease in CD4 cell count (>100 cells/μL per year), age greater than 60, or coinfection with hepatitis B or C [17].

Importantly, HAART is also recommended for symptomatic primary HIV infection to limit viremia or a rapid decline in CD4 cell count, as well as to preserve immune function and prevent further transmission. The panel also recommends considering HAART in asymptomatic patients with a primary infection irrespective of CD4 count, though deferring treatment remains an option in those patients with a CD4 cell count of >500/μL. A large, multinational cohort study has shown that HAART improves survival rates in all patients with HIV, arguing for initiation of HAART in all patients; however, the reduction in mortality is less for patients who have a higher CD4 count at diagnosis [17].

The decision of what antiretroviral medications to begin should be based on HIV resistance patterns, adverse side effects of medication, a patient's individual comorbidities, and the ease of dosing. Usually two nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent (a protease inhibitor, non-nucleoside reverse transcriptase inhibitor or an integrase inhibitor) are suggested; fixed dose or once-a-day regimens are preferred. The goal of therapy is to induce a viral load of less than 50 copies/mL as evaluated by polymerase chain reaction (PCR) at 24 weeks. Initiating therapy, monitoring a patient's immune status, and the decision to change a given regimen secondary to resistance, toxicity, or convenience should be performed in consultation with an infectious disease specialist [17].

5.3 HIV-Associated Dermatoses

HIV infection is associated with the development of atypical and uncommon dermatoses, as well as irregular or exuberant presentations of more common cutaneous disease. Two such conditions that may require prompt medical intervention, psoriasis and eosinophilic folliculitis, are discussed below.

5.3.1 Psoriasis

Psoriasis is an inflammatory dermatitis with multiple clinical manifestations, but classic psoriasis vulgaris is characterized by well-circumscribed, erythematous plaques with a thick silver scale commonly located on the extensor surfaces of the arms and legs. In immunocompetent patients, the pathogenesis of psoriasis is thought to be secondary to localized inflammation secondary to unrestrained activity of Th1 and Th17 subsets of helper T lymphocytes. Interestingly, though psoriasis is thought to occur in HIV+ patients at approximately the same frequency as in the immuncompetent population (between 1 and 3 %), its clinical features vary [18]. Notably, psoriasis in HIV+ patients often follows an explosive course: preexisting psoriasis can flare with new HIV infection or clinical progression to AIDS, and abrupt onset of severe psoriasis often occurs with HIV-associated immune dysfunction, requiring emergent intervention. Though psoriasis vulgaris is also the most common form of psoriasis in HIV+ patients, inverse, erythrodermic, guttate, rupioid, pustular (including keratoderma blennorrhagicum), and sebopsoriatic variants are not uncommon [19, 20]. In particular, inverse and palmoplantar forms occur more frequently in patients who develop psoriasis after contracting HIV. Furthermore, multiple morphologies can often be simultaneously present on the skin of the same patient, and an extensive amount of body surface area can be involved [19, 21–23]. HIV+ patients with psoriasis also appear to be more prone to developing accompanying arthritis. Interestingly, spontaneous resolution of psoriasis in patients with end-stage AIDS is also recognized [24].

Though HIV-associated psoriasis of varying severity can manifest at any CD4 T cell count, it often presents later in the course of disease when CD4 numbers decrease to below 100–350 [21, 25]. This paradoxical worsening of a disease driven by T cells is thought to be secondary to a decrease in the CD4:CD8 T cell ratio late in advanced HIV infection. Specifically, elevated CD8+ T cell counts and the absence of CD4+ T cells (including suppressor cells) may allow for unrestrained pro-inflammatory activity and the development of psoriasis even in the face of decreasing absolute T cell numbers [19]. Furthermore, staphylococcal and streptococcal infections in these immunocompromised hosts may induce flares of psoriasis [20]. Diagnosis of psoriasis can typically be done clinically, but histologic evaluation reveals proliferation of basal keratinocytes, acanthosis, and desquamation of the stratum corneum. In HIV+ patients, there is a predominance of plasma cells, and the presence of T cells and dyskeratotic keratinocytes is uncommon [18, 19]. The discovery of plasma cells on biopsy should therefore raise the suspicion of an associated HIV infection in patients with new-onset or abruptly worsening psoriasis.

Therapy for psoriasis in HIV+ patients is challenging as immunomodulating drugs—a mainstay of psoriasis therapy—may expose the patient to increased risk of opportunistic malignancy and infection. As a result, topical therapies including calcipotriene, corticosteroids, tazarotene, and calcipotriol/betamethasone are considered first line for mild to moderate disease [25]. Ultraviolet (UV) therapy and antiretrovirals are also thought to be safe and effective options for this subgroup of psoriatic patients. Second-line treatment consists of oral retinoids such as acitretin. Immunomodulating agents such as methotrexate, cyclosporine, and biologic agents are reserved for the most severe and recalcitrant cases [25]. These instances should be considered on a case-by-case basis, and close monitoring, as well as institution of antiretroviral therapy and prophylaxis

against infection, should be initiated when beginning immunosuppressant therapy.

5.3.2 Eosinophilic Folliculitis

Eosinophilic folliculitis (EF) is an extremely pruritic, follicular-based eruption of erythematous papules that is most commonly seen in HIV+ patients with low CD4 counts [26–28]. It has been reported as the primary presentation of HIV but more commonly serves to identify patients at risk for severe opportunistic infections. The presence of EF therefore indicates that urgent intervention is required to identify and/or treat an associated HIV infection [29]. The characteristic lesions of EF are 3–5 mm papules located primarily on the upper trunk, head, neck, and proximal extremities that are often excoriated or crusted as a result of associated pruritus [27–29]. Rarely, EF can present as erythematous plaques or urticaria [30]. A relative peripheral eosinophilia and elevated IgE levels may also be noted on laboratory studies [28]. The condition has a stark male predominance and has rarely been reported in women [27–29]. Interestingly, EF is associated with CD4 cell counts less than 250/μL; however, the initiation of HAART also appears to be a trigger of EF in these same patients [26, 27]. This tends to occur between 3 and 6 months after initiating HAART [27].

The differential diagnosis for EF includes multiple pruritic dermatoses such as scabies, papular urticaria, dermatitis herpetiformis, arthropod assault, and bacterial folliculitis [31]. In order to establish a diagnosis, skin biopsy of a papule is often helpful, though care must be taken to section the specimen appropriately so that an involved follicle can be evaluated. Histologic examination reveals a mixed perivascular or perifollicular infiltrate of eosinophils and lymphocytes with occasional neutrophils, often with rupture of the associated sebaceous gland [26, 28, 30]. Notably, infectious organisms are absent on both H&E and special stain examinations. A scabies preparation is also helpful to exclude this condition in patients who are immunosuppressed although typically scabies, even in severely immunosuppressed patients, spares the face.

The pathogenesis of EF remains unknown, though it is thought to occur secondary to the skewing of the immune system toward a Th2 phenotype in the context of extreme immunosuppression and immune dysregulation. Many common environmental antigens, including skin flora and medications, have been suggested to potentiate a hypersensitivity reaction that leads to the clinical appearance of EF.

Treatment of EF is challenging, and no consensus exists on the optimal treatment for this condition. Of foremost importance is the initiation of HAART, which, though it may potentiate EF when initiated in those with low CD4 cell counts, ultimately helps resolve the condition by restoring normal immune system function [27, 30, 32]. Among other therapeutic modalities, UVB therapy two to three times per week appears to most reliably provide improvement within 3–6 weeks, though weekly maintenance treatments are usually required [32]. High-potency topical steroids applied twice daily may also be effective, but given their side effects of skin atrophy, hypopigmentation, and telangiectasias, an effective alternative topical therapy such as tacrolimus may be a better option [28, 33]. Systemic therapies including itraconazole (begun at 200 mg/day), metronidazole (250 mg three times per day), and isotretinoin (0.3–1 mg/kg/day) have also been used to treat EF, with varying degrees of success [32]. Symptomatic control of pruritus can be achieved by using antihistamines such as cetirizine or doxepin, as well as through the application of topical lotions containing menthol [31, 32].

5.4 Infectious Complications of HIV Infection

Given the global immunosuppression associated with HIV infection and the depletion of CD4+ T helper cells, patients who are HIV+ are at an increased risk of both common and opportunistic infections. The most common and life-threatening infections are discussed below.

5.5 Tuberculosis and Other Mycobacterial Infections

Coinfection with HIV and *Mycobacterium tuberculosis* is a significant public health issue, as these two organisms have synergistically detrimental effects on individuals afflicted with both. Namely, weakening of the immune system by HIV allows latent *M. tuberculosis* infection to become active. In turn, tuberculosis (TB), which has become increasingly resistant to a greater number of pharmacologic therapies, is a leading infectious cause of death worldwide in HIV+ individuals [34–36]. HIV infection often prevents timely diagnosis of TB because of the atypical presentation of active TB in the immunosuppressed; HIV also promotes immune anergy and makes tests such as the tuberculin skin test less sensitive for diagnosis [34, 35].

Although cutaneous TB is rare, it appears to be more common in patients co-infected with HIV and therefore deserves special mention [37]. While scrofuloderma (suppurative, subcutaneous nodules of TB originating from an underlying nidus of infection such as a lymph node) can be seen in the context of immunosuppression, the more common appearance of cutaneous TB in patients with HIV/AIDS, particularly with CD4 cell counts <100/μL, is the disseminated miliary form, a.k.a. tuberculosis cutis miliaris acuta generalisata [36, 37]. Cutaneous miliary TB typically appears as macules, papules, and crusted ulcers, but papulovesicles, pustules, purpura, and subcutaneous nodules are also possible manifestations [36–39]. The distribution of these multiple lesions most often includes the buttocks, trunk, thighs, and extensor extremities. Other clinical signs of TB include fever, weight loss, and productive cough.

Diagnosis of cutaneous TB can be made via scraping of a lesion and visualizing acid-fast bacilli (AFB) under microscopy after Ziehl–Neelsen staining. Biopsy may be necessary, and reveals a superficial dermal infiltrate of neutrophils, histiocytes, and/or lymphocytes, though granuloma formation is uncommon given patients' weakened immune response. Special stains are often necessary to visualize AFB. Most importantly, physicians must simply be alert to the possible diagnosis of disseminated cutaneous TB in any HIV+ individual who presents with multiple nonspecific skin lesions [37].

Treatment of tuberculosis includes quadruple therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol, though sensitivities should be performed given increasing TB drug resistance; alternative medications may be required. HAART is also indicated in these patients, but there is considerable interaction between antituberculosis and antiretroviral medications; therefore treatment should be undertaken with an infectious disease specialist [35, 38].

Infection with other non-tuberculosis mycobacteria can also produce cutaneous findings. *M. kansasii*, *M. haemophilum*, and *M. avium*/*M. intracellulare* (the MAI complex) rarely cause cutaneous disease but are more likely to do so in immunocompromised hosts, including those with HIV. The clinical manifestations of these assorted mycobacteria are variable, and include firm red nodules, erythematous papules, pustules, ulcers, abscesses, sinus tracts, verrucous lesions, and firm annular plaques [40, 41]. It is therefore important for physicians to consider these atypical infections as a potential cause of persistent, nonspecific skin lesions in patients with HIV. Importantly, in the context of an unclear clinical diagnosis, biopsy sections should be cultured broadly and evaluated with special AFB stains so as not to miss the diagnosis of a mycobacterial infection [42]. As with tuberculosis, therapy and management should be performed in consultation with an infectious disease specialist, and evidence of a disseminated infection should be sought and managed as necessary.

5.6 Fungal Infections

5.6.1 Candidiasis

Candida species, in particular *Candida albicans*, are the most frequent cause of fungal disease in patients with HIV [43]. Typically, candidal disease presents as infection of the oropharynx, esophagus, or anogenital region, though intertriginous

involvement of the skin is not uncommon [43, 44]. Disseminated infections are rare in HIV-associated Candida in part due to a relatively more functional humoral immune system [43]. *Candida* infections present at moderate-to-advanced stages of HIV infection (with CD4 cell counts <200–300/μL), and often signify progressive disease and poor clinical outcomes [17, 43, 45].

There are four main manifestations of oropharyngeal candidiasis: pseudomembranous, erythematous/atrophic and hyperplastic forms, as well as angular cheilitis [43]. Pseudomembranous oral candidiasis (OC) presents as creamy white plaques present on multiple oropharyngeal surfaces, including the tongue, palate, and buccal mucosa; these lesions can be easily scraped away. Erythematous and atrophic lesions are common in older patients with HIV and present as red ulcers and erosions; they can often be found under oral accessories such as dentures [45]. The hyperplastic form and angular cheilitis are far less common and appear as thick yellow plaques or erythema and painful fissuring at the angles of the mouth, respectively. Patients with active oral Candida infections may note altered taste, and complaints of pain on swallowing should alert the physician to potential esophageal involvement, as well [45]. Vulvovaginitis, enteritis, and gastritis are also possible mucocutaneous manifestations of Candida infection [43]. Cutaneous candidiasis is marked by pink-red, thin plaques and patches with surrounding satellite pustules, found most commonly in skin folds, including the groin, inframammary, and axillary regions [43].

The diagnosis of candidiasis is often a clinical one, though KOH preparations demonstrating budding yeast and pseudohyphae, fungal culture, and biochemical tests can aid in diagnosis when uncertainty exists [43, 45]. In adults, treatment of oral candidiasis can be achieved by administering oral fluconazole at a dose of 100–200 mg/day until the patient has remained asymptomatic for 1–2 weeks; alternatively, a single dose of 750 mg can be given [46]. Clotrimazole troches and nystatin solution are other topical alternatives for treatment of oral candidiasis, while itraconazole, voriconazole, or posaconazole can be used as alternatives to fluconazole in unusually refractory cases or for esophageal involvement when systemic therapy is indicated [43–45]. Cutaneous candidiasis is typically responsive to Nystatin or topical azoles including ketoconazole or clotrimazole [43].

5.6.2 Cryptococcus and Other Invasive Fungal Infections

Infection with the encapsulated yeast Cryptococcus neoformans is a common occurrence in patients with AIDS, occurring in between 6 and 13 % of patients, typically with CD4 cell counts below 200/μL [4, 47]. Cryptococcal infection occurs following inhalation of the organism, which is found in soil or grass contaminated with pigeon droppings; from this primary pulmonary focus, the organism can disseminate hematogenously [47, 48]. Most often this dissemination manifests as meningitis associated with central nervous system involvement, but cutaneous involvement occurs in approximately 6–20 % of patients with disseminated disease, as well [4, 47]. Primary cutaneous disease secondary to external inoculation is overwhelmingly rare [47].

The primary lesions of cutaneous cryptococcal disease are protean in appearance, but most often present as umbilicated papules and nodules, often with a central hemorrhagic crust [4, 49]. Other potential morphologies include violaceous and crusted papules, plaques and nodules, scaly plaques, and less commonly ulcers or draining sinuses [4, 47]. These lesions occur primarily on the face and neck, though involvement of the extremities and trunk also occurs at a reduced frequency [4]. The differential diagnosis of these lesions includes molluscum contagiosum, Kaposi's sarcoma, basal cell carcinoma, and nummular eczema [4, 47]. Identification of an antecedent flu-like illness or symptoms indicating multi-organ system involvement, such as neurologic changes or pulmonary symptoms, may assist the astute dermatologist in making the correct diagnosis of cryptococcal infection.

Diagnosis can easily be established on biopsy with routine histology. Two primary histopathologic appearances manifest in the case of cryptococcal

infection: granulomatous or gelatinous, though individual biopsy specimens can also exhibit an overlap of these two patterns. In the granulomatous form, multiple histiocytes can be seen phagocytizing budding yeast that are surrounded by clear halos. The gelatinous form exhibits fungal organisms surrounded by a pool of mucin. These organisms can be found in a variety of distributions, from subepidermal foci to involvement of the entire dermis [4]. PAS stains may aid in identification of encapsulated yeast organisms. In instances where the diagnosis remains in question despite biopsy, other methods of identification can be used including culture on Sabouraud dextrose agar or identification of cryptococcal capsular polysaccharide antigen in serum [47, 49]. Microscopic or serologic examination of cerebrospinal fluid may also help in establishing the diagnosis in patients with concomitant meningitis or neurologic symptoms [49].

Treatment of disseminated cryptococcal infection in immunocompromised patients includes intravenous amphotericin B; adjunct therapy with fluconazole or flucytosine is often administered. Lifelong prophylactic therapy is subsequently indicated, most often with daily oral fluconazole.

Although less common, infection with other invasive fungi such as Histoplasma capsulatum (histoplasmosis), Blastomyces dermatitidis (blastomycosis), and Coccidioides immitis (coccidiomycosis) must also be considered in HIV+ patients with cutaneous manifestations, especially those who live in or have recently traveled to endemic areas.

Histoplasmosis is found primarily in the Ohio and Mississippi River valleys, blastomycosis in the Midwest and southeastern United States, and coccidiomycosis is most common in the southwestern United States [50]. For all of these diseases, infection occurs primarily after inhalation and by entry through the lungs; cutaneous manifestation therefore represents disseminated disease in the majority of patients, as primary cutaneous disease secondary to inoculation is rare [48, 50].

Like Cryptococcus, cutaneous histoplasmosis often presents on the face, and has a protean appearance. Red macules, necrotic papules, nodules and pustules, eruptions reminiscent of acne and rosacea, and even ulcers have all been reported in association with histoplasmosis [51]. Oral manifestations are also common, presenting most often as painful ulcerations or granulomatous lesions [52]. Blastomycosis can also present in a variety of forms, including papules, pustules, ulcers, and granulomatous masses [53, 54]. Similarly, cutaneous coccidiomycosis manifests typically on the face as papules, pustules, or nodules. If given time to expand and coalesce, these lesions can eventually transform into abscesses, ulcers, and verrucous or scarred plaques [51]. Given the nonspecific nature of these cutaneous findings and the considerable overlap in presentation between the various fungal organisms, these species must always be considered in HIV+ patients who present with any of the aforementioned cutaneous findings. Biopsy and serologic testing are indicated to quickly establish the appropriate diagnosis [50]. Treatment of all of these organisms should be guided by an infectious disease specialist but typically begins with amphotericin B, with azole therapy (typically with itraconazole or fluconazole) initiated after clinical stabilization. Patients subsequently require lifelong prophylaxis to prevent recurrence [48, 50].

5.6.3 Cutaneous Bacterial Infections that Can Be Emergencies

5.6.3.1 *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a rapidly emerging pathogen that has a higher prevalence of both colonization and skin and soft tissue infection in people infected with HIV. MRSA colonization is more highly associated with HIV-infected patients who have low CD4 counts, are intravenous drug users, and in men who have sex with men [55–58]. *Staphylococcus aureus* presents in the skin most frequently with folliculitis or furunculosis and can lead to more severe systemic infection. Although folliculitis and furunculosis are rarely emergencies, given the risk of bacteremia and internal abscesses, it is important to identify and treat cutaneous MRSA infections in HIV patients.

Antibacterial washes such as 4 % chlorhexidine can be used to decolonize the skin and treat mild folliculitis. When indicated, antibiotic therapy for cutaneous bacterial infections should be guided by cultures to assure the proper antibiotic choice. Furuncles and abscesses should be drained when possible. Antibiotic choices should be based on regional differences in susceptibilities. Since MRSA presents commonly with furunculosis, proper MRSA coverage (typically trimethoprim-sulfamethoxazole, a tetracycline, or clindamycin) should be started empirically while waiting for cultures if antibiotics are to be used. Dosing guidelines for skin and soft tissue infections should be followed, and patients should be monitored closely for clinical resolution as they may need more extended duration due to immunodeficiency.

5.6.3.2 Bacillary Angiomatosis

Bacillary angiomatosis (BA) is a bacterial infection caused by *Bartonella henselae* or *Bartonella quintana*. BA is nearly exclusively a manifestation of immunosuppression [59]. BA presents with papules and nodules that grow slowly in the skin and often ulcerate. The skin lesions often look distinctly vascular and can be mistaken for multiple pyogenic granulomas or Kaposi sarcoma. A high index of suspicion is vital, especially if an ulceration is cultured with conventional swab and does not yield a typical staphylococcal infection. Since BA can be an emergency with fever, fatigue, and disseminated lesions involving the liver, spleen, bone, and CNS, it is important to be able to recognize BA in the skin. BA is typically seen in patients with a CD4 count below 100 cells/μL [59]. Therefore, a diagnosis of BA should prompt a thorough workup for other diseases of extreme immunodeficiency such as *Pneumocystis carinii* pneumonia. Diagnosis of BA can be made with histology showing a vascular proliferation with protuberant cuboidal cells and positive staining of organisms with Warthin-Starry or Silver stains. PCR and immunoglobulin M detection can also be done where available [60]. Therapy is typically with erythromycin (500 mg every 6 h typically for 2 months). Tetracyclines are often used as a second-line agent, again for 2 months [61].

5.6.3.3 Syphilis

Syphilis is a bacterial infection caused by *Treponema pallidum*, which is most often sexually transmitted. The initial cutaneous manifestation of syphilis is the primary chancre that is commonly found in the perineum. In immunosuppressed HIV patients, the primary chancre may be deeper and longer lasting and there may be multiple chancres [62]. In addition, syphilis may predispose to easier transmission of HIV due to the chronic open wound with HIV shedding from the wound [63, 64].

Secondary syphilis is usually characterized by scaling papules and plaques on the trunk, palms, and soles but can include scattered ulcerations and condyloma lata. Later findings of cutaneous syphilis include large ulcerations (gummas). The risk of transition to neurosyphylis may be higher in patients with HIV, and therefore promptly recognizing and treating syphilis in HIV patients is vital [65]. Non-treponemal tests such as rapid plasma reagin (RPR) and venereal disease reference laboratory (VDRL) can be falsely positive or negative in patients with HIV but are still the preferred first-line tests. Biopsies of skin lesions with special stains as well as dark field examination and specific treponemal tests can help confirm the diagnosis [66].

5.6.3.4 Cancrum Oris (Noma)

Noma is a gangrenous infection of the oral cavity that typically affects young children. The infection typically starts with an ulceration on the gingiva which spreads to involve the mucosal and cutaneous lips. Noma is thought to be caused by a combination of poor nutrition and immunosuppression such as HIV. It is often polymicrobial and very challenging to treat. Noma can lead to significant morbidity and mortality due to the inability to eat and drink. Therapy is based on augmenting nutritional status and targeted therapy toward HIV as well as treating the infection based on cultures with antibiotics. Reconstructive surgery is also very important once the infection has been treated [67].

5.6.3.5 Viral Infections

Cutaneous viral infections are common and can manifest as typical self-limited infections in patients with HIV, especially if they have a normal CD4 count. This section reviews the atypical manifestations in patients with HIV and lowered immunity. Viral infections in immunosuppressed patients often present as more severe, disseminated, or chronic infections than in immunocompetent patients.

5.6.3.6 Herpetic Infections

Herpes simplex virus (HSV) typically affects mucous membranes including the mouth, eyes, perianal areas, perineum, and penis. This is because these areas are most likely to have microabrasions that can serve as portals of entry for the virus. HSV typically presents clinically with grouped vesicles that progress to grouped crusts and erosions as the vesicles rupture. In HIV patients with lowered immunity, the lesions will often be long standing or never fully resolve without therapy [68]. The resultant lesion is a non-healing ulcer, often in a typical location for HSV (perianal, perioral). These lesions can also become vegetative and exophytic requiring a high index of suspicion to diagnose.

HSV can present in an emergent fashion when cutaneous lesions disseminate hematogenously. Disseminated HSV can lead to widespread cutaneous erosions that can lead to secondary bacterial infection and sepsis. HSV can also disseminate widely (especially to the central nervous system or liver) leading to significant morbidity and possible mortality in severely immunosuppressed patients [69]. Diagnosis is typically with viral culture or more rapid tests such as PCR and direct fluorescent antibody. Therapy is based on the extent of involvement.

Varicella zoster virus (VZV) can be the first manifestation of new HIV infection. VZV is typically a self-limited widespread infection characterized by vesicles on an erythematous base ("dew drops on a rose petal"), especially in non-immunized people. In immunized patients or those with prior infection, widespread or exuberant VZV is rare. Instead, these patients may present with viral reactivation in one or two contiguous dermatomes. In HIV patients with lowered immunity, VZV may start as a typical reactivation within a dermatome (shingles) (Fig. 5.1). However, due to the lowered immunity, the cutaneous manifestations can be exuberant, last longer than the typical 1–2 weeks, or widely disseminate. Disseminated VZV is defined by having many lesions outside of the original dermatome or multiple noncontiguous dermatomes due to hematogenous spread. Disseminated VZV can lead to significant morbidity and mortality especially with involvement of the CNS, liver, or lungs [70]. Therefore disseminated VZV in a previously vaccinated or infected individual should prompt a workup for immunosuppression including HIV testing.

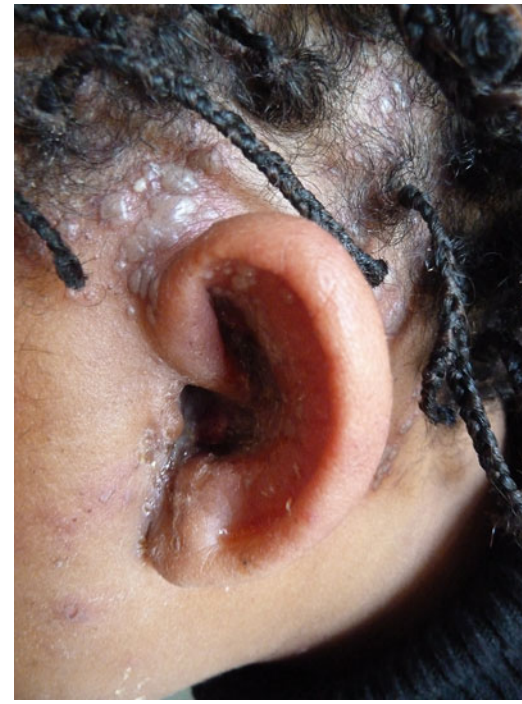

Fig. 5.1 Grouped vesicles involving the left cheek, ear, and ear canal consistent with herpes zoster infection

Cytomegalovirus (CMV) is another type of herpes virus that is typically self-limited in a normal host. In immunosuppressed HIV-positive patients, CMV can present as chronic ulcers (often oral or perianal) that are rarely emergent. Rarely digital necrosis has been reported in HIV-positive patients associated with CMV infection but the role of the CMV is not fully understood [71]. CMV is usually treated with gancyclovir

but should be guided by an experienced infectious disease specialist.

5.6.3.7 Molluscum Contagiosum

Molluscum contagiosum is caused by a DNA pox virus and most typically manifests as small flesh colored papules with central umbilication. Although molluscum is not a life-threatening infection, the virus can overgrow extensively in HIV patients. This overgrowth can lead to nodular lesions which can obstruct vision and become purulent and disfiguring [72]. Exuberant molluscum inflammation can also be a manifestation of immune reconstitution inflammatory syndrome (IRIS, discussed later in this chapter).

Viral infections can also be a precursor lesion to carcinomatous change. Chronic infection with human papillomavirus (HPV) infection that is recalcitrant to therapy and exuberant should raise suspicion for transition to verrucous carcinoma. Biopsy should be performed in immunosuppressed patients with especially recalcitrant warts, especially around the perineum.

5.6.4 Drug Reactions

Many medications used for the treatment of HIV and for AIDS-associated opportunistic infections are associated with cutaneous toxicities and can cause serious reactions, many of which are emergencies. Although the majority of cutaneous drug reactions are morbilliform, urticarial, or nonspecific reactions, clinicians need to be aware of the concerning features associated with more serious drug reactions. Patients with HIV have allergic reactions at a higher rate than the general population. Allergic reactions in HIV patients are likely to be multifactorial, and severe drug reactions need to be caught early to minimize morbidity and mortality [73, 74]. This is potentially difficult because of the multiple medications or combination regimens that are used to treat these patients making it difficult to identify the culprit medication.

The serious drug reactions that can occur include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug hypersensitivity syndrome (DHS) or drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). There are a few clinical signs and symptoms which can alert the clinician that one of these serious drug reactions might be occurring: high fever, skin pain, mucous membrane involvement, facial swelling, and internal organ involvement suggested by laboratory abnormalities. Table 5.2 provides a list of common medications used in the setting of HIV that may cause a serious drug reaction, including antiretrovirals and antibiotic regimens.

Table 5.2 Medications reported to cause a serious drug reaction in the setting of HIV

Abacavir
Amprenavir
Atazanavir
Didanosine
Indinavir
Isoniazid/rifampin combination therapy
Nevirapine
Ritonavir-boosted darunavir
Trimethoprim-sulfamethoxazole (TMP-SMX)
Zidovudine

5.6.5 Drug Hypersensitivity Syndrome

DHS has also been named Drug Reaction with Eosinophilia and Systemic Symptoms or DRESS. DHS is characterized by the triad of fever, skin eruption, and internal organ involvement in the setting of exposure to a medication [75]. Patients typically have a high fever (38–40 °C), malaise, facial edema, and lymphadenopathy. If suspected, laboratory testing should be performed to evaluate for internal organ involvement and should include a complete blood count (CBC) with differential looking for atypical lymphocytosis and eosinophilia; evaluation of liver abnormalities with special attention to transaminases, alkaline phosphatase, prothrombin time, and bilirubin; evaluation of kidney function with urinalysis and BUN and creatinine; and fecal occult blood test

to look for inflammatory colitis if gastrointestinal symptoms are present. Liver abnormalities are present in about 50 % of patients, and severe hepatitis and liver failure can occur [76]. Skin biopsy results in these situations are generally nonspecific but may allow the clinician to evaluate for underlying vasculitis, if suspected. In addition, because autoimmune thyroiditis occurring within 2 months of the onset of symptoms may result in hypothyroidism, thyroid function tests should be performed [76].

In the setting of HIV, abacavir hypersensitivity is a well-described, serious, and potentially fatal drug hypersensitivity reaction that can occur in both children and adults and affected approximately 5–8 % of people [77, 78]. It typically starts within the first 8 weeks of therapy and is characterized by two of the following: morbilliform rash, lymphadenopathy, fever, malaise, myalgias, gastrointestinal symptoms, and respiratory symptoms. Upon rechallenge, patients may experience hypotension and similar but worsened symptoms within hours which can result in death; because of this severity, hypersensitivity to abacavir is considered an absolute contraindication to future use [79]. Testing for HLA-B*5701 is recommended as positivity suggests a strong genetic predisposition for this hypersensitivity reaction [80]. Treatment of this syndrome includes prompt discontinuation of the medication. The use of systemic steroids also is recommended, at a dose of 1–2 mg/kg/day if symptoms are severe and should be used until laboratory abnormalities resolve. First-degree relatives should also be counseled to avoid these medications because of the increased risk to them. There are many other medications implicated in DHS including medications commonly used in HIV such as trimethoprim-sulfamethoxazole, dapsone, and nevirapine [81].

5.6.6 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN are other forms of severe hypersensitivity reactions that occur in the setting of HIV and are characterized by widespread blistering and sloughing of the skin (Fig. 5.2) and mucous membranes with mortality rates ranging from 5 to 30 % (typically depending on the amount of body surface area involved and time to treatment) [82–84]. These drug reactions are discussed in detail in other chapters.

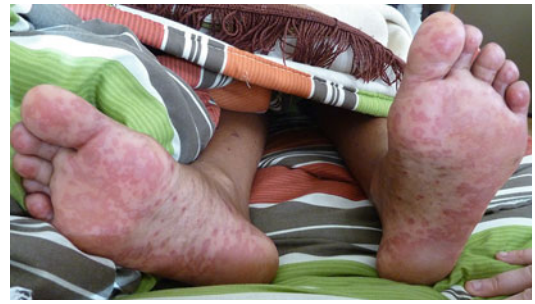

Fig. 5.2 Intact vesicles and target lesions on the plantar feet in a patient with SJS

Many HIV medications have increased risk of inducing SJS/TEN. Nevirapine is a non-nucleoside reverse transcriptase inhibitor for which severe life-threatening cutaneous rashes have been reported at a rate of 0.5–1 % [85–87]. Severe hepatotoxicity has been associated with the severe drug reactions and should be monitored for regularly. A review of the literature identified several antiretrovirals as potential culprit medications, which are included in Table 5.1 [88].

In addition to antiretroviral medications, serious drug reactions can occur with the use of sulfonamides as antibiotic therapy or for *Pneumocystis jiroveci* prophylaxis. The incidence of TEN due to trimethoprim-sulfamethoxazole was about fourfold compared to the general population and was 8.4 cases per 100,000 exposures [89]. Similarly, tuberculosis drugs can play a role in serious drug reactions as concomitant infection is not rare in this population [90].

SJS and TEN are most often caused by medications in HIV-positive patients, but severe forms of erythema multiforme and SJS have been described in association with infections including HSV and *Mycoplasma pneumoniae*, especially in pediatric populations, and should be considered if an inciting medication is not apparent [91–97]. Mycoplasma PCR and evaluation of HSV via PCR, direct-fluorescence antibody, or viral

culture can be performed if the timing of the drug reaction (patient has been on a medication for several years) or clinical scenario of mucosal predominant involvement, preceding cough and shortness of breath, or other information suggests an alternate diagnosis [91, 92, 98]. Treatment of SJS/TEN is discussed in detail in other chapters.

5.6.7 Acute Generalized Exanthematous Pustulosis

AGEP is a rare severe drug reaction characterized by a fever above 38 °C and a cutaneous reaction with non-follicular sterile pustules on an edematous and erythematous base. The onset of the reaction after drug administration can vary from 2 days to 3 weeks, depending on prior sensitization. The onset is typically extremely abrupt, starting on the face and extending to the trunk and then to the lower limbs. In addition, patients may have petechial purpura [101]. Laboratory studies should be performed and will reflect neutrophilia. Liver and kidney function should also be evaluated due to possible involvement in these organs. In the setting of HIV infection, the antiretrovirals reported to cause this condition are the protease inhibitors, ritonavir-boosted darunavir and atazanavir. Protease inhibitors have also been reported to be culprit medications when used for postexposure prophylaxis [102–104]. As overlap between AGEP and SJS/TEN or DRESS has been reported, clinicians should have a high index of suspicion when the constellation of symptoms with high fever and internal organ involvement is present, especially when a higher risk medication is used [105].

It also is important to note that a subgroup of patients with very low CD4+ counts (less than 50) also may exhibit drug reactions to every drug they are provided, which can pose a significant problem because these patients are on multiple new medications [106]. To help prevent these reactions, some of which are dangerous as outlined above, and enable the use of medications, a slow prednisone taper over 12 weeks while individual medications are added individually can help [107].

In summary, it is important for clinicians to have a high index of suspicion when HIV-positive patients present with cutaneous drug eruptions. Clues to a potentially serious underlying drug reaction include high fever, skin pain, facial swelling and lymphadenopathy, and mucous membrane involvement. General laboratory tests should be obtained to evaluate for underlying internal organ involvement. If a serious drug reaction is suspected, immediate cessation of the culprit medication is essential.

5.6.8 Malignancies

Malignancies are an increasingly recognized complication of HIV infection in all settings. There were five traditional AIDS-defining cancers including Kaposi sarcoma, cervical cancer, and three types of non-Hodgkin's lymphoma related to infection with the Epstein–Barr virus, including primary central nervous system lymphoma, immunoblastic lymphoma, and Burkitt lymphoma [108–110]. These are common and seen often, although some controversy about cervical cancer being AIDS-defining exists because it also can be commonly seen in HIV-negative individuals. Interestingly, all five of these tumors are associated with chronic oncogenic viral infection. There also are a wide variety of cancers that have been found to be more common in the setting of HIV, which have been termed non-AIDS-defining cancers including Hodgkin's lymphoma, lung cancer, and hepatocellular carcinoma [110]. Many of these malignancies are chronic and overall indolent, but some of them present as emergencies with cutaneous features as their presenting signs.

HIV-associated Kaposi sarcoma (KS) is caused by human herpes virus 8 and is primarily a disease of men who have sex with men. It classically presents as asymptomatic red-purple to brown papules, plaques, or tumors involving the head, neck, palate, chest, and extremities (Fig. 5.3) [111]. In children, prominent lymphadenopathy often is the presenting sign, and tissue pathology is essential to establish diagnosis and rule out infection or lymphoma [112]. Skin

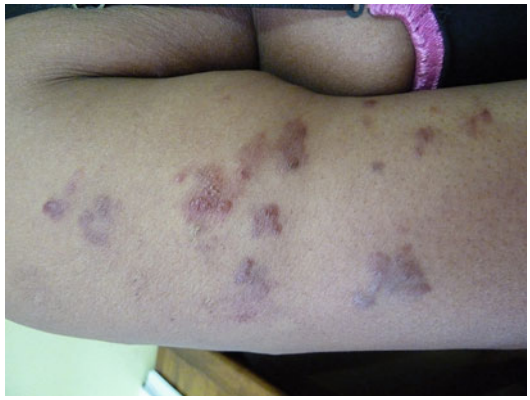

Fig. 5.3 Infiltrated red-purple papules and plaques of Kaposi sarcoma on the arm

biopsy may be necessary to differentiate KS from other vascular proliferations such as bacillary angiomatosis or lymphoma/leukemia cutis, and typically reveals a spindle cell proliferation with slit-like vascular spaces and increased red blood cell extravasation. Immunohistochemical stains with HHV8 will confirm the diagnosis. In advanced stages, there may be associated lymphedema, as well as aerodigestive tract, pulmonary, or gastrointestinal involvement. Internal involvement can be a poor prognostic factor indicative of rapid decompensation [113, 114]. The cornerstone of treatment and avoidance of this emergency is early detection and antiretroviral therapy [111, 115, 116]. In some advanced or emergent cases, collaboration with oncology and administration of doxorubicin/danorubicin chemotherapy may be important.

Cervical and anal cancer related to underlying human papilloma viral infection also is an AIDS-defining malignancy. Invasive cervical cancer was included as an AIDS-defining illness in 1993, and there is now good evidence that precursor lesions also are increased in women with HIV [109, 110, 117–119]. Although these changes can be slow-growing and chronic in nature, the extent of disease can become emergent as it interferes with underlying bowel and bladder dysfunction or metastasis. In most clinical situations, treatment of these diseases is the same as in immunocompetent women, although HIV-positive women and men often present with more advanced disease at presentation. Digital squamous cell carcinoma, also related to underlying HPV infection, can lead to amputation, which has significant morbidity [120]. Metastatic disease also can ultimately lead to death.

5.6.9 Immune Reconstitution Inflammatory Syndrome

IRIS is a condition that is characterized by paradoxical clinical deterioration in patients with HIV days to months after starting HAART and is due to the restoration of pathogen-specific immune responses [121, 122]. Opportunistic pathogens may grow unchecked in immunosuppressed patients. When the immune system recovers there may be an exuberant inflammatory response to these previously silent infections [123, 124]. Approximately 10–25% of individuals who start HAART experience this syndrome, and the skin is the most common organ system involved with 52–78% of manifestations involving the skin [123]. The presenting symptoms and dermatologic manifestations can be variable and include entities such as seborrheic dermatitis, psoriasis, acne vulgaris, folliculitis, molluscum contagiosum, and tinea versicolor or tinea capitis. More serious presentations can occur when there is a significant opportunistic infection or coinfection, and the inflammatory response can be detrimental. Frequently, differentiating this reaction from a medication reaction can be difficult. The opportunistic diseases most commonly associated with IRIS include mycobacterial diseases, including tuberculosis, *Mycobacterium avium* complex disease, leprosy, and a wide range of other nontuberculous mycobacterial diseases; deep fungal infections, especially cryptococcal meningitis; herpes viruses, including CMV retinitis, herpes zoster and herpes simplex; Kaposi Sarcoma (KS); and progressive multifocal leukoencephalopathy (PML) [41, 72, 125–135]. The diverse clinical manifestations and clinical sequelae of IRIS have been well documented. Early identification of HIV and institution of HAART may help prevent both the unmasking and worsening of preexisting

opportunistic infections by IRIS. For less dangerous dermatologic manifestations, general treatment guidelines as previously outlined in this chapter can be used.

5.7 Summary

In conclusion, there are many cutaneous manifestations of HIV and AIDS. Clinicians should be able to recognize and treat HIV early to prevent both serious illnesses and transmission. The cutaneous manifestations of HIV are often the most clinically evident since they can be seen easily. This chapter has reviewed the appearance of the initial eruption, dermatoses, infections, malignancies, and inflammatory reactions that should alert the clinician to recognize undiagnosed HIV as well as provide appropriate management in patients with known infection.

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Graft-Versus-Host Disease

6

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Graft-versus-host disease (GVHD) is a multisystem disorder combining features of both autoimmunity and immunodeficiency. It is a common and serious complication of hematopoietic stem cell transplantation (HSCT), and rarely solid organ transplantation, transfusion, and donor lymphocyte infusion. Because of its complex pathophysiology and diverse clinical manifestations, management of this challenging disease requires a multidisciplinary approach. Skin findings are the most common presenting sign, and they found in all forms of GVHD; therefore, the dermatologist plays an important role in diagnosis and therapy.

Research into HSCT began in the years following World War II in an effort to address fears over the deleterious effects of radiation exposure [1]. Animal research demonstrated that HSCT was able to replace radiation-damaged host cells with healthy, transplanted donor cells. This preclinical data provided impetus for future studies investigating HSCT following chemoradiotherapy in leukemic patients. The use of transplanted cells as a treatment option has driven research into stem cell graft types (autologous, syngeneic, and allogeneic) and graft sources (bone marrow, peripheral blood, and umbilical cord blood). Improvements in treatment have led to increased use of HSCT for a wide variety of disease (Table 6.1). Unfortunately, despite these improvements and research advances, GVHD remains a serious complication of this procedure.

6.1 Overview of HSCT

The process of bone marrow ablation is termed "conditioning." Conditioning reduces tumor burden, creating a physical space into which transplanted cells can migrate and proliferate, and it induces a state of immunosuppression so donor stem cells will not be rejected. Myeloablative conditioning consists of total body irradiation and/or chemotherapy. Specific conditioning regimens depend upon center protocols and the disease being treated. Myeloablative conditioning is associated with significant organ toxicity and is usually used in patients under 60 with good performance status. Non-myeloablative, minimally toxic conditioning regimens have been developed for use in older patients or those with

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Table 6.1 Indications for hematopoietic stem cell transplantation

Malignant disorders	Congenital disorders	Other disorders
· Multiple myeloma	· Severe combined immunodeficiency	· Aplastic anemia
· Non-Hodgkin lymphoma	· Hemophagocytic lymphohistiocytosis	· Primary Amyloidosis
· Hodgkin disease	· Hemoglobinopathies, i.e.,	· Autoimmune disorders, i.e.,
· Acute myeloid leukemia	o Sickle cell anemia	o Multiple sclerosis
· Acute lymphoblastic leukemia	o Thalassemia major	o Systemic sclerosis
· Chronic myeloid leukemia	· Inborn errors of metabolism, i.e.,	o Systemic lupus erythematosus
· Juvenile Chronic Myeloid Leukemia	o Porphyrias	o Crohn's disease
· Myelodysplastic syndromes	o Hunter's Syndrome	o Type I diabetes
· Other myeloproliferative disorders	· Congenital bone marrow failure syndromes, i.e.,	o Rheumatoid arthritis
· Medulloblastoma	o Fanconi anemia	o Juvenile idiopathic arthritis
· Germ-cell tumors	o Blackfan–Diamond anemia	o Hematologic immune cytopenias
· Ovarian cancer	o Shwachman–Diamond syndrome	o Pemphigus vulgaris
· Neuroblastoma	· Epidermolysis Bullosa, i.e.,	o Scleromyxedema
· Cutaneous T-cell lymphoma/ Sézary syndrome	o Recessive Dystrophic	
	o Junctional Variant	
	· Dyskeratosis congenita	
	· Bloom syndrome	
	· Paroxysmal noctural hemoglobinuria	
	· Wiskott-Aldrich syndrome	
	· POEMs syndrome[a]	
	· Osteopetrosis	
	· Griscelli syndrome	

[a]POEMS syndrome- Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes

significant comorbidities [2]. Conditioning usually takes 7–10 days.

After completion of conditioning, stem cells are infused intravenously, usually through a central venous line. Stem cells can be derived from bone marrow, peripheral blood or umbilical cord blood. If the patient himself provides stem cells, the transplant is said to be autologous. An allogeneic (*allos* means other in Greek) transplant means that stem cells are derived from another individual. If the other individual is an identical twin, the transplant is "syngeneic."

Extraction of bone marrow is usually done under general anesthesia as significant amounts of marrow (>70 ml) are obtained from the iliac crests. Extraction of stem cells from peripheral blood is logistically easier, and it avoids the risks of general anesthesia. Peripheral blood is the most common source of allogeneic stem cells in adult recipients (>20 years old), and bone marrow the most common in recipients under 20. Overall, peripheral blood is the most common source of stem cells [3]. The donor is primed with granulocyte-macrophage stimulating factor (GMSF), peripheral blood is removed, white blood cells (WBCs) are separated, and red blood cells (RBCs) are reinfused back into the donor. Stem cells can be frozen for prolonged periods without damaging their function or viability. Peripheral blood contains more T cells than bone marrow, thus increasing the risk of graft-versus-host disease (GVHD) [4, 5]. With umbilical cord blood, there is a lower incidence of GVHD, and a much lower risk of infection by latent viruses such as Epstein Barr (EB) or cytomegalovirus (CMV). One or two HLA disparities can be tolerated by the recipient, and cord blood is easily banked, typed and stored. The main disadvantage is that it contains low numbers of stem cells, and there may be failure of engraftment. Cord blood is mainly used in children [6–8] (Table 6.2).

Following infusion, stem cells migrate to the bone marrow. In the range of 2–4 weeks, they will "engraft" and start producing normal blood cells. The day of engraftment is defined as the first of three consecutive days in which the neutrophil count is greater than $0.5 \times 10(9)/l$. If engraftment does not occur by day 30, the graft is considered failed [9]. Hematopoietic function normalizes in a matter of weeks; however, immune function takes months, or even years to normalize [10]. From the start of conditioning to

Table 6.2 Characteristics of stem cell sources

	Stem cell content	Engraftment time	Risk of aGVHD	Risk of cGVHD
Bone marrow	Moderate	Moderate	Moderate	Moderate
Peripheral blood	High	Fastest	Moderate	Highest
Cord blood	Low	Slowest	Lowest	Lowest

the time of engraftment, the patient is in a state of pancytopenia and profound immunosuppression. The risk of lethal viral, bacterial or fungal infection is high. Infection can come about from external sources, from endogenous flora of the skin and gut, or through reactivation of latent viruses, particularly CMV [11]. Prophylactic antibiotics and careful supportive care are critical during this period. Mucositis can be severe during the pancytopenic phase, and total parenteral nutrition (TPN) may be necessary [12–14]. Following engraftment, there is recovery from pancytopenia and healing of mucositis; however, at this early stage the immune system remains weakened and dysregulated.

HSCT is a debilitating, emotionally taxing, high-risk procedure associated with significant treatment-related morbidity and mortality [15, 16]. In the months to years it takes for the engrafted stem cells to differentiate, proliferate and give rise to a functional immune system, patients suffer infections, fatigue and psychological debility. Children and young adults are most likely to experience complete immune reconstitution; however, complete immune recovery may never take place in older adults, particularly in patients who develop chronic GVHD (cGVHD) [17, 18]. Following HSCT, donor-derived, immunologically active cells are confronted with infection, residual malignant cells, and a variety of foreign proteins. Acute GVHD (aGVHD) results from this confrontation and is a major cause of morbidity and mortality following HSCT [19].

aGVHD occurs when donor T cells react against recipient HLA antigens and minor histocompatibility antigens (mHA). It occurs in 60–80% of patients in which there is an HLA mismatch, and in 20–50% of patients who receive stem cells from an HLA identical sibling donor [20]. In 1966, Rupert Billingham identified three preconditions that need to be met in order for GVHD to occur [21]. One, the graft must contain immunologically active cells, now known to be alloreactive T cells. Two, the recipient must express tissue antigens foreign to the donor. Three, the recipient must be incapable of mounting an immunological response against the donor cells. The incidence and severity of aGVHD relate to the extent of mismatch of HLA proteins [19]. Ideally, there will be high resolution matching for HLA-A, B, C and DR B1 between donor and recipient ("8/8 match") [19]. However, even if the donor is an identical twin, GVHD can still occur because of mismatch of minor histocompatibility antigens (mHA) [22, 23].

Every human being is genetically unique, and this uniqueness also applies to monozygotic twins in whom subtle, but medically significant genetic differences exist. For example, single nucleotide polymorphisms (SNPs) in the thiopurine methyltransferase gene have been identified in identical twins. These polymorphisms result in differences in metabolizing capacity between the twins. These genetic differences come about because of somatic mutations that occur in utero, meiotic and mitotic recombination, and biased gene conversions. Genes and genomes are in a state of constant evolution [22, 24].

Minor HAs are immunogenic peptides derived from genes outside the MHC. They arise through polymorphisms in homologous genes between recipient and donor [25]. Polymorphisms in recipient genes result in different amino acid sequences, which are recognized by donor T cells as non-self [19]. Approximately 30 mHAs have thus far been identified in humans [22]. For example, males express several H-Y antigens encoded on the Y chromosome. These antigens are recognized as foreign by lymphocytes from female donors, and aGVHD will result from gender mismatch [26]. Multiple other mHAs exist, all of which can trigger aGVHD [27]. Minor HAs

may play an important role in graft-versus-leukemia (GVL) effect because some of these antigens are only expressed on hematopoietic cells [28]. The success of HSCT in leukemia is due in part to GVL effect mediated by donor immune cells [25, 28]. The relapse rate of leukemia is lower in patients who develop GVHD compared to those who do not. It is also lower in patients receiving allogeneic versus syngeneic transplants because the former are more likely to develop GVHD than the latter.

6.1.1 Acute GVHD

GVHD has traditionally been divided into two forms, acute and chronic. aGVHD classically referred to disease that occurred in the first 100 days, and chronic, after day 100. This classification has proven inadequate because aGVHD can occur after day 100, particularly in patients who have undergone reduced intensity conditioning, and features of cGVHD are common in the first 100 days. This temporal division has been superseded by a new classification developed by experts in an NIH Consensus Development Project on Criteria for clinical trials in cGVHD [29] (Table 6.3). In the new classification, the two main categories remain, but each has two subcategories. aGVHD is subclassified into "classic" aGVHD occurring before day 100 following the transplant, or persistent, recurrent or late aGVHD occurring after day 100. cGVHD is subclassified into classic cGVHD, and an overlap syndrome in which features of aGVHD and cGVHD occur together. In the new classification system, clinical and pathologic manifestations take priority over time of onset.

Ferrara and associates have identified three distinct phases in the pathogenesis of aGVHD [19, 30, 31] (Fig. 6.1). Phase one involves induction of host cytokines and activation of host antigen presenting cells (APCs). Infections, conditioning regimens and underlying disease all cause cellular damage and release of pro-inflammatory cytokines such as TNF-α, IL-1,

Table 6.3 NIH criteria for clinical trials in chronic graft-versus-host disease

	Classic acute	Persistent, recurrent or late acute GVHD	Classic chronic	Overlap syndrome
Days post transplant	≤100	>100	N/A	N/A
Symptoms	Maculopapular rash, nausea, vomiting, anorexia, diarrhea, ileus, choestatic hepatitis	Maculopapular rash, nausea, vomiting, anorexia, diarrhea, ileus, choestatic hepatitis	At least one diagnostic clinical sign or manifestation confirmed by biopsy or other testing (see Table 6.3)	Features of both acute and chronic GVHD

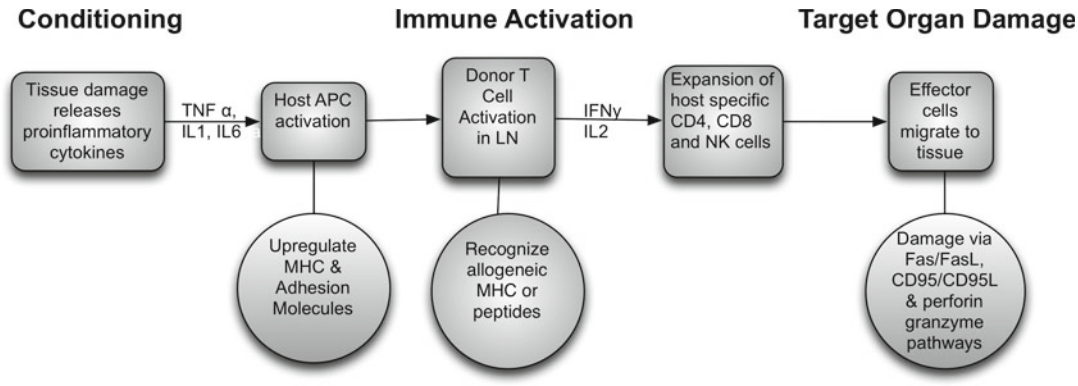

Fig. 6.1 Pathogenesis of acute GVHD

and IL-6. Increased serum levels of these cytokines upregulate adhesion molecules, MHC molecules and mHAs on APCs [30]. In addition, damage to the GI tract from conditioning results in translocation of immunostimulatory molecules such as lipopolysaccharide (LPS) and other bacterial products into the systemic circulation [32, 33]. Macrophages and other cells of the innate immune system recognize pathogen associated molecular patterns, and they secrete cytokines, chemokines, adhesion molecules and costimulatory molecules. The innate immune system is "primed." MHC molecules are upregulated, leading to enhanced antigen presentation by antigen-presenting cells [34]. Decontamination of the gastrointestinal tract has been associated with reduced incidence of aGVHD both clinically and in animal models, and in some centers, gut decontamination is standard procedure [34].

Phase two consists of antigen presentation to donor T cells. This occurs in recipient lymphoid tissue. In *direct* presentation, donor T cells recognize peptides bound to allogeneic MHC molecules on recipient APCs, or they recognize and react to the allogeneic MHC molecule itself without peptide [35]. In *indirect* presentation, donor APCs will degrade allogeneic MHC molecules into peptides, which are presented on the cell surface by donor-MHC molecules and recognized by donor T cells. In response to antigen presentation, activated donor T cells proliferate and differentiate. They then exit lymphoid tissue and traffic to target organs. Activated T cells secrete cytokines, in particular IL-2 and IFN-γ, both of which are important mediators of aGVHD. These cytokines trigger cytotoxic T lymphocyte (CTL) responses to alloantigens, and they also induce monocytes and macrophages to produce proinflammatory cytokines IL-1 and TNF-α [35].

During phase three, the effector stage, actual target organ damage takes place [30, 35]. CTLs are the predominant cellular effectors of aGVHD, and they cause tissue damage via the Fas/FasL and the perforin/granzyme pathway. TNF-α, IL-1, and nitric oxide (NO) are the main inflammatory cytokine effectors. TNF-α activates APCs, it enhances alloantigen recognition, and it recruits effecter cells to target organs [19]. It also directly causes tissue damage by inducing apoptosis of target cells after activation of the TNF-Fas activation pathway [36]. NO, produced by macrophages, inhibits proliferation of epithelial stem cells and thereby inhibits repair of target tissue [35]. Damage to the GI tract occurring during phase three causes more release of bacterial LPS, which further upregulates innate immune function. A feedback loop is created that enhances antigen presentation and activation of alloreactive donor T cells [30].

Natural killer (NK) cells appear to modulate aGVHD. NK cells are the first lymphocytes to recover to normal numbers after HSCT, and they play a role in both innate and adaptive immunity. Early animal models demonstrated that NK cells were not crucial for the development of GVHD and their role in GVHD was incompletely understood [37]. More recently, NK cells have been shown to decrease GVHD severity by inhibiting immature dendritic cells and suppressing alloantigen-driven proliferation of donor $CD4^+$ T cells [38, 39]. In addition, they can work in concert with T regulatory (Treg) cells to prevent cGVHD [39]. NK cell function may be more important in unrelated donor HSCTs compared to related donors as polymorphisms in NK cell receptor and ligand complexes have been linked to differences in GVHD and relapse rates. Patients undergoing unrelated HSCT with a graft containing high numbers of NK cells (CD56+) had a significantly reduced incidence of severe aGVHD compared to patients receiving grafts with lower numbers of NK cells [40]. This effect was not seen with related donors and did not seem to influence the graft-versus-leukemia (GVL) effect.

aGVHD can involve many organs; however, skin, intestine, and liver are the main targets [20]. Skin is usually the first organ involved with rashes occurring in at least 80% of patients [20]. Hepatic and intestinal manifestations appear a few days after the rash [41]. Extensive rashes are common in the post-transplant period, and these can include drug reactions, chemotherapy related toxicity, viral exanthems, toxin-mediated erythemas, engraftment syndrome, and intrinsic inflammatory skin diseases not related to the HSCT. These pathologic processes may occur simultaneously.

Dermatologists play a key role in sorting out post-transplant rashes. Diagnosis of aGVHD is based on clinical and histopathologic features. The main histopathologic features of cutaneous aGVHD include a lymphocytic interface dermatitis, vacuolar degeneration of the basal cell layer, and necrotic keratinocytes [42]. Histopathologic grading is based on the extent of keratinocyte necrosis, which ranges from subtle vacuolar alteration to complete epidermal necrosis [42] (Table 6.4). A skin biopsy can yield valuable diagnostic information with minimal risk to the patient (Figs. 6.2 and 6.3). In contrast, invasive endoscopic procedures and biopsies of intestine and liver carry significant procedural risks, particularly with respect to bleeding and infection post-transplant [23, 43, 44].

aGVHD usually manifests 2–6 weeks after transplantation. As a rough rule of thumb, rashes occurring in the first 20 days post-transplant are more likely drug reactions, reactions to conditioning, or infections rather than aGVHD. Acute cutaneous GVHD is heralded by a pruritic, sometimes painful "maculopapular" rash that tends to be acrally distributed (Figs. 6.4, 6.5, and 6.6). Involvement of the palms, soles, pinnae, and cheeks is common [45]. Involvement of the face, palms and soles together is strongly predictive of aGVHD rather than drug reaction [46]. The rash of aGVHD commonly affects the upper, sun-exposed areas of the body such as the face, arms and shoulders [43, 47]. Exanthematous drug reactions usually begin centrally and often do not involve the palms and soles. A follicular localization is also typical of aGVHD and an important clue to diagnosis [20, 48–50]. Atypical and severe skin manifestations of aGVHD may occur [51]. Acute grade IV cutaneous GVHD resembles SJS/TEN, and mucositis consisting of oral and lip erosions occurs in approximately 60% of these patients [51]. However, in milder forms of aGVHD, mucositis is not a prominent clinical feature [47]. Other mucosal manifestations of aGVHD include erythema and lichenoid lesions.

The liver is a common target organ in aGVHD. Abnormal liver functions and jaundice secondary to cholestasis comprise the typical clinical picture. Biliary epithelial cells are the primary target of alloreactive donor T cells recognizing foreign HLA antigens and minor HAs on the surface of

Table 6.4 Grading of the histopathological findings of cutaneous aGVHD

Grade	Skin changes
1	Vacuolar degeneration of epidermal basal cells
2	Vacuolar change with spongiosis and dyskeratosis
3	Epidermolysis and bulla formation
4	Total loss of epidermis

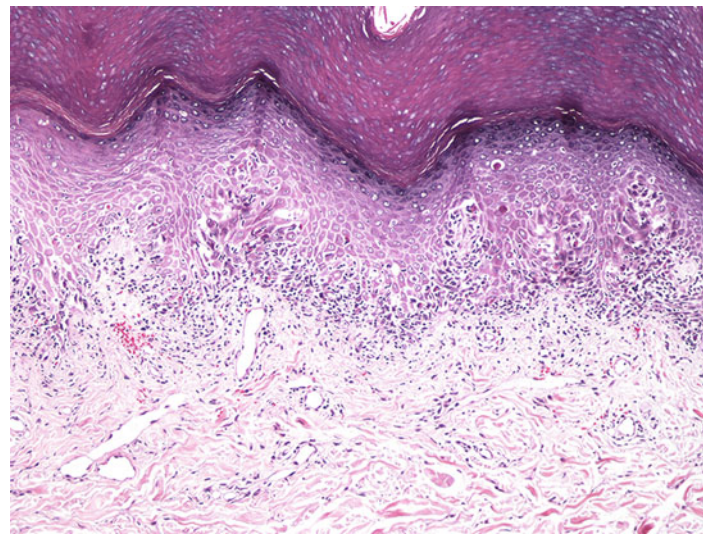

Fig. 6.2 Lymphocytic infiltration with necrotic keratinocytes (100×) (Photo Courtesy of Dr. Paul Chu, M.D.)

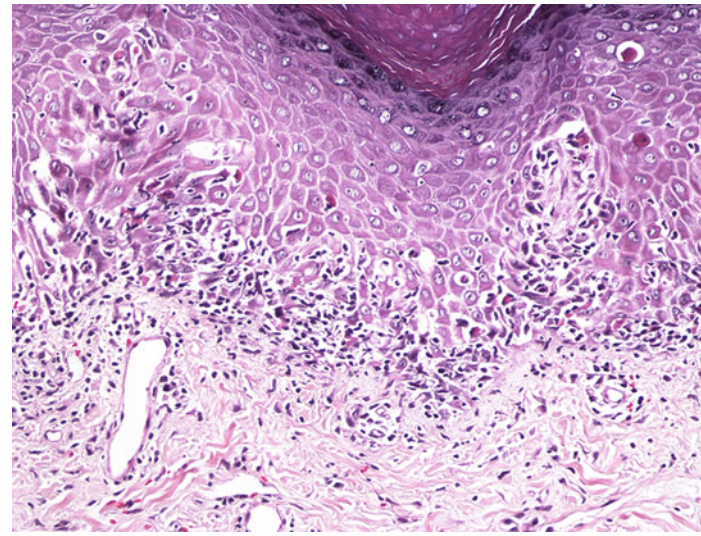

Fig. 6.3 Lymphocytic infiltration with necrotic keratinocytes (200×) (Photo Courtesy of Dr. Paul Chu, M.D.)

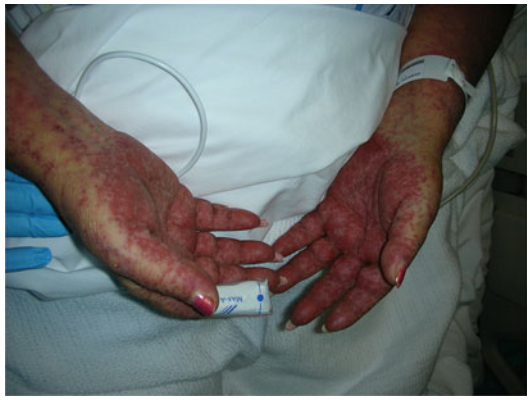

Fig. 6.4 A woman with acute GVHD showing erythematous macules and papules on the palms (Photo courtesy of Gil Cortes, M.D.)

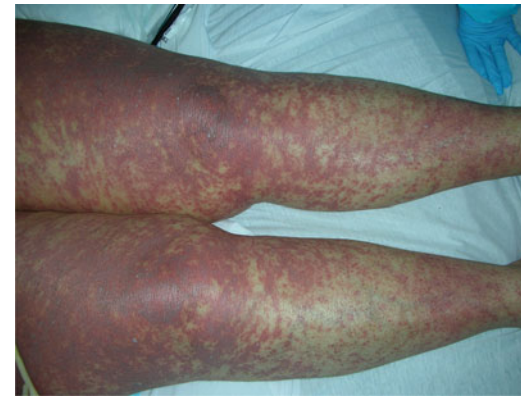

Fig. 6.5 A woman with acute GVHD with extensive erythematous follicular macules coalescing into dusky patches on the thighs (same patient as in Fig. 6.4) (Photo courtesy of Gil Cortes, M.D.)

these cells [52]. Histologically, there is lymphocytic infiltration of small bile ducts, nuclear pleomorphism, and apoptosis of epithelial cells [53]. Untreated, acute hepatic GVHD can lead to loss of bile ducts and worsening jaundice. A rising or persistent elevation of the bilirubin portends a poor prognosis. In some patients aGVHD can present with a hepatitis-like picture with elevation of aminotransferase enzymes [52, 53]. Fifty percent of patients with acute hepatic GVHD will develop chronic hepatic GVHD, and only 30% of patients with acute hepatic GVHD will experience complete resolution of liver abnormalities after initial immunosuppressive treatment [52]. The differential diagnosis of liver abnormalities in the post-transplant patient is complex and includes sinusoidal obstruction syndrome (SOS), acute viral hepatitis and other infections, biliary obstruction, drug induced liver injury, TPN hepatotoxicity, and numerous other conditions [53, 54]. Acute

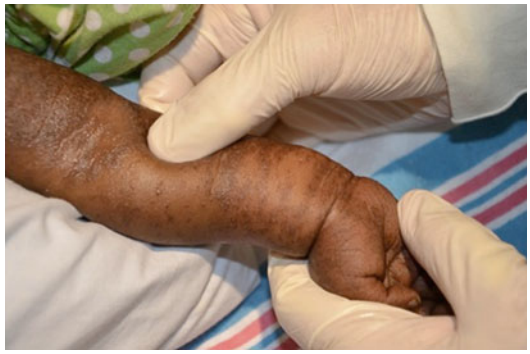

Fig. 6.6 An 11-month-old child presents 2 months post-HSCT with hemophagocytic lymphohistiocytosis and an overlap syndrome of acute and chronic GVHD. Note a lichenoid dermatitis with discrete and confluent violaceous papules involving palm and extending onto forearm (Photo courtesy of Jason Emer, M.D.)

hepatic GVHD usually does not occur in isolation, and other stigmata of aGVHD such as rash and GI abnormalities are part of the total clinical picture.

Timing is also an important consideration. If signs of liver damage occur in the first 20 days post-transplant, causes other than aGVHD are likely, especially SOS. SOS occurs following damage to the hepatic sinusoids from myeloablative conditioning, especially regimens containing cyclophosphamide, the metabolites of which are toxic to sinusoidal endothelial cells [52]. The condition is characterized by varying degrees of hepatomegaly, fluid retention, jaundice and biochemical abnormalities. Severe cases can be fatal.

The predominant clinical sign of acute intestinal GVHD is diarrhea. Vomiting, anorexia, abdominal pain and ileus may also be present. Diarrhea in the first 20 days after HSCT is usually associated with conditioning toxicity. From day 20 to day 100, aGVHD is most likely, and after day 100, an enteric infection should be considered [44]. Biopsy of intestinal mucosa in acute intestinal GVHD will show inflammatory changes associated with epithelial cell apoptosis, the presence of which is necessary for histopathologic diagnosis [44]. The rectosigmoid area is the optimum site for biopsy. In comparison to other sites in the GI tract such as stomach or duodenum, rectosigmoid mucosal biopsies have a sensitivity of 95.6% and a specificity of 100% [55].

In the post transplant period, a disorder known as engraftment syndrome (ES) can occur. ES shares some clinical features with classic aGVHD, and some authorities consider ES a variant of aGVHD. ES occurs after allogeneic or autologous HSCT at the time of neutrophil recovery [56]. Major features consist of generalized maculopapular rash, fever, and noncardiogenic pulmonary edema associated with hypoxemia. The clinical picture can be accompanied by diarrhea, weight gain secondary to fluid retention, hepatic or renal dysfunction, transient encephalopathy and keratitis [57, 58]. The reported incidence of ES varies from 7 to 59%. The wide disparity in numbers probably reflects differences in definition. In one large series of 328 patients undergoing peripheral blood autologous HSCT, the incidence was 12.8% [57].

ES is thought to result from release of proinflammatory cytokines and products of degranulation and oxidative metabolism of neutrophils [59]. This results in systemic endothelial cell damage [57, 59]. ES responds well to corticosteroids when given in a timely fashion and in adequate amounts; however, if treatment is delayed or inadequate, ES can progress to multiorgan failure and death [60]. Patients with ES have a 21% greater likelihood of non-relapse mortality in 5 years compared to those without ES. Steroid treatment does not reduce this increased mortality [60].

Autologous GVHD (autoGVHD) was first reported by Hood et al. in 1987 [61]. Seven patients receiving autologous bone marrow transplantations developed cutaneous eruptions compatible both clinically and histologically with grade II aGVHD. Also known as the "autoaggression" syndrome, autoGVHD tends to be milder than aGVHD following allogeneic HSCT. It usually involves skin alone and is generally self-limited; however, more severe forms involving the liver and intestine can occur. AutoGVHD is thought to result from loss of self-tolerance because of loss of regulatory T cells (Treg) and damage to the thymus from conditioning [62]. Treg cells are a subset of T cells that prevent self-reactive T cells that have escaped thymic deletion from reacting to self antigens. Treg cells establish

tolerance to both allo- and self-MHC antigens [63]. Myeloablative conditioning causes depletion of Treg cells [64]. In addition, cyclosporine (CSA) and other medications administered post-transplant interfere with the functional capacity of the thymus to delete T cells bearing autoreactive TCRs. This effect has been demonstrated in rodents, which are considered accurate models of human aGVHD [64, 65]. In the setting of autologous HSCT, loss of central tolerance coupled with the absence of peripheral Treg cells creates a permissive environment in which autoreactive T cells damage host tissue [62].

Although aGVHD causes considerable morbidity and mortality, it is associated with significant anti-tumor effects. It has been observed repeatedly that patients with aGVHD have lower disease relapse rates than those without. Because autoGVHD tends to be mild and limited to skin, investigations have been undertaken to harness graft-versus-tumor (GVT) effect by artificially inducing autoGVHD by post-transplant administration of CSA alone, or CSA plus IFNγ or IL-2. Unfortunately, no clear-cut anti-cancer benefit has thus far been shown in clinical trials [64, 66].

6.2 Acute GVHD Following Solid Organ Transplantation, Transfusion, and Donor Lymphocyte Infusion

aGVHD after solid organ transplantation is an uncommon, but serious complication with high mortality. It can occur with transplantation of any solid organ, but it is most likely to occur after small intestine transplant (5–10% incidence) or orthotopic liver transplant (OLT) (1–2% incidence) [67]. ("Orthotopic" means the donor organ is transplanted into the same place as the patient's original organ.) OLTs are performed much more commonly than intestinal transplants, so aGVHD associated with solid organ transplants generally refers to OLT [68]. Alloreactive lymphocytes are transplanted along with the organ, and liver and intestine contain the largest numbers. In fact, the number of lymphocytes transferred in an OLT is roughly equivalent to that in a bone marrow transplant [69].

Despite the large number of passenger lymphocytes, the incidence of GVHD is low. An important reason is that a high percentage of hepatic T cells express γδ receptors, 7–54% versus <6% in peripheral blood. These cells produce Th2 cytokines, which downregulate Th1 responses and suppress aGVHD [70]. In addition, patients receiving OLTs are immunosuppressed, not immunoablated. Donor T cells are rejected by a partially functioning immune system.

Skin rash is the major clinical sign associated with OLT-associated aGVHD [71]. Lesions erupt 1–8 weeks after transplantation. Skin lesions usually begin distally on the palms and soles and rapidly generalize [70]. Rapid progression to the GI tract and bone marrow follow [70]. Fever in association with the rash is a poor prognostic sign.

aGVHD associated with OLT differs from aGVHD following HSCT in several respects. The transplanted liver itself is not a target organ because alloreactive lymphocytes recognize transplanted liver tissue as self. On the other hand, bone marrow involvement manifesting as pancytopenia is a common and serious development [70]. Neutropenia can be a presenting sign of GVHD following OLT [70, 71]. Because of high mortality, and immunologic rejection of donor T cells, cGVHD following OLT is unusual [70].

A risk factor for aGVHD in the setting of OLT is HLA *compatibility* [68]. The more well-matched the graft, the greater the likelihood of aGVHD. If alloreactive hepatic T lymphocytes express shared HLA determinants with the recipient, they are less likely to be destroyed by the recipient immune system [70]. Age greater than 65, and large disparity in age between a young donor and an older recipient are also risk factors for the development of aGVHD following OLT.

Given the rarity of aGVHD following solid organ transplantation, diagnosis can be challenging. The usual presenting sign is rash, sometimes associated with fever. The differential diagnosis includes viral exanthem or other infection, drug eruption, and aGVHD [72]. A skin biopsy showing interface dermatitis, vacuolar degeneration of basal cells and necrotic epidermal cells is highly suggestive of GVHD [70]. Donor cell chimerism is also an important feature of GVHD associated with solid organ transplantation. Chimerism

refers to the presence of a mixed population of donor and recipient lymphocytes in tissue or peripheral blood. Although important, chimerism is not absolutely diagnostic. It is not present in all patients with solid organ aGVHD, and it is a frequent finding immediately after OLT [73]. Clinical response to treatment correlates with decrease or disappearance chimerism [69].

Transfusion associated aGVHD (TA-GVHD) occurs when transfused donor lymphocytes engraft in an immunocompromised host, or when the donor is homozygous for an HLA class 1 haplotype of the recipient, which allows donor lymphocytes to escape immunologic recognition by the recipient [74]. This sometimes happens when blood relatives donate blood to immunocompetent recipients [74–76]. Certain clinical situations are also high risk. Granulocyte transfusions contain large numbers of lymphocytes, and patients receiving them are usually neutropenic and immunocompromised. Infants receiving exchange transfusions for erythroblastosis fetalis receive a large volume of blood and cells, and their immune systems are immature. Patients with Hodgkin's disease, non-Hodgkin lymphoma (NHL), congenital immunodeficiency diseases, persons undergoing HSCT, and persons treated with purine analogues such as cytarabine are at risk for TA-aGVHD [74, 75, 77]. Patients with solid malignancies, hematologic malignancy other than Hodgkin's disease/NHL, and patients with AIDS are not considered to be at high risk [74].

TA-aGVHD begins abruptly with fever 3–30 days after the transfusion. Fever is followed by a generalized maculopapular rash, which can progress to erythroderma and bulla formation. Profuse diarrhea, vomiting, anorexia, right upper quadrant pain, jaundice, elevated liver enzymes, and pancytopenia complete the clinical picture [75]. The overall tempo of TA-aGVHD is more rapid than in HSCT-associated aGVHD [75]. Diagnosis is made by clinical signs and symptoms, the demonstration of chimerism in blood and tissue, and skin biopsy findings of interface dermatitis, basal cell vacuolization, and epidermal cell necrosis.

Unfortunately, treatment for TA-GVHD is generally ineffective, and the overall mortality exceeds 90% [74]. Prevention is the best and most effective management strategy. Prevention consists of identifying those at risk. Once identified, these patients should only receive blood and blood components that have been irradiated with 2,000 cGy or higher [74, 75]. Irradiation of blood and blood products blocks alloreactive lymphocyte proliferation, but it does not interfere with the function of RBCs, WBCs or platelets. Although some leakage of potassium has been observed in irradiated blood, there is no clinical evidence that irradiated blood is harmful to patients [74, 78].

Should leukemia relapse after HSCT, infusion of lymphocytes from the original donor can be used as a salvage treatment. Donor lymphocyte infusion (DLI) relies on graft-versus-leukemia effect, and it has proven quite effective in certain forms of leukemia, particularly in relapsed chronic myelogenous leukemia (CML) [79]. Complete molecular and cytogenetic remissions have been achieved using this modality in a substantial proportion of treated patients [80]. aGVHD and cGVHD can complicate DLI; however, GVHD following DLI tends to be mild to moderate, it is more responsive to treatment with immunosuppressive therapy, and the onset tends to occur later than GVHD following HSCT [79]. The reason is that the tissue damage and "cytokine storm" resulting from conditioning, infection and underlying disease are generally not present in the setting of DLI. However, the presence of either aGVHD or cGVHD following DLI is associated with a 2.3-fold risk of death in comparison to patients without GVHD [81]. cGVHD develops in 33–61% of patients following DLI [82].

6.3 Staging and Grading of Acute GVHD

Stratification of aGVHD severity is important in determining prognosis. It is also useful in determining entry into clinical trials and assessment of outcomes to particular regimens. In 1974, Glucksberg proposed a grading system for aGVHD severity [83]. The Glucksberg system is

intuitive, easy to apply, and has been in common use ever since. Severity of skin, liver and intestinal tract involvement is measured and assigned *stages* from one to four. To determine *grade*, the stages of the three organ systems, and a subjective one to four assessment of overall performance status are tabulated. The patient is then assigned a grade of severity from one to four. In the Glucksberg system there are 125 possible combinations when three organs plus performance status are staged one to four [84] (Table 6.5).

The International Bone Marrow Transplant Registry (IBMTR) severity index was created after it was noted that patients with the same Glucksberg grade but with different patterns of organ involvement had different outcomes [85]. For example, patients with grade II Glucksberg, but stage 3 skin involvement had significantly higher risk of death than patients with grade II Glucksberg with stage 0–2 skin involvement [85]. The IBMTR severity index assigns letter grades from A to D. The assigned grade is based on the maximum involvement in an individual organ regardless of involvement of other organ systems [85]. It relies only on objective measurement of organ involvement, thereby reducing inter-observer variability (Table 6.6). Thus, in the example above, a patient with stage three skin involvement would be assigned to level C even if liver and intestinal tract were stage one. In addition, the IBMTR severity index eliminates subjective assessment of performance status.

In a mixed retrospective and prospective study of 114 patients, Martino et al. found the IBMTR

Table 6.5 Glucksberg clinical stage and grade of aGVHD

Stage	Skin	Liver (Bilirubin mg/dl)	Intestinal tract
1	Maculopapular rash <25% BSA	2–3	>500 ml diarrhea/day
2	Maculopapular rash 25–50% BSA	3–6	>1000 ml diarrhea/day
3	Generalized erythroderma	6–15	>1500 ml diarrhoea/day
4	Generalized erythroderma with bullous formation and desquamation	>15	Severe abdominal pain, with or without ileus
Grade	Degree of organ involvement		
I	Stage 1–2 skin rash; no gut involvement; no liver involvement; no decrease in clinical performance		
II	Stage 1–3 skin rash; stage 1 gut involvement or stage 1 liver involvement (or both); mild decrease in clinical performance		
III	Stage 2–3 skin rash; stage 2–3 gut involvement or 2–4 liver involvement (or both); marked decrease in clinical performance		
IV	Similar to Grade III with stage 2–4 organ involvement and extreme decrease in clinical performance		

Reproduced with permission from Wolters Kluwer Health and Glucksberg et al. 1974 [83]

Table 6.6 Criteria for IBMTR severity index for aGVHD

	Skin involvement		Liver involvement		Gastrointestinal involvement	
Index (based on maximum involvement of any organ)	Stage (max)	Extent of rash (BSA)	Stage (max)	Total bilirubin (mg/dl)	Stage (max)	Volume of diarrhea (ml/dl)
A	1	<25 %	0	2–3	0	<500
B	2	25–50 %	1–2	3–6	1–2	550–1500
C	3	>50 %	3	6–15	3	>1500
D	4	Bullae	4	>15	4	Severe pain and ileus

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index superior to the Glucksberg grading system in predicting transplant related mortality and failure [86]. However, in a prospective study of 607 patients evaluating the two systems, Cahn et al. observed strong agreement between the two systems and no clear-cut advantage of one over the other [84].

6.4 Prophylaxis and Treatment of Acute GVHD

Risk factors for the development of aGVHD include histoincompatibility of MHC antigens (particularly class II antigens), older age of donor and recipient, gender mismatch (particularly female donor with male recipient), presence of infection, underlying disease stage and intensity of conditioning [9, 26]. To the extent possible, these risk factors should be modified. In addition, use of cord blood and decontamination of the gut are associated with lower incidence of aGVHD [6, 32].

GVHD prophylaxis usually consists of a combination of calcineurin inhibitor (CNI) plus methotrexate or mycophenolate mofetil (MMF) [23]. The purpose of prophylaxis is to inhibit the activity of alloreactive T cells. Without prophylaxis the incidence of aGVHD approaches 100% [27]. Tacrolimus appears to be somewhat superior to cyclosporine, and is less toxic [27]. MMF is associated with less mucositis than methotrexate. Antithymocyte globulin and anti-CD52 monoclonal antibody (alemtuzumab) have also been used for prophylaxis. Ex vivo depletion of T cells in the donor graft is associated with decreased incidence of aGVHD; however, this technique is associated with increased incidence of malignant disease relapse [27].

First line treatment of aGVHD consists of corticosteroids [23, 27, 30]. Patients are usually started on methylprednisolone 2 mg/kg/day, and the dose is slowly tapered depending on clinical response. Roughly 25% of patients will experience a complete response, and 50% a partial response. For corticosteroid nonresponders, a wide variety of therapies has been tried including PUVA, extracorporeal photophoresis, anti-TNF agents, anti-CD3, anti-IL2 receptor, denileukin difitox, sirolimus, antithymocyte globulin, pentostatin, and visilizumab, an anti CD-3 monoclonal antibody [23, 27, 30, 87]. Corticosteroid nonresponders have a poor prognosis.

6.5 Conclusion

HSCT ranks as one of the most radical interventions in the whole of medicine. The patient is given nothing less than an entirely new immune system, and he is potentially cured of hitherto untreatable, fatal diseases. New indications for HSCT are constantly arising, and the procedure is being performed with greater frequency. As with all drastic interventions, HSCT comes with a high cost: aGVHD. At high severity grades, aGVHD is a direct threat to life. Even with the best of care, mortality is high. Lower severity grades are associated with considerable morbidity, and there is a high chance of evolution into cGVHD. cGVHD in its own right is a serious, devastating disease associated with a huge panoply of medical and psychological problems. On the other hand, aGVHD is associated with GVT effect. A consistent observation is that patients with GVHD have a lower rate of leukemia and cancer relapse than those who do not. Thus far, all interventions that ameliorate or prevent GVHD lessen GVT effect. The "holy grail" of treatment is to separate the two by targeting GVHD while preserving GVT. This remains an area of intensive, ongoing research.

6.6 Chronic Graft-Versus-Host Disease

cGVHD can arise during or directly after an episode of aGVHD (progressive onset cGVHD), after a disease-free interval (quiescent cGVHD), or it can present de novo [88]. The condition usually occurs within 3 years after transplant, with an average onset of 5 months [89]. cGVHD is a multisystem disorder of immune dysregulation combining features of autoimmunity and immunodeficiency. It can affect virtually any

organ, and serious infection and secondary malignancy are constant threats. cGVHD profoundly damages quality of life, and patients with the condition suffer a variety of disabilities and impairments. cGVHD is associated with graft-versus-tumor (GVT) effect, a phenomenon in which alloreactive T cells attack host cancer cells in addition to normal tissue. Because of GVT effect, the incidence of cancer relapse is lower in patients who experience cGVHD. Ideally, treatment regimens for malignant disease aim to preserve GVT effect while preventing GVHD.

As previously stated, a 2005 NIH consensus conference established new guidelines for the diagnosis and staging of GVHD [29]. The new guidelines emphasized that clinical manifestations rather than time are the major criteria by which cGVHD is distinguished from late aGVHD (Table 6.3). The clinical manifestations of cGVHD are classified into four categories: diagnostic, distinctive, common and other (Table 6.7). *Diagnostic* features are considered pathognomonic for the disease, and when present they establish the diagnosis without any further testing. Diagnostic skin findings include poikiloderma, lichen planus-like eruption, deep sclerotic lesions, morphea-like lesions, and lichen sclerosus-like lesions. *Distinctive* lesions are those commonly seen in cGVHD, but not sufficiently unique to be considered diagnostic. These include depigmentation, sweat impairment, pruritus, maculopapular rash, and erythema. Distinctive features require further testing such as skin biopsy, or demonstration of cGVHD in another organ system. *Common* features are those that occur in both aGVHD and cGVHD and include maculopapular rash, pruritus, and erythema. *Other* features such as keratoses pilaris, hyperpigmentation and ichthyosis are nonspecific and cannot be used to establish the diagnosis. The diagnosis of cGVHD requires at least one diagnostic clinical sign, or one distinctive clinical sign plus a positive diagnostic test, and the exclusion of other possible diagnoses, particularly late-onset aGVHD, malignancy, drug reaction and infection. An "overlap" subtype encompasses features of both aGVHD and cGVHD.

The reported incidence of cGVHD following allogeneic HSCT varies, but the overall incidence is in the range of 50–70% [90, 91]. Incidence depends on multiple predisposing factors including prior aGVHD, older recipient age, intensity of conditioning, hematopoietic stem cell source (peripheral blood > bone marrow > umbilical cord blood), mismatched or unrelated donor, female donors with male recipients, graft manipulation (T-cell depletion), GVHD prophylaxis regimen and use of post-transplantation donor lymphocyte infusions [29, 89, 92]. In a multi-center cohort analyzing 5,343 HSCT recipients with cGVHD, the probability of overall survival was 72% at 1 year and 55% at 5 years with a non-relapse mortality (death unrelated to the original cancer) of 21% and 31% at 1 and 5 years, respectively [89]. Using multivariate analysis of overall survival and non-relapse mortality, the study further classified patients into risk categories and found several variables associated with a poorer outcome (Table 6.8). A prospective study comparing outcomes of patients with "overlap" GVHD versus those with classic cGVHD showed that overlap patients had greater functional impairment, higher symptom burden and increased non-relapse mortality [93].

cGVHD most commonly affects skin, mucosal surfaces, eyes, musculoskeletal system, gastrointestinal tract, lungs, liver, and bone marrow. Clinical findings often mimic autoimmune diseases, particularly scleroderma, systemic lupus erythematosus, and Sjögren's syndrome. Sclerodermoid, lichenoid lesions and lichen-sclerosus-like lesions are the characteristic skin manifestations of advanced cGVHD; however, subtle and nonspecific skin changes such as xerosis, maculopapular rash, and ichthyosis can characterize early disease.

Sclerotic variants range from superficial morphea or lichen-sclerosus-like lesions to deep, diffuse indurated plaques resembling scleroderma. An association exists between exposure to total body irradiation and the development of sclerotic cGVHD [94]. All forms of sclerotic GVHD can progress to disfigurement and impairment. Sclerosis of underlying subcutaneous tissues can lead to edema, joint stiffness, decreased range of motion, and contracture. Lichenoid cGVHD

Table 6.7 Signs and symptoms of chronic GVHD

Organ or site	Diagnostic (sufficient to establish the diagnosis of chronic GVHD)	Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other features[c]	Common (seen with both acute and chronic GVHD)
Skin	Poikiloderma	Depigmentation	Sweat impairment	Erythema
	Lichen planus-like features		Ichthyosis	Maculopapular rash
	Sclerotic features		Keratosis pilaris	Pruritus
	Morphea-like features		Hypopigmentation	
	Lichen sclerosus-like features		Hyperpigmentation	
Nails		Dystrophy		
		Longitudinal ridging, splitting, or brittle features		
		Onycholysis		
		Pterygium unguis		
		Nail loss (usually symmetric; affects most nails)[a]		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes)	
			Premature gray hair	
Mouth	Lichen-type features	Xerostomia		Gingivitis
	Hyperkeratotic plaques	Mucocele		Mucositis
	Restriction of mouth opening from sclerosis	Mucosal atrophy Pseudomembranes[a] Ulcers[a]		Erythema Pain
Eyes		New onset dry, gritty, or painful eyes[b]	Photophobia	
		Cicatricial conjunctivitis Keratoconjunctivitis sicca[b] Confluent areas of punctate keratopathy	Periorbital hyperpigmentation	
			Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features	Erosions[a]		

Organ or site	Diagnostic (sufficient to establish the diagnosis of chronic GVHD)	Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other features[c]	Common (seen with both acute and chronic GVHD)
	Vaginal scarring or stenosis	Fissures[a]		
		Ulcers[a]		
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus[a]		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea
				Weight loss
				Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2× upper limit of normal[a]
				ALT or AST >2× upper limit of normal[a]
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology[b]		BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis[b]	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia	
			Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions	

(continued)

Table 6.7 (continued)

Organ or site	Diagnostic (sufficient to establish the diagnosis of chronic GVHD)	Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other features[c]	Common (seen with both acute and chronic GVHD)
Other			Ascites	
			Peripheral neuropathy	
			Nephrotic syndrome	
			Myasthenia gravis	
			Cardiac conduction abnormality or cardiomyopathy	

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GVHD graft-versus-host disease, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BOOP* bronchiolitis obliterans-organizing pneumonia, *PFTs* pulmonary function tests, *AIHA* autoimmune hemolytic anemia, *ITP* idiopathic thrombocytopenic purpura
[a]In all cases, infection, drug effects, malignancy, or other causes must be excluded
[b]Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes)
[c]Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed

Table 6.8 Factors associated with a higher risk of mortality in chronic GVHD

Variable	Comment
Increasing recipient age	>30 years old
Presence of prior acute GVHD	Increased risk with higher grade
Early onset of chronic GVHD	Onset prior to 5 months
Elevated serum bilirubin	>2 mg/dl
Lower Karnofsky performance status	<80 (Functional Status Score 0–100)
Thrombocytopenia	Platelet count of $<100 \times 10^9$/L
Transplant from a HLA mismatched unrelated or related donor	Versus transplant from HLA-identical sibling donor
Intermediate or advanced disease status	Versus early disease
GVHD prophylaxis regimen	Better outcome with CSA + MTX ± other vs. Tacrolimus ± MTX ± other
Gender mismatch	Female donor to male recipient versus male donor to male recipient

presents with violaceous papules and plaques on extensor surfaces. The clinical presentation is virtually identical to that of idiopathic lichen planus. Other skin changes associated with cGVHD include depigmentation, poikiloderma, hypohidrosis with heat intolerance, erythema, and pruritus [95]. Pigment abnormalities can cause severe cosmetic disfigurement. Chronic cutaneous GVHD can be associated with an isomorphic or isotopic response. Sclerotic cGVHD often appears in areas of minor skin trauma (isomorphic response, or Koebner phenomenon), and lichenoid cGVHD sometimes follows another skin disease such as herpes zoster (isotopic response) [95, 96].

The main histopathologic features of lichenoid cGVHD lesions consist of hyperkeratosis, focal hypergranulosis, vacuolar degeneration of the basal cell layer, and a band-like infiltrate of lymphoid cells. Sclerodermatous lesions show epidermal atrophy and sclerosis of the dermis. The sclerosis can involve the dermis alone, or it can also involve subcutaneous fat and muscle. Lichen-sclerosis like lesions show epidermal atrophy, hyperkeratosis with follicular plugging and edema coupled with homogenization of the upper dermis. All three chronic cutaneous GVHD variants closely resemble both clinically and histologically their respective dermatologic conditions.

Oral and genital disease occurs in up to 80% patients [97]. Lichen planus-like lacy white plaques, ulceration, and scarring occur on the oral and genital mucosa of both women and men; however, genital lesions cause more functional impairment and more severe symptoms in women. Vulvovaginal lesions cause dyspareunia and interference with sexual function. Genital lesions are usually associated with concurrent oral involvement [98]. cGVHD commonly affects salivary glands with resultant xerostomia [99, 100].

Ocular manifestations of cGVHD include xerophthalmia, blepharitis, corneal ulcer, cicatricial conjunctivitis, scleritis, glaucoma, and infections. Xerophthalmia is the most common problem. Diagnosis is based on an abnormal Schirmer test and slit-lamp demonstration of keratoconjunctivitis sicca. Chronic ocular GVHD rarely affects visual acuity, and it is generally accompanied by other systemic findings [29, 101].

Nail changes are present in up to 50% of patients, and longitudinal ridging is the most common finding [102]. Periungual erythema, brittle nails, Beau's lines, pterygium, and complete nail loss are also features of cGVHD. Dermatoscopy reveals abnormalities in nailbed capillaries of patients with sclerodermoid cGVHD, but not in patients with lichenoid cGVHD. These abnormalities include enlarged capillaries, neovascularization, avascular areas and hemorrhage [103]. Both scarring and non-scarring alopecia occur in cGVHD, and poliosis is common. Hair abnormalities associated with cGVHD should be distinguished from chemotherapy or radiation effects.

Systemic cGVHD often involves the GI tract, liver, lungs and immune system. Nausea, vomiting, diarrhea, anorexia, weight loss, and abdominal pain are typical manifestations of gastrointestinal cGHVD. Endoscopic biopsy and characteristic radiographic findings confirm the

diagnosis. Chronic hepatic GVHD is usually associated with cholestasis, elevated bilirubin and elevated alkaline phosphatase. Definitive diagnosis requires positive liver biopsy findings plus a distinctive cGVHD manifestation in another organ system.

Pulmonary signs and symptoms include cough, wheezing, and dyspnea on exertion. These result from bronchiolitis obliterans (BO), an airway disorder in which bronchioles become obstructed by fibrous granulation tissue. BO is a diagnostic pulmonary manifestation of cGVHD, and diagnosis of BO is confirmed by biopsy and abnormal pulmonary function tests [29]. Lung dysfunction is serious, and its presence is invariably associated with the highest severity grades of cGVHD [104].

Thrombocytopenia and other cytopenias are harbingers of decreased survival [105]. Eosinophilia is common in cGVHD. Once thought to be a favorable predictor, reports now show no correlation between eosinophilia and outcome [106]. The effect of cGVHD on immunity can be devastating, and infection is a common cause of death. Immunosuppressant and immunomodulating medications worsen susceptibility to infection.

The pathophysiology of cGVHD is complex and current knowledge remains incomplete. A primary reason is the lack of animal models that recapitulate human disease as completely in cGVHD as they do in aGVHD [107, 108]. Several mechanisms have been identified that alone or in concert contribute to pathogenesis [88]. Damage to thymic epithelium from conditioning and aGVHD interfere with thymic deletion of self-reactive T cells, resulting in loss of self-tolerance. Failure of central tolerance can lead to autoimmune phenomena.

Under physiologic conditions, not all self-reactive T cells are eliminated in the thymus, and some make their way to the periphery. A subset of T cells, regulatory T cells (Treg), inhibit self-reactive T cells that have escaped thymic deletion from proliferating in response to self-antigens. Treg cells exert their effects through several cytokines including TGF-β and IL-10. Treg cells express CD4+ CD25+ and the transcription factor forkhead box P3 (FoxP3). In cGVHD, the numbers of CD4+ CD25+ FoxP3+ Treg cells are diminished [109, 110]. Strategies to increase numbers of Treg cells such as extracorporeal photophoresis and low dose IL-2 are associated with clinical improvement [91, 111].

B cell homeostasis is disturbed in cGVHD, and both host-derived and donor-derived B cells appear to play a role in pathogenesis [109, 112, 113]. The importance of B cells in cGVHD is evidenced by significant clinical improvement following use of rituximab, an anti-CD20 monoclonal antibody causing B cell depletion. Several case series of patients treated with rituximab for cGVHD have shown improvement with response rates varying from 43 to 80%. Manifestations of skin, mucosal and musculoskeletal cGVHD respond best [90, 114]. B cells perform multiple immunologic functions other than antibody production. B cells present antigen, produce cytokines and chemokines, and regulate immune reactivity [88, 90]. Autoreactive B cells in cGVHD secrete proinflammatory cytokines including IL-6, TNF-α, and IFN-γ that activate T cells, macrophages and NK cells [90]. The net result is potentiation of the inflammatory cascade. Antigen presentation by autoreactive B cells promotes autoimmune tissue damage independent of antibody production [90]. Patients with cGVHD have a higher frequency of autoantibodies, including antinuclear antibodies and antibodies to smooth muscle, cardiolipin, dsDNA, and platelet-derived growth factor receptor (PDGFR) [115, 116]. It is not entirely clear whether these autoantibodies are directly pathogenic or merely bystanders. Transfer of autoantibodies from cGVHD mice does not produce disease in normal mice [90]. However, autoantibodies to PDGFR have a stimulatory effect on fibroblasts and induce production of collagen. Stimulatory antibodies to PDGFR were found in 22 patients with extensive cGVHD, but not in HSCT patients without GVHD or in normal controls. Levels were highest in those with generalized skin involvement and lung fibrosis. Autoantibodies to PDGFR may contribute to fibrosis and the scleroderma-like phenotype in cGVHD [117].

B cell-activating factor of the TNF family (BAFF), also known as B-lymphocyte stimulator, is a cytokine that provides survival signals to B cells and prevents apoptosis [90, 113]. High levels are present in autoimmune diseases such as SLE, and a monoclonal antibody against BAFF (belimumab) is used in treatment of active lupus [90]. High levels of BAFF are also present in cGVHD. cGVHD is associated with low numbers of naïve B cells and high levels of activated, autoantibody-producing CD27+ B cells [118]. The high levels of BAFF enhance survival of activated alloreactive and autoreactive B cells, thus causing perpetuation of disease.

cGVHD in humans and in murine models is associated with expansion of Th2 CD4 lymphocytes and polarization to a Th2 cytokine profile [88, 108, 109]. aGVHD is thought to be a Th1 mediated disease with elevation of TNF-α and IFN-γ, whereas cGVHD is considered a Th2 mediated disease [45, 119, 120]. Fibrosis and chronic inflammation are the hallmarks of cGVHD, whereas necrosis in target organs is the predominant finding in aGVHD [108]. In murine models, transforming growth factor beta (TGF-β) plays an important role in the development of fibrosis. CD4+ T cells home to target tissue and secrete IL-13, a Th2 cytokine that stimulates macrophages. Activated macrophages produce TGF-β, which binds to receptors on fibroblasts causing collagen synthesis and fibrosis [108]. In patients with cGVHD, serum levels of TGF-β are significantly increased [121]. IL-13 itself can bind to fibroblast receptors and directly stimulate collagen synthesis. IL-4 (another Th2 cytokine) similarly binds to fibroblast receptors and stimulates collagen synthesis [122]. Thus, the fibrotic changes seen in cGVHD may be accounted for by a Th2 cytokine profile and by the presence of autoantibodies to PDGFR.

aGVHD is a strong predictor of subsequent cGVHD [123]. Therefore, steps to decrease the risk of aGVHD, such as ex vivo T cell depletion in the graft and optimization of HLA match, are undertaken. In addition, minimizing toxicity of conditioning reduces tissue damage, which can later become a target for cGVHD. For example, lesions of sclerotic, cutaneous cGVHD have been known to develop after localized radiation therapy [95]. This is thought to represent an isomorphic (Koebner) phenomenon. Similarly, Martires et al. showed an association between conditioning with total body irradiation and the development of sclerotic type cGVHD [94].

Patients with cGVHD should practice strict sun avoidance because of immunosuppression and a propensity to develop skin cancer. The incidence of cutaneous squamous cell carcinoma *and* melanoma is elevated in cGVHD, particularly in males and in those who have received total body irradiation [124]. Patients taking voriconazole, a systemic antifungal medication, are at especially high risk. Voriconazole is a potent photosensitizer and a strong exacerbating factor for development of squamous cell carcinoma and melanoma [125–127]. Squamous cell carcinoma associated with voriconazole can be aggressive and multifocal, with high metastatic potential [128–130].

Frequent skin and mucosal examinations should be performed to detect cancer, ulcers, or new areas of sclerosis. Serial photography is helpful in this regard. cGVHD patients with a history of skin cancer should be examined every 6 months [131]. The incidence of oral cancer is also increased, and examination of mucosal surfaces should be part of routine cancer surveillance [124]. Mucosal and cutaneous erosions must be treated promptly to prevent adhesions and infection [131]. The skin of cGVHD patients tends to be xerotic, and generous use of emollients is recommended. Treatment of chronic ocular GVHD consists of liberal and frequent use of preservative-free artificial tears [132].

If sclerodermoid change or faciitis are detected, physiotherapy is advised. Physiotherapy, which includes stretching, heat, and edema management, is considered a very important component of general cGVHD management. It should be started early to prevent contracture, reduced range of motion and disability. Fasciitis occurs in approximately 1% of patients and is characterized by rock-hard, subcutaneous induration. Fasciitis is progressive and can lead to serious functional impairment [131]. Myositis presents with muscle pain and weakness, usually in association with

skin findings. Evaluation includes electromyography, determination of creatine kinase and aldolase activity, and muscle biopsy [112, 133]. Cases of myocarditis with electrocardiographic abnormalities have been described [134].

Patients with cGVHD are immunosuppressed, and infection is a major cause of morbidity and mortality. Prophylactic antibiotics are an important adjunctive treatment [132]. Patients are at increased risk of infection by *Pneumocystis jirovecii* and by encapsulated organisms such as *S. pneumonia*, *H. influenzae* and *N. meningitides*. Those at high risk for fungal or viral infections should also be treated prophylactically with antifungal and antiviral medications. Patients lose protective immunity after HSCT, and vaccination should be instituted six months post-transplant [135]. However, patients and close contacts should avoid live vaccines until full immunocompetency is achieved.

6.6.1 Specific Treatments

Treatment of cGVHD is complex and multifaceted, and a multidisciplinary team consisting of oncologists, dermatologists, ophthalmologists, physical therapists, plastic surgeons and others with expertise in the disorder best serves the patient. For mild disease limited to skin, topical corticosteroids (TCS) and emollients alone will suffice. The lowest potency and frequency of application should be used to avoid local adverse cutaneous effects. Because immunosuppressive effects are minimal, topical therapy is particularly advantageous in patients at high risk of malignancy relapse. Topical calcineurin inhibitors (CNI) are useful for sensitive areas such as the face and groin [136, 137]. For oral mucosal involvement, TCS are also the mainstay of therapy. One study showed that the combination of topical dexamethasone and topical tacrolimus was particularly effective in reducing symptoms attributable to oral cGVHD [138].

Phototherapy has antiproliferative and immunomodulatory effects, and it is effective in cutaneous cGVHD. Ultraviolet A (UVA), psoralen with UVA (PUVA), and both narrow and broad band ultraviolet B (UVB) are all treatment options. Higher response rates to phototherapy have been observed in lichenoid disease as compared to sclerodermoid cGVHD [139]. Although PUVA is effective, UVA and UVB without a photosensitizer have the significant advantage of avoiding psoralen-related side effects [140, 141]. In addition, the risk of skin cancer in long-term treatment is lower in UVB than in PUVA [142]. In a small case series, Brazzelli et al. used narrow-band UVB to treat ten children with steroid-refractory cutaneous cGVHD. Eight had a complete response with resolution of skin lesions, while the other two showed a partial response [143]. Given its wide safety margin, phototherapy is an excellent choice for patients with solitary cutaneous involvement or persistent skin lesions unresponsive to systemic immunosuppression.

6.6.2 Systemic Therapies

If internal organs are affected, systemic treatment is required. Systemic corticosteroids alone or in combination with a CNI are first line therapy, with starting doses of prednisone at 1 mg/kg/day. Some groups recommend maintaining this dose for 2 weeks, after which a slow taper is begun [144, 145]. Approximately 50% of cGVHD patients will respond, but long-term side effects are a concern. The addition of a CNI does not necessarily reduce mortality, but it may reduce treatment-related morbidity. In a randomized trial of *low-risk* cGVHD patients without thrombocytopenia, combination therapy with prednisone and a CNI did not significantly reduce transplantation-related mortality compared to prednisone alone. Combination therapy did however reduce the incidence of steroid-related toxicities such as osteonecrosis [146]. Patients with cGVHD at high risk for adverse corticosteroid side effects may therefore benefit from the addition of a CNI to the initial regimen [146]. In another study of *high-risk* cGVHD patients with thrombocytopenia, the combination of a CNI and prednisone as first-line therapy conferred a distinct survival advantage [145, 147].

More than one third of cGVHD patients do not respond to corticosteroid therapy [148]. Steroid refractory and steroid dependent disease are typically defined by progression of cGVHD on prednisone ≥1 mg/kg/day for 2 weeks, stable disease on ≥0.5 mg/kg/day for 4–8 weeks or inability to taper the dose to ≤0.5 mg/kg/day. If a patient cannot be weaned from corticosteroids after 3 months, adjuvant therapies need to be considered; however, there is no established second-line treatment [91].

Inhibitors of the mammalian target of rapamycin (mTOR), sirolimus and everolimus, block response to interleukin-2 (IL-2) and prevent activation and proliferation of T and B lymphocytes. In addition, they may promote the generation of Treg cells [149]. Treatments of cGVHD with the combination of an mTOR inhibitor and prednisone have shown response rates of 60–70% [150, 151]. This combination is well tolerated and effective for patients with sclerodermatous cGVHD [151]. However, the addition of an mTOR inhibitor to a CNI appears to increase the risk of thrombotic microangiopathy [151, 152].

Extracorporeal photophoresis (ECP) is a procedure wherein peripheral blood mononuclear cells are collected from the patient, treated with 8-methoxypsoralen, irradiated with UVA, and then reinfused back into the patient [153]. The net result is that ECP causes apoptosis of donor effector lymphocytes while increasing donor Treg cells [154]. ECP is considered an immunomodulating treatment, not an immunosuppressive treatment [155]. It is effective for some cases of steroid dependent or refectory cGVHD, and one study showed lower non-relapse mortality in ECP responders [156]. Another study showed that most patients were able to achieve 50% improvement in cutaneous cGVHD lesions with bimonthly ECP sessions, and over 75% of the patients were able to reduce doses of systemic immunosuppressive medication after six months [157]. Sclerodermatous lesions responded better than lichenoid lesions. Given its excellent safety profile, ECP is a valuable adjunctive therapy.

Numerous other medications have been used in the treatment of steroid-refractory cGVHD. These include mycophenolate mofetil [149, 158], methotrexate [159, 160], azathioprine [161, 162], pentostatin, rituximab, and imatinib. Mycophenolate may be associated with a risk of thrombocytopenia, recurrent malignancy, infection, and gastrointestinal discomfort [163, 164]. Methotrexate is a reasonable option. It is effective, and side effects are predictable and manageable [159, 160]. Azathioprine is not often used because one study showed increased nonrelapse mortality when azathioprine plus prednisone was compared to prednisone alone [161]. Pentostatin inhibits adenosine deaminase resulting in apoptosis of dividing lymphocytes, and two phase II trials demonstrated response rates of about 50% [149, 165]. Side effects of pentostatin, however, are severe: serious infection, leukoencephalopathy, anemia, and gastrointestinal symptoms caused a 25% drop out rate in the trials. Rituximab has shown benefit in the treatment of cGVHD, and it may also be helpful in prevention [90, 108, 166]. A meta-analysis of 111 patients with cGVHD showed a combined response rate that approached 70% [167]. The most notable responses were seen with the cutaneous and musculocutaneous manifestations [168]. Imatinib mesylate is a tyrosine kinase inhibitor with activity against BCR-ABL-positive malignancies. It is also an inhibitor of PDGF and TGF-β signaling pathways. Several case reports and small series have shown usefulness in sclerodermatous cGVHD [149, 165, 169–172].

6.7 Emerging Therapies

Interleukin-2 (IL-2) is a cytokine necessary for the development, expansion and function of T cells, including Treg cells, which suppress autoreactivity and maintain tolerance to self-antigens. Treg cells are reduced in cGVHD and other autoimmune diseases [109, 110]. Koreth et al. treated 29 patients with glucocorticoid refractory cGVHD with daily *low-dose* subcutaneous IL-2 [91]. Of 23 patients available for analysis, 12 had major responses in several sites, including skin, and 3 patients had partial responses. All treated patients experienced a marked increase in Treg cells compared to

baseline values. None of the patients experienced recurrent malignancy, and several who continued this treatment were able to lower their glucocorticoid dose. The most common adverse effect was a dose-dependent flu-like syndrome. Serious adverse effects included renal dysfunction, thrombocytopenia, thrombotic microangiopathy, and infection. Daily low-dose IL-2 may prove to be an effective treatment, but safety and adverse side effects remain a concern [91].

Mesenchymal stem cells (MSCs) also show potential value for treatment of both aGVHD and cGVHD. MSCs are pluripotent bone marrow progenitor cells capable of developing into multiple mesenchymal cell lineages including osteoblasts, chondrocytes, adipocytes, cardiomyocytes, neurons, and endothelial cells [173]. They can repair various tissues by homing to damaged sites and differentiating into cells of that tissue [174]. They are also immunomodulators, and they inhibit T cell responses to create an immunosuppressive local microenvironment [175, 176]. MSCs inhibit B lymphocytes, NK cells, and dendritic cells, but they increase Treg cell numbers [176]. MSCs are obtained from bone marrow, umbilical cord blood, adipose tissue, and muscle. They exhibit immunomodulatory effects while maintaining low immunogenicity. Several studies have shown that they are safe to infuse intravenously, and HLA-compatibility between MSC donor and recipient does not appear to be important. MSCs are hypoimmunogenic, and they avoid allorecognition.

Investigations have been undertaken to determine whether MSCs can prevent GVHD. In an open-label, randomized clinical trial, Ning et al. co-administered an allograft and MSCs at the time of HSCT [177]. Although co-administration decreased the incidence of both aGVHD and cGVHD, it increased the risk of primary disease relapse [177]. However, other investigators suggest that co-administration of MSCs and allograft during HSCT is safe and may actually speed the engraftment process [178, 179].

MSCs are also being explored for treatment of established cGVHD. Weng et al. reported good response in 14 of 19 steroid-refractory cGVHD patients treated with MSCs. Four patients achieved a complete response and ten a partial response [148]. Moreover, 9 of the 14 patients were able to reduce or discontinue immunosuppressive therapy completely, and the 2-year survival approached 80%. Likewise, Zhou et al. treated four patients with sclerodermatous cGVHD by direct injection of MSCs into bone marrow. Following the injection, Th1 cells increased and Th2 cells decreased in all four patients. The reversal of Th1/Th2 ratio was accompanied by significant improvement in skin lesions and joint mobility. None of the patients showed evidence of cancer recurrence after 14 months [180]. Although MSCs appear promising, more clinical trials are needed to assess effectiveness and safety.

6.8 Conclusion

cGVHD is a major source of disability and impairment following HSCT, and it can have a profoundly negative impact on quality of life. Fibrosis is a hallmark feature and a significant cause of impairment. The immunosuppression accompanying cGVHD renders the patient susceptible to infection and cancer, the main causes of death in this condition. The pathogenesis of cGVHD is being elucidated, and promising new treatments are on the horizon.

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Erythroderma

7

Gillian Heinecke and Mark Lebwohl

7.1 Introduction

Erythroderma (exfoliative dermatitis) is a clinical syndrome characterized by extensive erythema involving greater than 90% of the skin surface. It may be the result of many different dermatological conditions including preexisting dermatoses, drug reactions, and malignancy. Hospitalization may be required for initial evaluation and treatment since many of these patients are elderly and the skin involvement is extensive leading to significant mortality risk. Patients need to be monitored to ensure that temperature, water, protein, and electrolyte homeostasis are maintained. Erythroderma accounts for 1% of all dermatologic hospital admissions [1].

7.2 Epidemiology

Erythroderma is a rare skin disorder with an estimated annual incidence of 1–2 patients per 100,000 population [2]. It is more common in males with a male to female ratio of 2:1 to 4:1 [2–4]. Erythroderma occurs more commonly in older adults, with affected patients usually over 45 years of age and a mean age of onset of 55 years, although it should be noted that most studies exclude pediatric cases of erythroderma [5]. Approximately 50% of cases are exacerbations of preexisting dermatoses such as psoriasis, atopic dermatitis, or pityriasis rubra pilaris. Other causative factors include drug reactions (20%), malignancies (11%), and idiopathic (17%) [3, 4, 8–15].

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7.3 Etiology

A wide range of cutaneous and systemic diseases can cause erythroderma. It is important to establish the correct diagnosis whenever possible because specific therapy other than corticosteroids or anti-inflammatory treatments may be necessary to improve the patient's condition [6]. Table 7.1 provides an overview of the major etiologies responsible for erythroderma [3, 4, 8–15].

7.3.1 Dermatoses

Erythroderma occurring secondary to a preexisting skin condition is the most common etiology. The underlying skin condition is commonly known prior to onset of the erythroderma; however, some may initially present with erythroderma. In analyzing the combined data from the studies listed in Table 7.1 [3, 4, 8–15], psoriasis was the most common (23.1%) followed by atopic dermatitis/eczema (9.5%), pityriasis rubra pilaris (3.4%), contact dermatitis (3.2%), actinic dermatitis

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Table 7.1 Major etiologies for erythroderma from ten series

Series (year)	Number of patients	Dermatoses (%)	Drug-induced reaction (%)	Malignancy (%)	Idiopathic (%)
Abrahams (1963) [11]	101	35	11	8	47
Nicolis (1973) [8]	135	27	40	21	12
King (1986) [12]	82	30	34	20	16
Sehgal (1986) [14]	80	53	25	0	23
Botella-Estrada (1994) [4]	56	63	16	13	9
Sigurdsson (1996) [9]	102	53	5	16	26
Pal (1998) [13]	90	74	6	6	15
Akhyani (2005) [3]	97	60	22	11	7
Rym (2005) [15]	80	72	11	9	8
Yuan (2010) [10]	82	72	17	5	6
Total	905	52	20	11	17

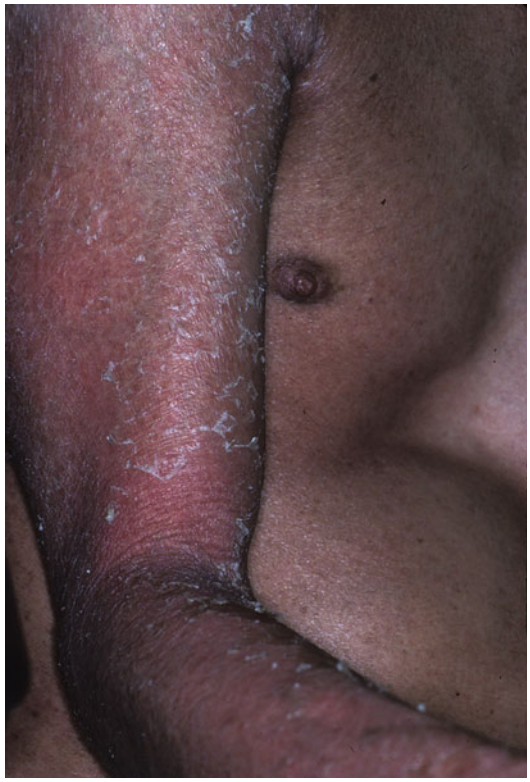

Fig. 7.1 Erythroderma secondary to congenital icthyosiform dermatitis. *Courtesy of Mount Sinai Dermatology collection*

(2.7%), and seborrheic dermatitis (2.5%). Additionally, pemphigus foliaceus, lichen planus, icthyosiform dermatitis (Fig. 7.1), phytophotodermatitis, stasis dermatitis, extensive dermatophytosis, Norwegian scabies, senile xerosis, and staphylococcal scalded skin syndrome account for the remaining cases. Table 7.2 lists the inflammatory dermatoses associated with erythroderma. It is important to consider other possible etiologies even in patients with clear preexisting dermatoses. Eugster et al. described that five out of seven patients with malignancy-induced erythroderma had a history of a preexisting dermatosis [16].

Table 7.2 Dermatoses known to cause erythroderma

Actinic dermatitis	Norwegian scabies
Bullous pemphigoid [17]	Pemphigus foliaceus
Candidiasis [18]	Perforating folliculitis [23]
Contact dermatitis	Phytophotodermatitis
Dermatophytosis	Pityriasis Rubra Pilaris
Eczema/atopic dermatitis	Psoriasis
Erythema gyratum repens [19]	Radiation recall dermatitis [24]
Hailey-Hailey [20]	Seborrheic dermatitis
Icthyosiform dermatitis	Senile xerosis
Impetigo herpetiformis [21]	Staphylococcal scalded skin syndrome
Lichen planus	Stasis dermatitis
Mastocytosis [22]	Subacute cutaneous lupus erythematosus [25]

7.3.2 Psoriasis

Erythrodermic psoriasis is a rare and severe form of psoriasis occurring in 1–2.25% of patients with psoriasis [26, 27]. It typically occurs in patients with established psoriasis with an average of 14 years between the onset of psoriasis and the first erythrodermic episode [26], although in some

cases, it can be the patient's initial presentation of psoriasis. Erythrodermic psoriasis may present acutely or may run a chronic course with frequent relapses [26]. There are a variety of medical and social conditions that may trigger outbreaks of erythroderma in previously localized psoriasis including systemic illness such as HIV infection, discontinuation of medications (including oral corticosteroids, potent topical steroids, methotrexate or biologics), emotional stress, UV burn, topical tar, and alcoholism [26, 28]. The classic plaques of psoriasis may be present in the early and remitting stages of erythroderma. The patient may also have the classical nail changes and arthritis associated with psoriasis [29].

7.3.3 Pityriasis Rubra Pilaris

Pityriasis rubra pilaris (PRP) may initially resemble a seborrheic dermatitis-like eruption of the scalp that then progresses into erythroderma over weeks to years. A similar picture of eruption on the scalp, with additional involvement of butterfly regions of the face and upper trunk can also be seen in early erythrodermic pemphigus foliaceus [6]. The erythroderma in PRP classically appears as generalized salmon-colored erythema with islands of sparing (Fig. 7.2). Islands of sparing may also be seen in psoriasis, cutaneous T-cell lymphoma and sarcoidosis [6]. Patients with PRP may also have underlying follicular papules and keratoderma of palms and soles.

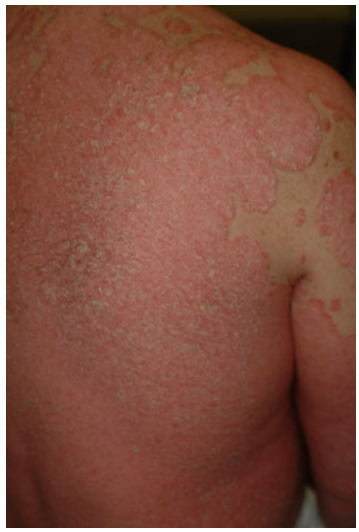

Fig. 7.2 Patient with erythroderma secondary to PRP with characteristic islands of sparing. *Courtesy of Mount Sinai Dermatology collection*

7.3.4 Drug Hypersensitivity Reactions

Both topical and systemic drugs are notorious for precipitating erythroderma, accounting for 20% of cases. While this list is constantly expanding, many of the implicated drugs come from single case reports. The most commonly implicated drugs include allopurinol, arsenicals, aspirin, carbamazepine, captopril, gold, hydantoins, mercurials, penicillin, phenothiazines, phenylbutazone, quinacrine, and sulfonamides. Additionally homeopathic, unani, ayurvedic, herbal, and home remedies have also been reported to cause erythroderma [14]. Interestingly, while carbamazepine is known to induce erythroderma, Smith et al. reported a case where the carbamazepine successfully cleared erythrodermic psoriasis [30, 31] (Table 7.3).

Drug-induced erythroderma typically occurs rapid and resolves quickly—on average 2–6 weeks after discontinuation of the drug. Drug eruptions that initially began as morbilliform, lichen planus-like or urticarial may evolve into erythroderma [8]. Nicolis et al. reported that erythroderma caused by sulfonamides, penicillins, antimalarials, barbiturates, arsenicals, and mercurials tended to have a more severe clinical course. Fever appears to be prominent in these cases, and moderate to severe liver degeneration can occur [8]. Drug-induced erythroderma due to dapsone or antileprosy agents can mimic the clinical and histolopathologic features of cutaneous T-cell lymphoma. In this situation, the erythroderma resolves with withdrawal of offending drugs [7].

7.3.5 Malignancy

Erythroderma may be a clinical expression of both hematological and internal malignancies, accounting for approximately 11% of cases. Cutaneous T-cell lymphoma is the most common etiology, accounting for 74% of the malignancy-induced erythroderma and 7.8% of all cases of erythroderma.

Table 7.3 Drugs reported to cause erythroderma

Antibacterial agents	*Cardiovascular agents*
Amoxicillin [10]	Amiodarone [29]
Aztreonam [29]	Captopril [5, 29]
Cefoxitin [32, 33]	Diltiazem [50]
Clofazimine [34]	Epoprostenol [51]
Dapsone [35, 36]	Isosorbide dinitrate [12]
Doxycycline [37]	Mexiletine [29]
Gentamicin [38]	Nifedipine [52]
Isoniazide [12, 14]	Quinidine [9]
Minocycline [29]	
Neomycin [29]	*Diuretic agents*
Penicillin [3, 4, 8, 10, 12, 15, 39]	Thiazides [12]
Ribostamycin [40]	
Rifampin [39]	*Antiepileptic agents*
Streptomycin [14]	Bupropion [53]
Sulfonamides [3, 8, 11, 12, 14]	Carbamazepine [3, 4, 9, 15, 39]
Teicoplanin [41]	Lamotrigine [54]
Thiacetazone [14]	Phenobarbital [3, 15]
Vancomycin [3]	Phenytoin [3, 9, 12]
Antifungal agents	*Psychotropic agents*
Terbinafine [42]	Chlorpromazine [39]
	Clonazepam [39]
Antiparasitic agents	Diazepam [39]
Chloroquine [11]	Etumine [4]
Quinacrine [8, 12]	Lithium [3]
Antiviral agents	*Miscellaneous*
Didanosine [43]	Allopurinol [4, 9, 12, 39]
Indinavir [44]	Bromodeoxyuridine [55]
Zidovudine [45]	Chlorpropamide [29]
	Cimetidine [56]
Analgesic and anti-inflammatory agents	Ephedrine [57]
Acetaminophen [15]	Erythropoietin [58]
Aspirin [39]	Fluidione [59]
Celecoxib [46]	Iodine [8]
Codeine [8]	Isotretinoin [60]
Diflunisal [47]	Omeprazole [61]
Indomethacin [10]	Pseudoephedrine [62]
Metamizole [48]	Rantidine [29]
Phenylbutazone [14]	Tar [14]
Piroxicam [49]	Terbutaline [12]
	Timolol eyedrops [63]
Chemotherapeutic	
Carboplatin [64]	
Cisplatin [65]	*Heavy metals*
Fluorouracil [29]	Arsenic [8]
Interleukin 2 [66]	Gold [9, 11]
Thalidomide [67, 68]	Mercury [8]

Table 7.4 Malignancies associated with erythroderma

Hematologic malignancies	Internal malignancies
Cutaneous T-cell leukemia • Sezary Syndrome • Mycosis fungoides	• Prostate [8, 76] • Lung [8, 9, 76] • Thyroid [8] • Liver [8, 77] • Breast [76] • Ovary [76] • Fallopian tube [78] • Rectum [76] • Esophagus [79] • Stomach [9, 10, 80] • Melanoma [65, 76, 81] • Buschke-Loewenstein tumor [82]
Leukemias • Acute myelomonocytic leukemia [69] • Adult T-cell leukemia [70] • Chronic lymphocytic leukemia [12] • Chronic eosinophilic leukemia [71]	
Lymphoma • Hodgkin's lymphoma [8, 12, 13, 72] • B-cell lymphoma [73] • Anaplastic large cell lymphoma [74]	
Miscellaneous • Reticulum cell sarcoma [11] • Myelodysplasia [75]	

Other malignancies include Hodgkin's lymphoma (11%), internal malignancy (8.5%), leukemia (4.2%), and non-CTCL, non-Hodgkin's lymphoma (2.1%). Table 7.4 lists the specific hematologic, and internal malignancies implicated in erythroderma. Malignancy should be considered in the differential diagnosis for erythroderma, especially when the disease is insidious, debilitating, or progressive in course, when the patient has no history of preexisting dermatoses, or when the erythroderma is refractory to treatment [5].

7.3.6 Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL), also known as mycosis fungoides, is the most frequently identified malignancy to cause erythroderma, and Sézary syndrome is the most common presentation associated with erythroderma. Sézary

syndrome is characterized by peripheral blood involvement of Sézary cells. The Sézary cell is an atypical lymphocyte with the characteristic morphology of a cerebriform nucleus and ample cytoplasm with vacuoles [83]. It is controversial how many Sézary cells are needed to define Sézary syndrome. The original NCI classification used the criterion of greater than 5%, but current practice at mycosis fungoides referral centers prefer greater than 20% or an absolute count of at least 100/mm^3 Sézary cells [84]. In both Sézary syndrome and non-Sézary mycosis fungoides, erythroderma may be accompanied by poikiloderma or frank tumors [84]. Patients also have intense pruritus which may be so severe as to interfere with daily activities. The diagnosis should be considered in all cases of erythroderma when the patient has infiltration of the skin, marked or asymmetric lymphadenopathy or splenomegaly. In severe cases of Sézary syndrome, patients may have leonine facies and hyperkeratosis of palms and soles with painful fissuring [85]. Erythroderma may be the first sign of CTCL, and its clinical and histological appearance may be identical to that of benign erythroderma [7]. In these cases, flow cytometry immunophenotyping of lymphocytes and T-cell receptor gene analysis are useful in identifying CTCL [86]. Sézary syndrome has a poorer prognosis than mycosis fungoides with a median survival of 2.5–5 years [85].

7.3.7 Internal Malignancy

Internal malignancies are implicated in 1% of all cases of non-CTCL-related erythroderma. Frequently, the malignancy is occult at the initial presentation of erythroderma. The common types of causative malignancies cited in the literature include carcinoma of the lung, prostate, thyroid, rectum, stomach, and liver [8–10, 76].

7.3.8 Miscellaneous Diseases

Erythroderma is also associated with several disorders that do not fit into the aforementioned groups. These disorders include graft-versus-host disease (GVHD), hepatitis, irradiation, reactive arthritis (formerly known as Reiter's syndrome), sarcoidosis, acquired immunodeficiency, congenital immunodeficiency syndrome, and disseminated histoplasmosis [6, 87, 88]. Japanese patients have been reported to develop a potentially fatal postoperative erythroderma caused by a unique form of transfusion-related GVHD and this can be prevented by the use of irradiated blood for transfusions [89]. The clinical findings in erythroderma caused by reactive arthritis may mimic the appearance of erythrodermic pustular psoriasis. Important distinguishing features of reactive arthritis include recent history of gastroenteritis, cervicitis in women or urethritis in men, mouth ulcers, or iridocyclitis [6]. The erythroderma that can occur secondary to progressive disseminated Histoplasma capsulatum infection can closely resemble CTCL. The diagnosis of Histoplasma should be suspected when chronic ulcers with an indurated base occur on the skin or oral mucosa or if characteristic chorioretinal lesions occur in the eyes [6].

7.4 Pathogenesis

One intriguing aspect of erythroderma is the fact that clinically distinct skin diseases can progress into erythroderma with a relatively uniform clinical picture. The pathogenesis of erythroderma is not completely understood and it is still unclear whether the underlying mechanisms leading to erythroderma are the same or different depending on the underlying disease [90]. The development of erythroderma is thought to be secondary to a complex interaction of cytokines and cellular adhesion molecules including interleukins (IL)-1, -2, -4, -5, and -10, tumor necrosis factor (TNF), interferon (IFN)-γ, intercellular adhesion molecule-I (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), selectin-E and -P [87, 90, 91]. Siggurdsson et al. found that while all types of erythroderma have a predominately CD4+ T-cell lymphocytic infiltrate in the skin, Sézary syndrome tends to have CD4+ T-cells that secrete

IL-4, consistent with the Th2 subset of T-helper (Th) cells while benign forms of erythroderma such as atopic dermatitis and psoriasis have a cytokine profile characterized by IFN-γ secretion, consistent with the Th1 subset [91]. Siggurdsson et al. also found that atopic dermatitis-induced erythroderma, CTCL-induced erythroderma, and idiopathic erythroderma all had increased levels of circulating adhesion molecules, and the types of adhesion molecules expressed were not significant between the different causes [90].

These molecular, cellular, and immunologic changes lead to increased mitotic rate and increased number of germ skin cells, resulting in a dramatic increase in the epidermal turnover rate. This increased turnover rate leads to greater loss of viable cellular material such as nucleic acids, amino acids, protein, and folic acid [5, 92, 93]. Erythroderma may increase daily protein loss through loss of keratinocytes and scaling by 25–30% in psoriatic erythroderma and by 10–15% in other causes of erythroderma [92].

7.5 Clinical Manifestations

Erythroderma is defined as generalized erythema and scaling of at least 90% of the patient's skin surface as seen in Fig. 7.3. The condition typically begins as patches of erythema accompanied by pruritus. These patches then enlarge and coalesce, eventually resulting in involvement of most of, or in some cases all of, the skin surface area. The palms, soles, and mucous membranes are generally spared [8]; however, erythroderma that is secondary to cutaneous T-cell lymphoma or pityriasis rubra pilaris may involve the palms and soles [29]. The character of erythema varies with the duration of the disorder with sudden-onset lesions typically bright red and more chronic lesions generally deeper, dusky red [6]. In darker-skinned patients, the erythema is darker from the onset. The degree of scaling can vary greatly between cases from virtually none to extensive. The scaling usually begins within several days of the onset of erythema, classically beginning in the flexures.

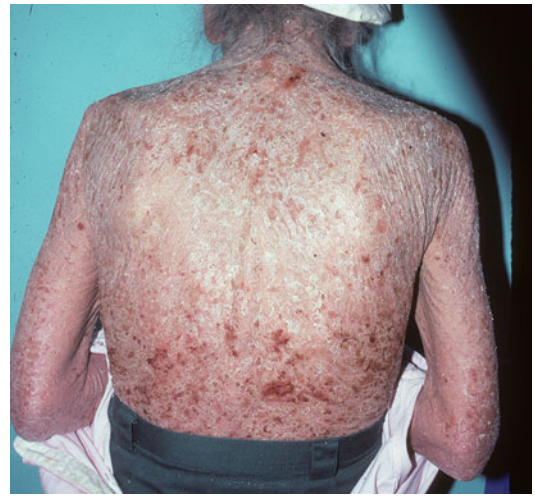

Fig. 7.3 Erythrodermic Psoriasis patient: This patient has the extensive erythema and scaling characteristic of erythroderma. *Courtesy of Mount Sinai Dermatology collection*

The size of the scale also varies with the duration of symptoms, with larger scale in acute cases and smaller scale in chronic [5]. Secondary bacterial infections are a frequent complication and can cause crusting, impetigo, or folliculitis [6].

Nail examination in erythrodermic patients frequently reveals dystrophy, especially in patients whose erythroderma is secondary to psoriasis. The nail plate is often thickened and lusterless with horizontal depressions (Beau's lines) [6]. Subungual hyperkeratosis, the accumulation of keratinaceous material under the nail plate, may occur leading to distal onchycholysis, separation of the nail plate from the nail bed. The entire nail plate may be shed in severe cases [6] (Fig. 7.4). Additionally, the patient's hair may also be affected. Alopecia occurs in 25% of patients and more often develops in patients with severe forms of exfoliation [8].

Most patients complain of pruritus, which may be mild to severe. Some patients also experience pain or a burning sensation of the skin [6]. Constitutional symptoms such as fever, chills, and malaise are common. Both hyperthermia and hypothermia may be observed. Heat loss is a major concern secondary to the defective skin barrier. There is loss of normal vasoconstrictive function of the dermis, decreased sensitivity of

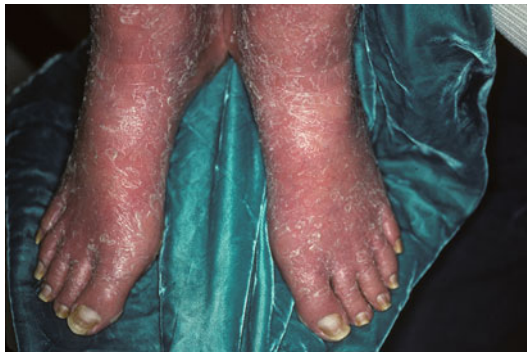

Fig. 7.4 Erythrodermic psoriasis patient showing characteristic nail involvement. The rapid keratinocyte turnover rate has lead to accumulation of keratinaceous material on the nail bed resulting subungual hyperkeratosis. *Courtesy of Mount Sinai Dermatology collection*

the shivering reflex and increased heat loss from evaporation of weeping fluids from the skin. These processes can lead to increased basal metabolic rate and a catabolic state resulting in significant weight loss [7]. Patients may develop either regional or generalized lymphadenopathy. Axillary and inguinal lymphodenopathy is more common than cervical lymphodenopathy [8]. Generalized lymphadenopathy is more common in patients whose erythroderma is secondary to malignancy. Mild hepatomegaly may occur in up to 20% of cases regardless of etiology; however, splenomegaly is usually only seen in patients with underlying malignancy, sarcoidosis, histoplasmosis, or severe hypersensitivity reactions. Other nonspecific clinical findings include peripheral edema, gynecomastia, and high output cardiac failure, which results from peripheral vasodilation [6].

7.6 Laboratory Findings

The laboratory findings are often not helpful in uncovering the underlying cause of erythroderma. Common abnormalities include mild anemia, leukocytosis, elevated sedimentation rate, hyperuricemia, hyperglobulinemia, hypoalbuminemia, and eosinophilia [4, 5, 8, 9, 12–14]. Mild anemia, with hematocrit values between 35 and 38% [12], is thought to be due to folic deficiency, iron deficiency, and a chronic inflammatory state [31]. More severe anemia is unusual [12]. Leukocytosis of greater than 20,000 leukocytes/mm^3 is seen in both benign and malignant forms of erythroderma [8]. Eosinophilia and increased IgE are frequently observed findings in erythroderma secondary to atopic dermatitis and drug reactions but are not diagnostic for these conditions [4, 8, 9, 14]. Griffiths et al. observed transient CD4$^+$ T-cell lymphocytopenia in HIV negative patients with acute erythroderma as a consequence of T-cell sequestration in the skin [5, 94].

For the diagnosis of Sézary syndrome, Sézary cell count analysis can be useful. In current practice, greater than 20% or absolute count of at least 100/mm^3 circulating Sézary cells is diagnostic for Sézary syndrome [84]. Less than 10% circulating Sézary cells is nonspecific and is seen in a variety of benign dermatoses including contact dermatitis, atopic dermatitis, psoriasis, lichen planus, discoid lupus, and parapsoriasis [83]. Differentiating Sézary syndrome from erythrodermic actinic reticuloid can be difficult since the two diseases can have similar clinical presentations and high levels of circulating Sézary cells in the peripheral blood [95, 96]. However, immunophenotyping and nuclear contour index (NCI) of blood lymphocytes can help differentiate the two since actinic reticuloid has increased CD8+ T cells and decreased NCI compared to Sézary syndrome [29, 95]. Additionally, actinic reticuloid patients are photosensitive. Looking for clonal T-cell populations in peripheral blood smears through T-cell receptor gene analysis can help to distinguish CTCL from benign erythroderma [96, 97]. This technique can also be applied to skin biopsies [98].

7.7 Histopathology

Skin biopsy is an important diagnostic tool for identifying the etiology of the erythroderma, but interpretations of these specimens may be difficult. This difficulty is due to the fact that the histopathological expression of the underlying disorder tends to be more subtle in the setting of erythroderma than in the conventional disease form [99]. Multiple

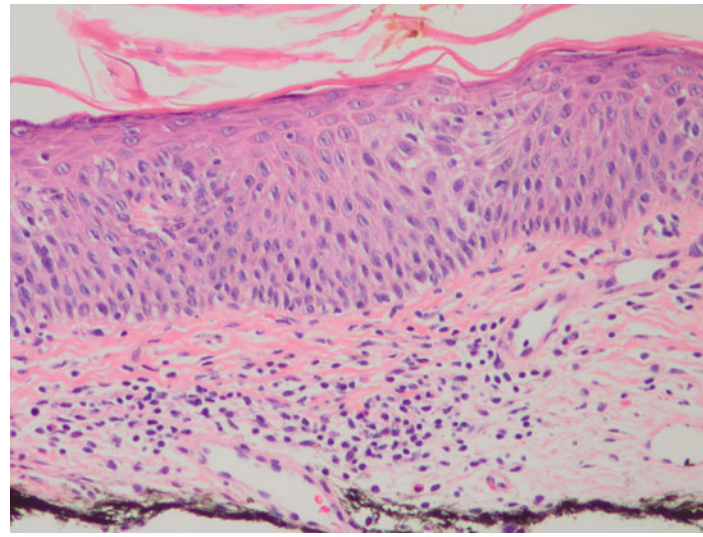

Fig. 7.5 Epidermis shows minimal acathosis, slight intercellular edema (spongiosis), and foci of parakeratosis characteristic of erythroderma secondary to dermatitis. *Courtesy of Mount Sinai Dermatology collection*

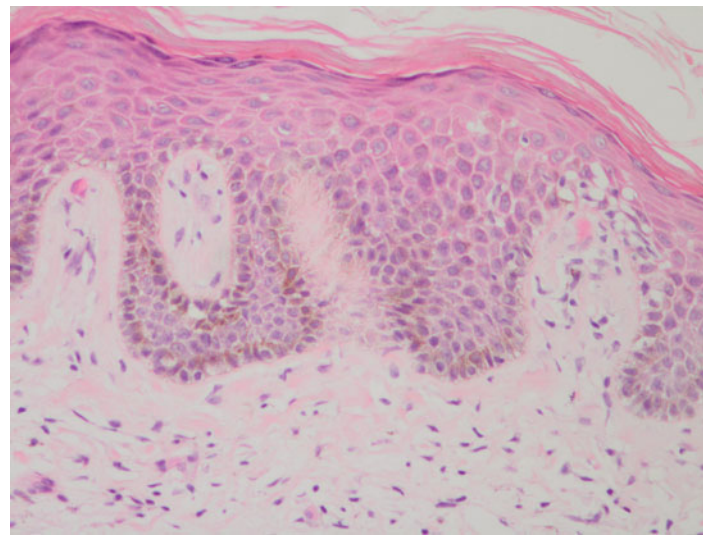

Fig. 7.6 Histopathology consistent with Erythrodermic psoriasis. The typical features of erythrodermic psoriasis includes suprapapillary thinning, exocytosis of neutrophils, subcorneal pustules, and edema of papillary dermis [90]. *Courtesy of Mount Sinai Dermatology collection*

skin biopsies submitted simultaneously can increase the accuracy of histopathological diagnosis, as the histopathological manifestations of the underlying disease are often heterogeneously distributed in the affected skin [99]. Studies comparing "blinded" microscopic diagnosis with final diagnosis found a 31–66% correlation [99–101]. Walsh et al. found that the correct pathological diagnosis is reached more often in patients with dermatitis (Fig. 7.5), CTCL, and psoriasis (Fig. 7.6) than in patients with drug eruptions or PRP [99].

It is especially important to differentiate benign inflammatory erythroderma from Sézary syndrome given the aggressive course of this lymphoma. Ram-Wolff et al. found that this distinction could be made with certainty in 57% of cases [100]. Distinguishing histopathological features of Sézary syndrome include Pautrier microabcesses, atypical lymphocytes (Fig. 7.7), basilar lymphocytes, and dense dermal infiltrate [100]. The basal lymphocytes seen in CTCL can be difficult to distinguish from the interface (dermal–epidermal) inflammation

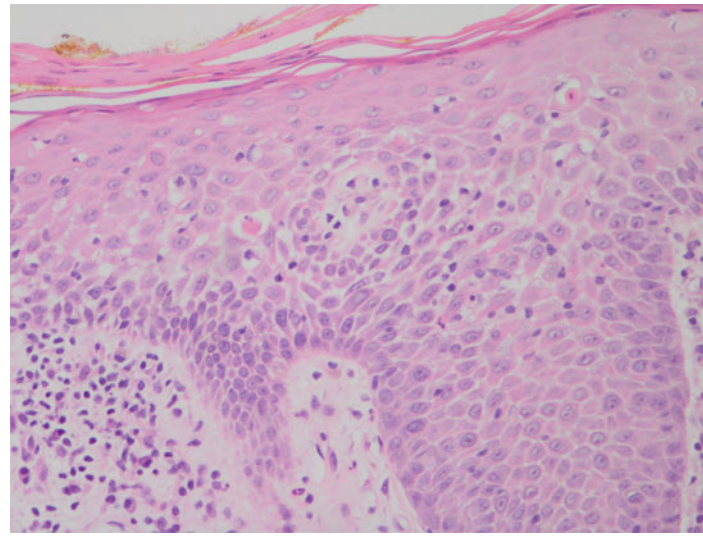

Fig. 7.7 Epidermal and dermal infiltrate of atypical T cells characteristic of CTCL. *Courtesy of Mount Sinai Dermatology collection*

seen in drug eruptions [99]. Identification of numerous dilated blood vessels favors a diagnosis of benign inflammatory erythroderma [100].

7.8 Treatment

All cases of erythroderma are considered a dermatological emergency, and hospitalization should be considered if fluid and electrolyte imbalance or cardiovascular or respiratory comprise occur. Regardless of the underlying etiology, the initial therapy for an erythrodermic patient should focus on fluid, electrolyte, and nutritional management as well as gentle skin care measures. If a drug reaction has not been ruled out, all nonessential medications should be discontinued if possible. Oatmeal baths and wet dressings to weeping or crusted sites followed by bland emollients and low-potency topical corticosteroids can help to reduce inflammation and pruritus [29]. High potency corticosteroids should be avoided due to increased systemic absorption from the extensive surface area involvement and increased permeability of erythrodermic skin [102]. Topical tacrolimus has also been shown to be systemically absorbed and blood levels should be monitored if used to avoid nephrotoxicity in an erythrodermic patient [103]. Sedating oral antihistamines can enhance this effect and relieve anxiety [5]. Patients require a warm and humidified environment to increase comfort, prevent hypothermia, and increase moisture to the skin [29]. Diuretics may be needed to treat edema, and systemic antibiotics may be required for secondary bacterial infections.

Patients who are refractory to topical therapy should receive systemic therapy directed at the underlying etiology. First-line treatment for erythrodermic psoriasis includes cyclosporine, infliximab, acitretin, and methotrexate with cyclosporine and infliximab being more rapidly acting agents [104]. While systemic corticosteroids should be avoided in patients with suspected underlying psoriasis because of the potential to induce a rebound flare, they are helpful in treating drug-induced and atopic dermatitis-related erythroderma. Pityriasis rubra pilaris-induced disease responds well to retinoids and methotrexate [5]. The best treatment regimen for Sézary syndrome depends on a variety of patient factors including burden of disease, impact on quality of life, and rate of disease progression. Systemic therapies such as extracorporeal photopheresis, interferon-α, bexarotene, low-dose methotrexate,

and denileukin diftitox can be used alone, or combined with skin-directed therapies such as phototherapy, topical nitrogen mustard, and total skin electron beam radiation [105].

When the etiology of erythroderma remains unknown, patients can be treated with empiric therapy which includes systemic corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil, and actretin. Until CTCL has been ruled out by up-to-date laboratory testing, immunosuppressive agents should be avoided [29].

7.9 Complications

Patients with erythroderma can suffer from a variety of serious complications including secondary infection, dehydration and electrolyte abnormalities, edema and high output cardiac failure. Patients with erythroderma have increased skin colonization of Staphylococcus aureus when compared to healthy controls [106]. This colonization may explain the high incidence of staphylococcal septicemia in patients with erythrodermic psoriasis and CTCL [107, 108]. The rapid turnover of the epidermis leads to increased daily protein loss of 25–30% in psoriatic erythroderma and 10–15% in other causes of erythroderma which can lead to a net negative nitrogen balance as seen by muscle wasting, hypoalbuminemia, and edema [92]. Increased cardiac output has been demonstrated in patients with erythroderma secondary to dilation of cutaneous blood vessels in the diseased skin which can lead to heart failure especially in patients with underlying cardiac disease or the elderly [109].

7.10 Prognosis

The prognosis of erythroderma depends on the underlying disease. Drug-induced erythroderma often resolves quickly once the offending agent is removed, while CTCL often has a chronic and refractory course [29]. While older series report high mortality from erythroderma ranging from 5 to 64% [4, 8, 11, 12], this mortality has been likely reduced due to advances in diagnosis and therapy.

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Vesiculobullous Dermatoses

8

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8.1 Introduction

The vesicobullous diseases in dermatology are numerous and quite distinct from one another; the unifying feature, intuitively, is the histologic feature of separation either intraepidermally or subepidermally. Vesicobullous diseases can be mediated through infections, allergic causes, physical insults, or may occur as a result of autoimmune and hereditary disorders. The majority of vesicobullous diseases are acquired, wherein autoantibodies target specific cellular adhesion molecules resulting in separation of keratinocytes. In contrast, inherited vesicobullous diseases due to genetic loss of either adhesion molecules or basic structural proteins, lead to loss of cell–cell adhesion following minor or insignificant trauma or traction to the skin. The term "acantholysis" refers to intraepidermal pathology, whereas "blister" is traditionally used to delineate subepidermal disease. Whether acquired or inherited, vesicobullous diseases are a major source of patient morbidity and mortality in dermatology, either due to inherent disease processes or from therapeutic complications.

Several clinical characteristics including age of onset, family history, exposure history, and known systemic or other dermatologic disease can provide clues as to the etiology of a blistering disease [1]. Advanced clinical recognition of vesicobullous diseases takes lesion morphology, distribution, evolution, and presence of Nikolsky sign into consideration; however, diagnosis strictly relies on histological and immunologic criteria through application of specialized immunohistologic techniques [2, 3]. Despite this clinical armamentarium, blistering diseases are often misdiagnosed and delay in diagnosis or institution of appropriate treatment can sometimes result in death [4].

8.2 Intraepidermal Blistering Diseases

Intraepidermal blistering diseases include the acquired pemphigus family and the inherited epidermolysis bullosa simplex. Pemphigus is a group of rare, life-threatening autoimmune blistering diseases characterized by widespread bullae and erosions of the skin and mucous mem-

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branes. The pemphigus family can be divided into three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Other pemphigus subtypes exist such as pemphigus vegetans and Fogo selvagem, all of which will be reviewed in this chapter. Dysfunctional desmosomal proteins leading to acantholysis within the epidermis with subsequent flaccid blister formation characterize the pemphigus family of disorders. Epidermolysis bullosa is a spectrum of inherited and acquired blistering diseases; heritable keratin defects found in Epidermalysis Bullosa Simplex lead to acantholysis and will be discussed in this section, whereas the remainder lead to subepidermal disease and will be discussed later in this chapter.

8.3 Pemphigus

Before the advent of corticosteroids, pemphigus was associated with a high mortality rate. Today, pemphigus remains a possible dermatologic emergency; however, with new therapeutics, mortality rates have decreased, yet it still conveys significant morbidity. The most classic form of pemphigus is pemphigus vulgaris (PV). PV is also known as "deep" pemphigus, as blisters develop in the deeper portion of the epidermis just above the basal cell layer. Of the entire pemphigus family PV is the most potentially life threatening [5].

The prevalence of pemphigus vulgaris in men and women is nearly equal and the mean age of onset is 50–60 years, although the range is broad and disease arising in the elderly and children has been described [6]. Available data is limited in regards to the incidence of PV, although one review cited an annual incidence of 0.42 per 100,000 [7]. In the general population, the incidence ranges from 0.76 to 5 new cases per million per year. However, the incidence is much higher in people of Mediterranean, South Asian, and Jewish ancestry, reported at 16–32 cases per million per year [8]. PV is more common than other forms of pemphigus such as pemphigus foliaceus. In Japan with an incidence of 3.5 cases per million per year, the ratio of vulgaris to foliaceus is 2:1, whereas the majority of all cases (73%) are due to vulgaris in France where the incidence is 1.7 cases per million per year [9].

The exact etiology of PV remains unknown; however, the interaction between environmental factors and genetic background is thought to contribute to its development. Predisposition to PV is linked to genetic factors. For example, certain major histocompatibility complex (MHC) class II molecules, specifically the alleles of human leukocyte antigen DR4 and DRw6, are more common in patients with PV [10–15]. Despite this, predisposing genetic factors alone may not be sufficient to trigger the autoimmune response seen [16]. Clinical evidence supports the role of dietary factors in the exacerbation of pemphigus [17, 18]. Suspected culprits capable of inducing PV as reported in the literature include thiol compounds (garlic, leek, chives) and phycocyanins (Spirulina platensis alga) [18, 19]. Another cause of pemphigus reported in the literature is medications including thiol drugs, phenol drugs, and nonthiol nonphenol drugs. The thiol drugs known to cause pemphigus include captopril, penicillamine, and gold. The phenol group includes culprits such as aspirin, rifampin, levodopa, and heroin, while nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and dipyrone are examples of nonthiol nonphenol medications known to induce pemphigus [20].

In PV, blister formation is associated with IgG antibodies against desmoglein 3 and 1, key adhesion proteins found in both the skin and mucous membranes [20]. Patients with active disease have circulating and tissue-bound autoantibodies of both the immunoglobulin G1 (IgG1) and immunoglobulin G4 (IgG4) subclasses [21, 22]. Autoantibody binding directly interferes with cell–cell adhesion, leading to suprabasilar acantholysis. The target antigen affected—desmoglein 1 or 3 (Dsg1 or Dsg3)—dictates the clinical phenotype seen in pemphigus. For example, individuals with the mucosal-dominant type of PV have only anti-Dsg3 IgG autoantibodies, whereas patients with the mucocutaneous type of PV have both anti-Dsg1 and anti-Dsg3 IgG autoantibodies [23].

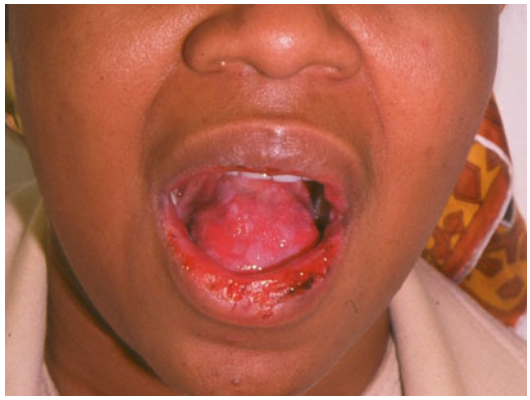

Fig. 8.1 Mucosal lesions in pemphigus vulgaris seen on the mucosal lips, tongue, and buccal mucosa

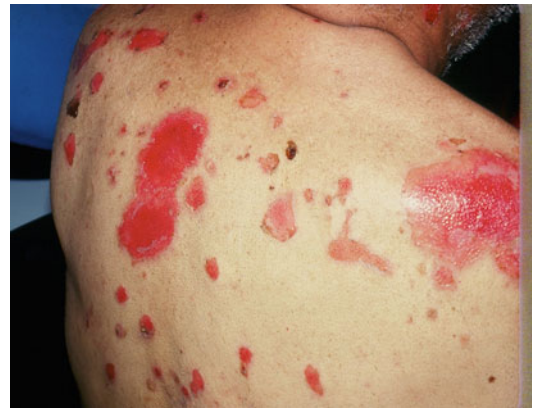

Fig. 8.2 Pemphigus vulgaris. Coalescing epidermal erosions on the trunk. Crust reminiscent of the flaccid blister

All patients with PV have mucosal membrane erosions, and in 50–70% of patients, the disease begins with the development of oral lesions [24]. In acute PV, patients often present to the ER or their primary care physician complaining of severe dysphagia. On physical exam, there are usually ill-defined erosions of the lips, tongue, buccal mucosa, gingiva, or hard/soft palate (Fig. 8.1) [25]. Those unfamiliar with PV may diagnose the patient with herpes gingivostomatitis, apthous stomatitis, oral lichen planus, Stevens-Johnson syndrome, or traumatic ulceration. In misdiagnosed and therefore untreated PV, the oral erosions show little or no tendency to heal. This leads to hypoalimentation secondary to patient fear of pain with eating and subsequent malnutrition and unintended weight loss. Other mucous membranes can be involved including the conjunctivae, nasal mucosa, esophagus, vagina, penis, and anus [26]. More than half of all patients will also have cutaneous erosions and/or flaccid bullae. Common cutaneous locations include the head, upper torso, and intertriginous areas (Fig. 8.2) [25, 27].

In patients with suspected pemphigus vulgaris, a biopsy specimen for routine histology should be obtained from lesional skin. Histology findings in PV include suprabasilar blister formation, acantholysis, and minimal inflammation [25]. In addition to routine histology, a direct immunofluorescence (DIF) of perilesional skin should be obtained against monkey esophagus substrate. An intercellular "fishnet" pattern of IgG antibody and C3 deposition is virtually diagnostic (Fig. 8.3). An indirect immunofluorescence (IIF) is not necessary for diagnosis; however, a baseline is useful before therapy is initiated [25]. Antibody titer usually parallels disease activity in PV and can be used to track therapeutic response [28]. In the past 10 years, serum enzyme-linked immunosorbent assay (ELISA) testing has become widely available for PV and has been shown to be more sensitive than convential IIF [29]. Similar to IIF titers, ELISA values may be used to track disease activity [30].

As previously mentioned, the diagnosis of PV can be missed, as there are simulators of this disease. The differential diagnosis for pemphigus vulgaris includes distinguishing it from other variants of pemphigus including pemphigus foliaceus and paraneoplastic pemphigus. Additionally, the differential can be divided into two main categories—only oral lesions present versus both oral and cutaneous lesions present. The list of diseases on the former includes aphthous stomatitis, erythema multiforme, herpes simplex, erosive lichen planus, and cicatricial pemphigoid, while the latter differential includes Stevens-Johnson syndrome/toxic epidermal necrolysis, bullous pemphigoid, linear IgA dermatitis, and epidermolysis bullosa acquisita.

Before the advent of corticosteroids in the 1950s, pemphigus vulgaris had been a deadly disease with mortality rates between 90 and

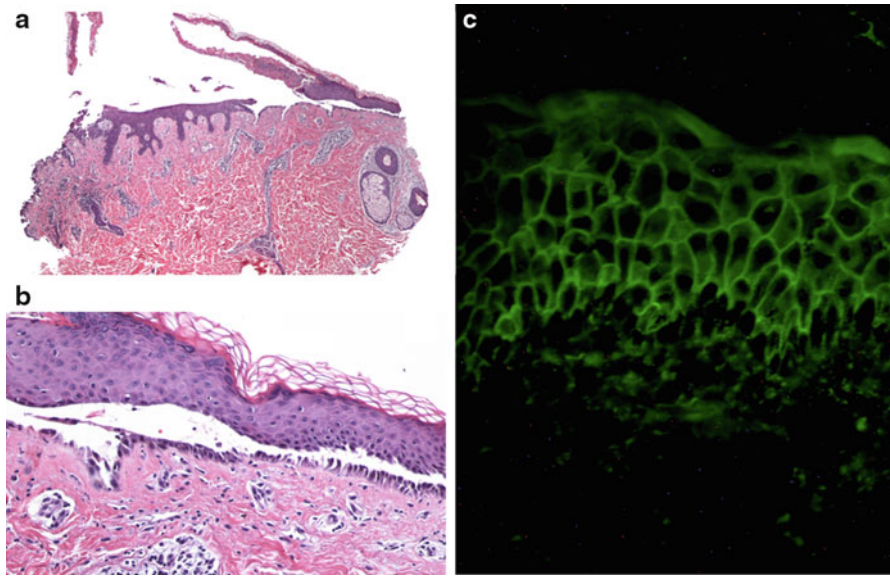

Fig. 8.3 (**a**) Low power H&E view of Pemphigus Vulgaris showing suprabasilar acantholysis. (**b**) High power view showing "tombstoning" of basilar keratinocytes. (**c**) Direct Immunofluorescence

100% of affected patients within 2 years of disease onset. Death largely resulted from sepsis secondary to loss of skin barrier, leading to loss of body fluids or serving as a nidus for secondary bacterial infections [31]. PV is almost universally fatal in the absence of therapy, and studies demonstrate higher mortality among the elderly; therefore, early intervention is essential [25]. With the vast array of treatment options available today including systemic glucocorticoids, nonsteroidal systemic immunosuppressives, biologics, and immunomodulatory procedures, mortality is now less than 10% [32].

If the disease appears nonprogressive and restricted to one body area such as the mouth, topical therapy alone may be adequate [26]. Corticosteroid gels or ointments such as fluocinonide, desoximetasone, or clobetasol can be initially used two to three times per day [33]. Gels are often more easily applied and better tolerated when used within the oral cavity. It should be advised that daily applications should initially occur two to three times per day when symptoms are severe and gradually tapered once relative improvements are seen. Q-tip or fingertip application is recommended, rubbing the gel or ointment onto the affected areas gently for 30 s with abstention from food or drink for 30 min thereafter. It should also be noted that patient should be aware that these topical therapies are used off-label and products often claim "for external use only" [26]. A prosthetic device such as a dental tray that fits over the teeth and gingiva can be fashioned by a dentist to make application of a topical corticosteroid preparation easier. When these topical medicines are applied under a dental tray their potency is increased [34]. There are few recognized adverse effects associated with the use of topical corticosteroids in the oral cavity including oral candidiasis and reactivation of herpes simplex virus (HSV). The former can be treated with antifungal agents such as clotrimazole lozenges five times per day for 1 week, nystatin swish and swallow four times per day until the patient is asymptomatic for 48 h, or oral fluconazole dosed twice weekly. When HSV reactivation occurs, treatment with topical acyclovir six times per day for 1 week is appropriate with lesions limited to the oral cavity; however, if life-threatening HSV reactivation occurs intravenous acyclovir may be necessary. Intralesional corticosteroid injections can be used in the treatment of PV with some success using triamcinolone 5–10 mg/mL every 2–4 weeks [26].

Excellent oral care is integral in patients with PV. Such care includes gently brushing the teeth twice daily using a soft-bristle toothbrush, daily flossing, and professional teeth cleaning every 3–6 months [26]. Ahmed et al. have recommended gentle debridement of necrotic mucosal tissue to prevent infection [35]. Therefore, it is important to have a dentist involved in those patients with PV. Topical analgesics or anesthetics and antiseptic mouthwashes are recommended as further treatment. Various elixirs containing combinations of viscous lidcaine, diphenhydramine, and antacids can be used as an oral rinse to decrease mouth pain [35, 36]. Oral trauma can easily lead to new erosions and should be avoided as much as possible. Poorly fitted dentures, dry crackers, and hard candies have all been implicated in giving rise to trauma of the oral mucosal surface [26].

Systemic corticosteroids are the mainstay of therapy and often first-line for PV, while immunosuppressive agents are used to aid in disease remission and decrease the need for long-term systemic steroids. The goal of therapy is to control the disease with the lowest possible dose of corticosteroids. Systemic corticosteroid therapy usually in the form of oral prednisone is standard treatment. Therapeutic effects are assessed by the number of new blisters per day, and their rate of healing with gradual tapering of prednisone. Once clinical remission is obtained, changes in the titer of circulating autoantibodies are helpful in estimating the dose of prednisone [37]. Should the disease flare at any point during the attempted taper, patients should return to the steroid dose prior to the disease flare and be maintained at that dose for 4 weeks before attempting another taper. Patients with PV often require several months of high-dose corticosteroid therapy before a taper can be attempted, irrespective of whether adjuvant therapy is administered. Therefore, patients should be counseled at length on the adverse effects of systemic corticosteroids. Treating physicians should protect against recognized sequelae of prolonged corticosteroid treatment [26]. Such precautions include use of an H2-blocker or proton pump inhibitor for ulcer prophylaxis, as well as a bisphosphonate and calcium with vitamin D supplementation for osteoporosis prophylaxis. Other adverse events to consider include steroid-induced glaucoma or elevated intraocular pressure (IOP) and osteonecrosis. While an every other day dosing schedule mitigates the occurrence of several steroid-induced side effects, it only decreases the risk of cataract development without fully eliminating the risk, and does not affect the risk of osteoporosis/osteonecrosis at all [38].

A rapid response is usually noted once systemic glucocorticoids are initiated; however, prolonged therapy is often required to achieve clearance. With a long course comes many side effects and the elderly are particularly susceptible to these adverse effects. As such, the management of elderly patients mandates the lowest effective dose of corticosteroids with early initiation of adjuvant therapy. Examples of adjuvant therapies include immunosuppressive agents such as azathioprine and mycophenolate mofetil, and antibiotics such as dapsone. Such agents allow for a decreased dose of systemic corticosteroid needed to achieve disease control and their expedited tapering [26].

Prior to initiating any systemic immunosuppressive, a complete physical examination and age-appropriate malignancy screening should be performed. Baseline laboratory data may be helpful in selecting a steroid-sparing agent. Monitoring for potential adverse effects include a complete blood count (CBC) with differential, serum chemistry, liver function tests (LFT), fasting lipid profile, urinalysis, tuberculin skin test, hepatitis panel, glucose-6-phosphate dehydrogenase (G6PD) enzyme level (for dapsone), and thiopurine methyltransferase (TPMT) enzyme level (for azathioprine) [26]. Bone densitometry is indicated for those patients on a daily dose of prednisone 5 mg or more for longer than 6 months [38]. Blood pressure, blood glucose, and stool guaiac should also be monitored [39]. Prophylaxis for Pneumocystis carinii pneumonia (PCP) should be considered in patients on long-term oral corticosteroids or other immunosuppressives with the exception of dapsone [40]. However, recent data has shown that routine prophylaxis for PCP may not be necessary, recommending physicians who prescribe immunosuppressants for dermatologic

indications to consider it on a case-by-case basis [41]. Regardless, patients should be monitored closely for signs and symptoms of infection or malignancy in general, and if either occurs, appropriate treatment should be instituted early and aggressively [26].

Tetracycline along with nicotinamide has been used with some success in patients with mild pemphigus vulgaris, using tetracycline 2 g daily along with nicotinamide 1,500 mg daily [39]. This antibiotic regimen has a minimal side effect profile and is ideally suited for elderly patients. Side effects of tetracycline include gastrointestinal upset and phototoxicity; administration should be avoided in patients with renal impairment. The main adverse effects of nicotinamide include flushing and pruritus. Although this regimen is particularly useful in the elderly, it should be avoided in patients with renal impairment and in children less than 9 years old, as tetracyclines are associated with permanent tooth discoloration in the pediatric population [26].

Dapsone, historically used as a therapy for leprosy, is another antibiotic that can be used as adjuvant therapy for PV. Although some studies have shown no statistically significant difference in remission when dapsone was compared to placebo, dapsone has been documented to be extremely useful in controlling mild to moderate PV if introduced early in disease evolution [26]. Dapsone is contraindicated in patients with low G6PD levels. In patients with normal levels, the degree of hemolytic anemia and associated symptoms may be avoided by gradually increasing the dose of dapsone. The drug can be started at 25–50 mg/day and increased every third day by 25 mg until 100 mg is reached. Dapsone 100 mg should be taken for 1 week before increasing to a target maintenance dose of 125–150 mg daily [42]. This gradual titration allows for the bone marrow to adapt to the hemolytic insult.

Other important adverse effects of dapsone include methemoglobinemia, agranulocytosis, and hypersensitivity syndrome. Patients should be counseled to expect a 1–2 g drop in hemoglobin. Most patients can tolerate such a mild anemia, and this often does not necessitate discontinuation of the medication; however, decreases greater than 2 g may require discontinuation [26]. Baseline CBC including reticulocyte count should be obtained prior to initiation then frequently checked thereafter in order to monitor for this potential complication in addition to screen for agranulocytosis, which affects 1 in 400 patients and most often occurs after 8–12 weeks of therapy. Any significant rise in reticulocyte count (i.e., 5% higher than baseline) may warrant discontinuation of the drug [43, 44]. Dapsone hypersensitivity syndrome is an idiosyncratic reaction characterized by fever, generalized eruption, hepatitis, and peripheral eosinophilia, typically occurring 8 weeks after drug initiation. When this occurs, discontinuation of the offending agent is required [26]. Dapsone can also cause a distal motor peripheral neuropathy, which is usually reversible upon discontinuation. Therefore, patients should be monitored for hand and/or leg weakness or muscle atrophy throughout treatment duration [33].

Numerous immunosuppressive agents have been used as adjunctive therapy, particularly when there is severe disease or when disease extends beyond the oral cavity. Such agents include azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, and cyclosporine with monotherapy of the chosen immunosuppressive agent as the eventual goal [26]. The use of azathioprine when combined with corticosteroids may result in gaining early control of disease and increased percentage of clinical remissions [4, 45]. Remission rates of 28–45% and mortality rates of 1.4–7% have been reported when azathioprine and systemic corticosteroids are used [26]. Azathioprine has been used alone; however, its long latency of onset (up to 8 weeks) limits its use as initial monotherapy [45, 46]. The main adverse effects include hepatotoxicity, hypersensitivity syndrome, and neutropenia. Patients with low TPMT levels are at greater risk of neutropenia. Therefore dosing should be individualized based on the patient's TPMT enzyme activity level [39]. Individuals with high TPMT enzyme activity levels require higher doses to achieve clinical effect [47]. Regular laboratory monitoring should include LFTs and CBC with differential. Azathioprine

should not be prescribed in patients who take allopurinol unless unavoidable, since allopurinol interferes with the metabolism of azathioprine increasing plasma levels of 6-mercaptopurine, which may result in potentially fatal blood dyscrasias.

Mycophenolate mofetil is another adjuvant immunosuppressive used to treat PV [26, 48]. Similar to azathioprine, therapeutic effect takes approximately 6–8 weeks; however, mycophenolate mofetil has less hepatotoxicity and myelosuppression, but more gastrointestinal toxicity than azathioprine [49]. Laboratory parameters including CBC with differential and LFTs should be checked regularly. Both azathioprine and mycophenolate mofetil can be used in conjunction with dapsone should the latter provide only partial control.

Cyclophosphamide is another adjunctive immunosuppressive agent used to treat pemphigus vulgaris. Its combination with systemic corticosteroids may result in gaining early control of disease and increased percentage of clinical remissions [4, 50]. Although cyclophosphamide is still typically used in combination with systemic corticosteroids, numerous case series have reported utilizing it as monotherapy with clinical effect in acute disease at doses of 50–200 mg/day [26]. Cyclophosphamide has a higher incidence of adverse effects including hemorrhagic cystitis, infertility, and bladder cancer when compared to azathioprine or mycophenolate mofetil [26]. Regular laboratory monitoring includes CBC with differential and urianalysis. Given its potential risk of toxicity, it should only be used as short-term therapy with transition to an alternative adjuvant once disease activity is controlled [51]. Furthermore, intravenous administration is available in those patients who cannot tolerate oral intake.

Methotrexate should be considered in patients where other adjuvant medications have failed or are contraindicated. The major adverse effect of methotrexate is total cumulative dose-dependent hepatotoxicity. Additional side effects include anemia, leukopenia, pulmonary toxicity, mucositis, and nausea. Doses ranging from 10 to 17.5 mg once weekly are typically used to treat PV. The final adjunctive immunosuppressive cyclosporine is used concomitantly with prednisone in the treatment of pemphigus vulgaris [52]. Known adverse effects include hypertension, nephrotoxicity, hepatitis, and neurologic changes. With such a toxicity profile, cyclosporine should be not considered first-line adjuvant therapy, but may be used to achieve rapid initial control.

Two final medications used to treat pemphigus vulgaris—one more recently debuted, the other more historic—are rituximab and gold. The former has activity against tumor necrosis factor alpha (TNF-α), and recently emerged as a choice for refractory cases to more standard immunosuppressive therapy because of its ability to target plasma cell precursors responsible for antibody production [25, 53]. Most patients respond within 3 months after starting rituximab; however, delayed response after a year of treatment has been reported [54]. Its use is limited by cost, infusion route of delivery, and potential for serious immunosuppression and infection. Other biologics such as etanercept and infliximab have been investigated in treating PV; however, results are variable [25]. Gold has been used to treat mild to moderate cases of PV as monotherapy or with oral glucocorticoids [26]. Two early studies reported complete remission in 15–44% in a total of 44 PV patients; however, it was considered ineffective in 15–28% of patients, while 17–35% discontinued the due to side effects [55, 56]. Gold is rarely used today because of its delayed onset of action, side effect profile, and relative ineffectiveness compared to other treatments available.

Immunomodulatory procedures such as intravenous immunoglobulin (IVIg), plasmapheresis and extracorporeal photopheresis have all been employed in the management of pemphigus vulgaris. High-dose IVIg (2 g/kg per cycle) may be necessary in patients with rapidly progressive, extensive, or treatment resistant PV [26, 57]. IVIg has a very rapid onset of action, and has been used with oral corticosteroids and an immunosuppressant drug in patients with refractory PV; however, consensus on its efficacy remains controversial, as well as duration of treatment [26]. Plasmapheresis plays a limited role in the management of PV, but can be considered in

difficult cases. Plasmapheresis is useful for quickly reducing very high titers of autoantibodies and should be considered in severe presentations if unresponsive to a combination of immunosuppressants and corticosteroids [32, 51]. Extracorporeal photopheresis has been used in patients with PV; however, clinical efficacy is variable [26]. One final medication with cytokine-modulating effects recently reported in treating PV is thalidomide. The report showed it to be a very effective treatment option deserving further evaluation. The recommendation was to consider the use of this drug for patients in whom standard therapy, IVIg, and rituximab have all failed [58]. Table 8.1 outlines therapeutic options in the treatment of most autoimmune blistering diseases.

8.4 Pemphigus Vegetans

Pemphigus vegetans, a rare clinical variant of pemphigus vulgaris affecting 1–2% of patients, is thought to represent a reactive pattern of the skin to the autoimmune insult of PV. Pemphigus vegetans is characterized by the occurrence of hypertrophic, papillomatous, or verrucous vegetating skin lesions predominately involving the intertriginous areas [59, 60]. In general, flaccid blisters become erosions with subsequent formation of fungating vegetative plaques (Fig. 8.4).

Two clinical subtypes of pemphigus vegetans are recognized: the Neumann type and the Hallopeau type. The former is more severe with longstanding and refractory erosions that transform into vegetating lesions, while the latter is a milder presentation characterized by the initial appearance of pustules and rapid evolution to verrucous vegetative plaques with persistent peripheral pustules. Diagnosis may be difficult in patients with chronic vegetations, but the DIF staining is identical to that seen in classic PV [61]. As in PV, systemic corticosteroids are the principal treatment for pemphigus vegetans. Patients with the Neumann subtype have a similar disease course to PV, mandating higher steroid doses with multiple remissions and relapses, while patients with the Hallopeau subtype have a benign disease course, only needing low doses of steroids with longer remissions [59]. As such, morbidity and mortality is similar to PV for the Neumann subtype.

8.5 Pemphigus Foliaceus

Like pemphigus vulgaris, pemphigus foliaceus (PF) is one of the originally characterized classic forms of pemphigus. PF is generally a more benign variant; however, localized lesions tend to persist for months to years carrying a significant amount of morbidity for some patients. Although PF is not often associated with considerable mortality, the disease can progress to erythroderma (see Chap. 7) representing a true dermatological emergency. These patients require prompt hospitalization to prevent serious and sometimes fatal complications from high output cardiac failure and metabolic instability [62].

Sporadic PF is a rare disease accounting for 20–30% of pemphigus cases. Its incidence in the USA and Europe is estimated at less than 1 case per million inhabitants per year [61]. The prevalence of PF is approximately equal between men and women affecting all races and ethnicities with an average age of onset between 40 and 60 years old [62]. The epidemiologic statistics exhibit considerable variation when examining the endemic forms of PF as discussed later. The exact cause of sporadic PF remains unknown; however, extensive UV exposure, burns, and various drugs have all been implicated in its development. Penicillamine and captopril are the two medications in particular that are associated with PF, and in patients receiving penicillamine, PF is seen more commonly than PV with a ratio of approximately 4:1 [20]. Similar to PV, one dietary factor has also been reported in giving rise to PF seen in a patient taking herbal supplements with phycocyanin [63]. An overlap syndrome exists that exhibits characteristics of both PF and systemic lupus erythematosus called Senear-Usher Syndrome or pemphigus erythematosus. The name was used to describe patients with overlapping immunologic features of both diseases (IgG and C3 deposition and circulating antinuclear antibodies); however, only a few patients have

Table 8.1 Therapies used in bullous dermatoses

Therapy	Use	Standard dose	Notes
Topical corticosteroids (e.g., fluocinonide, clobetasol)	PV, PF, BP, PG, MMP	0.05% gel or ointment	-Useful in mild, localized cases including disease in the oral cavity
Nicotinamide with tetracycline	PV, BP, MMP	1.5–2 g/day for both	Useful in mild cases Higher doses of nicotinamide required in MMP (3 g/day) Not for pediatric use
Dapsone	PV, PF, BP, MMP, LABD	125–150 mg/day	Useful in mild cases Start 25–50 mg/day and titrate slowly 100 mg/day is mean dose for disease control in LABD but may need higher dose of 300 mg/day Watch for G6PD deficiency, hemolysis, and methemoglobinemia
Systemic corticosteroids (e.g., prednisone)	PV, PF, BP, PNP, PG, MMP, LABD	0.75–1 mg/kg/day	Usually initial therapy Maintenance use in moderate to severe cases Lower dose in PG and LABD at 0.5 mg/kg/day
Azathioprine	PV, PF, BP, MMP	2–4 mg/kg/day	Useful in severe cases Steroid-sparing adjuvant First-line adjuvant in MMP Check TPMT levels Care with concomitant use of Allopurinol
Cyclophosphamide	PV, PF, BP, MMP	1–3 mg/kg/day	Useful in severe cases Steroid-sparing adjuvant; Consider use in very aggressive cases as efficacy achieved faster compared to other adjuvants Risk of infertility and GU malignancy
Mycophenolate mofetil	PV, PF, BP, MMP	2–3 g/day in two divided doses	Useful in severe cases Steroid-sparing adjuvant Less hepatotoxic
Methotrexate	PV, BP, MMP	7.5–20 mg/week	Not commonly used but helpful in some patients Steroid-sparing adjuvant
Cyclosporine	PV, MMP	5 mg/kg/day	Useful in severe cases Steroid-sparing adjuvant Topical formulation used in ocular MMP

(continued)

Table 8.1 (continued)

Therapy	Use	Standard dose	Notes
IVIG	PV, BP, MMP	400 mg/kg/day for five consecutive days	Used in refractory cases May need to repeat dose Especially helpful in progressive ocular MMP Controversial efficacy in PV
Plasmapheresis	PV, BP, MMP	1–2 times per week	Short bridging therapy to decrease autoantibody levels in extremely difficult cases
Extracorporeal photopheresis	PV	2 days per month	Useful in refractory or treatment resistant cases Variable outcomes
Rituximab	PV, PNP, BP, MMP	375 mg/m^2 IV once weekly for 4 weeks 1,000 mg IV at day 0 and day 14	Useful in patients resistant or intolerant to standard therapies (e.g., systemic steroids and adjuvants) After induction, long-term therapy with infusions every 4–12 weeks may be continued
Etanercept	MMP	25 mg SQ twice weekly	Reported success in case reports and small case series
Infliximab	MMP	5 mg/kg	Reported success in case reports and small case series Infusions are given at 0, 2, and 6 weeks and then every 8 weeks thereafter
Gold	PV	50 mg IM once weekly	Used in mild to moderate cases of PV either alone or with glucocorticoids
Thalidomide	MMP	100 mg/day	Reported success in a single case of refractory MMP
Subconjunctival mitomycin C	MMP	0.02 mg per injection	Last resort in rapidly progressive ocular MMP unresponsive to oral agents No more than 1–3 injections

IVIG = intravenous immunoglobulin; PV = pemphigus vulgaris; PF = pemphigus foliaceus; BP = bullous pemphigoid; PNP = paraneoplastic pemphigus; PG = pemphigoid gestationis; MMP = mucous membrane pemphigoid; LABD = linear IgA bullous dermatosis; g = gram; mg = milligram; kg = kilogram; SQ = subcutaneous; IM = intramuscular; G6PD = glucose-6-phosphate dehydrogenase; TPMT = thiopurine methyltransferase

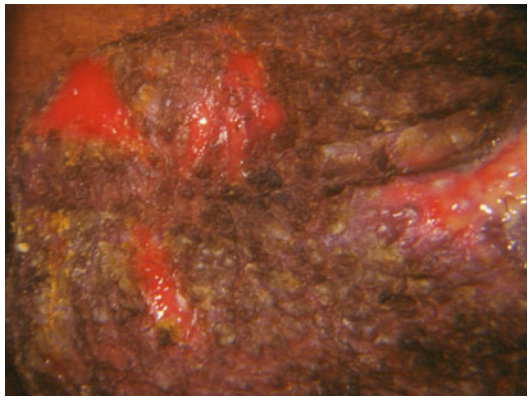

Fig. 8.4 Pemphigus Vegetans. Verrucous and eroded plaques in the axilla

been reported to actually have the two diseases concurrently [64].

In pemphigus foliaceus, blister formation is associated with IgG antibodies against desmoglein 1 only, which is essential to keratinocyte cohesion only in the most superficial layer of the epidermis [25]. DIF is similar to that in PV, but a stronger staining has been described in the upper epidermal portion. IIF shows mainly IgG4 antibodies best detected using guinea pig esophagus [25]. Anti-desmoglein 1 antibodies are frequently detected with ELISA assays on serum of PF patients in more than 90% of cases. Desmoglein 1 values parallel the course of the disease [61]. Antibodies directed against desmoglein 3 are not detected as it has been clearly demonstrated that autoantibody reactivity is restricted to desmoglein 1 in PF [61, 65].

Clinically, the primary lesions seen in pemphigus foliaceus are flaccid superficial vesicles and bullae confined to the skin. Such lesions may not necessarily be seen at time of presentation since they are both transient and fragile. Therefore, secondary lesions are more often seen including shallow erosions with extensive crusting [62]. Lesions are typically well demarcated and have a seborrheic distribution favoring the face, scalp, upper trunk, and back (Fig. 8.5) [25].

Therapy for pemphigus foliaceus is usually less aggressive than that of PV because of lower morbidity and mortality rates [66]. In general, the treatment is similar to PV when patients with PF

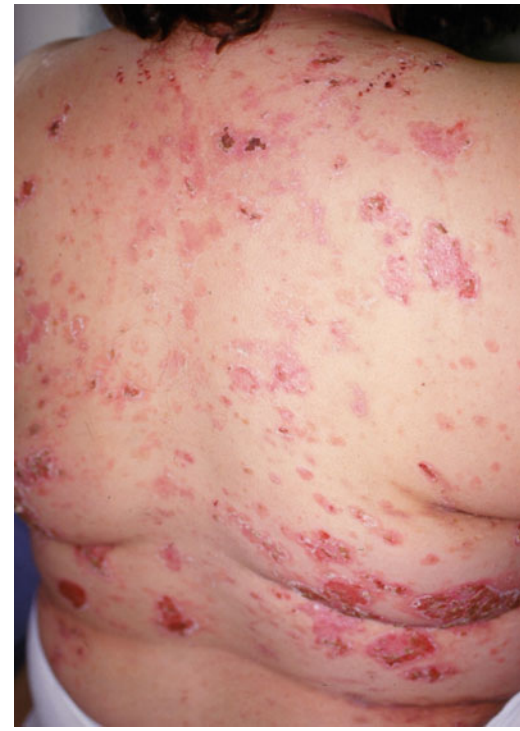

Fig. 8.5 Pemphigus Foliaceus. Eroded and crusted plaques. Vesicles are transient and are rarely seen due to superficial nature of blisters

present with active and widespread disease. Such extensive cases may require adjuvant immunosuppresants such as systemic corticosteroids, azathioprine, cyclophosphamide, or mycophenolate mofetil [67, 68]. In some patients with PF, disease activity may remain localized for many years and topical high potency corticosteroids may provide sufficient control [69]. Dapsone might be considered when neutrophils are dominant histologically [70].

8.6 Fogo Selvagem

Fogo selvagem (FS) is an endemic subtype of pemphigus foliaceus. Endemic PF differs from the sporadic form of the disease in its geographic distribution, high familial incidence, and younger age of onset [71]. Patients are clinically, histologically, and immunopathologically similar to patients with sporadic PF; however, a higher incidence of more severe, generalized exfoliative

dermatitis is related to a higher morbidity and mortality seen in FS [62].

Fogo selvagem occurs with a high frequency in Central and Southwestern Brazil where as many as 50 cases per million per year are seen. Some endemic regions of Brazil exhibit a prevalence equal to 3% of the population, where the ratio of FS to PV is 17:1 [72]. FS affects a larger number of children and young adults without sex predilection as symptoms usually begin during the second or third decade of life [62]. Another focus of endemic PF exists in the northern part of Columbia. The prevalence of Columbian PF is close to 5% and greater than 95% of those affected are men [61]. A third focus of endemic PF has also been described in Tunisia. There, the overall incidence is 6–7 cases per million per year; however, the incidence dramatically increases up to 20 cases per million per year in some areas in south Tunisia, particularly affecting young adult women from 25 to 34 years old as evidenced by a female to male ratio of 4:1 [61, 62].

The exact cause of fogo selvagem is unknown. FS frequently occurs in genetically related family members, and more than 50% of normal individuals in certain areas of Brazil have antidesmoglein 1 IgG autoantibodies [73]. In addition to genetic propensity, FS is thought to be triggered by the bite of an insect, where antibodies produced against this unidentified antigen may cross-react with desmoglein 1 in genetically susceptible individuals, leading to the development of FS [62]. More recent research has focused on the study of a protein transmitted from the saliva of Simulium nigrimanum, a type of black fly [74]. Dietary factors have also been implicated as increased amounts of tannins dissolved in the water systems directly serving Amazonian natives could explain the occurrence of FS in Amazonian Brazil [75].

The target antigen in fogo selvagem is desmoglein 1 with similar DIF and IIF staining patterns as seen in PF. Clinically, patients with FS exhibit the same characteristics as patients with PF. Some patients with chronic disease may develop verrucous plaques on the trunk and extremities, which have also been described in patients with Columbian endemic pemphigus. Hyperkeratosis on the soles and palms is also frequently observed [61]. Therapeutics are similar to those used in PF.

8.7 Paraneoplastic Pemphigus

Of the entire pemphigus family, paraneoplastic pemphigus (PNP) is the most severe [76]. PNP carries significant morbidity and mortality, partially due to development in the setting of malignancy and also the associated often extensive mucosal involvement. When PNP is associated with malignancy, mortality is estimated at 93% usually from sepsis, bronchiolitis obliterans, or progression of the underlying malignancy [25].

Epidemiological data on the prevalence and incidence of PNP is scarce. One review reported approximately 150 cases in the literature 10 years ago. The age range for PNP is from 7 to 83 years, although the majority of patients are between the ages of 45 and 70 years [77]. The mean age at onset is 60 years without predilection of sex or race. PNP occurs in the setting of malignancy including, in decreasing order of frequency, non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman disease, thymoma, Waldenstrom macroglobulinemia, and spindle-cell sarcomas [25].

PNP patients display autoantibodies to desmoglein 1 and 3, as well as desmosomal proteins of the plakin family including desmoplakin I and II, envoplakin, periplakin, plectin, BP antigen 230, and a 170-kDa protein that has not been further identified [25, 78]. DIF reveals IgG, C3, or both in an intercellular pattern like PV, but in addition, linear/granular IgG or C3 may be present at the basement membrane zone. Results of IIF are similar to PV but autoantibodies may also demonstrate binding to simple or transitional epithelium substrates like rodent bladder, which is considered unique and diagnostic of PNP [25].

Severe involvement of multiple mucous membranes is the major clinical feature and hallmark of this disease. The most constant clinical feature is severe and intractable stomatitis consisting of erosions and ulcerations that affects all surfaces of the oropharynx, characteristically extending to the vermilion lip (Fig. 8.6) [25, 77]. Mucosal

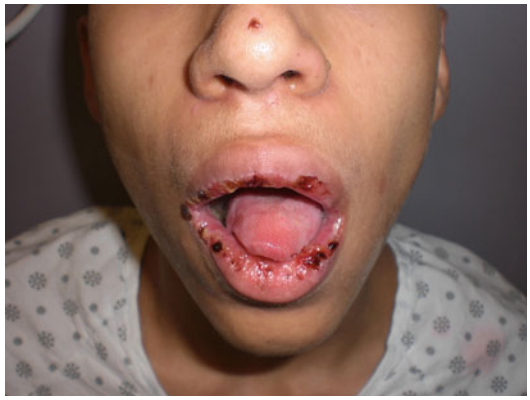

Fig. 8.6 Paraneoplastic pemphigus presented as intractable mucosal ulcerations

involvement may also include the conjunctiva, genitalia, or tracheobronchial tree [25]. Such extensive mucosal involvement is a considerable source of morbidity in PNP patients as the conjunctival fornices may become scarred and obliterated leading to synblepharon, while esophageal ulceration may lead to hypoalimentation and malnourishment. The cutaneous findings are by definition polymorphous and may present as erythematous macules, flaccid blisters and erosions resembling PV, tense blisters resembling bullous pemphigoid, erythema multiforme, or lichenoid dermatitis [25].

Treatment is aimed at the underlying malignancy, but the course of PNP does not correlate with the course of the underlying neoplasm [25]. Patients with benign tumors such as a thymoma or localized Castleman's disease should have them surgically excised, as the majority of these patients will significantly improve [79]. There is no consensus on a standard effective therapeutic regimen for patients with malignant tumors. Cutaneous lesions respond more rapidly to therapy in contrast to the stomatitis, which is generally refractory to most treatment measures. Aggressive combinations of immunosuppressants including systemic corticosteroids, rituximab, and others have been used but are frequently unsuccessful [25]. Yet another source of morbidity in these patients with PNP is the susceptibility to infection caused by the loss of skin integrity, exacerbated by the potent immunosuppressants used to treat the condition.

8.8 Epidermolysis Bullosa Simplex

Epidermolysis bullosa simplex is one of three major forms of inherited epidermolysis bullosa (EB), which is the prototypic mechanobullous disease, characterized by the development of blisters after trivial trauma to the skin. Most epidemiologic data is derived from the work of the National EB Registry stating that 50 EB cases occur per million live births and approximately 92% are classified as EB simplex [80]. EB simplex is mostly transmitted in an autosomal dominant fashion and appears to be the result of mutations within the gene for either keratin 5 (K5) or keratin 14 (K14), which are present primarily within the basal layer of the epidermis [81]. Transmission electron microscopy (TEM) distinguishes among the three major EB types by the identification of the ultrastructural level of cutaneous blister formation. TEM can also be used to quantitatively and qualitatively assess specific structures such as basilar tonofilaments, hemidesmosomes, subbasal dense plates, anchoring filaments, and anchoring fibrils [80].

EB simplex is characterized by mechanically fragile skin, tense fluid-filled blisters, erosions, and crusts with subsequent atrophic scarring (Fig. 8.7). These features are seen beginning at birth or soon after. The more severe subtype of EB simplex known as EB simplex herpetiformis, or Dowling-Meara, is characterized by grouped blisters often in an arcuate or polycyclic array, and also associated with the most significant mucosal membrane involvement and increased mortality. Morbidity and mortality of EB simplex relates to the consequences of repeated damage, ulceration, and poor healing of the skin. Malnutrition and growth stunting is consistently seen in patients with EB simplex [16]. This may be due to oral blistering and ulcerations, digestion and absorption problems, or loss of blood and protein through open skin blisters [82–84]. Although more common over a decade ago, bacterial sepsis and subsequent death is now relatively rare; however, it can still occur in the EB simplex Dowling-Meara subtype, and hypermetabolism resulting in increased heat loss and

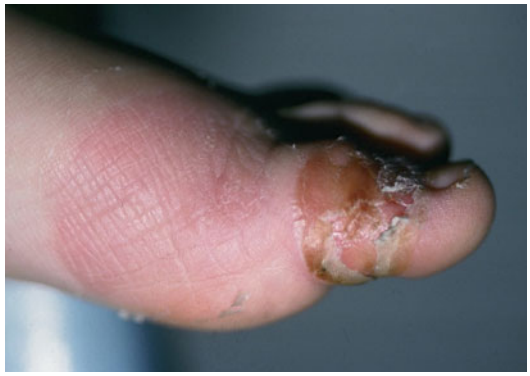

Fig. 8.7 Mechanicobulla seen in Epidermolysis Bullosa Simplex

protein turnover is especially common in the setting of skin infections [85].

There are no FDA approved therapies for any form of inherited EB, but two clinical trials involving molecular therapy are currently underway and specific treatment may become a reality for at least some types or subtypes of EB in the near future. One clinical trial is investigating bone marrow transplantation and immunosuppression to deliver corrective skin cells in the patient, while the other clinical trial is examining retroviral-mediated type VII collagen gene transfer. For now, daily management revolves around the prevention of both mechanical trauma through the use of padded bandages and loose-fitting garments, in addition to the prevention of infection via mild, broad-spectrum topical antibiotic ointments or creams. Experience in a few patients suggests that systemic tetracycline might be of clinical benefit in EB simplex [86]. Most of the extracutaneous complications of EB can be surgically or medically managed. In patients with significant malnutrition, aggressive nutritional supplementation facilitated by placement of a gastrostomy tube can be performed when necessary [87]. Genetic counseling should be considered as genetic information from mutation analyses on epidermolysis bullosa candidate genes provides an immediate benefit to families of patients with the disease. Prenatal diagnosis of epidermolysis bullosa in affected families is a genetic-based protocol, providing that the patient identified as the original proband has had identification of the defective gene, and chorionic villus sampling as early as 8–10 weeks or amniocentesis in the second trimester are both used to aid in diagnosis.

8.9 Subepidermal Blistering Diseases

Subepidermal blistering diseases often requiring emergent attention include bullous pemphigoid, gestational pemphigoid, cicatricial pemphigoid, linear IgA bullous dermatosis, and epidermolysis bullosa acquisita in addition to two heritable disorders known as junctional epidermolysis bullosa and epidermolysis bullosa dystrophica. All the acquired disorders are characterized by circulating and tissue-bound autoantibodies against various components of the dermo-epidermal anchoring complex (hemidesmosome), whereas the inherited disorders result from various defects in these hemidesmosomal proteins [88].

8.10 Bullous Pemphigoid

Bullous pemphigoid (BP) is the most commonly encountered autoimmune, subepidermal blistering disease of the skin, most commonly affecting the elderly. Elderly individuals are more likely to have comorbid conditions, and the presence of such conditions complicates the selection of and effect of therapy and may also dramatically influence both prognosis and outcome [89, 90]. Elderly patients also frequently have suboptimal nutritional states that can adversely affect prognosis and further complicate care [91]. The morbidity and mortality in BP is also influenced by its chronicity with periodic remissions and exacerbations with a profound impact on quality of life. Among studies of patients with BP published in the past two decades, 1-year mortality rates ranged from 15 to 41% [92].

Previously published case series have documented an age of onset range from 68 to 82 years [25]. The annual incidence of BP is estimated to be at least 6–7 new cases per million per year with a rapid increase after the age of 60 years, and expected to rise given the advancing age of the

population. The relative risk for patients over 90 years of age appears to be about 300-fold higher than for those 60 years of age or younger with an apparent predominance in men. Certain HLA class II alleles are more prevalent in patients with BP than in the general population including DQB1 in Caucasians and DRB1 in Japanese [93].

Most cases of BP occur sporadically without any obvious precipitating factors; however, several reports have implicated various triggers such as UV light, radiation therapy, percutaneous endoscopic gastrostomy, thermal burn, amputation stump, and adhesive dressings [94–97]. BP has also been reported to develop in associated with other autoimmune diseases like diabetes mellitus and pernicious anemia, chronic inflammatory skin diseases such as lichen planus and psoriasis, and various malignancies [98]. Despite the various case reports of BP associated with renal cell carcinoma, gallbladder malignancy, and colon and breast cancers, large population studies have reported conflicting evidence. Therefore, the relationship between BP and malignancy is still a matter of debate. Medications associated with bullous pemphigoid include furosemide, ibuprofen and other NSAIDs, captopril, penicillamine, and antibiotics [98].

The target antigens in BP are components of the hemidesmosome in cutaneous basal cells. Most BP patients have bound and circulating IgG antibodies directed towards the extracellular noncollagenous domain of collagen type 17, a transmembrane protein in basal cells also known as BP180 (BPAg2). Patients with BP also exhibit autoreactivity to a cytoplasmic plakin family protein known as BP230 (BPAg1), which is also a structural part of the hemidesmosome [25]. DIF studies are generally considered more sensitive than IIF because circulating antibodies may not be detectable in a small but significant portion of patients; however, if the DIF does not display the characteristic pattern (i.e., deposition of IgG and/or C3 at the basement membrane zone), serum for IIF on salt-split skin and/or BP180 ELISA may be necessary to differentiate BP from the inflammatory variant of epidermolysis bullosa acquisita, bullous systemic lupus erythematosus, and mucus membrane pemphigoid (MMP) [99].

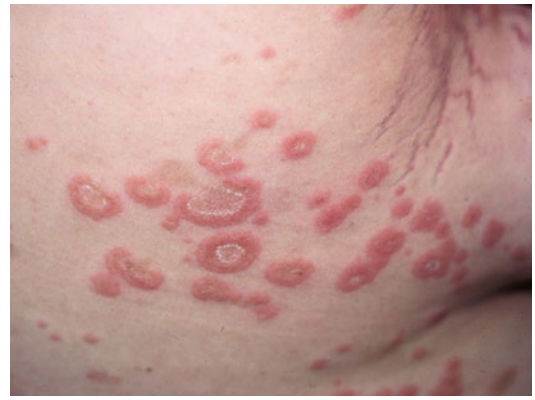

Fig. 8.8 Urticarial papules and plaques on the lower abdomen in early Bullous Pemphigoid. Overlying scale suggests early blister formation

The clinical presentation of BP is highly variable. Patients may seek medical attention during the initial nonbullous phase, which is often a simple complaint of pruritus or urticarial patches, plaques and erythema with no evidence of bullae (Fig. 8.8). When blisters eventually develop, they are classically 1–4 cm in size, tense, bilateral, and symmetric with predilection for the flexural proximal extremities and trunk (Fig. 8.9). Pruritus is common and mucosal involvement can occur in a minority of patients and often limited to the oral cavity [25]. Several variants of BP exist, and many carry unique morbidity and mortality characteristics. For example, dyshidrosiform pemphigoid—a localized variant of BP often presenting with recurrent, painful vesicles, and bullae of the palms and/or soles—can lead to significant functional impairment, whereas erythrodermic pemphigoid tends to induce a high output cardiac failure placing patients at risk for sepsis and subsequent death. Interestingly, the overall trend in mortality over a 24-year period was found to increase in pemphigoid but decrease in pemphigus, while mortality in the black population was significantly higher for every bullous disorder [30].

Systemic corticosteroids are the most effective therapy for BP, and prednisone given at doses ranging from 0.5 to 0.75 mg/kg/day is generally sufficient for disease control [100]. More recent reports have been published in regards to the efficacy of topical corticosteroids in the treatment

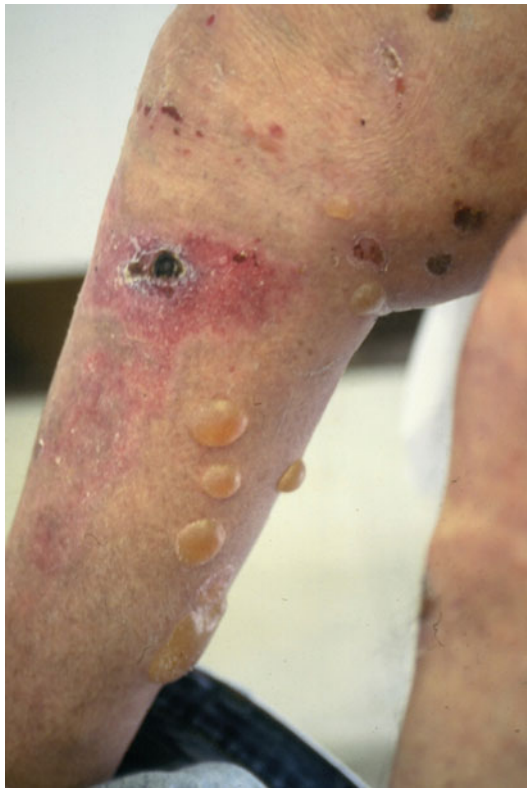

Fig. 8.9 Tense blisters on the lower extremities in Bullous Pemphigoid

of BP; however, it is still unclear whether topical steroids are unequivocally better than systemic regimens [25]. Additional therapies for BP with documented efficacy include azathioprine, methotrexate, and tetracycline with nicotinamide [101]. In treatment resistant cases, IVIg, plasma exchange, or rituximab are all potential options, discussed more extensively in the pemphigus vulgaris section.

8.11 Pemphigoid Gestationis

Pemphigoid gestationis is one of the dermatoses of pregnancy that places both mother and fetus at risk, and emergent diagnosis and treatment is paramount in order to prevent any significant morbidity to either. It is intensely pruritic and generally develops in the third trimester or the immediate postpartum period [102]. Case reports have documented an association with pemphigoid gestationis and subsequent development of choriocarcinoma [103, 104]. The mother is also at increased risk for enduring the same eruption with subsequent pregnancies. Fetal morbidity and mortality includes low birth weight for gestational age and prematurity. In addition to the possibility of fetal adrenal insufficiency and transient neonatal pemphigoid exist from transplacental antibody transfer exist, although much less common [102].

The incidence of pemphigoid gestationis is estimated to be 1 in 50,000 pregnancies in North America [105]. Only 14% of cases develop in the postpartum period [106]. An increased risk for the development of this disease has been delineated in patients with HLA-DR3 and HLA-DR4 alleles. Those patients with this same haplotype also have a higher relative prevalence of other autoimmune diseases including Hashimoto thyroiditis, Graves disease, and pernicious anemia [102]. Pemphigoid gestationis appears to be caused by an anti-basement membrane zone (BMZ) serum factor that induces C3 deposition along the dermal–epidermal junction. The majority of patients also have antibodies to BP180 (as seen in BP patients) of the IgG1 subclass. The gold standard in diagnosing pemphigoid gestationis is DIF on perilesional skin, which shows a bright linear deposition of C3 along the BMZ in 100% of cases, an immunopathologic hallmark [102]. IIF shows circulating IgG antibodies in 30–100% of cases, and in salt-split skin, staining remains with the epidermal fragment as seen in patients with BP [107].

The initial clinical findings of pemphigoid gestationis are characterized by the presence of severe pruritus and erythematous urticarial papules, which coalesce into plaques. The typical localization of the lesions is on the abdomen and exclusively within or proximate to the umbilicus. In atypical cases, the lesions tend to cluster over the limbs, palms, or soles [102]. Lesions spare abdominal striae unlike the lesions in pruritic urticarial papules and plaques of pregnancy (PUPPP) that have a predilection of involving abdominal striae. As lesions progress over the course of days to weeks, tense blisters develop, and a generalized pemphigoid pattern of eruption becomes evident.

The bullae are similar to those found in BP—tense with serous fluid and often leaving widespread erosions. The entire skin surface can be involved, but the face, palms, soles, and mucous membranes are usually spared [108]. Systemic corticosteroids are the cornerstone of therapy and most patients respond to prednisone 0.5 mg/kg/day. Maintenance therapy is generally held at a lower dose and may not even be required throughout gestation depending on response. Interestingly, many patients will experience spontaneous disease regression during the third trimester, only to experience a flare during childbirth [102].

Many pregnant women become concerned with the risks of systemic steroids on fetal well-being, and these apprehensions should be appropriately addressed. There is an increased inclination to develop fetal risks such as small for gestational age and prematurity suggesting a low-grade placental insufficiency; however, it has recently been shown that these risks seem to be more associated with antibodies binding to the placenta rather than the effect of systemic steroids. The other potential risk to consider is adrenal insufficiency, especially in those women treated with systemic steroids over longer periods of time; however, the maternal–fetal gradient of prednisone is only 10:1 and fetal adrenal suppression is only a rare consequence [102].

8.12 Mucous Membrane (Cicatricial) Pemphigoid

Mucous membrane pemphigoid (MMP) is a chronic inflammatory subepidermal blistering disease. MMP is characterized by the presence of antibodies targeting subepidermal BMZ structural components of mucosal surfaces. The morbidity and mortality for this disease are significant, and serious sequelae can develop including scarring and fibrosis of the involved mucous membranes [25]. The disease course is often slow and progressive interrupted with periods of explosive inflammatory activity.

MMP is rare but most often affects elderly individuals with a 2:1 female preponderance aged 60–80 years, and an average age ranging from 62 to 66 years [25, 109]. However, MMP has also been reported in children [26]. The incidence of MMP is estimated to be between 1 in 12,000 and 1 in 20,000 in the general population. Although no geographic or racial predilection has been described, several studies have demonstrated an increased risk in patients with an HLA-DQw7 haplotype [109]. No specific diseases or predisposing factors have been noted in association with MMP, with the exception of colon cancer in patients with antilaminin 5 (epiligrin) MMP [101].

Laboratory evidence suggests that the autoantibodies in MMP can target multiple different structural components of the extracellular portions of the hemidesmosomal adhesion complex in the skin and mucosal surfaces [25]. The various target antigens can include BP180, BP230, laminin 5, laminin 6, and integrin alpha-6/beta-4 subunit [25, 26]. Patients with antibodies against the integrin subunits predominantly exhibit ocular disease. Patients with antibodies against laminin 5 have no specific phenotype, and whereas those with BP180 autoantibodies can exhibit cutaneous involvement [25].

Similar to BP, immunofluorescence studies are the gold standard for diagnosis. Biopsy for DIF is best obtained from perilesional uninvolved mucosa such as the lower labial mucosa which is easily accessible [25]. In general, MMP is characterized by the linear deposition of IgG, IgA, and/or C3 along the epidermal BMZ in mucosal and/or cutaneous biopsy specimens [26]. IIF is positive in approximately 20–30% of cases in contrast to the much higher detection rate seen in BP [25]. Given the lower detection rate with IIF on human split skin, western blotting, immunoprecipitation, and ELISA using various cell-derived and recombinant proteins are pivotal diagnostic tools for MMP. Despite a low detection rate, laminin 5 detected on the dermal side of salt split skin differentiates it from all other pemphigoids [65].

The diagnosis of MMP should be entertained in patients with erosive or blistering mucosal lesions, especially if evidence of scarring is present. Erythema multiforme, erosive lichen planus, and PV should be considered and can be differentiated by histology and immunofluorescence studies. BP, epidermolysis bullosa acquisita, and linear IgA

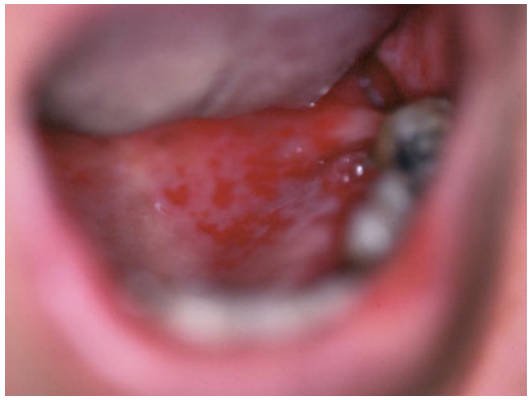

Fig. 8.10 Erosive blisters on the floor of the mouth in a Cicatrical Pemphigoid (MMP)

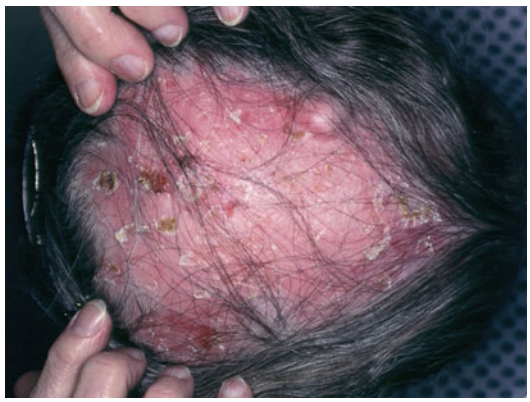

Fig. 8.11 Scarring blistering dermatosis on the scalp in Cicatrical Pemphigoid

bullous dermatosis should also be included in the differential diagnosis [25].

The most common sites of MMP involvement are the oral mucosa and conjunctival mucosa, but the nasopharynx, esophagus, larynx, and anogenital mucosa can also be affected (Fig. 8.10) [25, 26]. Approximately 25% of patients will display cutaneous involvement, typically scalp (Fig. 8.11), but mucosal disease predominates in true cases of MMP. Any part of the mouth can be affected including the attached gingiva, hard palate, and buccal mucosa. A common clinical presentation is that of a painful, erosive gingivitis, and intact blisters are usually not apparent. Symptoms and clinical findings in early ocular MMP are often nonspecific, and patients may complain of burning, pain, or foreign body sensation [25].

MMP carries significant morbidity and mortality often resulting from severe consequences arising from untreated disease. Chronic and progressive ocular inflammation can lead to scar formation, ultimately resulting in blindness. Laryngeal webs may develop causing sore throat, hoarseness, and possible loss of speech. Supraglottic stenosis secondary to erosions, scar formation, and edema may necessitate a tracheostomy as the airway becomes progressively compromised. Esophageal strictures can result in dysphagia, odynophagia, hypoalimentation, malnourishment, and subsequent weight loss [25, 26]. And finally, involvement of the anogenital mucosa may lead to urinary stricture and sexual dysfunction [110].

Several treatment modalities exist, and most patients with extensive disease will require long-term therapy. Excellent oral and ocular care should be emphasized in patients diagnosed with MMP. Therefore, patient care should coordinate the services of both an ophthalmologist and dentist (see Sect. 8.3 for more information on oral care). In regards to ocular care, frequent lubrication with artificial tears to prevent dryness is recommended, and topical cyclosporine can be considered for extreme dryness although burning may limit compliance. Placement of lacrimal punctal plugs is recommended if patients do not already have occluded puncta secondary to scarring. It is also important to clean debris and exudate that accumulates in order to prevent secondary infection. Cleaning can also be achieved with artificial tears, but buffered preserved saline solutions are also available for patients that need an extra cleanse [26].

For MMP localized to the oral cavity with or without cutaneous involvement, the first-line therapy has been topical corticosteroids such as dexamethasone swish [25]. Other vehicles have been used such as corticosteroid gels, which are more easily applied and better tolerated within the oral cavity. There are few recognized adverse effects associated with steroid use in the oral cavity including oral candidiasis and herpes simplex virus reactivation [26]. Topical corticosteroids should not be used alone and are not effective in controlling disease progression in

ocular MMP [111]. Although corticosteroid injections have been used for ocular MMP, it only achieves short-term results and carries a risk of cataract formation. Subconjunctival injections should only be performed by an ophthalmologist, but are rarely used in clinical practice [26].

Dapsone can be used as first-line therapy in localized MMP or slowly progressing, extensive disease as it can take 10–12 weeks before producing benefit [42]. Systemic corticosteroids are the first-line therapy for treatment of extensive MMP, rapidly progressive MMP, or in patients with ocular, laryngeal, esophageal, severe anogenital, or severe gingival involvement causing loosening of teeth [33]. However, systemic corticosteroids alone are frequently inadequate for disease control and adjuvant immunosuppressants are often required [25]. Azathioprine is the first choice of adjuvant therapy in MMP, provided the disease is not rapidly progressive and threatening vision [33]. Mycophenolate mofetil has also demonstrated efficacy as an adjuvant therapy; however, cyclophosphamide is used in aggressive MMP, as it achieves efficacy sooner than either azathioprine or mycophenolate mofetil [110].

Other treatment modalities include the use of IVIg, which has a very rapid onset of action and found to be especially helpful in patients with progressive ocular MMP suffering from active deterioration of vision [112, 113]. There has been reported success using etanercept and infliximab in the management of MMP [114–116]. Rituximab has been reported to be successful in three cases of recalcitrant MMP [117–119]. A single case of thalidomide use in refractory MMP has been reported, which may be considered in patients that are not responding to conventional therapies [120]. Subconjunctival mitomycin C injections have been used by ophthalmologists in the treatment of ocular MMP and reserved as an option of last resort [121]. Despite the numerous treatment options available, decisions must be heavily weighed against the potential adverse effects of therapy, and particularly in elderly patients with multiple comorbidities [25].

8.13 Linear Iga Bullous Dermatosis

Linear IgA bullous dermatosis (LABD) is an autoimmune subepidermal blistering disease with a heterogenous clinical presentation often idiopathic or drug induced affecting both adults and children. The morbidity and mortality of this disease largely rests on whether mucous membranes as these lesions will tend to heal with scarring. Desquamative gingivitis may secondarily damage teeth, while ocular involvement can potentially lead to blindness as seen in MMP [122]. Adults often deal with higher morbidity rates as the disease course is prolonged as compared to children.

The true incidence of LABD is unknown, but the incidence in southern England has been estimated to be 1 in 250,000 per year [122]. Incidence in the USA has not been reported. LABD can occur at any age, but there are two peaks of onset: an average age of onset at 60 years in adults, and an average age of 4.5 years in children [123–125]. Many drugs have been reported in association with LABD, but nearly half the cases are due to vancomycin [25]. Other important inducers of LABD include captopril, penicillins, cephalosporins, and nonsteroidal anti-inflammatory agents [126]. Another factor affecting the morbidity and mortality of LABD includes the documented association with malignancy seen in B-cell lymphoma, chronic lymphocytic leukemia, and carcinoma of the bladder, thyroid and esophagus [122, 127].

Linear IgA disease antigen-1 (LAD-1), the 120-kDa cell-derived soluble ectodomain of BP180 is the major target antigen of IgA autoantibodies in patients with linear IgA disease. BP230 is an additional target antigen in the disease [65]. The diagnosis of LABD is based on histology, which invariably shows a subepidermal blister with a superficial dermal infiltrate of neutrophils. DIF is confirmatory with homogenous, linear IgA deposits at the BMZ. Rarely, weak deposits of IgG and C3 at the BMZ may also be present [25]. IIF can be either negative or detect low levels of IgA BMZ autoantibodies that would react with the epidermal, dermal, or both

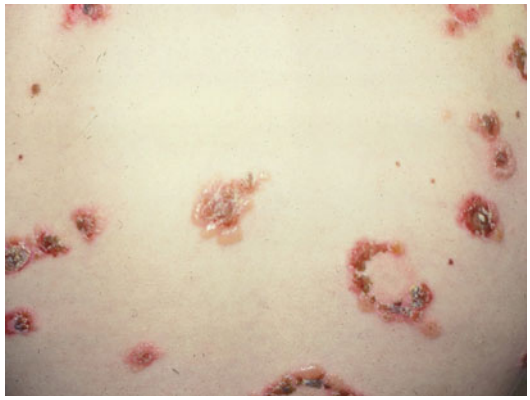

Fig. 8.12 Annular arrangement of bullae ("cluster of jewels" sign) on the trunk in Linear IgA Bullous Dermatosis

sides of the blister when tested on salt-split skin substrate [128].

As previously mentioned, LABD can vary in its clinical presentation; however, patients classically present with symmetric, grouped, annular vesicles, and bullae on the trunk and extensors that are usually pruritic and often excoriated. Annular arrangement at the periphery showing a tendency to heal in the center is a characteristic feature of LABD known as the "cluster of jewels" sign (Fig. 8.12) [25]. Atypical presentations of LABD have been described including forms that resemble erythema multiforme, toxic epidermal necrolysis, and a morbilliform eruption [129]. Mucosal involvement can occur, but is less commonly seen in drug-induced LABD, which appears within 7–14 days of starting the offending agent [25].

The majority of LABD cases will respond to either oral dapsone or sulfapyridine therapy, and most patients have a clinical response within 48–72 h. The average dose of dapsone needed for disease control is 100 mg daily, however, doses as high as 300 mg may be required [130]. On occasion, the addition of oral prednisone in doses up to 40 mg daily for complete control of the disease may be required [128]. The treatment for drug-induced LABD involves discontinuation of the suspected causative agent, and improvement is usually evident within 3 weeks [25].

8.14 Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is an extremely rare, acquired subepidermal blistering disorder, associated with significant morbidity resulting from involvement of various skin and mucosal surfaces including similar irreversible complications as seen in MMP such as blindness and esophageal strictures. Tracheal involvement and upper airway obstruction requiring tracheostomy has been described. Indeed, more aggressive cases of EBA are often difficult to control and associated with a significant mortality rate. EBA is a chronic disease that is difficult to treat and for which there is no cure [131].

The exact incidence and prevalence of EBA is unknown, but it seems rare overall. Few available studies showed an incidence of 0.22 cases per million per year in Germany, 0.26 per million per year in France, 0.23 per million per year in Kuwait, and a slightly higher incidence of 0.5 per million per year in Singapore [132–134]. EBA may occur in patients of any age with an average age at onset of 40 years, and unlike BP does not exhibit a predilection for the elderly [25]. The disease does seem to be slightly more common in women and black patients [135]. The cause is unknown, but genetic predisposition is likely given its association with specific haplotypes HLA-DR2 and HLA-DRB1 [136]. A number of disorders have been anecdotally reported with EBA including systemic lupus erythematosus, amyloidosis, autoimmune thyroiditis, diabetes mellitus, and multiple endocrinopathy syndromes [137]. The most frequent association is with inflammatory bowel disease [25].

EBA is characterized by IgG autoantibodies targeting type VII collagen, which is unique to stratified squamous epithelium and is the primary component of the anchoring fibril in the BMZ connecting the lamina densa to the papillary dermis of skin and mucosa [25, 138]. Two clinical types of EBA exist—the classic form and inflammatory form. The latter contains varying degrees of inflammation with lymphocytes, neutrophils, and eosinophils distinguishing it from

the former on histology. Inflammatory EBA is a great mimicker of BP; thus, the distinction between the two can only be made with immunofluorescence studies and clinical course. DIF microscopy reveals linear deposits of IgG along the BMZ, with variable presence of linear C3, IgA, and IgM. The intensity of IgG is generally greater than the other substrates [25]. IIF can be useful in differentiating EBA from BP since circulating IgG antibodies along the dermal side of salt-split skin can only be detected in 10–30% of cases of EBA [25, 139]. Furthermore, a more sensitive ELISA for the detection of antibodies against type VII collagen is also available [129].

The differential diagnosis of classic EBA includes variants of porphyria, pseudoporphyria, and hereditary forms of epidermolysis bullosa, while inflammatory EBA must be distinguished from BP, LABD, MMP, bullous drug eruptions, and bullous lupus [25]. Disruption of type VII collagen function results in the clinical manifestations seen with this disease and also found disrupted in bullous lupus, although the latter often presents with a known history or other signs or symptoms of systemic lupus erythematosus. Patients with classic EBA present with blisters, arising in areas of the skin where frequent and minor trauma can occur on noninflammed skin including the dorsum of the hands, knuckles, elbows, knees, sacral area, and feet. Healing results in scarring and milia formation [25]. Approximately half of all patients present with inflammatory EBA, which constitutes a vesiculobullous eruption most prominent over the trunk and flexural skin. As opposed to classic EBA, skin fragility is not a characteristic feature of inflammatory EBA with minimal to absent scar and milia formation. Mucous membrane involvement can occur either exclusively or with cutaneous lesions, making it very difficult to clinically distinguish from MMP [25, 140].

Treatment of EBA is both challenging and often unsatisfactory, as no clear therapeutic ladders have been established. Prevention of blister formation through avoidance of trauma and prompt attention to ulcerations is extremely important in order to reduce the possibility of secondary infection. Dapsone, colchicine, and standard immunosuppressant agents such as corticosteroids, azathioprine, and methotrexate have been used with varying success [25]. In addition, variable efficacy has been reported in using photopheresis, infliximab, or high-dose IVIg.

8.15 Junctional and Dystrophic Epidermolysis Bullosa

Junctional epidermolysis bullosa (JEB) and dystrophic epidermolysis bullosa represent the two other major types of inherited EB. The main focus will include the JEB-Herlitz subtype and the recessive dystrophic EB (RDEB) subtype in particular. According to a National Epidermolysis Bullosa Registry report, 50 EB cases occur per one million live births, and of these cases 5% are classified as dystrophic while only 1% are classified as junctional [141]. All subtypes of JEB are transmitted in an autosomal recessive manner, while dystrophic EB is transmitted in either an autosomal dominant or autosomal recessive manner. Evidently, RDEB is transmitted in an autosomal recessive fashion. The most severe subtype of JEB is JEB-Herlitz, which leads to a mutation in the protein subunits of laminin 5, a key component of the lamina lucida of the dermo-epidermal junction [142]. RDEB usually results in a mutation within the type VII collagen gene [143].

Similar to the clinical features seen in EB simplex, JEB and RDEB also exhibit mechanically fragile skin tense fluid-filled blisters, erosions, and crusts at birth with subsequent atrophic scarring (Fig. 8.13). A unique characteristic of JEB-Herlitz includes excessive granulation tissue usually in a symmetric distribution involving periorifacial skin, axillary vaults, and the upper back and nape of the neck [144]. It is practically impossible to make a strict clinical diagnosis comparing the several entities of epidermolysis bullosa; therefore, TEM is also used to aid in the diagnosis of JEB and RDEB as seen in EB simplex. An exact diagnosis is preferred because each entity of epidermolysis bullosa carries different prognoses, unique morbidities, and specific management strategies.

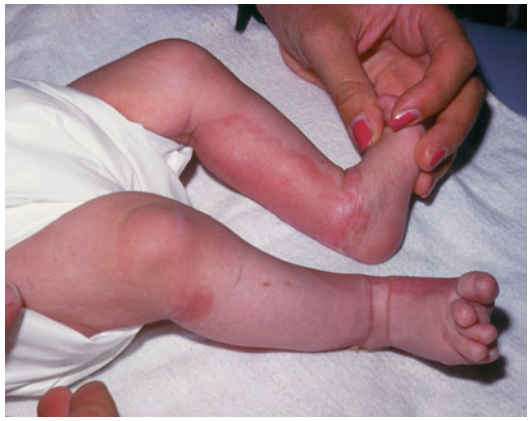

Fig. 8.13 Infant with Dystrophic Epidermolysis Bullosa exhibiting blisters on legs

Morbidity and mortality of JEB and RDEB relates to the consequences of repeated damage, ulceration, and poor healing of the skin in addition to extracutaneous complications. Malnutrition and growth stunting is consistently seen in patients with JEB and RDEB but even more severely than in patients with EB simplex [16]. This may be due to oral blistering and ulcerations, digestion and absorption problems, or loss of blood and protein through open skin blisters [82–84]. In addition vitamin and mineral deficiencies have been reported more readily in patients with JEB and RDEB including low iron levels, zinc deficiency, deficiencies in selenium and carnitine, and vitamins A, C, D, and E [16]. Although more common over a decade ago, bacterial sepsis and subsequent death is now relatively rare; however, it can still occur in the either JEB or RDEB, and hypermetabolism resulting in increased heat loss and protein turnover is especially common in the setting of skin infections [85, 145].

More unique characteristics of morbidity and mortality also arise in either JEB or RDEB. For example, enamel hypoplasia is a characteristic feature of JEB, and if left untreated, teeth are lost during childhood as a result of excessive caries [145, 146]. Pseudosyndactyly can occur in RDEB, although it may also occur in JEB [147]. Osteoporosis is a common finding in both RDEB and JEB, which is readily detectable on DEXA scan. A few patients with severe RDEB have developed a cardiomyopathy, and it has been suggested that this may be due to selenium deficiency [148]. Finally, failure to thrive is common among infants with JEB and may lead to death, and another major cause of death in JEB during the first 6 years of life is acute airway obstruction secondary to blisters within the trachea [149]. A major complication of RDEB is the development of multiple cutaneous squamous cell carcinomas, which arise in chronic nonhealing wounds or hyperkeratotic lesions. The risk of cutaneous malignancy is not solely limited to patient with RDEB, and an increased risk of skin cancer exists for all individuals with any chronic blistering disorder. Melanoma has also arisen in a small number of children with RDEB with a cumulative risk of 1.5% by the age of 12 years [150].

Similar to EB simplex, no specific treatment options are currently available. For now, the daily precautions should be taken with careful avoidance to prevent trauma and careful surveillance for and prevention of infection. Other treatment modalities have been used historically as well including systemic phenytoin administration in patients with dystrophic EB or JEB [151, 152]. Interestingly, systemic retinoids in low doses may very well have a role in effectively treating patients with RDEB, although little data exists on this issue [153, 154]. Aggressive nutritional supplementation should be considered in patients with JEB or RDEB who are severely malnourished. In addition, esophageal and urethral strictures may be successfully dilated through appropriate procedures. Since the risk of acute life-threatening airway obstruction is practically guaranteed in JEB, tracheostomy is considered standard of care in such patients. Finally, squamous cell carcinomas should be treated with conventional wide excision in those patients with RDEB who are at increased risk for developing such lesions [155].

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Vasculitis

9

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9.1 Introduction

Vasculitis is defined as inflammation of blood vessel walls. There are many types of vasculitis, lending to its variable clinical presentation, with or without systemic involvement. The diagnosis of specific vasculitides can be difficult, given much overlap in clinical manifestations, serum laboratory tests, and tissue histopathology. In addition, it is essential to differentiate benign, self-limited forms of vasculitis from those that may be life-threatening.

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9.1.1 Classification

Several classification systems have been used. One common system is based on vessel size [1] (see Table 9.1). Large vessels encompass the aorta, as well as its branching large arteries and veins that are directed toward major body regions, such as the carotid arteries and their branches. Giant cell arteritis and Takayasu arteritis mainly involve these vessels. These large arteries are not found in the skin, although skin manifestations can be seen in these vasculitides [2]. Medium vessels are the main visceral (renal, hepatic, coronary, and mesenteric) vessels; these vessels are implicated in entities such as polyarteritis nodosa and Kawasaki disease. They may also be involved in Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangitis, and cryoglobulinemic vasculitis. Small vessels are arterioles, venules, and capillaries. These vessels are involved in many types of vasculitis such as cutaneous leukocytoclastic vasculitis, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangitis, Henoch-Schonlein purpura, and others accounting for the majority of visible cutaneous disease.

Two classification schemes are those of the American College of Rheumatology (ACR) and the Chapel Hill Consensus Conference (CHCC). The ACR criteria of 1990 are a set of clinical and histological features that classify vasculitides (see Table 9.2) [3–10]. The CHCC definitions of 1992 provide histological definitions for ten

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Table 9.1 Size-based classification of vasculitis [1]

Vessel size	Vasculitides
Small	Cutaneous small vessel vasculitis Henoch-Schonlein purpura Urticarial vasculitis
Small and medium	Cryoglobulinemic vasculitis Microscopic polyangitis Wegener's granulomatosis Churg-Strauss syndrome Malignancy-associated vasculitis Infection-associated vasculitis Drug-associated vasculitis Connective tissue disorder-associated vasculitis
Medium	Polyarteritis nodosa
Large	Takayasu's arteritis Giant cell arteritis

types of vasculitis (see Table 9.3) [11]. Both of these classification schemes were designed as research tools. CHCC definitions are based on histology and have limited value for clinical diagnosis. The ACR criteria are more amenable to clinical diagnosis, but these criteria have a positive predictive value of only 17–29% for the diagnosis of specific vasculitides [12]. An expert group from the European League Against Rheumatism (EULAR) has recently suggested that new diagnostic and classification criteria should be developed with more consideration given to current diagnostic testing. While this group did not propose a new classification system, they proposed 17 points to consider in the development of such a system. These points include biopsy, laboratory testing, radiologic testing, nosology, definitions, and research agenda [13].

9.1.2 Pathogenesis

Vasculitis may be caused by a Type III hypersensitivity reaction which leads to deposition of immune complexes in blood vessel walls. This deposition is an early event in pathogenesis and is followed by activation of complement. Complement may directly damage the endothelium and also provides a chemotactic signal for the recruitment of inflammatory cells. The immune complexes themselves are also thought to activate polymorphonuclear leukocytes (PMNs) and increase production of tumor necrosis factor-alpha (TNF-alpha), Fas ligand, and perforin. Vessel damage may occur during diapedesis of PMNs from the luminal side of the vessel wall [14].

In the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangitis), antibodies directed against myeloperoxidase (MPO) or proteinase 3 (PR3) are present. Anti-MPO antibodies increase leukocyte adhesion to endothelial cells and migration into renal and pulmonary tissues. These antibodies also activate MPO; this generates an oxidative stress which leads to damage of endothelial cells. PR3 bound to the neutrophil membrane plays a proinflammatory role, and anti-PR3 antibodies increase the expression of membrane-bound PR3 in neutrophils during cell adhesion. Anti-PR3 also activates epithelial cells and increases epithelial cell production of proinflammatory cytokines (interleukin (IL)-6, IL-8, monocyte chemoattractant protein 1, and TNF) [14].

Cell-mediated immune responses may also play a role in giant cell arteritis, Takayasu's arteritis, Wegener's granulomatosis, and Churg-Strauss syndrome. CD4+ T cells are activated by antigens in vessel walls or in the circulation. These cells produce chemotactic cytokines which recruit monocytes. Monocytes mature into macrophages which produce lysosomal enzymes that damage endothelial cells [14].

9.1.3 The Emergent Nature of Vasculitis

Vasculitis is an emergency because of systemic complications which can be life-threatening. Renal, gastrointestinal, pulmonary, and cardiac complications can be seen with specific vasculitides. Urgent diagnosis of vasculitis can ensure prompt initiation of appropriate treatment.

Table 9.2 ACR criteria for classification of vasculitis [4–10]

Disease	Criteria
Hypersensitivity vasculitis (diagnose with 3/5 criteria; three or more criteria with sensitivity of 71.0% and specificity of 83.9%)	1. Age >16 years at disease onset 2. Medication taken at the onset of symptoms that may have precipitated the event 3. Palpable purpura 4. Maculopapular rash 5. Biopsy including arteriole and venule with granulocytes in a perivascular or extravascular location
Henoch-Schonlein purpura (diagnose with 2/4 criteria; two or more criteria with sensitivity of 87.1% and specificity of 87.7%)	1. Palpable purpura 2. Age less than or equal to 20 years at disease onset 3. Bowel angina 4. Vessel wall granulocytes on biopsy
Wegener's granulomatosis (diagnose with 2/4 criteria; two or more criteria with sensitivity of 88.2% and specificity of 92.0%)	1. Nasal or oral inflammation 2. Abnormal chest X-ray with nodules, fixed infiltrates, or cavities 3. Urinary sediment with microscopic hematuria (>5 red blood cells per high power field) or red cell casts 4. Granulomatous inflammation on biopsy
Churg-Strauss syndrome (diagnose with 4/6 criteria; four or more criteria with sensitivity of 85.0% and specificity of 99.7%)	1. Asthma 2. Eosinophilia (>10%) 3. Mononeuropathy or polyneuropathy 4. Nonfixed pulmonary infiltrates 5. Paranasal sinus abnormality 6. Extravascular eosinophils
Polyarteritis nodosa (diagnose with 3/10 criteria; three or more criteria with sensitivity of 82.2% and specificity of 86.6%)	1. Weight loss greater than or equal to 4 kg 2. Livedo reticularis 3. Testicular pain or tenderness 4. Myalgias, weakness, or leg tenderness 5. Mononeuropathy or polyneuropathy 6. Hypertension with diastolic blood pressure >90 mmHg 7. Renal impairment with elevated blood urea nitrogen (>40 mg/dl) or creatinine (>1.5 mg/dl) 8. Hepatitis B Virus 9. Abnormal arteriography 10. Biopsy of small or medium-sized artery containing polymorphonuclear leukocytes
Takayasu's arteritis (diagnose with 3/6 criteria; presence of three or more criteria with sensitivity of 90.5% and specificity of 97.8%)	1. Age at disease onset less than or equal to 40 years 2. Claudication of extremities 3. Decreased brachial artery pulses 4. >10 mmHg difference in systolic blood pressure between arms 5. Bruit over subclavian artery or aorta 6. Abnormal arteriogram
Giant cell arteritis (diagnose with 3/5 criteria; presence of three or more criteria with sensitivity of 93.5% and specificity of 91.2%)	1. Age at disease onset greater than or equal to 50 years 2. New headache 3. Temporal artery abnormality (tenderness to palpation or decreased pulsation) 4. Elevated erythrocyte sedimentation rate (greater than or equal to 50 mmHg) 5. Abnormal artery biopsy showing vasculitis

Table 9.3 CHCC definitions of vasculitis [11]

Disease	Definition
Cutaneous small vessel vasculitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis
Henoch-Schonlein purpura	Vasculitis with IgA-dominant immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis
Cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with cryoglobulins in serum. Skin and glomeruli are often involved
Microscopic polyangitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common
Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and eosinophilia
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
Kawasaki's disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50
Giant cell arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica

9.2 Types of Vasculitis

9.2.1 Cutaneous Small Vessel Vasculitis

Cutaneous small vessel vasculitis, also known as cutaneous leukocytoclastic angiitis, is caused by inflammation in post-capillary venules. Lesions often occur in crops on the lower extremities. Palpable purpura is the classic clinical finding, but macules, urticarial lesions, and vesicles can also be seen (Fig. 9.1). Once mature, these lesions do not blanch with diascopy. Patients may develop fever, malaise, arthralgia, and myalgia. Underlying causes include infections, medications, foods (gluten, milk proteins), chemical exposure (petroleum products, insecticides), autoimmune disease, and malignancy. Despite the numerous causes, no specific etiologic factor is identified in up to 60% of patients [15].

9.2.2 Henoch-Schonlein Purpura

Henoch-Schonlein purpura (HSP) is a small vessel vasculitis that is associated with immunoglobulin A immune complex deposition. It accounts for approximately 10% of cases of small vessel vasculitis [16]. HSP is the most common type of vasculitis in children. It classically occurs in boys 4–8 years of age. Peak incidence is in winter months, and patients often have an upper respiratory tract infection 1–2 weeks prior to the development of symptoms [17]. A recent study by Weiss et al. has shown temporal association between hospitalizations for Group A beta-hemolytic streptococcus, Staphylococcus aureus, and Parainfluenza and hospitalization for HSP. Despite this temporal association, a causal role for these organisms has not yet been established [18].

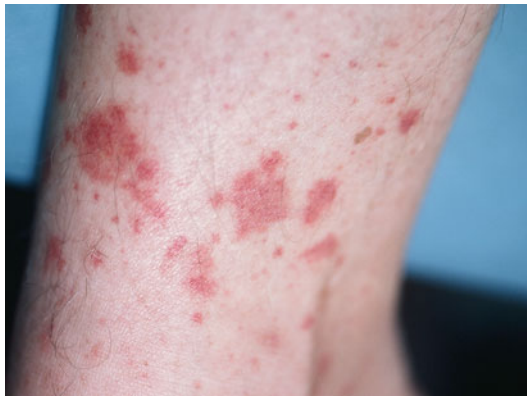

Fig. 9.1 Early purpura on the ankle

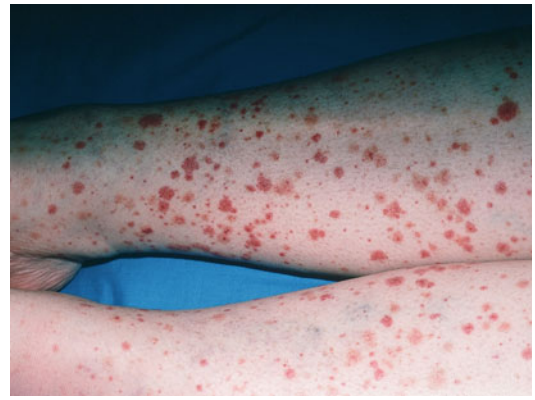

Fig. 9.2 Symmetrically distributed palpable purpura on the lower extremities due to Henoch-Schonlein purpura

The classic tetrad of HSP includes palpable purpura, arthritis, nephritis, and gastrointestinal tract involvement with abdominal pain or bleeding. All patients with HSP have skin involvement. In a study of 100 children with HSP, 83% had arthritis, 63% had abdominal pain, 33% had gastrointestinal bleeding, and 40% developed nephritis [19]. Adults commonly present with joint or kidney involvement, but gastrointestinal manifestations are less common. Adults may be more refractory to treatment than children [20, 21].

Palpable purpura is the classic cutaneous finding. Lesions may begin as macular erythema or urticaria that develops into nonblanching erythematous macules and papules. Lesions are symmetrically distributed, and dependent areas such as the lower extremities and buttocks are the most common sites of involvement (Fig. 9.2). Individual lesions generally resolve within 10–14 days [17]. While this condition is self-limited in most patients, the physician must take care to evaluate for renal involvement. Long-term renal impairment is seen in 1.8% of all children with HSP and in 19.5% of children who develop nephritic or nephrotic syndrome [22]. In a study by Coppo et al., end stage renal disease was seen in 15.8% of adults and 7% of children with HSP nephritis [23]. The use of systemic therapy to decrease the likelihood of renal complications remains controversial. In one study by Ronkainen et al., prednisone did not prevent renal disease from occurring although it led to faster resolution of disease once it occurred. Prednisone was also effective in decreasing the intensity of abdominal pain and joint pain in this study [24]. A more recent study from these authors compared the outcomes of patients 8 years after treatment with prednisone or placebo at disease onset. This study found no beneficial effect from early prednisone treatment, and the authors concluded that prednisone should not be routinely used [25].

9.2.3 Urticarial Vasculitis

Urticarial vasculitis is a small vessel vasculitis that is seen in 1–10% of patients with chronic urticaria [26]. It has a predilection for women and is most common in the fourth or fifth decades [27].

Patients with urticarial vasculitis have wheals and erythematous plaques that persist in the same location for more than 24 h. Patients often complain of burning pain in these lesions. These features contrast with the evanescent pruritic lesions seen in classic, allergic urticaria, which is IgE-mediated. Lesions of urticarial vasculitis favor the proximal trunk and extremities. Petechiae or purpura are often seen, and lesions frequently resolve with postinflammatory pigmentary alteration (Fig. 9.3) [28].

Normocomplementemic urticarial vasculitis tends to be limited to the skin. It is often self-limited and may be regarded as a subset of cutaneous small vessel vasculitis [17]. Low complement levels are seen in 18–32% of patients

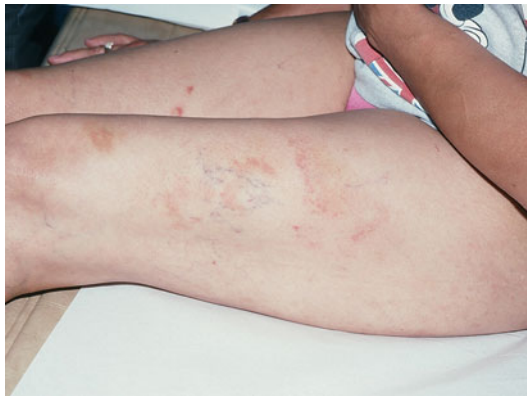

Fig. 9.3 Residual hyperpigmentation after resolved urticarial vasculitis. The post-inflammatory changes and duration of lesions help distinguish this from allergic urticaria

with urticarial vasculitis [27]. Patients with hypocomplementemic urticarial vasculitis have more severe disease with involvement of the joints (50% of patients), the gastrointestinal tract (20% of patients), and the airways with asthma and obstructive airways disease (20% of patients) [29]. Some patients with severe disease may be considered to have hypocomplementemic urticarial vasculitis syndrome (HUVS). Patients with this syndrome may have renal involvement with glomerulonephritis or ophthalmologic involvement with uveitis or episcleritis in addition to the above symptoms [30]. All patients with this syndrome have anti-C1q precipitins, and 24% may have anti-double stranded deoxyribonucleic acid (dsDNA) antibodies [17]. There are overlapping features of HUVS and systemic lupus erythematosis (SLE). Fifty percent of patients with HUVS are subsequently diagnosed with SLE; HUVS is seen in 7–8% of patients with SLE [31]. Another syndrome associated with urticarial vasculitis is Schnitzler syndrome. This syndrome is characterized by urticarial vasculitis, immunoglobulin M monoclonal gammopathy, fever, lymphadenopathy, arthralgia, bone pain, hepatosplenomegaly, elevated erythrocyte sedimentation rate, leukocytosis, and abnormal bone radiology studies. This syndrome also has overlapping features with SLE. Urticarial lesions in SLE may be more pruritic and difficult to control than those of Schnitzler syndrome. Schnitzler syndrome also commonly shows a neutrophilic leukocytosis, while SLE may have neutropenia and positive antinuclear antibody (ANA). Schnitzler syndrome is benign in most patients although there is a risk of development of lymphoproliferative disorders [32].

9.2.4 Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis affects both small- and medium-sized vessels. Cryoglobulins are immunoglobulin molecules that precipitate in cold temperatures. This precipitation occurs in vitro and may be due to intrinsic characteristics of the immunoglobulin components [33]. Type I cryoglobulins are monoclonal immunoglobulin (Ig) M and less commonly IgG. These cryoglobulins are associated with hematologic conditions such as multiple myeloma or Waldenstrom's macroglobulinemia. Type I cryoglobulins are associated with cold-induced vasculopathy but are not associated with vasculitis. Vasculopathy refers to vascular occlusion without blood vessel wall inflammation. The cryoglobulins associated with vasculitis, types II and III (the mixed cryoglobulins), are monoclonal IgM directed against polyclonal IgG and polyclonal IgM directed against polyclonal IgG, respectively. Fifteen percent of patients with cryoglobulins have cryoglobulinemic vasculitis. This vasculitis results from deposition of immune complexes in blood vessel walls with subsequent complement activation and inflammation [17].

In a study of 443 patients with cryoglobulinemia, underlying infection was seen in 75%, autoimmune disease in 24%, and hematologic disease in 7% [34]. Hepatitis C virus is the most common infection associated with cryoglobulinemia [33]. Hepatitis B and human immunodeficiency virus are less frequently associated. Associated autoimmune diseases include Sjögren's syndrome, systemic sclerosis, SLE, rheumatoid arthritis (RA), and primary antiphospholipid syndrome. Hematologic associations include non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, and myelodysplasia [34].

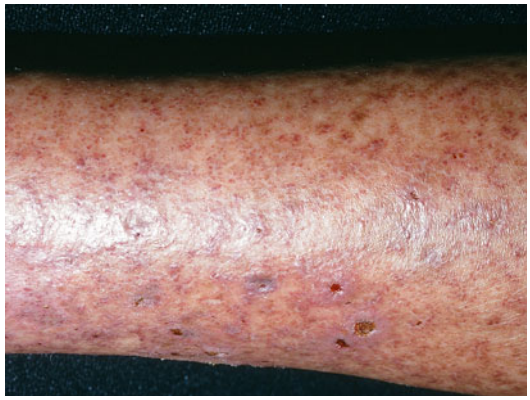

Fig. 9.4 Purpuric ulcers on the lower extremity due to cryoglobulin deposition

Cryoglobulinemic vasculitis often presents with palpable purpura localized to the lower extremities. Other cutaneous manifestations include erythematous papules, dermal nodules, ecchymoses, skin necrosis, bullae, urticarial lesions, ulcers, and livedo reticularis (Fig. 9.4). In contrast to the vasculopathy associated with type I cryoglobulins, cold temperatures induce lesions in only 10–30% of cases [17]. Common extracutaneous manifestations include joint involvement, peripheral neuropathy, and renal involvement. Patients may also have weakness, fever, lymphadenopathy, central nervous system, pulmonary, and gastrointestinal tract involvement. Central nervous system involvement may lead to devastating complications such as cerebral ischemia, spinal cord complications, or cranial nerve palsy [34].

Detection of cryoglobulins requires careful handling of specimens. Two red-topped tubes (without anticoagulant) must be drawn and transported to the laboratory at 37°C. This may be achieved by submerging the tubes in warm water or carrying the specimen in the axilla. The sample is allowed to clot at 37°C for 1 h prior to centrifugation. Type I cryoglobulins may precipitate within 24 h, but it may take several days for precipitation of mixed cryoglobulins. Many labs observe specimens for up to 7 days [35]. Rheumatoid factor can serve as a surrogate marker for Type II and III cryoglobulins because this test looks for IgM directed against IgG in the blood.

9.2.5 Microscopic Polyangitis

Microscopic polyangitis is a necrotizing vasculitis that affects small- and medium-sized vessels. It is most frequently associated with perinuclear-antineutrophil cytoplasmic antibody (pANCA; anti-myeloperoxidase antibody), although cytoplasmic-antineutrophil cytoplasmic antibody (c-ANCA; anti-proteinase 3 antibody) is less frequently seen [17]. p-ANCA has a sensitivity of 58% and specificity of 81% in the diagnosis of microscopic polyangitis; c-ANCA has a sensitivity of 23% [36]. It may be slightly more common in men, and the average age of onset is 57 [37].

The first symptoms of microscopic polyangitis are typically fever, weight loss, arthralgia, and/or myalgia which may begin months to years before other disease manifestations. Palpable purpura is the most common cutaneous manifestation and is seen in 45% of patients at diagnosis [38]. Other skin findings include splinter hemorrhages, nodules, livedo reticularis, and palmar erythema [27]. Renal involvement, seen in 79–90% of patients, manifests as a focal segmental necrotizing glomerulonephritis. Pulmonary involvement occurs in 25–50% of patients, and pulmonary hemorrhage is seen in 12–29% of patients [17].

Microscopic polyangitis must be differentiated from other causes of pulmonary-renal syndrome which include the other ANCA-associated vasculitides (Wegener's granulomatosis, Churg-Strauss syndrome), Goodpasture syndrome (a clinical condition in which patients develop diffuse pulmonary hemorrhage and rapidly progressive glomerulonephritis), and SLE. Serology may be helpful in this endeavor; ANCA will be positive in the ANCA-associated vasculitides, while anti-basement membrane antibody is seen in Goodpasture syndrome. Microscopic polyangitis may be differentiated from Wegener's granulomatosis by the lower incidence of severe upper respiratory tract and ocular disease as well as lack of granulomatous inflammation. Unlike Churg-Strauss syndrome, microscopic polyangitis is not associated with asthma or eosinophilia.

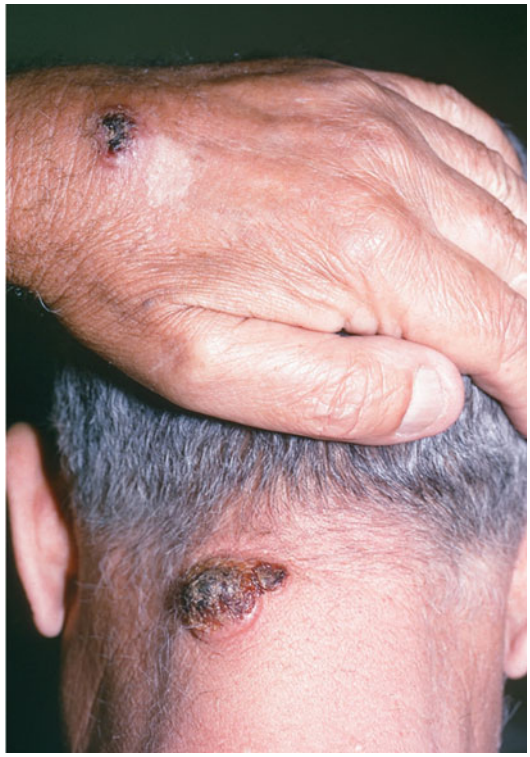

Fig. 9.5 Papulonecrotic lesions in Wegener's granulomatosis

9.2.6 Wegener's Granulomatosis

Wegener's granulomatosis is a triad of necrotizing vasculitis of small vessels, necrotizing granulomatous inflammation of the upper and lower respiratory tract, and pauci-immune glomerulonephritis. It is associated with c-ANCA in 75–80% of patients; those who are negative for this antibody are more likely to have a better prognosis with more localized disease. p-ANCA is seen in only 10–15% of patients [17]. c-ANCA has a sensitivity of 64% and specificity of 95% in the diagnosis of Wegener's granulomatosis; p-ANCA has a sensitivity of 21% in this disease [36]. Wegener's granulomatosis is slightly more common in women. Ninety-eight percent of patients in one study were Caucasians, and the peak age of onset is from 45 to 65 years [39].

Palpable purpura and oral ulcers are common cutaneous manifestations of Wegener's granulomatosis. Other skin findings include subcutaneous nodules, ulcers, or papulonecrotic lesions (Fig. 9.5). The skin is involved in 46–66% of patients with Wegener's granulomatosis, and cutaneous manifestations may be the initial finding in 10% of patients [17]. Systemic disease in Wegener's granulomatosis can be severe. The upper and lower respiratory tracts are frequently involved at the time of diagnosis. Upper respiratory tract involvement can manifest as epistaxis, ulcerations of mucosa, nasal septal perforation, or saddle nose deformity; symptoms of lower respiratory tract involvement include cough, hemoptysis, dyspnea, and pleuritis. Glomerulonephritis is less common at presentation, although it may develop in up to 77% of patients [40]. Causes of death include rapidly progressive renal disease and pulmonary disease with hemorrhage [17]. Other less common systemic findings include ocular (proptosis, optic nerve ischemia leading to loss of vision, entrapment of extraocular muscles), musculoskeletal (myalgia, arthralgia, arthritis), nervous system (mononeuritis multiplex, cerebrovascular accident, cranial nerve palsies), and cardiac (pericarditis, cardiac muscle or vessel involvement) manifestations [40].

9.2.7 Churg-Strauss Syndrome

Churg-Strauss syndrome, also known as allergic granulomatosis, is a necrotizing granulomatous vasculitis of small- and medium-sized vessels. It is classically associated with asthma and peripheral blood eosinophilia. It is associated with p-ANCA in 55–60% of patients and c-ANCA in 10–15% of patients [17]. It is slightly more common in women and has an average age of onset of 35 [1].

Churg-Strauss syndrome often occurs in three phases. In the first phase, patients have symptoms of allergic rhinitis and asthma. This phase may last for years to decades [17]. In the second phase, peripheral eosinophilia develops with eosinophilic infiltration of tissues, and in the third phase, patients develop vasculitis [41]. There is often a long delay between phase one and phase three; the average length of the delay is 3 years, but in some patients this delay may be as long as 30 years [17]. Symptoms may develop following the use of leukotriene inhibitors, abrupt discontinuation of steroids, or vaccinations such as hepatitis B vaccine [17, 42]. It is unclear whether leukotriene inhibitors

directly cause Churg-Strauss syndrome. The use of these agents in the treatment of asthma may allow for tapering of corticosteroid doses with subsequent unmasking of Churg-Strauss symptoms [43].

Dermatologic manifestations occur in 40–70% of patients. Common lesions include palpable and retiform purpura, petechiae, ecchymoses, hemorrhagic bullae, subcutaneous nodules often located on the scalp or extremities, urticaria, and livedo reticularis (Fig. 9.6) [27]. Pulmonary, cardiac, neurologic, renal, gastrointestinal, and rarely urologic systems can be involved. Renal involvement may take the form of focal segmental glomerulonephritis. It is seen in 16–49% of patients with Churg-Strauss syndrome. Peripheral neuropathy, usually mononeuritis multiplex, is very common and occurs in 53–75% of patients. Potentially fatal cardiovascular complications result from granulomatous infiltration of the myocardium and coronary vessel vasculitis [44]. Cardiovascular manifestations include cardiac arrest, myocardial infarction, valvular heart disease, congestive heart failure, pericardial effusion, and constrictive pericarditis [41].

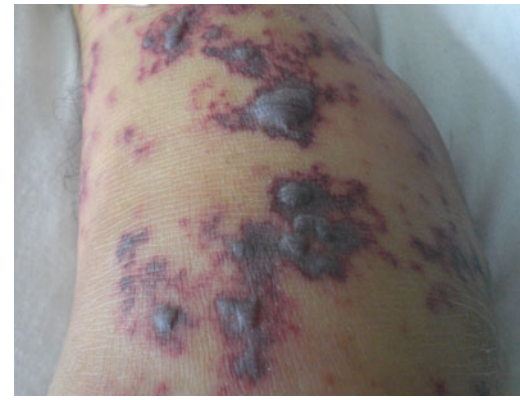

Fig. 9.6 Retiform purpura in a patient with Churg-Strauss syndrome. Similar lesions may be seen in other small- to medium-sized vessel vasculitides and other entities

9.2.8 Malignancy-Associated Vasculitis

Vasculitis may occur in the setting of malignancy, and metastases may mimic vasculitis (Fig. 9.7). It is more common with hematologic malignancies, although it can also occur with solid tumors. Malignancies that have been associated with vasculitis include hairy cell leukemia, leukemia, multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, sarcomas, malignant histiocytosis, lung cancer, cervical cancer, melanoma, breast cancer, prostate cancer, and renal cancer. Therapy for cancer may also result in vasculitis; chemotherapy agents, radiation, and bone marrow transplantation have all been associated with vasculitis [45].

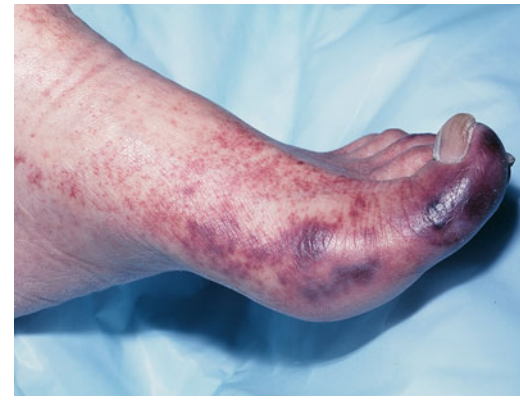

Fig. 9.7 Metastatic bowel cancer mimicking cutaneous vasculitis

9.2.9 Infection-Associated Vasculitis

Vasculitis may occur secondary to bacterial, viral, fungal, or parasitic infection (Fig. 9.8). Causative organisms include Group A beta-hemolytic

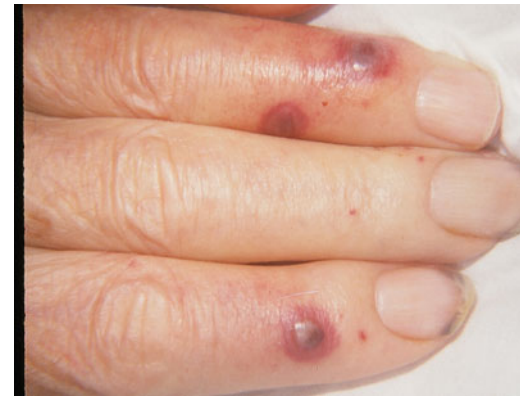

Fig. 9.8 Acral or septic vasculitis

Streptococcus, Staphylococcus aureus, Mycobacterium, hepatitis A virus, hepatitis B virus, hepatitis C virus, herpes simplex virus, influenza virus, Candida albicans, Plasmodium malariae, Schistosoma mansoni, Schistosoma haematobium, and Onchocerca volvulus [15].

9.2.10 Drug-Associated Vasculitis

Numerous drugs have been implicated as causal agents in vasculitis. The timing of the onset of vasculitis is variable, and cases may occur hours to years after the initial drug exposure. It often develops following increases in dose or following rechallenge with a given medication [46].

Drugs that induce ANCA-negative vasculitis include methotrexate, isotretinoin, and colony stimulating factors. ANCA-negative drug-associated vasculitis is often limited to the skin and typically presents a few days to weeks after initial drug exposure. Other drugs induce an ANCA-associated vasculitis; common examples are propylthiouracil, allopurinol, hydralazine, minocycline, penicillamine, and phenytoin. Retiform purpura and visceral involvement with severe systemic complications may be seen with these medications [27].

Levamisole-adulterated cocaine has also been shown to cause an ANCA-associated vasculitis which typically presents with purpuric lesions on the face in a reticular, retiform, or stellate pattern (Fig. 9.9). In one study, 50% of patients presented with a rash on their earlobes [47]. Similarly, patients treated with levamisole for nephritic syndrome presented with a rash on their earlobes [48–50]. Patients should immediately discontinue cocaine use in order to accelerate the healing process; in some cases this may be sufficient treatment. It is unclear whether steroids are useful in this type of vasculitis [47].

9.2.11 Connective Tissue Disorder-Associated Vasculitis

The most common connective tissue disorders associated with vasculitis are RA, SLE, and Sjögren's syndrome. Vasculitis can also occur secondary to systemic sclerosis, Behçet's disease, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, and antiphospholipid antibody syndrome. The presence of vasculitis correlates with increased activity of the underlying connective tissue disease and suggests a poorer prognosis [51].

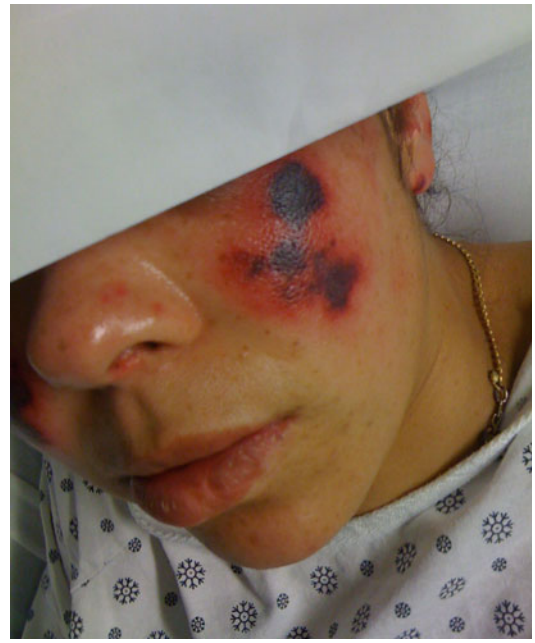

Fig. 9.9 Necrotic purpura in a cocaine abuser. Note the earlobe involvement

9.2.12 Polyarteritis Nodosa

Polyarteritis nodosa is a necrotizing vasculitis of medium-sized blood vessels. It is more common in men and most frequently occurs in patients 40–60 years of age [17]. Systemic polyarteritis nodosa has been associated with hepatitis B virus [44]. Cutaneous polyarteritis nodosa has been associated with Group A beta-hemolytic Streptococcus, Parvovirus B19, hepatitis B virus, hepatitis C virus, and Mycobacterium tuberculosis. It can also be seen in association with inflammatory bowel disease (IBD) or minocycline use [52].

In the systemic variant, livedo reticularis, ulcers with a "punched-out" appearance, and

tender erythematous subcutaneous nodules are seen [17]. Systemic findings include fever, weight loss, malaise, fatigue, arthralgias, and myalgias. Renal involvement may present with proteinuria, renal failure, or hypertension. Gastrointestinal involvement may lead to abdominal pain, nausea, vomiting, or bleeding. Mononeuritis monoplex is a typical neurologic manifestation. The heart, testicles, and eyes may also be involved [53]. Orchitis is particularly common in patients with polyarteritis nodosa secondary to hepatitis B virus. Of note, there is no respiratory involvement in classic polyarteritis nodosa [17].

In cutaneous polyarteritis nodosa, livedo reticularis, subcutaneous nodules, and ulcers are seen. A burst pattern of livedo reticularis surrounding an ulcer is very suggestive of cutaneous polyarteritis nodosa. Painful subcutaneous ulcers are more common than in the systemic form. Systemic symptoms are limited to constitutional symptoms, arthralgias, myalgias, and neuropathy [52].

9.2.13 Kawasaki Disease

Kawasaki disease is a vasculitis that is commonly seen in children. Most cases occur in children between 6 months and 5 years, and the peak incidence is from 13 to 24 months. It is most common in Japanese, Korean, and Asian-American children [54]. It is slightly more common in boys with a male:female ratio of 1.4:1. It is most common in the late winter and spring which has led some to propose an infectious etiology. An alternative theory suggests that superantigens may play an etiological role [55].

The diagnosis of Kawasaki disease requires a fever that lasts at least 5 days and four of the following: polymorphic exanthem; peripheral extremity manifestations including erythema, edema, and induration in the acute phase and desquamation in the convalescent phase; bilateral nonexudative conjunctival injection; oropharyngeal manifestations including marked erythema of lips, fissuring of lips, and strawberry tongue; and nonsuppurative cervical lymphadenopathy with at least one lymph node greater than 1.5 cm in diameter. Patients with fewer than four of these criteria may be diagnosed with atypical Kawasaki disease if coronary artery abnormalities are present [55].

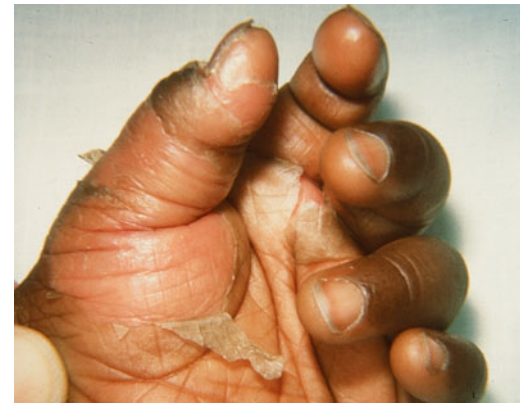

Fig. 9.10 Late desquamation of the palms in a child with Kawasaki disease

The exanthem of Kawasaki disease occurs in over 90% of patients. It may manifest as a scarlatiniform rash, generalized erythema, papules, acral pustules, or erythema multiforme-like lesions. This rash may be noted at the onset of fever, and it typically persists throughout the acute stage of the illness. As mentioned above, other cutaneous manifestations of Kawasaki disease include erythema and induration of the palms and soles with fusiform swelling of the digits, desquamation of digits beginning at the fingertips (Fig. 9.10), perineal rash with erythema and desquamation, strawberry tongue, and fissured erythematous lips [55].

Kawasaki disease is thought to proceed through four stages. In the first stage (days 1–9) a small vessel vasculitis is present along with intimal inflammation in larger blood vessels. The second stage (days 12–25) is characterized by thrombosis with inflammation of the coronary arteries. In the third stage (days 28–31) the inflammation regresses, and in the fourth stage (day 40 to 4 years after the onset of illness) scar formation and reorganization of thrombi occur. Death may occur in the first and second stages from cardiac arrhythmias, myocarditis, acute myocardial thrombosis, or rupture of coronary artery aneurysms. In the third and fourth stages death may occur from sudden myocardial

infarction. Because of the risk of cardiovascular complications, echocardiography and electrocardiography (ECG) are recommended for all patients. Coronary arteriography may be pursued in those patients with persistent ECG changes or symptoms of cardiac ischemia [55]. Kawasaki disease may have cardiac effects even years after the acute illness. Adults with history of Kawasaki disease may have increased risk of endothelial dysfunction and premature atherosclerosis, and thus long-term follow-up may be warranted in these patients [56].

Treatment with intravenous immunoglobulin (IVIG) has been associated with improved outcomes in this condition [55]. Treatment with aspirin is somewhat controversial. Aspirin has been used because of its anti-inflammatory and antithrombotic effects. Typical regimens use high doses of 80–100 mg/kg/day during the acute febrile phase and a maintenance dose of 3–5 mg/kg/day once the fever subsides [55]. A retrospective study by Hsieh et al. found that treatment without aspirin had no effect on fever duration, response to IVIG, or incidence of coronary artery aneurysms in patients with acute Kawasaki disease who were treated with high-dose IVIG (2 g/kg) [57]. A Cochrane review from 2006 found that there was insufficient evidence to determine whether or not children should continue to receive aspirin in the treatment of Kawasaki disease [58]. Studies have shown that corticosteroids may be added to IVIG with improved clinical and cardiac outcomes [59]. Such improved outcomes are especially seen in patients who are at high risk to be IVIG nonresponders [60].

9.2.14 Takayasu's Arteritis

Takayasu's arteritis, also known as pulseless disease, is a vasculitis that affects large arteries. It is typically a disease of young women with peak incidence between 10 and 24 years of age. It is most common in Asia [61].

Clinical manifestations are typically divided into pre-pulseless and pulseless phases. In the pre-pulseless phase patients may experience fever, fatigue, weight loss, headache, myalgia, arthralgia, and exertional dyspnea. Patients develop syncope, congestive heart failure, angina, hypertension, Raynaud's phenomenon, and claudication of the upper or lower extremities in the pulseless phase. Physical exam may reveal arterial bruits and tenderness over the sites of large arteries [61].

Skin manifestations are seen in 8–28% of patients. Cutaneous findings include erythema nodosum, erythema induratum, and pyoderma gangrenosum. These manifestations are typically localized to the lower extremities [62].

9.2.15 Giant Cell Arteritis

Giant cell arteritis (temporal arteritis) is a form of large vessel vasculitis that involves the aorta and its major branches. It is most common in individuals older than 50 years. It occurs most frequently in women and Caucasian individuals of Northern European descent [63].

Giant cell arteritis can present with temporal headache, claudication of the jaw, and visual changes including visual loss. Nonspecific symptoms such as fever, malaise, night sweats, anorexia, and weight loss may also be present. It can result in serious complications such as permanent visual loss, aortic aneurysm, stroke, and limb claudication, and thus early detection is essential [64]. Cutaneous findings include scalp tenderness, blanching of the temporal scalp, cord-like thickening of the temporal artery, and decreased or absent temporal arterial pulse [27].

9.3 Clinical Evaluation

9.3.1 History

A detailed history is essential in the diagnosis of vasculitis, and a thorough review of systems should be performed. Symptoms suggestive of systemic involvement include fever, malaise, weight loss, arthritis, arthralgia, myalgia, hemoptysis, cough, shortness of breath, sinusitis, abdominal pain, melena, hematochezia, hematuria, and paresthesias [17]. One should also consider possible causes of vasculitis. Patients

should be asked about preceding illnesses, medications, vaccines, chemical exposures, and symptoms of connective tissue disease or malignancy.

9.3.2 Physical Exam

Palpable purpura is pathognomonic for vasculitis. Palpable purpura consists of elevated, nonblanching erythematous lesions. Not all vasculitis presents with palpable purpura, however, and a variety of dermatologic lesions may be seen including macules, papules, wheals, vesicles, bullae, and ulcers [65]. Specific clinical manifestations reflect the size of the involved vessels. Small vessel vasculitis commonly presents with purpura, erythema, urticaria, vesiculobullous lesions, superficial ulcers, and splinter hemorrhages. Medium-vessel vasculitis can present with subcutaneous nodules, erythematous nodules, deep ulcers, livedo reticularis, pitted palmar scars, gangrene of the digits, or infarcts. Review of vital signs may show hypertension if there is renal artery involvement, and thorough neurologic exam may reveal deficits consistent with mononeuritis. Large vessel vasculitis often has no skin manifestations; common findings on physical exam include asymmetric blood pressure, absence of pulses, and bruits [27].

The important finding of retiform purpura deserves special mention. Retiform purpura consists of nonblanching erythematous lesions in a reticulate, branching, serpentine, or stellate pattern. Retiform purpura is caused by complete loss of blood flow in the dermal and subcutaneous blood vessels. It may be caused by vasculitides such as cryoglobulinemic vasculitis, connective tissue disorder-associated vasculitis, polyarteritis nodosa, microscopic polyangitis, Wegener's granulomatosis, and Churg-Strauss syndrome. It may also be caused by vasculopathies. The differential diagnosis includes antiphospholipid antibody syndrome, protein C or S deficiencies, disseminated intravascular coagulation, coumadin necrosis, heparin necrosis, cholesterol embolization, calciphylaxis, and type I cryoglobulinemia [66, 67].

9.3.3 Pathologic Evaluation

Biopsy confirms the diagnosis of vasculitis and identifies the size of the involved vessel. In order to obtain the most information, the most purpuric, erythematous, and tender skin should be biopsied. It is also important to biopsy lesions that are less than 48 h old; after 48 h lymphocytes and macrophages replace initial inflammatory cells regardless of the underlying type of vasculitis. This is also true for direct immunofluorescence specimens as the likelihood of finding immunoglobulins decreases after 48–72 h [68]. One must also take care when deciding on the type of biopsy to perform. The subcutaneous tissue must be included if a medium-sized vessel vasculitis is suspected. A deep biopsy of the central white area should be performed for livedo reticularis. In cases in which ulcers are present, one should attempt to biopsy nonulcerated sites or the edge of a superficial ulcer. In cases in which deep ulcers are present, biopsy of the subcutaneous tissue can be taken from the central portion of the ulcer. In addition to hematoxylin and eosin staining, a sample may be sent for direct immunofluorescence [27]. See Table 9.4 for histologic findings in specific types of vasculitis [61, 63, 69].

9.3.4 Laboratory and Radiologic Evaluation

Thorough laboratory evaluation is required in patients with systemic disease or chronic vasculitis. Laboratory evaluation should include complete blood count with differential, blood urea nitrogen and creatinine, liver function tests, hepatitis B and C serologies, ANCA, ANA, rheumatoid factor, immunoglobulin levels, complement levels, antiphospholipid antibodies, cryoglobulins, urinalysis, and stool for occult blood [27]. In patients with fever and/or a heart murmur, blood cultures and echocardiography may be warranted. Anti-streptolysin O titers can also be checked and may be particularly useful in children. The physician must be aware of the possibility of false-negative test results, particularly with

Table 9.4 Histologic findings in specific vasculitides [59, 61, 67]

Vasculitis	Histologic findings on H&E	Direct immunofluorescence
Cutaneous small vessel vasculitis	Small vessel neutrophilic vasculitis affecting the superficial dermal plexus (see disruption of vessels by inflammatory cells, deposition of fibrin in vessel walls or lumen, and nuclear debris)	Typically small granular deposits of IgM, IgG, and C3 in vessel walls
Henoch-Schonlein purpura	Small vessel neutrophilic vasculitis affecting superficial dermis; occasionally may have involvement of whole dermis	IgA vascular deposits
Urticarial vasculitis	Focal nuclear debris or vascular fibrin deposits, with or without extravasated red blood cells	
Cryoglobulinemic vasculitis	Small vessel neutrophilic vasculitis affecting superficial dermis and subcutis vessels; some cases with neutrophilic muscular-vessel vasculitis	Vascular immunoglobulins (IgM) and complement
Microscopic polyangitis	Small vessel neutrophilic vasculitis	
Wegener's granulomatosis	Necrotizing vasculitis in small- and medium-sized vessels	
Churg-Strauss syndrome	Small vessel eosinophil-rich neutrophilic vasculitis affecting dermal venules and arterioles; less commonly muscular vessel eosinophil-rich arteritis or histiocyte-rich granulomatous arteritis of the dermo-subcutaneous junction or subcutis	
Infection-associated vasculitis	Small vessel neutrophilic vasculitis affecting superficial dermis; increased frequency of pustules (subcorneal, intraepidermal, or subepidermal), tissue neutrophilia; fewer lymphocytes and eosinophils	Predominant IgA vascular deposits
Drug-associated vasculitis	Superficial dermal small vessel neutrophilic or lymphocytic vasculitis; tissue eosinophilia	
Connective tissue disorder-associated vasculitis	Mixed neutrophilic vasculitis affecting both small and muscular vessels; may see pathologic findings from underlying disease	
Polyarteritis nodosa	Muscular vessel neutrophilic vasculitis affecting arterial branch points at the dermo-subcutaneous junction or in the subcutis	
Takayasu's arteritis	Large vessel vasculitis with granulomatous inflammation of the vessel wall and infiltration of inflammatory cells into the adventitia	
Giant cell arteritis	Large and medium vessel vasculitis with lymphocytic infiltrate with activated macrophages and multinucleated giant cells	

cryoglobulins and complement levels. It is suggested that these labs be sent on at least three separate occasions [17].

9.4 Treatment

Many cases of cutaneous vasculitis will be self-limited and short-lived. The first step in treatment is to reverse the underlying cause of the vasculitis, if possible. Symptomatic treatment with antihistamines, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), leg elevation, ice packs, and avoidance of tight-fitting clothing may be sufficient. In a study of 95 patients with hypersensitivity vasculitis, 54 patients did not require treatment, and another 26 cases resolved with NSAIDS only [70]. It is important to note that NSAIDS have limited value in vasculitides with renal involvement. These agents cause vasoconstriction of the afferent arteriole which decreases renal perfusion and

can exacerbate renal failure. In patients with itching or burning or in those with refractory or recurrent skin disease, dapsone (titrated from 25 to 50 mg daily), colchicine (0.5–0.6 mg twice daily or three times daily), or pentoxifylline (400 mg three times daily) may be tried [71].

Systemic immunosuppression may be required in patients who develop systemic symptoms, extensive disease, or persistent lesions. Agents that may be used include prednisone (15–80 mg daily or 1–1.5 mg/kg daily), methotrexate (5–20 mg weekly), azathioprine (50–200 mg daily or 0.5–2.5 mg/kg daily based on thiopurine methyltransferase (TPMT) level), hydroxychloroquine (400 mg three times daily), mycophenolate mofetil (2 g daily), cyclosporine (2.5–5 mg/kg daily, divided twice a day), or cyclophosphamide (2 mg/kg daily) [15, 71].

Therapy for the ANCA-associated vasculitides has been studied in depth. Before the use of cyclophosphamide, Wegener's granulomatosis was a fatal disease with death typically occurring within 5–12 months of disease onset. The introduction of cyclophosphamide and corticosteroids increased survival to 80% [72]. A randomized controlled trial of 149 patients with ANCA-associated vasculitis showed that pulse cyclophosphamide (15 mg/kg every 2–3 weeks) was as effective as daily oral cyclophosphamide (2 mg/kg) in inducing remission; in addition, fewer cases of leukopenia were seen with the pulse regimen [73].

In some patients, methotrexate may be an alternative to cyclophosphamide for induction of remission. A randomized trial of 100 patients found similar remission rates at 6 months of therapy (methotrexate 89.8% and cyclophosphamide 93.5%). However, remission was delayed in patients with lower respiratory tract involvement or more extensive disease. Patients treated with methotrexate had a higher rate of relapse (69.5%) than patients treated with cyclophosphamide (46.5%), and relapse occurred sooner in those treated with methotrexate (13 months) than in those treated with cyclophosphamide (15 months). In this study both treatments were tapered and stopped by 12 months; the high rates of relapse lead the authors to conclude that therapy should be continued longer than 12 months [74].

Cyclophosphamide may be associated with serious adverse effects such as infection, bone marrow toxicity, cystitis, transitional cell carcinoma, myelodysplasia, and infertility [72]. An important study by Jayne et al. showed that exposure to cyclophosphamide could be safely reduced by substitution of azathioprine after remission was achieved. In this study, comparable rates of relapse were seen in patients who continued on cyclophosphamide after remission (13.7%) and those who were switched to azathioprine (15.5%) [75]. Methotrexate has been shown to be an alternative to azathioprine in maintenance therapy. A study by Pagnoux et al. showed that the two drugs had similar rates of adverse events (azathioprine 29/63 patients, methotrexate 35/63) and relapse (azathioprine 23/63, methotrexate 21/63). Of note, 73% of these relapses occurred after the study drugs were discontinued [76]. Mycophenolate mofetil appears to be less effective than azathioprine for maintenance of remission. In a study of 156 patients, relapse was seen in 30/80 patients treated with azathioprine and 42/76 patients treated with mycophenolate mofetil ($p=0.03$) [77].

Novel biologic therapies targeted against specific components of the immune system may be used in patients in whom conventional therapy has failed. Agents such as infliximab (chimeric antitumor necrosis factor-alpha (TNF-alpha) monoclonal antibody), etanercept (fusion protein of the p75 TNF-alpha receptor and IgG1), adalimumab (fully humanized IgG1 anti-TNF-alpha monoclonal antibody), rituximab (chimeric anti-CD20 monoclonal antibody), anakinra (recombinant interleukin-1 receptor antagonist), and IVIG may be used in refractory disease [78, 79]. Prospective studies of infliximab and adalimumab combined with standard therapy of cyclophosphamide and corticosteroids in patients with ANCA-associated vasculitis have shown that these agents may reduce corticosteroid requirements. Mean prednisolone doses decreased from 23.8 mg/day to 8.8 mg/day at week 14 with infliximab [80]. In patients with ANCA-associated vasculitis and renal involvement, adalimumab reduced mean prednisolone doses from 37.1 to 8.1 mg/day at week 14 [81]. A randomized controlled trial of 174 patients found that etanercept was not more

effective than placebo in maintenance treatment of Wegener's granulomatosis. Sustained remission was seen in 69.7% of patients treated with etanercept and in 75.3% of patients in the control group ($p=0.39$) [82]. A recent study by the European Vasculitis Study Group found that rituximab and cyclophosphamide-based induction regimens for ANCA-associated renal vasculitides had similar rates of sustained remissions and adverse effects. Sustained remission was seen in 76% of patients in the rituximab group (treated with glucocorticoids, rituximab for 4 weeks, and 2 cyclophosphamide pulses) and in 82% of patients in the control group (treated with glucocorticoids and cyclophosphamide for 3–6 months followed by azathioprine). Severe adverse effects occurred in 42% of patients in the rituximab group and 36% of patients in the control group; 18% of patients in each group died [83]. The RAVE-ITN Research Group found that rituximab may be superior to cyclophosphamide for inducing remission in relapsing disease. Disease remission at 6 months (without corticosteroids) was seen in 67% of the rituximab group versus 42% of the control group treated with cyclophosphamide ($p=0.01$) [84].

9.5 Conclusion

The vasculitides are a heterogeneous group of diseases. While some forms of vasculitis are limited to the skin, the physician must always consider the possibility of systemic involvement. A thorough history, physical examination, and biopsy increase the likelihood of making a correct diagnosis. While some forms of vasculitis progress slowly, others can lead to fatal complications rapidly; the prompt recognition of vasculitis and determination of extent of disease are crucial so that appropriate therapy can be initiated.

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Skin Manifestations of Internal Disease

10

Daniel Behroozan and Hana Jeon

10.1 Introduction

As the largest organ in the body, the skin may reveal the first manifestations of internal disease. The astute clinician can often use dermatologic findings to diagnose an underlying systemic disease. This chapter outlines some of the most important skin manifestations of internal disease. Common yet clinically important systemic diseases will be reviewed, and their most notable skin findings will be delineated.

10.2 Hyperlipidemia

Hyperlipidemia is a well-known risk factor for coronary artery disease. Hyperlipidemia may be a primary disorder or secondary to another cause. Primary hyperlipidemia consists of dyslipidemia syndromes while secondary hyperlipidemia may be associated with endocrine disorders, renal disorders, chronic liver disease, medications, and pregnancy. Xanthomas and xanthelasmas are dermatologic manifestations indicative of a possible abnormality in lipid metabolism.

10.2.1 Xanthomas

Xanthomas appear as yellowish or pink papules, plaques, or nodules. Histologically, dermal accumulations of lipid-laden macrophages are characteristic. Eruptive xanthomas are small papules that appear suddenly on the buttocks, hands, or extensor surfaces, sometimes accompanied by pruritus or tenderness [1] (Fig. 10.1). They are associated with very high triglyceride levels and clear rapidly when serum lipid levels are lowered. They can also be secondary to uncontrolled diabetes. Patients with eruptive xanthomas are at risk of developing severe pancreatitis and should be appropriately managed with dietary and pharmacologic interventions such as statins to normalize serum lipid levels [2].

Tuberous xanthomas tend to be larger and deeper than eruptive xanthomas and evolve slowly. They appear on the knees, palms, or extensor surfaces of the body. The lesions are painless and due to cholesterol accumulation within the tissues. Tuberous xanthomas are associated with primary hyperlipoproteinemias with elevated cholesterol levels, such as familial hypercholesterolemia and familial dysbetalipoproteinemia. Tendinous xanthomas, which are similar lesions found in extensor tendons such as the Achilles tendon, may also be present in these patients. Treating the underlying

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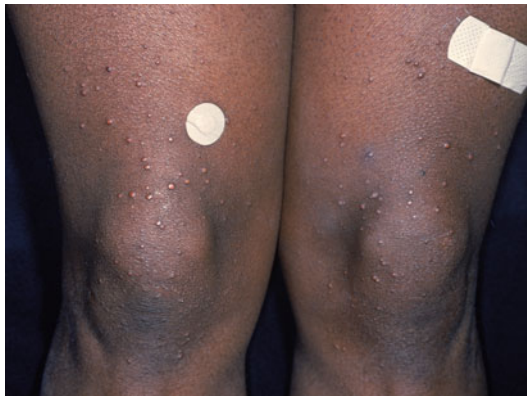

Fig. 10.1 Diffuse yellow papules and small plaques consistent with eruptive xanthomas. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

condition is essential in conjunction with dietary changes, exercise, and pharmacologic intervention. While eruptive xanthomas can resolve within weeks of initiating systemic medical treatment, and tuberous xanthomas can resolve after months of similar treatment, tendinous xanthomas may persist for years despite treatment and may even need surgical intervention to alleviate infrequent but obvious swelling which can rarely lead to chronic morbidity.

10.2.2 Xanthelasma

Xanthelasmas, also known as xanthelasma palpebrarum, are yellowish plaques that are most commonly found on the inner canthi. More common in women and older individuals, xanthelasmas are the most common of all xanthomas [3]. The lesions can be soft, semisolid, or calcified, and are characterized by a tendency to be symmetric, permanent, progressive, multiple, and coalescent [4]. They tend to grow slowly with time, and the diagnosis can often be made clinically. Histologically, the lesions are composed of foamy, lipid-laden histiocytes that tend to be located in the superficial dermis in perivascular and periadnexal locations.

Although roughly 50% of patients with xanthelasma have normal serum cholesterol levels, studies have shown that the presence of xanthelasma is a risk factor for mortality from atherosclerotic disease regardless of cholesterol level. It has also been reported that patients with xanthelasmas in the setting of normal levels of cholesterol and triglycerides may have elevated LDL and VLDL and decreased HDL. Therefore, xanthelasma should be considered a marker of dyslipidemia, and a full lipid profile should be considered to identify those with more subtle lipid abnormalities that are still associated with increased risk of cardiovascular disease. Familial hypercholesterolemia or familial dysbetalipoproteinemia should be considered especially in those patients who develop xanthelasma at a young age.

Xanthelasmas are not known to cause serious complications expect in rare instances in which the lesions become large and obstruct vision [5]. Although the classic method of treatment is surgical excision, surgical scarring can occur. This has led to investigations of other methods of treatment including trichloroacetic acid peeling, electrodessication, and laser therapy, all of which result in varying success [6]. Regardless of the mode of treatment, recurrence of xanthelasma is common, especially in cases of familial hyperlipoproteinemia where involvement of all four eyelids, or more than one recurrence, is common [7].

10.3 Kidney Disease

10.3.1 Half-and-Half Nails

Half-and-half nails (also known as Lindsay's nails) are associated with chronic renal failure. This nail finding is a result of nail bed edema and characterized by apparent leukonychia in the proximal half of the nail which fades upon application of pressure [8]. These nail changes are thought to be an occasional but very specific finding of chronic renal failure, and it is estimated that up to 40% of patients with renal insufficiency have the nail changes during the course of their disease [9]. It has been proposed that the distal dark color is caused by melanin deposition resulting from stimulation of nail matrix melanocytes by acidosis and uremia [10]. Others have proposed that changes in the nail bed rather than in the nail

produced the change, such as an increase in the number of capillaries and a thickening of the capillary walls in the nail bed [11].

10.3.2 Uremic Pruritus

While pruritus is infrequent in patients with acute renal failure, it is a common symptom in patients with chronic renal failure [12]. The pathogenesis of uremic pruritus is unknown, with various proposed mechanisms including nitric oxide, pruritogenic cytokines, and altered skin innervations secondary to neuropathy [13].

Before initiating treatment, a specific diagnosis should first be made as patients with chronic renal failure may experience pruritus secondary to other skin conditions such as infections or contact dermatitis from dialysis catheters. Secondary hyperparathyroidism due to chronic renal failure has also been associated with uremic pruritus (parathyroidectomy in dialysis patients with secondary hyperparathyroidism has been reported to decrease pruritus), though PTH itself does not seem to be pruritogenic. Thus, surgery should be considered for pruritus in association with secondary hyperparathyroidism. In cases without a specific cause, treatment includes optimizing dialysis, as well as the use of emollients and topical analgesics such as pramoxine. Ultraviolet light B therapy has also been shown to be effective.

10.3.3 Uremic Frost

Uremic frost is a rare dermatologi manifestation of severe azotemia which clinically manifests as characteristic white, crystalline, and friiable depostis arising in the head and neck area.. The lesions form as a result of the accumulation of urea and other nitrogenous waste products in sweat which then crystallize after evaporation [14]. Today, this dermatologic finding is rarely seen in developed countries due to the availability of hemodialysis [15]. Uremic frost should be differentiated from eczema, postinflammatory desquamation, and retention keratosis. A history of severe azotemia as well as the presence of characteristic lesions help to make the diagnosis. To verify the composition of the lesions, scrapings can be taken and diluted in normal saline, and then tested for elevated urea nitrogen levels.

10.4 Diabetes

10.4.1 Necrobiosis Lipoidica

Necrobiosis lipoidica is present in approximately 0.3% of patients with diabetes. It may be seen in both type I and type II diabetes with about two-thirds of cases occurring in type II [16]. Although not all patients with necrobiosis lipoidica have diabetes, studies have shown that majority of those without diabetes had abnormal glucose tolerance tests, subsequently developed diabetes, or had a strong family history of diabetes [17]. Most patients are females. The pathogenesis remains unknown. Proposed mechanisms include vascular abnormalities, collagen abnormalities, sweat gland and nerve disturbances, and abnormal leukocyte function.

Necrobiosis lipoidica initially presents as an oval violaceous patch, most often in the pretibial region. It slowly evolves into a larger lesion with an erythematous advancing border and central epidermal atrophy (Fig. 10.2). Subsequent ulceration is common. Histologically, the lesions demonstrate layers of interstitial granulomatous inflammation and fibrosis with multinucleated histiocytes involving the entire dermis. Diagnosis can often be made clinically.

At this time, there is no consistently effective treatment for necrobiosis lipoidica. Treatment options include corticosteroids, fibrinolytics, antiplatelet agents, and surgical treatments (i.e., excision and grafting). Diabetic glycemic control does not seem to result in the resolution of necrobiosis lipoidica.

10.4.2 Bullae Diabeticorum

Although most commonly seen in patients with long-standing diabetes, bullosis diabeticorum may also occur as the initial presentation of diabetes [18]. The lesions are characterized by

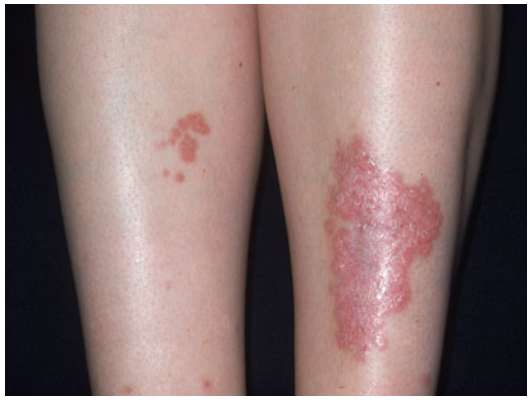

Fig. 10.2 Erythematous to violaceous atrophic plaques of the pretibial legs consistent with necrobiosis lipoidica. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

the rapid onset of tense, painless blisters on the feet, legs, or hands. They vary in size from 0.5 to 3 cm, can be unilateral or bilateral [19], and usually heal in 2–4 weeks [20]. The pathogenesis of bullosis diabeticorum is unknown. Proposed mechanisms include nephropathy, immune-mediated vasculitis, and disturbed metabolism of calcium, carbohydrates, or magnesium.

The diagnosis is made clinically as there is no specific diagnostic test for bullosis diabeticorum [21]. Histologically, subepidermal bullae are observed, and direct immunofluorescence is usually negative [22]. The differential diagnosis includes other blistering disorders such as bullous pemphigoid, porphyria cutanea tarda, pseudoporphyria, drug-induced bullous eruptions, and friction/burn blisters.

The goal of treatment is to prevent secondary infection and to allow the lesions to heal on their own [23]. While some clinicians suggest topical therapies are not necessary, others suggest aspirating the blisters to reduce discomfort and applying petroleum jelly or a topical antibiotic ointment to prevent secondary infection.

10.4.3 Acanthosis Nigricans

About 30–50% of patients with diabetes have acanthosis nigricans. Acanthosis nigricans is characterized by velvety, hyperpigmented plaques most commonly involving the axillae and/or neck creases, as well as other intertiginous areas such as the groin, and less frequently the flexural extremities, periorally, and periorbitally. High levels of circulating insulin promote increased liver production of insulin-like growth factor, which binds to epidermal growth factor receptors to produce thickening of the epidermis and hyperkeratosis [24]. These lesions are most often asymptomatic, but can be malodorous or painful. Histologically, acanthosis nigricans is characterized by hyperkeratosis, mild acanthosis, and papillomatosis. The hyperpigmentation results from thickness of the keratin-containing superficial epithelium rather than a change in melanocytes. Acanthosis nigricans is classified either as benign when it occurs in the context of insulin resistance, or as malignant when it is a paraneoplastic sign of an internal malignancy, most commonly gastric adenocarcinoma [25]. Thus, evaluation for an internal malignancy should be considered if patients with acanthosis nigricans are found not to have insulin resistance. Because obesity is an important cause of insulin resistance, weight control and dietary changes play an important role in therapy. Common pharmacologic therapies to improve insulin sensitivity such as metformin or long-term treatment with octreotide (a synthetic analog of somatostatin) to reduce insulin secretion and eventually reduce insulin binding to insulin-like growth factor may be helpful. Topical treatment includes retinoids, ammonium lactate, and calcipotriene.

10.5 Thyroid Disease

10.5.1 Graves' Disease

Graves' disease is an autoimmune hyperthyroidism caused by autoantibodies that bind to thyrotropin (also known as thyroid-stimulating hormone, TSH) receptors in the thyroid gland resulting in increased thyroid hormone synthesis. Pretibial myxedema is a specific sign of Graves' disease, but occurs in only 3–5% of patients with the disease [26]. It is characterized by indurated tan to brownish-red plaques over the pretibial areas (Fig. 10.3). Histologically, there is

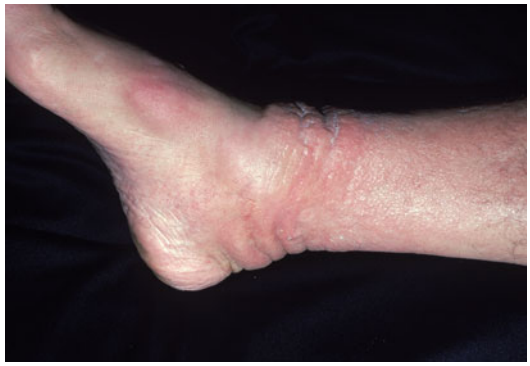

Fig. 10.3 Indurated waxy plaques of the pretibial leg in a patient with hyperthyroidism. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

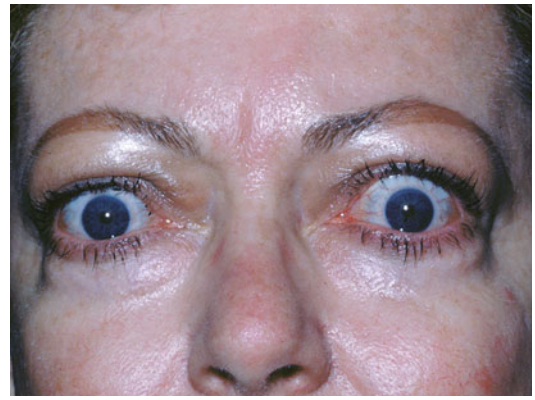

Fig. 10.4 Physical finding and eye changes seen in patients with Graves' disease. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

infiltration by mucopolysaccharides (mucinous ground substance), thought to be caused by stimulation of TSH receptors that are present in the pretibial connective tissue. Treating hyperthyroidism does not alter the presence of pretibial myxedema because treatment of Graves' disease treats hyperthyroidism rather than the underlying autoimmune disease [27].

Graves' ophthalmopathy (proptosis) may be the first sign of hyperthyroidism. Associated symptoms include photophobia, tearing, and sensation of a foreign material in the eye [28] (Fig. 10.4). It is thought to be caused by infiltration of retrobulbar tissues and extraocular muscles by mononuclear cells and mucopolysaccharides.

Dermatologic manifestations of hyperthyroidism may generally be characterized by warm, moist skin and separation of the nails from the nail bed (onycholysis). The nail changes are characterized by rapid growth, softening, and friability, and often reverse following successful therapy of hyperthyroidism. Hair caliber may be fine and thin; frank alopecia is also seen, though the severity of alopecia does not correlate with the severity of hyperthyroidism.

10.5.2 Hypothyroidism

Dermatologic manifestations of hypothyroidism include dry, scaly, and cold skin. Some patients may be severely xerotic and develop an acquired ichthyosis. The loss of the outer third of the eyebrows is considered a classic hair loss pattern for patients with hypothyroidism. Hair may be coarse and brittle, with slowed growth rate (increase in telogen hairs) [28]. In severe hypothyroidism, enlargement of the lips and tongue as well as diffuse thickened skin may be observed. The thickened skin, also called myxedema, differs from pretibial myxedema of Graves' disease; myxedema of hypothyroidism has a generalized distribution with smaller quantities of mucin. The skin of hypothyroid patients may appear yellow due to impaired hepatic conversion of carotene to vitamin A, resulting in excess deposition of serum carotene in the stratum corneum. There may be cutaneous pallor caused by both vasoconstriction and alteration of the fraction of incident light, which results from increased water and mucopolysaccharide content in the dermis [28]. About 90% of patients with hypothyroidism have some degree of nail changes. The nails are brittle, slow growing, and striated either longitudinally or horizontally. Onycholysis is more common in hyperthyroidism but has been reported in association with myxedema.

10.6 Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. Skin manifestations occur in approximately 25% of cases and may be

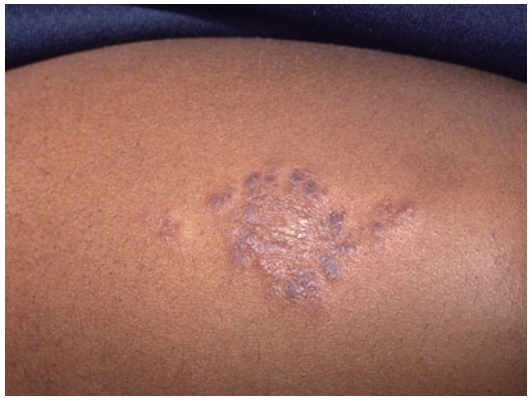

Fig. 10.5 Common nonspecific skin findings seen in Sarcoidosis. Note the annular pattern of lesions. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

the first sign of sarcoidosis. The lesions are classified as either specific or nonspecific, based on the presence or absence of non-caseating granulomas on histology, respectively.

The most common skin findings are small, smooth dermal papules of varying colors such as tan, red, violaceous, or brown (Fig. 10.5), though in African Americans, they may be hypopigmented. Lesions are most commonly located around eyelids, nasal alae, nasolabial folds, and neck [29]. The papules sometimes enlarge or coalesce to form annular lesions or plaques [30]. Uncommon but specific skin lesions of sarcoidosis include subcutaneous nodules, ulcerations, dystrophic nails, scarring alopecia, verrucous lesions, pustular lesions, and rarely erythroderma [29].

Lupus pernio is a distinct form of cutaneous sarcoidosis presenting as purplish plaques around the nose, ears, lips, fingers, and face [31]. The lesions appear insidiously and progress to result in scarring, fibrosis, and deformity. Lupus pernio is associated with the involvement of the upper respiratory tract, pulmonary fibrosis, as well as severe bony disease. Patients with lupus pernio often have persistent and progressive pulmonary manifestations [30].

Erythema nodosum is the most common nonspecific skin lesion of sarcoidosis. It is characterized by erythematous and tender subcutaneous nodules most often located in the pretibial areas. It is thought to be caused by a delayed hypersensitivity response, and studies have shown involvement of T-lymphocytes as well as reactive oxygen intermediates in producing the tissue damage and inflammation [32]. Erythema nodosum is typically associated with a subacute transient course of sarcoidosis. Löfgren's syndrome describes an acute form of sarcoidosis associated with erythema nodosum in the setting of asymptomatic bilateral hilar lymphadenopathy, uveitis, fever, and arthritis. It most often resolves without treatment. Erythema nodosum is usually self-limiting or improves with treatment of the underlying disorder. Symptomatic treatment to relieve the discomfort associated with the skin lesions can be achieved with salicylates or nonsteroidial anti-inflammatory drugs. Although the mechanism is unclear, potassium iodide (400–900 mg daily) has been reported to be beneficial in refractory cases.

Sarcoidosis is diagnosed by a combination of clinical, radiologic, histopathologic, and laboratory findings. In patients with asymptomatic bilateral hilar lymphadenopathy or Löfgren's syndrome, clinical presentation may be sufficient. Following diagnosis, patients should be thoroughly assessed to evaluate the extent of the disease.

Approximately 70% of cutaneous sarcoidosis resolve without treatment in 1–2 years. For mild disease, potent topical corticosteroids such as clobetasol or intralesional corticosteroids may be considered. For extensive cutaneous disease, prednisone is the drug of choice [33]. For refractory sarcoidosis, methotrexate is most commonly used as a nonglucocorticoid immunosuppressive agent. Other antimetabolites such as azathioprine and leflunomide are also used when patients fail or cannot tolerate methotrexate. Other options for patients who fail glucocorticoid treatments include antimalarial drugs with immunomodulating properties (e.g., chloroquine, hydroxychloroquine) and tumor necrosis factor alpha (TNFα) inhibitors (TNFα is thought to play a role in maintenance of granuloma formation in sarcoidosis by accelerating the inflammatory process).

10.7 Cushing's Syndrome

Cushing's syndrome refers to a state of excess glucocorticoids and has various dermatologic findings. Thinning and atrophy of the skin, easy bruising,

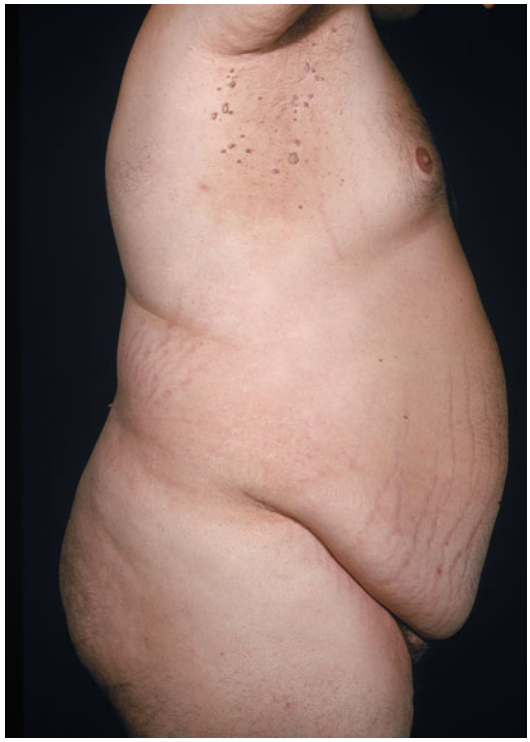

Fig. 10.6 Characteristic striae and body habitus of a patient with Cushing's syndrome. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

and inhibition of wound healing may be observed. A reduction in epidermal and dermal components of the skin leads to atrophy; there is decreased collagen synthesis, elastic fibers, and dermal mucopolysaccharides [34]. The epidermis is shiny and may show scaling [35]. High levels of glucocorticoids impair wound repair and cause easy damage to the skin with subsequent ulceration and infection. Additionally, increased vascular fragility results in petechiae and ecchymoses.

Large, violaceous striae may appear in areas of stretched skin such as the abdomen and buttocks (Fig. 10.6) due to weak dermal connective tissue and the failure of normal regenerative capacity of the skin [35]. The striae of Cushing's are increased in depth, breath, and intensity of color as compared to the striae of adolescence or pregnancy.

Excess deposits of fat in the clavicles, posterior neck (buffalo hump), cheeks (moon facies), and abdomen result in the characteristic body habitus. Patients with Cushing's syndrome can also develop steroid-induced acne characterized

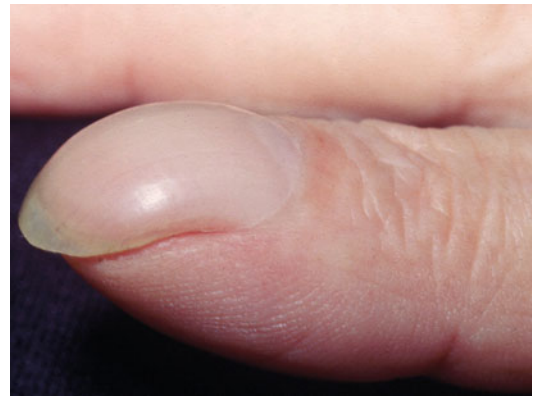

Fig. 10.7 Hyper-convexity of the nail consistent with clubbing. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

by erythematous papules and pustules uniform in their stage of development and without comedones. They spare the face and appear on the trunk, arms, and shoulders. Hypertrichosis is also common most often on the face. Hair tends to be laguno-like rather than true beard growth [35].

Hypercortisolism could be due to iatrogenic administration of glucocorticosteroids, pituitary or ectopic adrenocorticotropic hormone (ACTH) production, or adrenal tumors [35]. Although the most common cause is therapeutic administration of exogenous systemic glucocorticoids, it has been reported that the use of potent topical corticosteroids can induce similar skin changes [36]. Some suggest limiting the usage of potent topical glucocorticoids to 50 g/week in adults and 15 g/week in children to avoid such adverse reactions [36]. The skin changes caused by Cushing's syndrome are only partially reversible with treatment of the underlying disease.

10.8 Pulmonary Disease

Clubbing is characterized by increased convexity of the nail due to proliferation of the soft tissues in the distal phalanx (Fig. 10.7). The emergence angle of the nail becomes equal to or greater than 180° [37]. The nail plate enlarges in size. About 80% of nail clubbing is associated with respiratory diseases such as lung cancer, sarcoidosis, mesothelioma, empyema, cystic fibrosis, and interstitial lung disease.

Fig. 10.8 Absent lunulae, absent cuticles, thickening with curvature to the sides, and yellowing of nails in a patient with yellow nail syndrome. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

In the evaluation of clubbing, it is important to verify that the patient has true clubbing rather than pseudoclubbing, which involves only a single digit and is usually due to a subungual mass [37]. In those with true clubbing, a chest X-ray should be considered to rule out underlying pulmonary causes.

Hypertrophic osteoarthropathy is an important entity to consider when evaluating nail clubbing. It is a syndrome that consists of simple clubbing, peripheral neurovascular disease, acute bone pain, muscle weakness, joint pain, and hypertrophy of the extremities. The presence of these findings is associated with malignant tumors of the pulmonary system 90% of the time. The syndrome mostly affects males with a familial predisposition. Pamindronate may be considered in treating painful osteoarthropathy [38].

Yellow nail syndrome is also associated with pulmonary diseases such as tuberculosis, pulmonary malignancies, and asthma. The classic triad of yellow nail syndrome is lymphedema of the lower extremity, nail changes, and pleural effusion. The nail changes consist of absent lunulae and cuticles, nail thickening with lateral curvature, and yellowing (Fig. 10.8). The syndrome usually involves all 20 nails. Nail growth is slowed to less than 0.2 mm/week [39]. Total nail plate detachment may occur (secondary onycholysis), as well as colonization by Pseudomonas aeruginosa that may produce green-to-black discoloration of the nail plate. In patients with paraneoplastic yellow nail syndrome, the nails often return to normal when the underlying tumor is treated. The exact pathogenesis of the yellow nail syndrome remains unknown. One possible mechanism is a congenital abnormality of the lymphatic vessels, which explains the nail pathology characterized by ectatic lymphatics in the nail bed as well as matrix dermis [37].

10.9 Gastrointestinal

10.9.1 Pyoderma Gangrenosum

Pyoderma gangrenosum is a severe ulcerative skin condition that is associated with inflammatory bowel disease and chronic infectious hepatitis, as well as other non-gastrointestinal conditions such as rheumatoid arthritis, lupus erythematosus, and HIV infection. It is estimated that about 5% of patients with ulcerative colitis develop pyoderma gangrenosum. In some patients, pyoderma gangrenosum may develop years before the onset of inflammatory bowel disease.

The lesion begins as a small tender pustule, but eventually breaks down and forms an expanding ulcer. It can grow rapidly and extend to fat, fascia, and muscle. The ulcers can become very

large before healing with a thin and atrophic scar [40]. While not specific to pyoderma gangrenosum, patients may exhibit pathergy, a phenomenon where skin trauma or injury can trigger the development of skin ulcerations which may be resistant to healing. Pathergy may also lead to non-healing wounds at sites of surgical incisions. Facial pydoerma gangrenosum tends to be more superficial and less destructive.

The pathogenesis of pyoderma gangrenosum remains largely unknown. It is thought that abnormal neutrophil trafficking and immunologic dysfunction are involved. Pyoderma gangrenosum is a diagnosis of exclusion; culture for bacterial, viral, and fungal agents should be done. Therapy involves treating the associated disease and administration of systemic steroids (predinosolone 1–2 mg/kg daily with tapering as healing occurs) and other immunosuppressive agents such as cyclosporine. However, treatment is often recalcitrant when an underlying systemic condition cannot be identified and subsequently treated. More recently, the use of TNF-α inhibitors, specifically infliximab (5 mg/kg infusion at weeks 0, 2, and 6 and every 8 weeks after that), has also been shown to be effective in management of this difficult condition.

10.9.2 Pancreatic Panniculitis

Pancreatic panniculitis has been associated with both acute and chronic pancreatitis as well as pancreatic carcinoma, but overall is a rare associated finding in patients with pancreatitis. Pancreatitis results in the outpouring of digestive enzymes, such as pancreatic lipase, phospholipase, trypsin, and amylase, that may migrate into tissue to cause pancreatic panniculitis [41]. Tender, fluctuant, red subcutaneous nodules develop on the lower legs. Occasionally, the nodules rupture discharging a thick and oily liquid which may be a result of autodigestion of the subcutaneous fat by the pancreatic enzymes. Histologically, a mixed lobular and septal panniculitis with lipocyte necrosis ("ghost cells") and basophilic saponification may be seen. Prognosis depends on the underlying pancreatic disease, treatment of which may help to treat the skin lesions; the nodules may regress as the level of lipolytic pancreatic enzymes decreases.

10.9.3 Dermatitis Herpetiformis

Dermatitis herpetiformis, a cutaneous marker of gluten-sensitive enteropathy, is characterized by pruritic grouped papules and vesicles symmetrically distributed on the elbows, knees, scalp, buttocks, and extensor forearms [42]. Men are more often affected than women, and dermatitis herpetiformis usually first occurs at a young adult age. Gluten is the main adhesive substance of many grains, and gliadin is the most important sensitizing protein as well as the substrate for tissue glutaminase. Autoantibodies against tissue glutaminase also cross-react with epidermal transglutaminase leading to the formation of the cutaneous lesions. There is a strong HLA association with 90% of patients possessing HLA-DQ2.

The diagnosis can be made by histologic examination of an early blister and direct immunofluorescence of non-lesional skin in which IgA is seen in the dermal papillae. Suppressive therapy using dapsone is the mainstay of treatment. Dapsone is effective in rapidly clearing the rash, but relapse upon discontinuation of the medication is also rapid. Therapy should also include a gluten-free diet, which can be difficult, but essential in treating the underlying disease as well as dermatitis herpetiformis.

10.9.4 Hepatobiliary/Cirrhosis

10.9.4.1 Spider Angiomas

The cutaneous signs of liver disease generally correlate with the severity of the disease [43].

Cirrhosis distorts the normal liver anatomy causing decreased blood flow through the liver resulting in portal hypertension. Portal hypertension, in turn, results in ascites, peripheral edema, and varices. There is also impaired biochemical function; albumin as well as clotting factor synthesis are decreased. This results in purpura and ecchymoses.

Spider angiomas result from hyperestrinism, and develop in at least 75% of patients with cirrhosis. The lesion is characterized by centralized red macule or papule with outward vascular extensions resembling a spider web. The center is a coiled central arteriole, and the extensions are smaller vessels radiating outward. Spider angiomas are most often planar, but can enlarge to form hemangioma-like masses [43]. They are found on the face, neck, trunk, and upper extremities. The lesions are usually associated with chronic liver disease, but may be associated with pregnancy and oral contraceptives, as well. Thus, spider angiomas are not considered to be pathognomonic of liver disease.

10.9.5 Terry's Nails

Terry's nails occur in patients with liver disease, and are characterized by nails that turn opaque white except for the distal portion which remains pink in color. The discoloration stops suddenly at about 1–2 mm from the distal edge of the nail, leaving a reddish brown transverse band [44]. These nail findings are not specific to patients with cirrhosis, and may also be found in some normal women younger than 20 years of age. It is thought that hypoalbuminemia results in edema of the connective tissue in the distal nail bed, converting it into a loosely knit rather than highly compact collagenous structure. This change in turn stimulates the organization of the lunula producing a white color of the nail. Histologically, there are changes in vascularity, and specifically distal telangiectasias [44]. The recognition of Terry's nails may serve as an important clue to early diagnosis of hepatic disease.

10.10 Amyloidosis

Amyloidosis refers to a group of conditions characterized by the extracellular deposition of an abnormal protein [45]. While most of proteins in humans and other species are synthesized in an alpha-helical structure, amyloid protein is synthesized in a much less biodegradable beta-pleated sheet structure. There are many proteins that can be precursors for amyloid fibril deposition in the skin: light-chain monoclonal protein, beta-2 microglobulin, serum protein A, prealbumin, and keratin. Amyloidosis can be classified according to the type of amyloid protein deposition and clinical presentation.

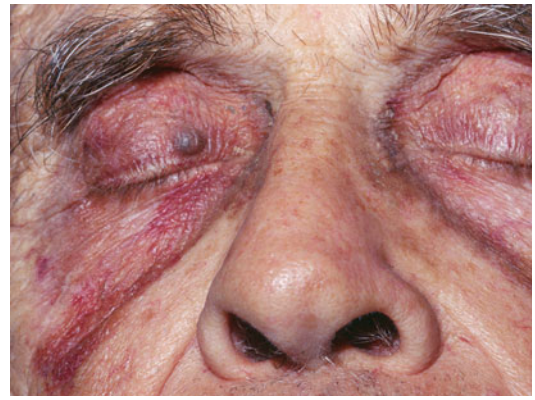

Fig. 10.9 Periorbital spontaneous purpura in a patient with systemic amyloidosis. Images courtesy of the Victor D. Newcomer, M.D. collection at UCLA and Logical Images, Inc

About 30% of patients with primary or myeloma-related systemic amyloidosis have cutaneous manifestations. The dermatological signs of systemic amyloidosis can be helpful in diagnosis because these signs may be the only manifestations before systemic amyloidosis develops into a late-stage disease [46]. As amyloid infiltrates and weakens blood vessels, patients develop purpura, petechiae, or ecchymoses occurring spontaneously on skin folds (e.g., the eyelids, axillae, and anogenital area). "Pinch purpura" in which pinching the skin produces purpuric lesions may occur. Periorbital pupura may form following coughing or the valsalva maneuver (Fig. 10.9). When amyloid infiltrates travel to the dermis, subcutaneous nodules or plaques may form. The lesions appear hemorrhagic, though they may also appear smooth and waxy.

Lichen amyloidosis, the most common type of localized cutaneous amyloidosis, is characterized by tan to brown pruritic papules which may coalesce to form plaques [47]. The lesions most commonly form on the shins.

Various stains of a biopsied specimen can be used to diagnosis amyloidosis. Congo red, for

example, shows doubly refractive and apple green amyloid when examined in polarized light.

Although treatments are usually ineffective, topical corticosteroids could be tried as an antipruritic measure. PUVA or systemic retinoids may be considered as well. In macular amyloidosis, pruritic macular hyperpigmentation occurs in the interscapular area. Treatment is similar to lichen amyloidosis. Topical capsaicin once daily for long periods of time has helped some patients. Both lichen amyloidosis and macular amyloidosis are variants of primary localized cutaneous amyloidosis and occur most often in patients from Asia, the Middle East, and Central and South America.

10.11 Malignancy

10.11.1 Sister Mary Joseph's Nodule (Colon Cancer)

Sister Mary Joseph's nodule is a nodular umbilical metastatic tumor (Fig. 10.10). It was named after Sister Mary Joseph, the first surgical assistant to Dr. William Mayo and the superintendent of St. Mary's Hospital in Rochester, Minnesota, who noted the association between metastatic intraabdominal cancer and paraumbilical nodules [48]. Sister Mary Joseph's nodule is associated with cancers of the gastrointestinal tract and ovary. The most commonly associated malignancy is stomach (20%), followed by large bowel (14%), ovary (14%), and pancreatic tumors (11%). In about 20% of patients, the primary site cannot be identified.

In general, cutaneous metastasis is a poor prognostic sign and may signify widespread internal metastasis [49]. While the prognosis is dependent on the primary tumor, a study found that the average life expectancy after developing skin metastases was 3 months (Figs. 10.11 and 10.12).

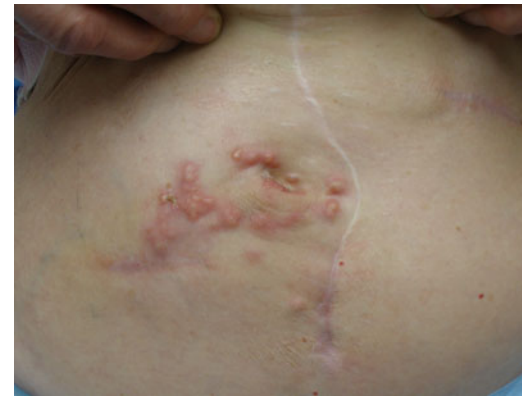

Fig. 10.10 Periumbical metastatic tumors consistent with a diagnosis of Sister Mary Joseph nodule. The diagnosis was made by an incisional biopsy. From the personal collection of Daniel Behroozan, M.D

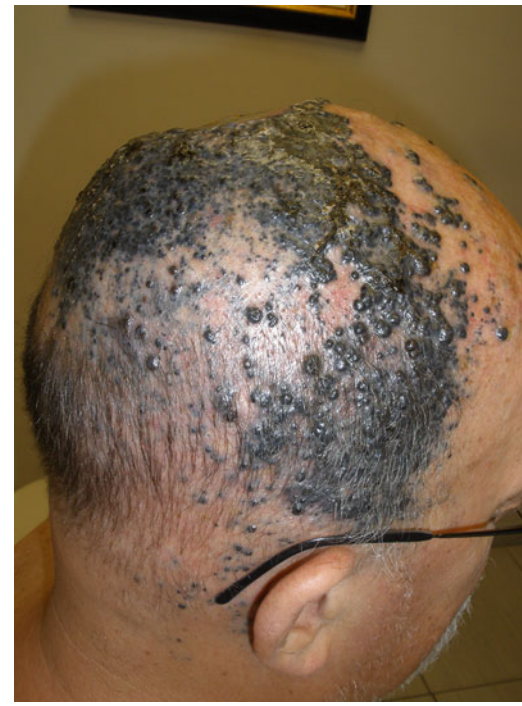

Fig. 10.11 Diffuse and disseminated blue nodules in two patients with metastatic melanoma. From the personal collection of Daniel Behroozan, M.D

10.11.2 Malignant Acanthosis Nigricans

Acanthosis nigricans (previously discussed under the diabetes section) is called malignant acanthosis nigricans when there is a sudden onset of widespread acanthosis nigricans with weight loss, suggesting an underlying malignancy [50]. About 60% of patients who develop malignant acanthosis nigricans have been found to have adenocarcinoma of the stomach, and most often

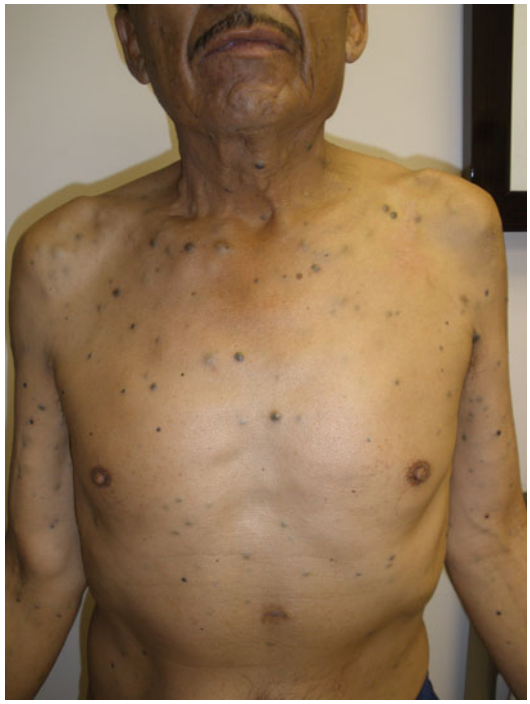

Fig. 10.12 Diffuse and disseminated blue nodules in two patients with metastatic melanoma. From the personal collection of Daniel Behroozan, M.D

are at an advanced stage of the disease. "Tripe palms," acanthosis nigricans of the palms, is characterized by a velvety furrowing of the palmar surfaces and is also often associated with internal malignancy. It is thought that acanthosis nigricans appears due to an epidermal growth factor that is secreted by the tumor. The evidence for this has been shown in some cases where successful resection of the adenocarcinoma results in regression of the acanthosis nigricans [50].

10.11.3 Sweet's Syndrome

Sweet's syndrome is commonly associated with hematopoietic malignancies including acute myelogenous leukemia (the most common), chronic myelogenous leukemia, lymphocytic leukemia, T- and B-cell lymphomas, and polycythemia [51]. No clinical or histopathologic differences exist between patients with and without associated malignancy. Sweet's syndrome most commonly occurs in women 30–60 years of age. It is characterized by skin lesions, fever, malaise, and leukocytosis. About 20% of patients have an associated hematopoietic malignancy. The classic cutaneous manifestation of Sweet's syndrome is sharply demarcated and painful plaque that often has papulovesicles and pustules on the surface. The plaques are present on the face, neck, upper trunk, and extremities. Lesions may be present in the oral mucous membrane and eyes as well. As in pyoderma gangrenosum, the phenomenon of pathergy (hypersensitivity reaction developing at the site of minor skin trauma) may be seen.

The laboratory abnormalities include leukocytosis (present in 60% of patients), elevated sedimentation rates, anemia, thrombocytopenia, and increased number of segmented neutrophils.

Sweet's syndrome responds well to systemic corticosteroids (e.g., prednisolone 60 mg daily tapered over two to four weeks), but recurs in about 25% of cases. Various alternatives such as potassium iodide, clofazimine, or colchicine may be considered in recurrent cases.

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Cutaneous Findings of Collagen Vascular Disease and Related Emergent Complications

11

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11.1 Introduction

Collagen vascular diseases are disorders of unknown etiology, with features of autoimmunity, in which the immune system loses the capacity to distinguish self from nonself. This loss of immune tolerance can result in varied and protean clinical manifestations, ranging from mild constitutional symptoms to major organ failure. Skin changes may be the initial manifestation of, or have pathognomonic features, for specific collagen vascular diseases, and are often invaluable to diagnosis. In this chapter we focus on identifying features of collagen vascular diseases, with an emphasis on cutaneous findings and emergent complications.

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11.2 Lupus Erythematosus

Lupus erythematosus is a broad term used to describe a spectrum of clinical entities ranging from localized cutaneous manifestations to potentially life-threatening, multi-organ systemic involvement, caused by pathogenic autoantibodies, leading to immune complex formation in target tissues.

Systemic lupus erythematosus (SLE) is diagnosed clinically, as proposed by the American College of Rheumatology (ACR) criteria. Patients must fulfill 4 of the 11 criteria [1, 2] (Table 11.1).

Constitutional symptoms including fatigue, weight loss, and fever are common during active lupus. Fatigue may persist even when lupus is "quiescent" [3, 4].

Arthritis, presenting as joint swelling and pain, and arthralgias, or joint pain without synovitis, are one of the most common, and early features of SLE, and are often present at sometime during the disease course (Table 11.2), specifically with a lupus flare [5].

Hematologic manifestations are also common, including leukopenia (46%), anemia (42%), and thrombocytopenia (7–30%) [6, 7]. When leukopenia is secondary to active lupus, the WBC rarely decreases to <1,500 and the bone marrow is usually normal, with a greater drop in neutrophil count than lymphocyte count, though isolated lymphocytopenia is a more frequent finding. Anemia is frequent and often multifactorial, usually secondary to chronic disease or iron deficiency [8, 9].

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Table 11.1 1997 American College of rheumatology revised criteria for classification of systemic lupus erythematosus

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	(a) Pleuritis—convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion OR (b) Pericarditis—documented by ECG, rub or evidence of pericardial effusion
Renal disorder	(a) Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantitation not performed OR (b) Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	(a) Seizures—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance OR (b) Psychosis—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
Hematologic disorder	(a) Hemolytic anemia with reticulocytosis OR (b) Leukopenia—less than 4,000/mm^3 total WBC on two or more occasions OR (c) Lymphopenia—less than 1,500/mm^3 on two or more occasions OR (d) Thrombocytopenia—less than 100,000/mm^3 in the absence of offending drugs
Immunologic disorder	(a) Anti-DNA antibody to native DNA in abnormal titer OR (b) Anti-Sm: presence of antibody to Sm nuclear antigen OR (c) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; (2) a positive test result for lupus anticoagulant using a standard methods; or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test (FTA-ABS)
Antinuclear antibody (ANA)	An abnormal titer of antinuclear antibody by immunofluorescence (or an equivalent assay) at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

11.2.1 Emergent Complications

Occasionally SLE patients can have severe life-threatening thrombocytopenia in the setting of a lupus flare, which can be refractory even to aggressive therapy. Thrombocytopenia may be part of the antiphospholipid syndrome or thrombotic thrombocytopenic purpura (TTP), which includes microangiopathic hemolytic anemia (suggested by schistocytes on peripheral smear), CNS deficits, renal failure, and fever [10].

Cardiopulmonary involvement is not infrequent. Pleuritic chest pain occurs in up to 50% of lupus patients at some time during their disease [11]. Pericarditis is another common cause of chest pain in SLE patients, occurring ultimately

Table 11.2 Cumulative prevalence of 16 clinical and lab manifestations in 2,000 lupus patients [6]

Clinical or lab manifestation	Percentage
Positive ANA	97%
Arthritis, arthralgia, or myalgia	80%
Skin changes	71%
Low complement	51%
Cognitive dysfunction	50%
Fever	48%
Elevated anti-dsDNA	46%
Leukopenia	46%
Pleuritis	44%
Proteinuria	42%
Anemia	35%
Antiphospholipid antibody	35%
Elevated gamma globulin	32%
Pleural or pericardial effusion	12%
CNS vasculitis	12%
Adenopathy	10%

in 19–48% of patients [12]. Tamponade and myocardial disease is rare [13]. Clinicians should consider pulmonary embolism as the cause of cardiopulmonary symptoms in patients with lupus anticoagulant or anticardiolipin antibodies [14]. Pulmonary hemorrhage is a rare, yet life-threatening emergency in SLE, presenting with marked hypoxia along with abnormal chest imaging [15]. This complication is usually the result of either pneumonitis or pulmonary embolus and is associated with high mortality in the range of 50–90% [16]. Lupus patients are at higher risk for coronary artery disease, and myocardial infarction is now the most common cause of death in SLE patients in the Western world [17, 18].

Kidney involvement is a major cause of morbidity and hospital admissions. The most common manifestation of lupus nephritis is proteinuria [19, 20]. Nephritic or nephrotic syndrome can be observed in 30% of patients. Rapidly progressive glomerulonephritis occurs in less than 5% of patients with SLE [21].

Neuropsychiatric manifestations are seen in up to 60% of patients. Symptoms include seizures, personality changes, and cerebrovascular accidents, and are a major cause of morbidity [22–24].

11.2.1.1 Cutaneous Lupus

Cutaneous lupus is seen in 59–85% of SLE patients [25] and can be classified as LE-specific skin disease and LE-nonspecific skin disease. LE-specific skin disease has characteristic histopathologic changes, including epidermal atrophy, hyperkeratosis, liquefactive degeneration of the basal epidermis, and mononuclear cell infiltrate [26]. The three main categories of LE-specific cutaneous disease are acute cutaneous (ACLE), subacute cutaneous (SCLE), and chronic cutaneous (CCLE).

LE-nonspecific lesions, such as vasculitis and alopecia, do not have the characteristic LE histopathological changes, and can found in other medical conditions besides lupus.

It is important to note that not all cutaneous lupus patients have systemic lupus. Of patients with discoid lupus erythematosus (DLE) lesions, only 5–10% will go on to develop SLE. Conversely, 25% of patients with systemic lupus develop DLE lesions at some point in their disease course. Of patients with SCLE, about 10–15% develop SLE. Presence of acute cutaneous lupus lesions usually indicates underlying SLE [27, 28].

11.2.2 LE-Specific Skin Disease

11.2.2.1 Acute Cutaneous Lupus Erythematosus

Acute cutaneous lupus erythematosus (ACLE) can present in localized or generalized distributions and often occurs in the setting of acutely flaring SLE [29]. The most common form of ACLE is localized symmetric, confluent erythema and edema over the malar region and the bridge of the nose, sparing the nasolabial folds, also known as the "butterfly" rash (Fig. 11.1). The malar butterfly rash is present at time of SLE diagnosis in 20–60% of patients [25, 30]. The eruption fluctuates with disease activity and can be differentiated from acne rosacea or seborrheic dermatitis by its lack of papules and pustules and by its distribution. Painless oral and/or nasal mucosal ulcerations (Fig. 11.2) frequently accompany lesions of ACLE [31].

Table 11.3 Extra-articular involvement of RA [163, 164, 167]

Ocular	Keratoconjunctivitis sicca, scleritis, ulcerative keratitis
Hematologic	Anemia of chronic disease, thrombocytosis, lymphadenopathy, Felty syndrome
Renal	Mild membranous glomerulonephritis, secondary amyloidosis
Neurologic	Cervical myelopathy from atlantoaxial subluxation, mononeuritis multiplex, peripheral neuropathy
Pulmonary	Pleural effusions, interstitial lung disease, pulmonary nodules
Cardiac	Pericarditis—usually asymptomatic, aortic root dilatation, coronary arteritis from rheumatoid vasculitis

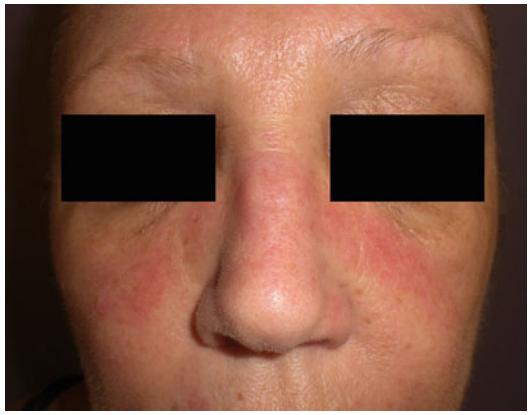

Fig. 11.1 Malar rash of acute cutaneous lupus erythematosus (ACLE) also called the "butterfly" rash

Generalized ACLE presents similar to a viral exanthem or drug eruption, as a widespread morbilliform eruption, with diffuse edema and erythema of the face, upper trunk, or extremities (Fig. 11.3). The lesions develop rapidly and last for hours to days. There may be associated edema and erythema of the hands over the dorsal and interphalangeal areas, with pathognomonic sparing of the skin overlying the knuckles, in contrast to Gottron's papules of dermatomyositis. Generalized ACLE can affect up to a third of patients with SLE [29]. Severe forms of generalized ACLE can present with vesiculobullous skin changes, due to widespread apoptosis of epidermal keratinocytes, clinically resembling toxic epidermal necrolysis (TEN). However, unlike TEN, bullous ACLE is photosensitive, occurring predominantly over sun-exposed areas, has a more insidious onset, and may or may not involve mucosa [32]. Outside of the skin, there can be bullous LE involvement of ocular, esophageal, or laryngeal tissue, potentially leading to corneal blindness and laryngoesophageal stenosis. Histopathology and immunofluorescence studies are necessary to delineate bullous SLE from other blistering diseases in the lupus patient [29]. A patient presenting with vesiculobullous lesions should be treated emergently regardless of etiology (see vesiculobullous diseases and drug eruptions chapters).

11.2.2.2 Subacute Cutaneous Lupus Erythematosus

Subacute cutaneous lupus erythematosus (SCLE) presents as erythematous macules and/or papules that evolve into hyperkeratotic, papulosquamous annular plaques often occurring often over the neck, shoulders, upper extremities, and trunk (Fig. 11.4), resembling psoriasis [33]. About 70% of SCLE patients have positive anti-Ro/SSA antibodies. SCLE patients are, in general, more likely to progress to SLE than those with chronic cutaneous lupus [34]. Severe systemic manifestations such as systemic vasculitis, renal disease, and CNS occur in less than 10% of patients with SCLE [29]. Risk factors for the development of SLE in a patient with SCLE lesions include papulosquamous SCLE, leukopenia, and antinuclear antibody (ANA) titer greater than 1:640 [35]. SCLE is drug-induced in 12% of cases. It resembles idiopathic SCLE clinically and histopathologically, but resolves when the offending drug, most often an antihypertensive or antifungal agent, is withdrawn [33, 34].

11.2.2.3 Chronic Cutaneous LE

The most common form of chronic cutaneous LE (CCLE) is discoid lupus, which begins as red-purple macules and papules that evolve into coin-shaped, erythematous plaques with scale extending into the openings of dilated hair follicles (Fig. 11.5).

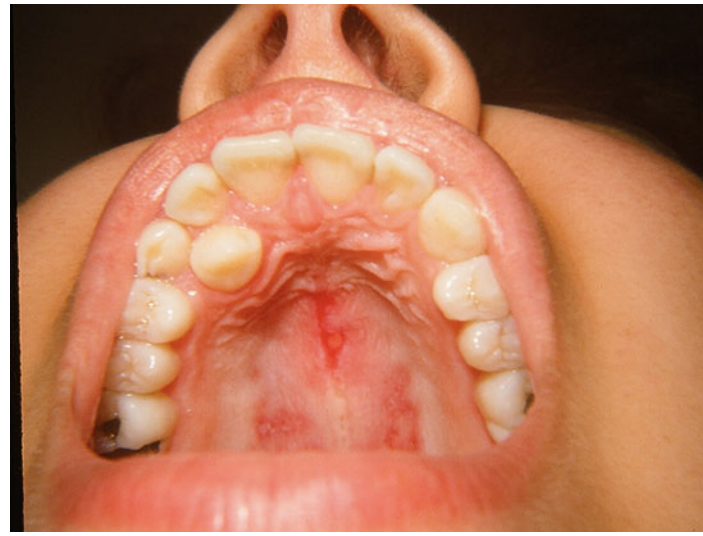

Fig. 11.2 Oral ulcerations of ACLE

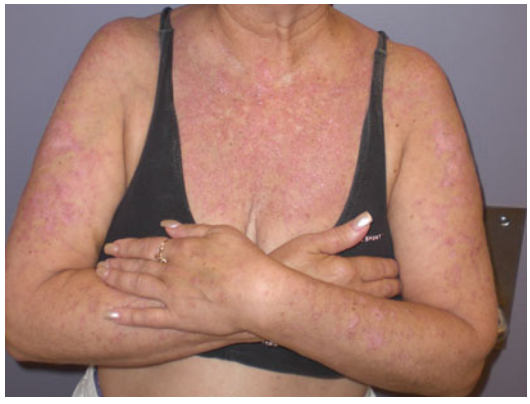

Fig. 11.3 Generalized rash of ACLE, which is typically photosensitive, occurring mainly over sun-exposed areas

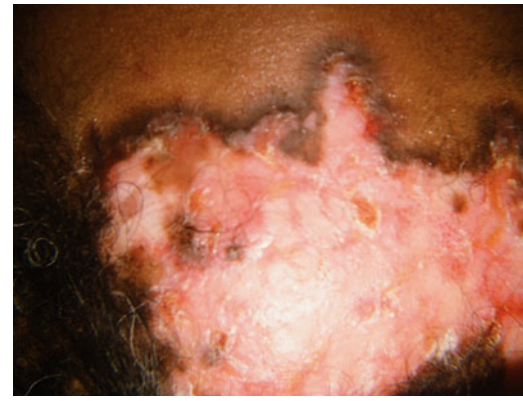

Fig. 11.5 Discoid lesions of chronic cutaneous lupus erythematosus

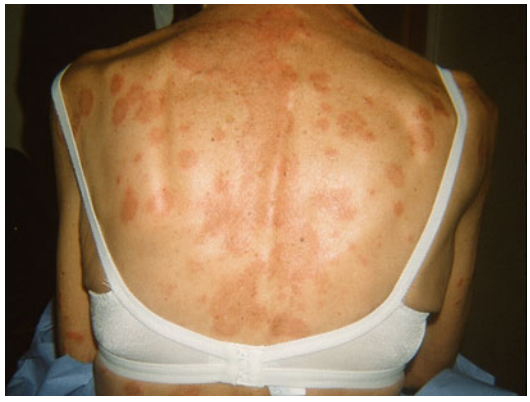

Fig. 11.4 Subacute cutaneous lupus erythematosus

Central scarring, telangiectasias, and hypopigmentation are the post-inflammatory hallmarks of these lesions, most striking on darker skinned patients, and can be very disfiguring. DLE is commonly found on the head and neck and extensor aspects of the arms, similar to ACLE, but is neither edematous nor transient. There can be mucosal DLE involvement of the oral and genital mucosa and the conjunctiva [36]. The small percentage of DLE patients that progress to develop SLE are more likely to do so within the first 5 years of DLE diagnosis and usually have generalized DLE distribution (lesions both above and below the neck) [37]. SLE patients with DLE skin lesions tend to have less severe systemic lupus activity.

Other variants of CCLE are lupus panniculitis, lupus tumidus, and chilblains lupus. Lupus panniculitis (or lupus profundus) presents as firm, depressed nodules, extending into the deep dermis, and is seen in 1–3% of CCLE patients (Fig. 11.6) [38]. About 10–40% of those with LE panniculitis have mild manifestations of SLE [39]. Lupus tumidus presents as erythematous, urticarial plaques with minimal surface change and no follicular plugging (Fig. 11.7) [40]. Lupus tumidus patients rarely have clinically evident SLE and are usually ANA negative. Chilblain lupus, a rare form of DLE, presents as violaceous plaques and papules on the tips of fingers and toes, exacerbated by cold exposure (Fig. 11.8). Twenty percent of chilblain lupus patients go on to develop SLE [41].

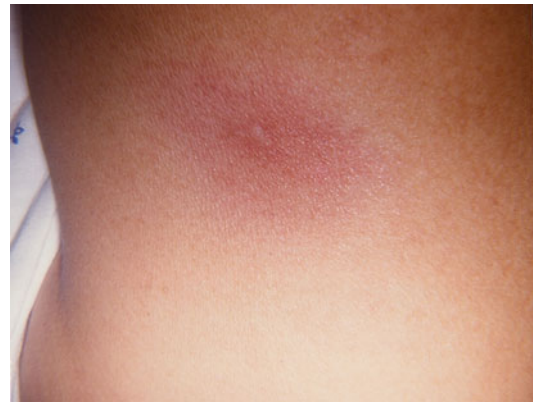

Fig. 11.6 Lupus panniculitis/lupus profundus

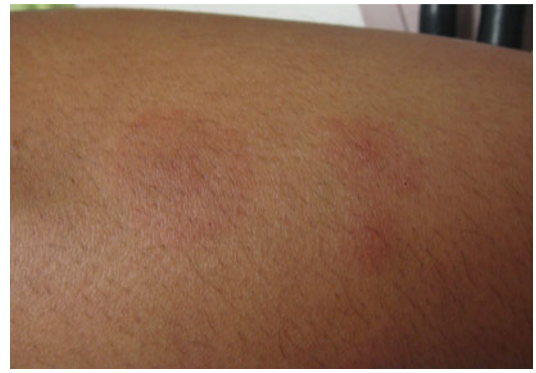

Fig. 11.7 Lupus tumidus

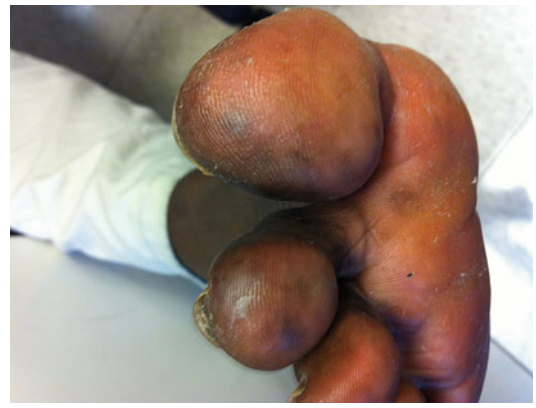

Fig. 11.8 Chilblain lupus

11.2.3 LE-Nonspecific Skin Disease

Cutaneous vasculitis is reported to occur in 11% of SLE patients (Fig. 11.9) [42]. Palpable purpura is common, often in the lower extremities, although a generalized or acral distribution can also be observed [29]. Less-dependent areas of the skin can exhibit urticarial vasculitis. Additionally, fingertip gangrene, splinter hemorrhages, periungual telangiectasia, and purpuric lesions of the palm can be seen. Antiphospholipid syndrome or infective endocarditis should be kept in the differential when evaluating these patients [42]. Cutaneous vasculitis may be a predictor of the future development of LE nephritis [43].

Alopecia is common in lupus patients [44]. Telogen effluvium can occur with systemic flares and tends to resolve with lupus treatment. Discoid lupus can cause a scarring alopecia [29]. Nonscarring alopecia is seen in 24% of patients with SLE [30].

Cutaneous mucinosis is an unusual nonspecific presentation of SLE, presenting as asymptomatic papules and nodules on the trunk and arms, with increased mucin deposition in the dermis on histology. In one study, this occurred in 1.5% of SLE patients. Another study found that 80% of patients with this presentation had underlying SLE, though it can also be seen in other connective tissue diseases, such as dermatomyositis and scleroderma [45, 46].

Other nonspecific cutaneous findings include Senear-Usher syndrome, or pemphigus erythe-

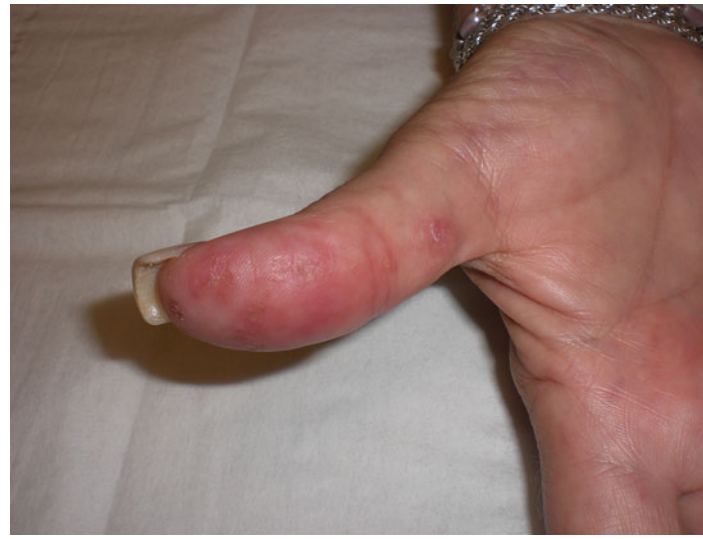

Fig. 11.9 Cutaneous vasculitis of SLE

matosus, which manifests as pemphigus foliaceous-like lesions in a seborrheic distribution in the setting of LE, and Rowell syndrome, in which erythema multiforme-like lesions are seen in patients with LE [31, 47].

11.2.4 Laboratory Findings

Whereas ANA may or may not be positive in isolated cutaneous lupus patients, ANA >1:160 is present in virtually all SLE patients [27]. Anti-double-stranded DNA antibodies (dsDNA), seen in 70% of patients, and anti-Smith antibodies (anti-Sm), seen in 25% of patients, are both highly specific for SLE [25]. Along with falling complement levels, rising anti-dsDNA titers are markers for an acute or impending SLE flare. With a lupus flare, the CBC may reveal leukopenia, hemolytic anemia, and/or thrombocytopenia [7, 25, 48].

All lupus patients should be monitored for proteinuria and active urinary sediment, such as cellular casts and hematuria, which are indicative of lupus nephritis [49]. As ACLE often occurs in the setting of active systemic lupus, these patients should have thorough evaluation for underlying disease activity including a history and physical examination, complete blood count, comprehensive metabolic panel, urinalysis, complement levels, and autoantibody profile.

11.2.5 Treatment

Antimalarials, particularly hydroxychloroquine, are used almost universally in SLE patients, except in those with intolerance or G6PD enzyme deficiency [50]. Hydroxychloroquine is safe in pregnancy and lactation, prevents and decreases severity of lupus flares, and has the added benefit of increased survival, decreased thrombosis, and improved lipid levels in patients who take the medication compliantly [51, 52]. Patients on antimalarials should be screened for maculopathy and neuromyopathy. Another side effect is increased blue-gray skin pigmentation with chronic hydroxychloroquine ingestion [25, 53, 54].

Lupus flares are treated according to severity and risk to major organ function, with glucocorticoids being the cornerstone of treatment. Mild to moderate flares, arthritis, and serositis can be treated with low-dose prednisone 10–20 mg/day, while moderate to severe flares require higher doses. Steroids are tapered according to patient response [55]. For patients who flare with steroid tapering, or have recurrent lupus flares, or severe

organ manifestations, maintenance immunosuppression with azathioprine or mycophenolate mofetil [25, 56], among others, should be considered. For patients who fail these standard therapies, the newest FDA-approved medication for moderate to severe SLE, IV Belimumab, a B-lymphocyte stimulator-specific inhibitor, may be considered.

Most hospitalized patients and those with severe flares are treated with the equivalent of prednisone 1 mg/kg/day, or pulse doses of IV methylprednisolone: 1 g/day for 3 days, particularly for cases of rapidly progressive lupus nephritis or life/organ-threatening manifestations. For patients with life-threatening organ manifestations such as severe lupus nephritis or neuropsychiatric disease, six monthly doses of IV cyclophosphamide may be added to high-dose steroids. Due to concern over cyclophosphamide toxicity, azathioprine can be substituted for milder forms of lupus nephritis, and mycophenolate mofetil can be effective in induction treatment for even moderate to severe proliferative lupus nephritis, especially in African Americans and Hispanics [57]. Intravenous immunoglobulin (IVIG) has shown benefit in autoimmune hemolytic anemia and thrombocytopenia and can be used for other severe lupus manifestations, without increasing risk for secondary infection [58].

Because cutaneous lupus is highly photosensitive, sun protection is paramount, including the use of sunblocks and sunscreens, as well as hats and sun-protective clothing [59]. Initial therapy usually includes topical glucocorticoids and/or intralesional steroid injection. Antimalarials such as hydroxychloroquine with or without quinacrine are added first as systemic therapy or in combination if topical or local therapy is inadequate [60]. Patients with extensive skin involvement may require oral corticosteroids, and if needed, azathioprine, methotrexate, mycophenolate mofetil, dapsone (particularly for bullous lesions), or thalidomide can be added [25, 29].

11.3 Neonatal Lupus

One-third of SLE patients have antibodies to the SSA/Ro and SSB/La antigens. Neonatal lupus (NLE) is caused by placental transfer of either SSA/Ro or SSB/La antibodies and/or U1-RNP to the fetus [61]. The risk of a baby being born with NLE to an SSA/Ro+mother is roughly 20%, and increases to 25% in women who have previously given birth to an affected child. Unlike classic SCLE, the SCLE-like rash of neonatal lupus can scar (Fig. 11.10). Congenital heart block occurs in 1–3% neonatal lupus, thought to result from anti-Ro/La antibodies attacking cardiac conduction tissue [62]. Congenital heart block can be diagnosed by fetal echocardiography, usually starting at gestational week 18, and is treated with IV steroids administered to the mother [61, 63]. Fetal mortality from congenital heart block is roughly 20–30%. There is also a risk of liver failure secondary to hepatobiliary disease and thrombocytopenia. Most deaths occur in utero or within the first 3 months after birth [61, 62, 64]. NLE without cardiac involvement usually spontaneously resolves within 2–6 months, though during that period, maternal antibodies persist and can precipitate new skin lesions upon exposure to UV light [65].

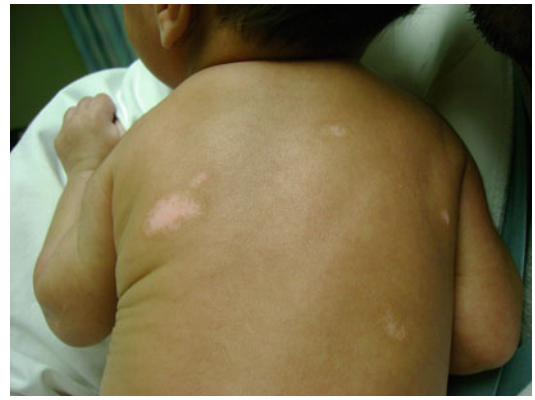

Fig. 11.10 Atrophic plaques of previously acute neonatal lupus erythematosus

11.4 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is defined by persistent serum antiphospholipid antibodies [anticardiolipin (ACL), lupus anticoagulant (LAC), or anti-β2-glycoprotein I antibodies (anti-β2GPI)], along with vascular thromboses and/or pregnancy morbidity [66]. Primary disease occurs

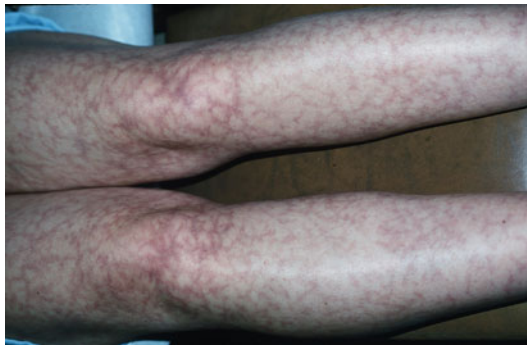

Fig. 11.11 Livido reticularis

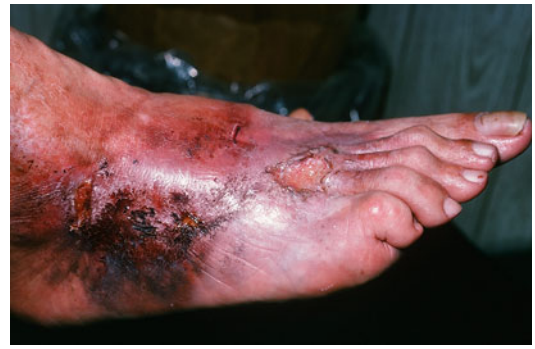

Fig. 11.12 Lower extremity ulceration secondary to thrombosis in acute antiphospholipid antibody syndrome

in 1% of the population [11]. Patients with concomitant autoimmune disease such as lupus are labeled as "secondary APS." Of lupus patients with antiphospholipid antibodies, 10–15% have clinical manifestations of APS [67, 68].

Up to 50% of APS patients have nonbacterial cardiac valvular thickening or vegetations, known as marantic or Libman-Sacks endocarditis. Though severe cardiac manifestations requiring valvular replacement are rare, dermatologic manifestations are common. Livedo reticularis is seen in 22–35% of SLE patients [42], particularly those with antiphospholipid syndrome (Fig. 11.11). Other nonspecific APS skin manifestations include atrophie blanche, painful extremity ulcers that heal as a white atrophic scar (Fig. 11.12), and embolic phenomenon leading to acral purpura and gangrene [69].

11.4.1 Emergent Complications

Thrombosis may occur in large, medium, and small vessels of the venous and arterial circulation. Venous thromboses are most common in the legs, but have been reported in varied sites not limited to the renal, mesenteric, axillary, and sagittal veins. Arterial events can be the result of either primary thrombosis or from emboli originating from valvular vegetations. Transient ischemic attacks are the most frequent manifestation of arterial thrombosis in APS [66, 70].

APS is a significant cause of recurrent pregnancy loss in lupus patients. Pregnancy morbidity can manifest as unexplained consecutive spontaneous abortions before the 10th week of gestation, death of a normal fetus beyond the 10th week of gestation, or premature birth of a normal neonate prior to 34th week of gestation due to eclampsia, severe preeclampsia, or placental insufficiency. Those occurring after 10 weeks of gestation are most associated with aPL. Patients with a history of previous fetal loss and high titer IgG aCL are at 80% risk for loss of their current pregnancy. Other obstetric manifestations of APS include premature delivery, oligohydramnios, and intrauterine growth restriction [71, 72].

Catastrophic antiphospholipid syndrome (CAPS) is defined as positive antiphospholipid antibodies along with three or more organ thromboses occurring over a short period of time. Occlusion of small vessels, or thrombotic microangiopathy, is characteristic. CAPS should be distinguished from TTP and disseminated intravascular coagulation. CAPS is rare, occurring in only 0.8% of patients with APS, but is significant due to high mortality rate [73].

11.4.2 Laboratory Findings

APS laboratory criteria require at least one of the three following tests, present on two or more occasions in a period of 12 weeks: lupus anticoagulant, IgG, or IgM anticardiolipin antibodies in medium-high titers, or IgG, IgM, or anti-®2-GPI antibodies above the 99th percentile [66, 74–76].

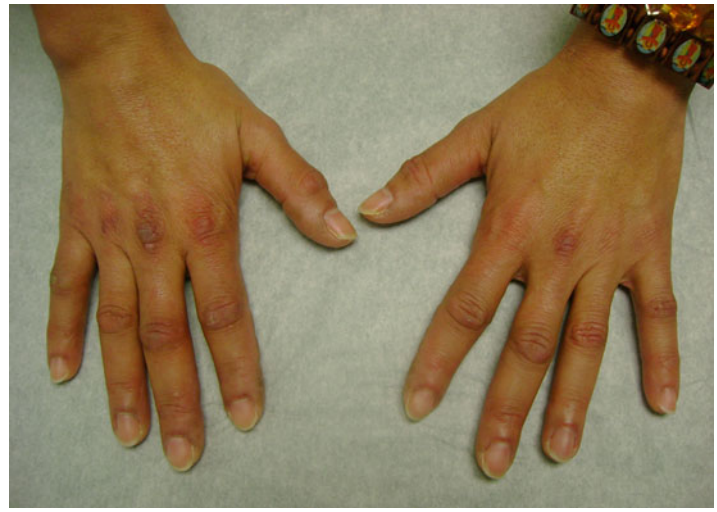

Fig. 11.13 Gottron papules of dermatomyositis (DM)

False-positive tests for syphilis often indicate the presence of underlying antiphospholipid antibodies. Besides being associated with autoimmune disease, APS antibodies and can be drug-induced or infection related [76]. Medications associated with aPL are hydralazine, procainamide, and phenytoin. Bacterial infections, including syphilis, Lyme disease, post-streptococcal rheumatic fever, and viral infections, such as hepatitis A, B, C, mumps, HIV, varicella zoster, EBV, and parvovirus can all result in IgM anticardiolipin in the serum [77].

Other lab abnormalities seen in APS are thrombocytopenia (typically mild), and less commonly, Coombs-positive hemolytic anemia. Antiphospholipid antibodies with thrombocytopenia and autoimmune hemolytic anemia are known as Evans syndrome [78].

11.4.3 Treatment

Patients with APS and history of thrombosis require lifelong anticoagulation at an INR of 2–3 for venous events. There is controversy over whether the INR should be kept at a higher level for arterial thrombosis [79]. Some studies suggest that APL antibody positive SLE patients may benefit from prophylactic aspirin therapy [80]. Severe cases of APS-associated thrombocytopenia are treated with steroids, IVIG, or splenectomy if resistant [81, 82].

CAPS patients are in general very ill, and require anticoagulation, high-dose steroids and plasma exchange [83].

Women with APS and recurrent miscarriages are treated with low-dose aspirin along with either heparin or low molecular weight heparin (LMWH) during subsequent pregnancies [84]. Anticoagulation is continued for 6 weeks after delivery [85]. Intravenous immunoglobulin with or without steroids is also being evaluated in clinical trials for use in preventing pregnancy losses in women with APL. Pregnant APS patients are at risk for and should be monitored for preeclampsia. The fetus should be monitored for placental insufficiency the last weeks of the third trimester [85].

11.5 Dermatomyositis

Dermatomyositis (DM) is an inflammatory muscle disease associated with characteristic skin manifestations. The cutaneous findings pathognomonic for DM are Gottron's papules, violaceous or pink papules of the dorsal metacarpal and interphalangeal joints (Fig. 11.13), and Gottron's sign, macular erythema over extensor surfaces such as the elbows and knees (Fig. 11.14). Lesions resemble cutaneous lupus in that they are sensitive to UV light and have similar histopathologic findings. Also frequently occurring are the

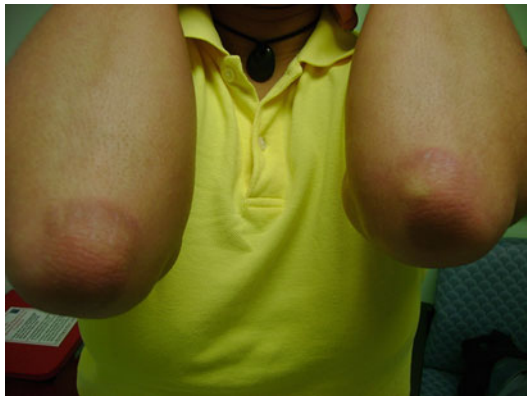

Fig. 11.14 Gottron sign of DM

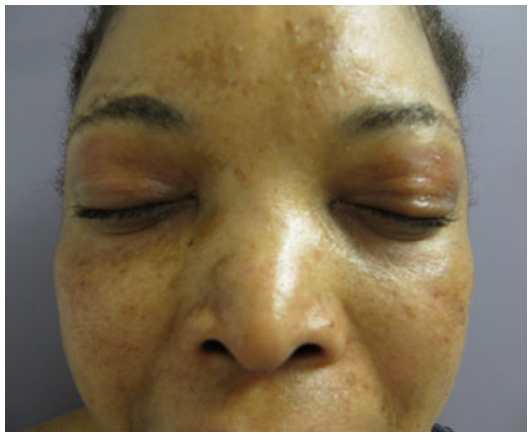

Fig. 11.15 Heliotrope rash of DM

heliotrope rash, presenting as periorbital violaceous erythema (Fig. 11.15), and erythema extending over the shoulders (the "shawl sign") or the anterior chest (the "V-sign"), which can later progress to poikiloderma. Nail fold changes are also common, including periungual erythema and telangiectasias [86].

DM is most commonly diagnosed using the Bohan and Peter Criteria. According to the criteria, a patient has definite DM if presenting with a typical DM skin rash, and any three of the following: symmetric proximal muscle weakness, elevated skeletal muscle enzymes, characteristic electromyogram, or myositis on muscle biopsy [87]. Amyopathic DM is defined as a characteristic DM rash, without clinical, laboratory or histologic evidence muscle involvement for at least 2 years following initial presentation [88].

11.5.1 Emergent Complications

Interstitial lung disease (ILD) is the most frequent cause of morbidity and mortality in DM [89, 90] and is usually associated with the presence of anti-Jo1 antibody. An important subset of myositis is the antisynthetase syndrome: inflammatory myositis associated with the presence of anti-Jo1 antibody, along with ILD, fever, Raynaud's phenomenon, arthritis, and "mechanics hands" (rough erythema on the sides of the fingers and palm) [91, 92]. Of amyopathic DM patients, up to 25% have ILD and must be screened with annual pulmonary function tests [93]. The natural course of ILD is gradual and progressive, though acute deteriorations can occur [92, 94]. Besides ILD, dyspnea can be due to weakness of the diaphragm and thoracic muscles, or from myositis of the striated esophageal muscles, which can lead to aspiration pneumonia.

Cardiac myositis, another complication of DM, is usually subclinical, presenting with mild rhythm disturbances. Congestive heart failure from myocarditis or fibrosis is rare. Myocardial involvement, pharyngeal weakness, malignancy, ILD, and delayed initiation of steroids are associated with poor survival [95, 96]. Several population-based studies have documented a higher than expected risk of malignancy in patients with adult-onset DM [97–99]. Risk of malignancy increases with age, male gender, and elevated serum creatine kinase levels [100]. The most commonly associated malignancies are ovarian, breast, lung, pancreatic, stomach, colorectal cancer, and non-Hodgkin lymphoma [101]. Risk of malignancy appears to approach that of the general population if no malignancy is discovered within the first 2 years of diagnosis [102].

DM can also occur in the pediatric population, with a similar rash as adult DM, except with a more frequent incidence of soft tissue calcinosis and cutaneous or gastrointestinal ulceration and

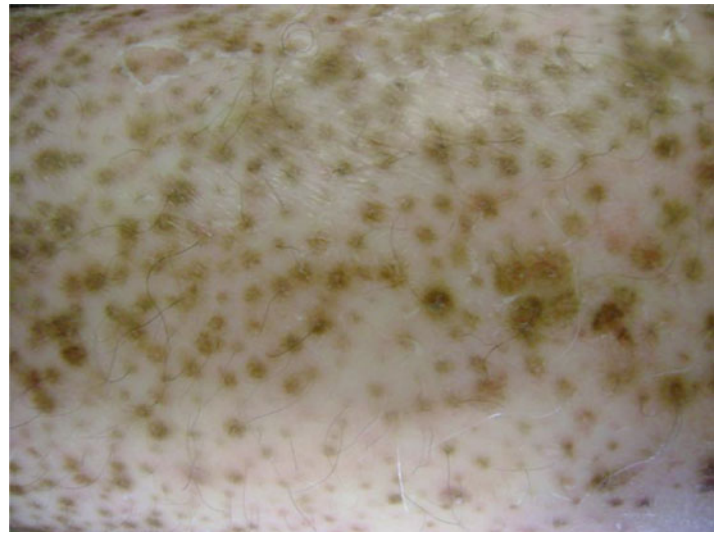

Fig. 11.16 "Salt and pepper" appearance of the skin in systemic sclerosis (SSc)

vasculitis [103]. Unlike adult dermatomyositis, malignancy is rarely associated with juvenile dermatomyositis. Up to 15–24% of adult individuals with dermatomyositis are diagnosed with malignancy either at time of diagnosis of DM or soon thereafter, in contrast to only 1% of pediatric patients with juvenile dermatomyositis [104].

11.5.2 Laboratory Findings

Evidence of myositis includes elevated creatine kinase (CK), aldolase, and liver function tests. CK is most often used for monitoring of disease activity and response to therapy [105].

11.5.3 Treatment

Initial pharmacologic therapy for DM consists of high-dose glucocorticoids, tapered once muscle enzymes normalize [106]. Steroid sparing agents may be added, most commonly azathioprine and/or methotrexate, particularly in patients with major organ involvement, delayed diagnosis or treatment, or severe myositis. For treatment resistant myositis, IVIG, mycophenolate mofetil, and rituximab may provide benefit [107, 108].

The rash of dermatomyositis often responds to myositis treatment, along with sun avoidance, topical steroids, and hydroxychloroquine. Malignancy-associated myositis and DM rash are generally refractory to steroids, resolving only with treatment of the underlying cancer [101, 109].

11.6 Systemic Sclerosis

Systemic sclerosis (SSc), also known as scleroderma, is characterized by microvascular injury and excessive collagen deposition and fibrosis of the skin and internal organs. The extent of skin sclerosis determines whether the patient has a diffuse or limited systemic sclerosis. Each subset has unique serologic markers and variable associations with underlying organ manifestations.

Diffuse systemic sclerosis (dSSc) is defined by skin changes extending from the fingers and toes proximally to the elbow and knees, often involving the chest and abdominal wall. With progressive skin tightening and fibrosis, certain areas of the skin may become hypo- or hyperpigmented. Often, pigment is maintained around the hair follicle, leading to a "salt and pepper" appearance of the skin (Fig. 11.16). Disease presentation is usually abrupt, and symmetric hand edema and Raynaud's phenomenon are closely related to the onset of sclerosis. While skin sclerosis is the most severe in the first 18 months of disease and can subsequently

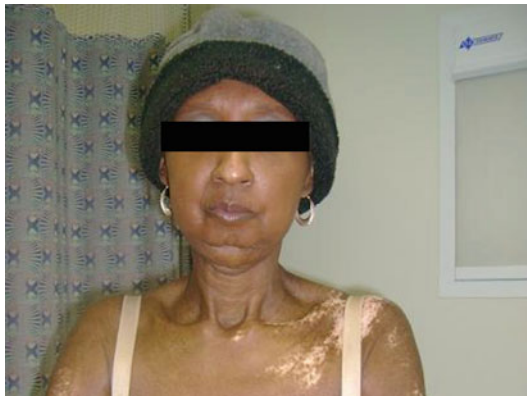

Fig. 11.17 Taut facial skin yielding a mask-like appearance and small oral aperture of SSc

improve, disease involvement of internal organs continues to progress with time [110, 111].

Limited systemic sclerosis (lSSc) presents with a more indolent course than dSSc. Patients often have a longstanding preexisting history of Raynaud's phenomenon, later presenting with skin thickening and fibrosis distal to the elbows and knees. Both diffuse and limited SSc can have taut facial skin yielding a mask-like appearance, with a small oral aperture (Fig. 11.17). Besides Raynaud's, other lSSc features include subcutaneous calcinosis, gastrointestinal reflux and esophageal dysmotility, sclerodactyly, and telangiectasias, also known as CREST syndrome. One percent of cases can develop internal organ involvement without characteristic skin changes [112]. Limited SSc is associated with a higher risk of pulmonary hypertension, but overall prolonged survival when compared to dSSc [113, 114].

Scleroderma can overlap with other autoimmune diseases, including the inflammatory myopathies, SLE, and Sjögren's syndrome.

11.6.1 Emergent Complications

Until the development of ACE inhibitors, scleroderma renal crisis (SRC) was the most serious and lethal complication of SSc [115]. SRC, arising from vessel narrowing and ischemic kidney disease, presents almost exclusively during the first 5 years of diffuse SSc, as new-onset hypertension, acute renal failure, and microangiopathic hemolytic anemia [116].

Nowadays, most disease-related SSc mortality is from cardiopulmonary involvement: ILD, subsequent pulmonary fibrosis, and pulmonary artery hypertension (PAH). Patients are monitored for lung disease with pulmonary function tests and/or imaging [117]. The greatest decline in lung function from ILD occurs in the first 4–6 years of scleroderma onset [118, 119].

Pulmonary arterial hypertension (PAH) can occur in any subset of scleroderma, but as mentioned earlier, is more frequent in limited SSc, usually occurring years after diagnosis. Patients are monitored for PAH by echocardiography, and diagnosis is confirmed by right heart catheterization [120].

Besides PAH, other cardiac features include pericardial effusions, arrhythmias, and diastolic dysfunction. Myocardial ischemia, fibrosis, and myocarditis have been noted as well [121, 122].

Empiric treatment with a proton pump inhibitor is recommended to prevent SSc gastrointestinal complications, including dysmotility, reflux, and stricture formation. [123]. SSc patients may have gastrointestinal blood loss from mucosal telangiectasias, such as gastric antral vascular ectasia (GAVE), described endoscopically as "watermelon stomach" [124]. There is an association between primary biliary cirrhosis (PBC), which often has an associated anticentromere antibody, and limited scleroderma. Without ursodiol treatment, there can be progression to secondary cirrhosis [125]. Intestinal fibrosis can yield dysmotility, giving rise to bacterial overgrowth, abdominal pain, and bloating.

Finally, Raynaud's phenomenon of scleroderma is typically severe and resistant to treatment, leading to critical digital ischemia, ulceration, gangrene, and ultimately, auto-amputation (Fig. 11.18). Ischemic pain and decreased capillary refill with or without signs of visible tissue damage is a sign of ongoing ischemia and requires immediate treatment. Care should be taken to not mistake either digital calcinosis, or sores from microtrauma of taut atrophic skin covering joints, for digital ulcerations [126].

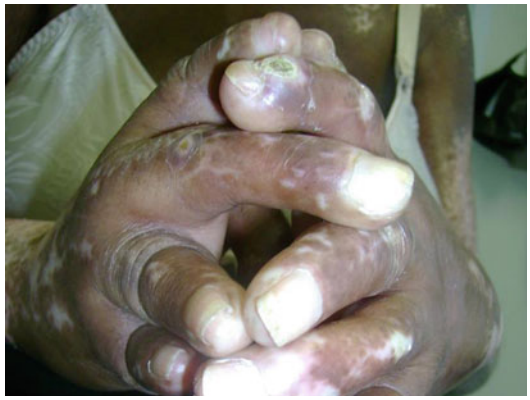

Fig. 11.18 Digital ischemia and ulceration in SSc

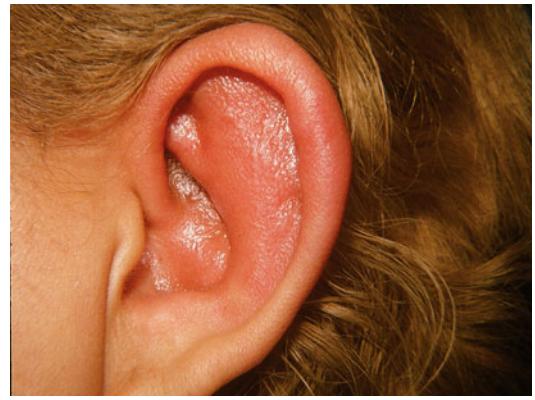

Fig. 11.19 Auricular chondritis of relapsing polychondritis

11.6.2 Laboratory Findings

Most SSc patients will have a positive ANA. A negative ANA should alert the clinician to consider other diagnoses such as nephrogenic systemic fibrosis, scleromyxedema, scleredema, graft versus host disease (GVHD), and toxin-mediated sclerotic syndromes [127]. The anti-centromere antibody is almost exclusively seen in lSSc. Anti-Scl antibody is more characteristic of dSSc, especially those with ILD, and is found in 20–30% of patients. Anti-RNA polymerase I/III antibodies are linked to SRC [128, 129].

11.6.3 Treatment

Most treatment is directed towards a specific organ and/or symptom. For Raynaud's, vasodilatation and increased blood flow to the digits is the goal of treatment and can include any combination of calcium channel blockers, angiotensin receptor blockers, nitropaste, or even sildenafil and/or bosentan, if resistant secondary ulcers are present.

Proton pump inhibitors are beneficial for esophageal dysmotility, strictures, and esophagitis. Promotility agents such as metoclopramide alternating with antibiotics can alleviate symptoms of bacterial overgrowth.

Many immunosuppressant agents have been used as disease modifying treatments in systemic sclerosis, including mycophenolate mofetil, azathioprine, and methotrexate, but only cyclophosphamide has been shown in randomized controlled studies to be of benefit in SSc ILD, albeit modestly [117, 130]. Corticosteroids play a minimal role in the management of scleroderma and are used mainly for the treatment of associated inflammatory arthritis [131].

Depending on the severity of PAH, oral endothelin receptor antagonists, phosphodiesterase inhibitors, inhaled iloprost, or prostacyclin can be used [132, 133].

11.7 Relapsing Polychondritis

Relapsing polychrondritis (RP) is characterized by painful inflammation of cartilage throughout the body. Autoantibodies and cell-mediated immunity towards extracellular matrix components, including collagen types II, IX, and XI, have been implicated in the pathogenesis. Episodes last days to weeks and can resolve spontaneously. The classic finding in RP is acute uni- or bilateral auricular chondritis (Fig. 11.19). Recurrent attacks of auricular chondritis can result in the floppy "cauliflower ear," and attacks of nasal cartilage can yield a depressed "saddle nose" deformity. Nasal involvement is common, presenting as a tender, warm, and red nasal bridge. Up to 12% of patients may present with nonspecific dermatologic findings, including erythema nodosum, purpura, livedo reticularis, and distal necrosis [134, 135].

11.7.1 Emergent Complications

Involvement of the cartilaginous rings of the respiratory tract is a major cause of mortality, and can occur in over 50% of patients [136]. Though there is little correlation between severity of clinical symptoms and the extent of airway involvement, clinicians should consider laryngotracheal involvement in any RP patient with respiratory complaints, including hoarseness, nonproductive cough, wheezing, dyspnea, or stridor. Flow-volume loop studies should be obtained for all patients diagnosed with RP and be repeated every 6–12 months to evaluate for subacute airway strictures and narrowing. During an acute attack, CT scan may show edema and thickening of the trachea. Recurrent pneumonias or bronchiectasis may suggest a collapsed bronchus [137, 138].

Less than 10% of cases have cardiovascular involvement. Aortic regurgitation secondary to aortic root dilatation can occur [139]. Other manifestations include mitral regurgitation and conduction abnormalities [140].

Renal dysfunction is seen in up to one quarter of patients, manifesting as IgA nephropathy, tubulointerstitial nephritis, or segmental necrotizing crescentic glomerulonephritis [141]. Renal involvement is associated with extrarenal vasculitis, arthritis, and overall worse prognosis [142].

Ocular inflammation is found in up to 60%. Episcleritis and scleritis are most frequent, followed by keratoconjunctivitis, sicca, uveitis, and ulcerative keratitis. Although rare, blindness can result from corneal perforation, retinal vasculitis, and optic neuritis [143].

There is an association between myelodysplasia and RP, especially in patients who are male, have dermatologic manifestations and an older age at onset of disease [133, 144].

11.7.2 Laboratory Findings

There is no specific screening autoantibody for RP. Anti-collagen antibody tests are not always readily available and may not be positive in all cases. A positive ANA is seen in 22–66% of patients. In atypical cases, biopsy of involved cartilage may be needed to confirm diagnosis [133].

11.7.3 Treatment

Initial treatment of relapsing polychondritis consists of low-dose prednisone for mild auricular or nasal chondritis, or arthritis, while more serious manifestations such as laryngeotracheal or ocular symptoms require higher doses. For steroid dependent or refractory cases, anecdotal evidence suggests dapsone and colchicine, or if severe, cyclophosphamide, azathioprine, cyclosporine, or mycophenolate mofetil may be helpful. Biologics such as infliximab and the IL-1 receptor antagonist, Anakinra, have been used as well. Localized steroid therapy can be used in the form of eye drops, inhaled steroids, or intra-articular or intralesional injections [145–148].

11.8 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis, with a predilection for the small joints of the hands, feet, and wrists. The arthritis is commonly symmetric, affecting upper and lower extremity joints, with associated morning stiffness lasting for hours. If left untreated, or suboptimally treated, chronic untreated joint inflammation can progress to a secondary osteoarthritis and deforming arthritis with bone erosions on imaging. Among the more common cutaneous findings in RA are rheumatoid nodules, seen in 20–30% of patients. Rheumatoid nodules are painless, firm, flesh-colored subcutaneous nodules, occurring over extensor surfaces, believed to occur from small vessel vasculitis with fibrinoid necrosis. Rheumatoid nodules portend a more severe disease course and higher risk of developing extraarticular disease. Rheumatoid nodules are more common in males and rheumatoid factor (RF) positive patients [149]. Neutrophilic dermatoses can also present in patients with RA, including

pyoderma gangrenosum, Sweet's syndrome, rheumatoid neutrophilic dermatitis, erythema elevatum diutinum, and palisading neutrophilic and granulomatous dermatitis [150, 151].

Bywater's lesions are small brown to purpuric painless lesions on the nail fold, nail edge, or digital pulp that represent nail fold infarctions, and do not require intense immunosuppression [152–154].

11.8.1 Emergent Complications

RA is associated with exudative pleural effusions with low fluid glucose levels that can be mistaken for empyema. Patients with cutaneous rheumatoid nodules can have associated pulmonary nodules, which are usually asymptomatic, but can rarely cavitate and cause bronchopleural fistulas or pneumothorax. Symptomatic ILD is reported in up to 10% of RA population studies. Some forms of RA-associated ILD such as cryptogenic obstructive pneumonia are very steroid responsive, whereas usual interstitial pneumonitis is progressive despite treatment [155].

Cervical spine involvement is frequent in patients with severe RA. Patients complaining of neck pain or upper extremity paresthesias should alert the clinician to possible cervical spinal cord compression from atlantoaxial subluxation. Other symptoms include sensation of the "head falling off," weakness, incontinence, and positive Babinski reflex. Atlantoaxial subluxation occurs as a result of a lax C1 transverse ligament or from erosion of the odontoid process. Diagnosis is confirmed with a lateral flexion–extension X-ray, in which the space between the C1 anterior arch and C2 odontoid process is greater than 5 mm. Basilar invagination can also occur, from upward migration of the odontoid process into the foramen magnum. Both processes can lead to vertebral artery compression [157].

Active RA can be associated with episcleritis, scleritis, and peripheral ulcerative keratitis. Scleritis, when untreated, can progress from eye redness and pain to necrotizing scleritis, which is associated with underlying vasculitis, vision loss, and high mortality [213].

Felty's syndrome, consisting of RA, leukopenia and splenomegaly, occurs in 1%of RA patients, mainly those with long-standing, seropositive, erosive, and deforming RA [158]. Patients with Felty's syndrome frequently have lower extremity ulcers as well as an increased risk of melanoma, lymphomas, and leukemias. Leukopenia portends a 25% mortality risk from sepsis [158–160].

Rheumatoid vasculitis is uncommon (<5%), and typically occurs in patients with long-standing, erosive RA with RF seropositivity and rheumatoid nodules. Cutaneous manifestations are digital gangrene and leg ulcers along the lateral malleolus or pretibial region, and nonspecific erythema, hemorrhagic blisters, livedo reticularis, erythema elevatum diutinum, and atrophie blanche [163, 164]. Visceral involvement of different organ systems (eye, heart, lung, GI) and the peripheral nerves can occur [161]. Features include scleritis, pericarditis, myocardial infarction, neuropathy, and acute abdomen [161, 166, 167]. Decreased survival has been noted in patients with a younger age at diagnosis, delayed diagnosis, abnormal urinary sediment, and hypergammaglobulinemia. Cardiac involvement, gangrene, bowel infarctions, and mononeuritis multiplex also suggest poor prognosis [168]. As the pathogenesis is immune complex mediated, it has been suggested that direct immunofluorescence of skin biopsy may detect early or subclinical vasculitis in RA patients [156].

11.8.2 Laboratory Findings

Rheumatoid factor is an autoantibody against IgG, seen in 80% of RA patients, but can also be seen in Sjögren's syndrome, cryoglobulinemia, and SLE among others diseases. Low titers may also be seen in the elderly, and patients with long-standing infection. Anti-citrullinated peptide antibodies (anti-CCP antibody or ACPA) can be seen in up to 85% of RA patients later in the course of the disease, and has higher specificity for RA than the RF does [170].

The 2010 ACR/EULAR classification incorporates joint involvement, serology, duration of

symptoms and acute phase reactants for diagnosis. The acute phase reactants, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) are also used in monitoring disease activity [165].

11.8.3 Treatment

Once rheumatoid arthritis is diagnosed, aggressive therapy with disease-modifying antirheumatic drugs (DMARDs) should be initiated, in order to prevent further joint damage and subsequent permanent deformity.

Methotrexate is considered the anchor drug. If disease control is not achieved, other DMARDs such as leflunomide, or sulfasalazine with hydroxychloroquine can be added, or biologic agents can be employed. Adjunctive treatments for helping with pain and function include glucocorticoids, NSAIDs, and physical and occupational therapy.

Treatment of rheumatoid vasculitis requires high-dose glucocorticoids with or without cyclophosphamide. Methotrexate is not only a DMARD, but is also used to improve Felty's syndrome associated cytopenias. Splenectomy is indicated for recurrent infections or noncorrecting leukopenia, and may also improve leg ulcers [165, 171].

Scleritis requires topical or local steroids with or without systemic immunosuppressants. Hematologic findings such as anemia of chronic disease and thrombocytosis, tend to resolve as the RA comes under control with immunosuppression. Peripheral neuropathy from inflamed synovial entrapment will also improve with RA treatment. Atlantoaxial subluxation greater than 8 mm from cervical involvement usually requires surgical intervention [163, 173–175].

11.9 Sjögren's Syndrome

Sjögren's syndrome (SS) is an autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, primarily manifesting as xerophthalmia and xerostomia. Sjögren's syndrome can be a primary disorder, or can be seen in association with other autoimmune diseases such as SLE and RA [176]. The disease can manifest with a variety of cutaneous signs, the most common being xerosis. Cutaneous vasculitis, including cryogolubulinemia, may suggest more serious systemic and extraglandular involvement [177].

Lymphocytic infiltration of various organs can yield interstitial pneumonitis, pericarditis, and interstitial nephritis. These features usually appear early in the disease and follow a benign course. Arthritis and arthralgias are seen in over half of patients. PBC and celiac sprue have also been noted to be associated with SS [178, 179].

11.9.1 Emergent Complications

There is a 10- to 40-fold increased risk of lymphoma in SS patients. The overall risk of developing lymphoma is 5% in patients with SS. Patients with SS also have a predilection for vasculitis, and in particular type II cryoglobulinemic vasculitis is associated with lymphoma (most commonly non-Hodgkins type) both independently and in those with SS. Other risk factors for lymphoma include C4 hypocomplementemia and hard enlargement of parotid or lacrimal glands [180]. Neurologic complications include sensorimotor neuropathy, though cranial neuropathies, central demyelinating disease, and optic atrophy have also been described. Central nervous system vasculitis is uncommon [181].

Three prognostic factors for adverse outcomes in primary SS are purpura, hypocomplementemia, and cryoglobulinemia, as identified in several prospective studies of SS pts. Such outcomes include systemic vasculitis, B cell lymphoma, and death [182, 183, 184].

11.9.2 Laboratory Findings

The presence of SSA/Ro and SSB/La antibodies are part of the diagnostic criteria, and occur in high frequency, along with RF and ANA. Elevated ESR is seen in most patients, as is hypergammaglobulinemia [177].

11.9.3 Treatment

Ocular and oral disease is treated symptomatically with preservative-free artificial tears, lubricating ointments, methylcellulose drops, good dental hygiene, and antifungal medications if needed. Muscarinic stimulants such as pilocarpine and cevimeline can aid with salivary gland secretion though side effects such as diaphoresis, nausea, and diarrhea can be limiting. For Sjögren's associated arthritis, hydroxychloroquine can be helpful. Corticosteroids and immunosuppressives such as cyclophosphamide and azathioprine can be used for severe extraglandular disease, but are not helpful for alleviating symptoms of xerosis [185–187].

11.10 Behçet's Disease

Behçet's disease is a systemic vasculitis, with an increased prevalence along the old "silk route," specifically Turkey, Iran, and Japan. Though there is no diagnostic test for Behçet's disease, criteria have been developed by the International Study Group for Behçet's disease, which include recurrent oral aphthous ulcers (Fig. 11.20) as the major criterion, and any two of the following minor criteria: recurrent genital ulcers (most commonly of the scrotum in males (Fig. 11.21) and labia majora of women), eye lesions (uveitis, retinal vasculitis), cutaneous findings such as erythema nodosum, papulopustules, pseudofolliculitis, acneiform lesions, or a positive pathergy test. The pathergy reaction is characterized by papule or pustule formation 1–2 days after skin trauma, such as a needle prick. Behçet's differs from other autoimmune diseases in its lack of B-cell hyperreactivity or T-cell dysfunction, and lack of association with Raynaud's phenomenon or secondary Sjögren's syndrome [188, 189].

11.10.1 Emergent Complications

Ocular disease occurs in 70% of cases of Behçet's disease; approximately 25% may lose their vision despite therapeutic intervention. Males are more likely than females to have severe ocular involvement. Ocular inflammation is the initial manifestation in about 20%. Anterior uveitis is seen more commonly in females, while posterior uveitis is more common in males [190, 191].

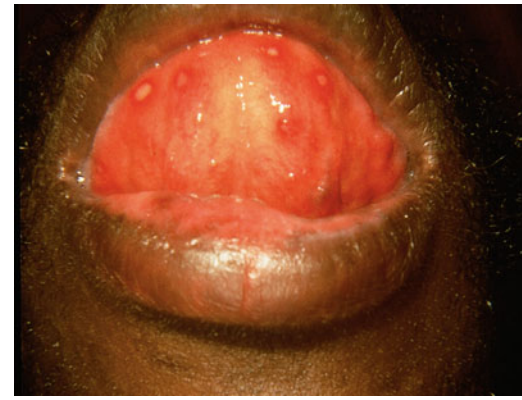

Fig. 11.20 Oral aphthous ulcers of Behçet's disease

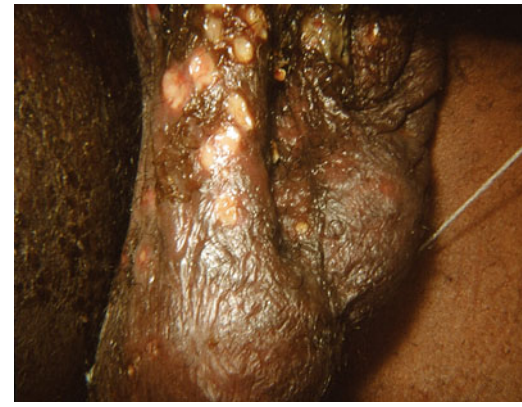

Fig. 11.21 Scrotal ulcers found in Behçet's disease

An important cause of morbidity in patients with Behçet's disease is major vessel disease, particularly arterial aneurysm and/or occlusions, hepatic vein occlusion (Budd-Chiari syndrome), and thrombophlebitis of superficial and deep veins of the legs. Behcet's syndrome is the only vasculitis that causes pulmonary artery aneurysms, which is the primary cause of mortality.

Significant neurological involvement can be seen, including central nervous system disease, especially involving the brainstem, aseptic meningitis, and cerebral venous sinus thrombosis [192–195].

11.10.2 Laboratory Findings

Laboratory findings are usually nonspecific, and also found in other inflammatory diseases, such as anemia of chronic disease, and elevated acute phase reactants. Autoantibodies are typically negative [189].

11.10.3 Treatment

Mild to moderate mucocutaneous disease can be treated with topical or intralesional corticosteroids, topical sucralfate, and local anesthetics. For more severe cases, colchicine, thalidomide, or azathioprine can be used. The nonerosive arthritis of Behçet's can be managed with colchicine. Ocular disease is treated with prednisone and azathioprine [196, 197]. As it is believed that vascular inflammation is the cause of venous thromboses, treatment strategy is aimed toward immunosuppression rather than anticoagulation. Vascular involvement is treated with systemic corticosteroids alone, or in combination with other immunosuppressives such as azathioprine, chlorambucil, cyclophosphamide, cyclosporine, and interferon-α. Mycophenolate mofetil, IV immunoglobulin, and anti-TNF-α agents have also been used [198, 199].

11.11 Reactive Arthritis

Reactive arthritis (ReA), formerly known as Reiter's syndrome, is a multisystem disease characterized by a sterile oligo- or monoarthritis and either urethritis, cervicitis, or bilateral conjunctivitis following a urogenital or enteric infection. Triggering organisms include Chlamydia trachomatis (or less frequently, Chlamydia pneumoniae), Salmonella, Shigella, Campylobacter, and Yersinia. The pathogenesis is not clearly understood, but it is thought that bacterial components may trigger the disease in genetically susceptible individuals, perhaps via molecular mimicry [200, 201].

There are many classic skin findings. Keratoderma blennorrhagicum (10%) is a scaly, often pustular, eruption that manifests 1–2 months after the start of arthritis, usually involving the soles of the feet (Fig. 11.22), but can affect the legs, hands, nails, and scalp. Circinate balanitis (25%) is most frequently seen in Chlamydia-associated ReA, and presents as either hyperkerototic plaques on circumcised males, or shallow ulcers on uncircumcised males, typically on the glans penis, or on the shaft or scrotum (Fig. 11.23). Yersinia infection can be associated with erythema nodosum. Oral ulcers can also be seen in ReA [200, 202].

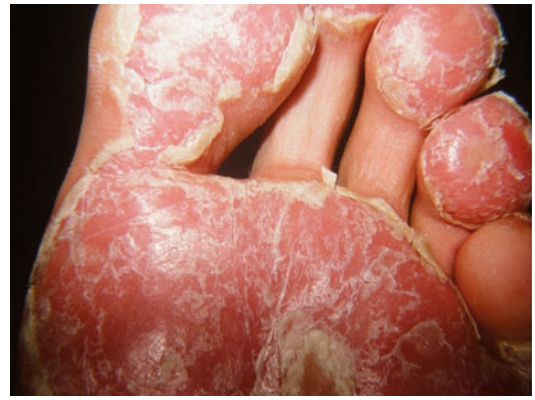

Fig. 11.22 Keratoderma blennorrhagicum of reactive arthritis (ReA)

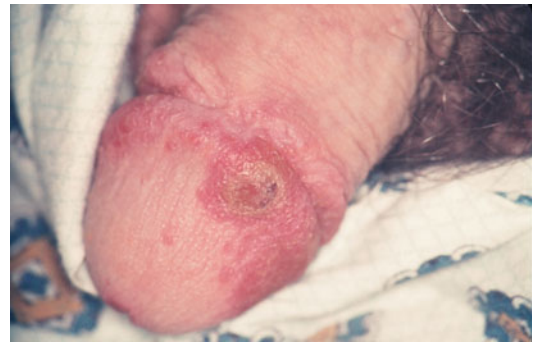

Fig. 11.23 Circinate balanitis of ReA

11.11.1 Emergent Complications

Conjunctivitis is the most common eye finding, but anterior uveitis (iritis), often unilateral, is also seen. Topical glucocorticoid eye drops and a mydriatic agent may be needed to dilate the involved eye and prevent synechiae formation between the pupil and lens.

Acute reactive arthritis may be severe enough to mimic septic arthritis and be associated with high fevers and extreme malaise. Septic arthritis can occur in Campylobacter and Salmonella infections. Furthermore, gonococcal arthritis (a septic arthritis) must be distinguished from an aseptic arthritis arising in a patient developing ReA with a gonococcal infection. Synovial fluid gram stain and culture helps distinguish the two [202].

11.11.2 Laboratory Findings

Diagnosis relies on finding the triggering infection. Chlamydia trachomatis can be found in morning urine or by genital swab. By the time arthritis presents, enteric organisms may not be identifiable in the stool. There is a strong association between the genetic marker HLA-B27 and reactive arthritis. Furthermore, HLA-B27 can be predictive of future development of spondyloarthritis and uveitis [203].

11.11.3 Treatment

Patients infected with C. trachomatis and their sexual partners should be treated with azithromycin or doxycycline. The arthritis itself can be treated with NSAIDs, and with local glucocorticoid injections for mono- and oligoarthritis and enthesitis. Systemic corticosteroids can be used if there are systemic symptoms. The role of antibiotics in the treatment of reactive arthritis is questionable. Although it may be helpful in the infective phase, once the arthritis has developed, antibiotics typically do not modify the disease course. As half of affected patients recover from reactive arthritis within the first 6 months, the use of disease-modifying antirheumatic drugs are often not considered, though sulfasalazine may be helpful in achieving faster remission if used in the first few months and for those with chronic reactive arthritis. Cutaneous lesions can be treated with topical steroids [202, 204–206].

11.12 Adult-Onset Still's Disease

Adult-onset Still's disease (AOSD) is an uncommon febrile autoimmune disease, typified by high spiking fevers, polyarthritis, and a transient rash. The etiology of AOSD is unknown, and it typically affects adults in the second and fourth decades of life with equal incidence between males and females. A similar syndrome occurs in the systemic subset of juvenile idiopathic arthritis. Other AOSD symptoms include pharyngitis which can be a presenting symptom, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, elevated transaminases, and serositis [207].

Fever of unknown origin is the most frequent cause for investigation, as high fever is the initial symptom in most patients. The classic fever pattern is one–two spikes exceeding 39 °C, most often late in the day, and resolving within hours, also known as quotidian fever [207, 208]. AOSD can be mistaken for sepsis, and other disorders such as hepatitis and reactive hemophagocytic syndrome must be excluded. The classic AOSD rash is maculopapular and salmon-colored, mainly over the trunk and proximal extremities, most pronounced during febrile episodes. Dermatographism is present in up to 60% of patients with the rash [207].

11.12.1 Emergent Complications

Chronic AOSD can lead to joint destruction akin to seropositive rheumatoid arthritis, with resultant severe functional impairment [207]. Up to 5% of patients can develop amyloidosis within 10 years of the disease onset [209]. Macrophage activation syndrome is reported in 5–10% of patients. This massive, potentially deadly immune response is associated with cytopenias, disseminated intravascular coagulation, and liver dysfunction [210].

11.12.2 Laboratory Findings

AOSD is typically seronegative for ANA and RF. However, acute phase reactants such as ferritin, ESR, and platelets are often elevated. Ferritin levels more than five times the upper limit of normal is specific for AOSD. Serum albumin is commonly low. A majority of patients have leukocytosis, mild anemia of chronic disease, and thrombocytosis. Patients with hepatomegaly may have elevated LFTs [207].

Histology of skin lesions is nonspecific with a mild perivascular infiltrate in the superficial dermis consisting of lymphocytes and histiocytes. Myalgias and joint pains also worsen with the rash and fever [207].

11.12.3 Treatment

NSAIDs are first-line treatment for the symptoms of adult-onset Still's disease, but most affected individuals need oral corticosteroids to treat the acute systemic symptoms. About 20% of patients have chronic relapsing disease, which may require steroid-sparing agents, namely methotrexate for polyarthritis. Cyclosporine, IVIG, biologics such as anti-TNF-α agents, rituximab, and the IL-1 receptor antagonist anakinra have been used successfully as well [211].

11.13 Conclusion

The connective tissue diseases span a broad clinical spectrum with varied presentations in multiple organ systems. As such, the diagnosis of connective tissue disease is difficult, and can be delayed, leading to deleterious end organ effects. The clinical picture is further muddled by the fact that patients with underlying collagen vascular diseases may develop unrelated disease processes, which can mimic a disease "flare" or exacerbation. Cutaneous findings often provide an invaluable clue to diagnosis and management, and are thus critical to preventing the multitude of associated secondary complications.

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Burn and Other Exposure Injuries

12

Alexander M. Sailon and Peter J. Taub

12.1 Introduction

Man's primitive fascination with fire has led to affliction with burn injuries since the dawn of our history. Therapy has evolved from the application of mud and excrement in Egyptian times, to dressings impregnated with pig fat and resin in the Roman era, to the emergence of a relatively modern concept of first aid from the military battlefield [1]. Still today, burn injuries and their sequelae represent one of the most potentially devastating and challenging conditions in medicine. Over one million burns occur annually in the USA, with the majority being treated in an outpatient setting. Children up to 4 years of age and working age adults comprise nearly 90% of patients with burn injuries. Injuries to children largely involve scald injuries, whereas flame burns are predominant in the working age population [2]. Presentation may vary considerably, from simple sunburns requiring no more than counseling and a topical agent to extensive tissue loss resulting in multi-organ system failure and a protracted ICU course. In more serious cases, it is imperative that burn care extend far beyond the initial insult. Burns can significantly alter quality of life and are a common cause of disability. Debilitating contractures and cosmetically unacceptable scars may have long-lasting physical and psychological consequences, requiring continued physician involvement and support.

12.2 Evaluation

Burns occur via numerous etiologic insults and may damage the skin and appendageal structures at various depths. Skin may be harmed by contact with heat, noxious chemicals, and/or electrical current.

With the exception of minor injuries, all burn patients should be treated as trauma patients. Initial evaluation should assess life-threatening conditions and focus on the airway, vital signs, neurological status, etc. A careful history identifying the cause, type, and exact time of injury is paramount in determining initial fluid resuscitation, expected clinical course, and disposition.

Exposure to smoke or heated gas may cause airway edema which can quickly progress to obstruction. Facial burns, carbonaceous sputum, elevated blood carboxyhemoglobin, and tachypnea should raise concern for airway injury. Progressive hoarseness often indicates impending airway obstruction. Intubation by an experienced anesthesiologist or emergency room physician should be ideally performed prior to

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Table 12.1 American Burn Association criteria for referral to a burn center

Partial thickness burns greater than 10% total body surface area (TBSA)
Burns that involve the face, hands, feet, genitalia, perineum, or major joints
Third-degree burns in any age group
Electrical burns, including lightning injury
Chemical burns
Inhalation injury
Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
Any patients with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient may be initially stabilized in a trauma center before transfer
Burned children in hospitals without qualified personnel or equipment for the care of children
Burn injury in patients who will require special social, emotional, or rehabilitative intervention

the development of a complete obstruction. A history of smoke exposure in an enclosed space or for a prolonged time merits screening for carbon monoxide poisoning via measurement of blood levels. Although standard blood tests suffice, noninvasive pulse carbon monoxide oximetry should be used where available. The clinician should be aware that standard pulse oximetry and arterial blood gases erroneously report normal oxygen levels in the setting of carbon monoxide poisoning. Specific and severe burn injuries require immediate transfer to a burn center once the patient has been stabilized (Table 12.1) [3].

A thorough full-body assessment is critical in major injuries to avoid missing any areas of soft tissue damage. For electrical injuries, potentially hidden points of entry and exit should be sought. These commonly occur on the palms and soles since electrical cables are inadvertently grasped and the current travels to the ground. In these cases, damage along the path of the current is hidden but should be suspected.

12.2.1 Depth of Burn Injury

Careful assessment of burn depth is the next critical step in determining appropriate management and can help predict prognosis and long-term scarring. It is important to keep in mind that most burns represent a mixture of different depths. Superficial or first-degree burns involve only the epidermis. They are painful and have an erythematous, glistening appearance without blister formation. Capillary refill is brisk, as is bleeding on pin-prick. The classic example is a sunburn, although superficial burns are frequently caused by flash burns (i.e., brief, intense thermal exposure) as well.

Partial-thickness or second-degree burns involve the epidermis and part of the dermis. They are further subdivided into superficial and deep partial thickness burns depending on the depth of dermal involvement. Superficial partial-thickness burns are pink and painful with delayed capillary refill. They will generally heal in 2–3 weeks without significant scarring, although depigmentation of the affected skin is possible. Scald burns typically result in superficial partial-thickness burns.

Deep partial-thickness burns are characterized by injury extending into the reticular dermis. They appear “cherry red” or pale and dry with mottling (Fig. 12.1). The neural plexus in the deep dermis is often injured resulting in variable sensation and burns that are generally less painful to touch. They will not blanch with gentle pressure, and bleeding from pin-prick will be delayed. The rate of healing is variable depending on the number of intact adenxal structures left in the skin. As a result, thin, hairless skin (e.g., eyelids) will heal more slowly than thick or hairy skin (e.g., back, scalp). Typically, these burns will heal in 1–3 months, but with a significant amount of scarring and possible contractures because follicular structures needed for re-epithelialization may be destroyed. Often, they are best treated by excision and grafting.

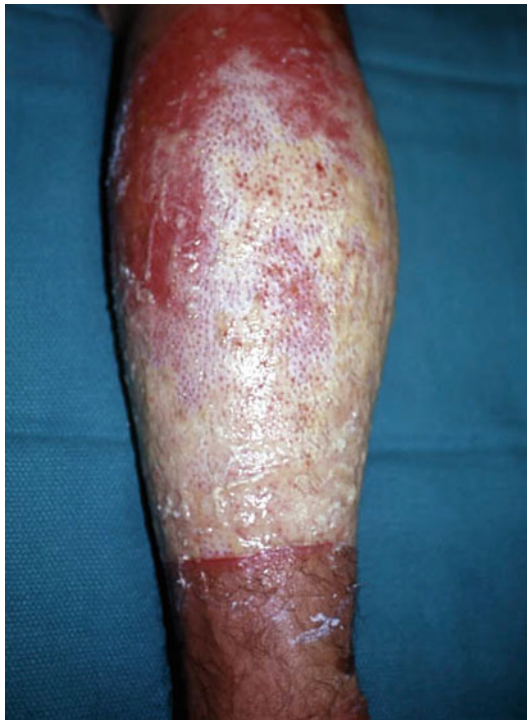

Fig. 12.1 Contact burn exhibiting a mixture of deep partial thickness injury on the distal aspect of the leg and superficial partial thickness injury proximally. Note the rapid demarcation to normal skin secondary to protection from the patient's footwear

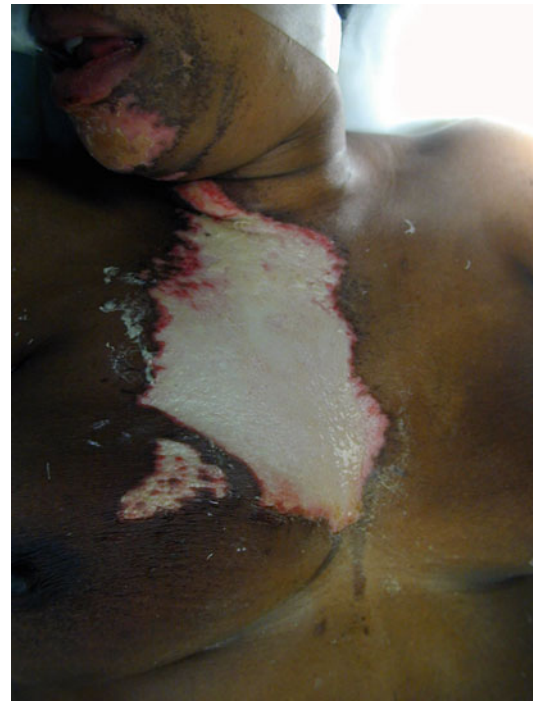

Fig. 12.2 Full-thickness burn to the chest, neck, and chin

Full-thickness or third-degree burns extend through the entirety of the dermis (Fig. 12.2). They appear dry, leathery and can be white, brown, or black. These wounds are insensate, do not blanch, and do not bleed upon pin-prick. Thrombosed vessels may be visible and are pathognomonic for third-degree burns. Fourth-degree burns extend completely through the skin and subcutaneous tissues, affecting underlying muscle and bone [4].

Assessing burn depth requires experience and often takes several days of observation to determine the appropriate management. Patients may be admitted for observation and reexamined every day as the appearance of the wound becomes clearer. Serial debridement of necrotic tissue may be required to accurately assess the degree of injury. Generally, the wounds that appear likely to heal within 3 weeks can be managed conservatively, whereas those that will take longer are best treated by excision and grafting.

12.2.2 Determining Total Burn Surface Area

Calculating total burn surface area (TBSA) is the next critical step as it serves to guide initial fluid resuscitation, nutritional requirements, and appropriate triage. Of note, partial thickness burns covering more than 10% of TBSA and those in anatomically sensitive areas (i.e., genitalia, hands, crossing joints) should be immediately referred to a burn center (Table 12.1). It can be estimated by either of two methods. Regardless of the technique employed, it is important to note that only areas of partial- and full-thickness injury (second- and third-degree burns) should be counted. Superficial burns involving only the epidermis (i.e., first-degree burns) need not be considered. The "rule of nines" is the most popular method and divides the adult body into anterior torso (18%), posterior torso (18%), legs (18% each), arms (9% each), head/neck (9%), hands (1% each), and perineum (1%) (Fig. 12.3). The percentage assigned to a body area reflects its total area, therefore a burn

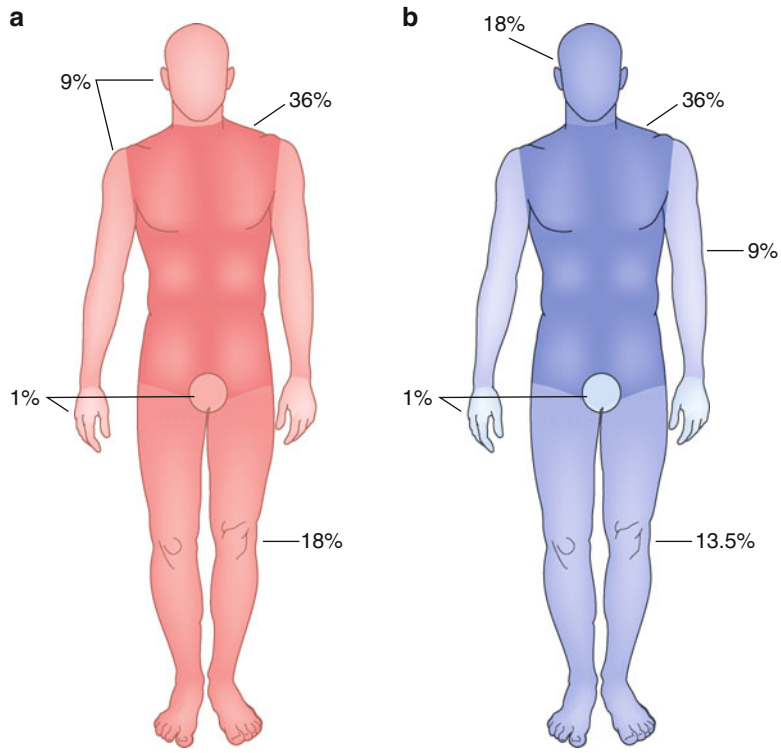

Fig. 12.3 Rule of nines to calculate total burn surface area in (**a**) adults and (**b**) children

involving one-third of the leg should be considered a 6% TSBA burn. A modified rule of nines is used for children dividing the body into anterior torso (18%), posterior torso (18%), head/neck (18%), legs (13.5% each), arms (9% each), hands (1% each), and perineum (1%). Because the proportions for infants and children differ significantly from each other and adults, Lund and Browder charts are available to provide a more precise estimate of TBSA based on the patient's age. For small or scattered burns, a second technique for calculating burn area involves using the patient's hand (note: not the examiner's). The patient's hand represents approximately 1% of the body surface area and can be used to estimate TBSA by counting how many "hands" are required to cover the area of a burn [5].

12.2.3 Zones of Injury

The initial effect caused by a burn can be generally divided into three distinct zones based on histology, degree of tissue damage, and blood flow. The zone of coagulation is the portion of the wound that was most directly affected by the insult and is characterized by irreversible tissue damage. The zone of stasis is the surrounding ischemic area that is potentially salvageable. Fluid resuscitation seeks to increase perfusion in this area and prevent progression to skin necrosis. The zone of hyperemia is the most peripheral area and is characterized by inflammation leading to increased blood flow and increased vascular permeability causing edema. This area invariably recovers rapidly over the course of a few days [2].

12.3 Management

12.3.1 Fluid Resuscitation

Historically, high early mortality rates seen following burn injury were in part related to unrecognized fluid loss and inadequate resuscitation. Hypovolemia develops quickly due to evaporation

Table 12.2 Parkland Formula: used to determine fluid resuscitation in the first 24 h

Parkland formula
Total fluid volume = 4 (cc/kg) × weight (kg) × TBSA (%)

One-half of the total fluid volume should be administered in the first 8 h, the second half in the subsequent 16 h. Total burn surface area (TBSA)

from a compromised skin barrier and extravasation of fluid into unburned tissue. Today, burns of significant size (greater than 10% total body surface area) are managed with fluid replacement according to one of several described protocols. The more widely used Parkland Formula calculates the amount of total fluid requirement over the first 24-h period following the injury. Total fluid volume is calculated as the patient's weight in kilograms multiplied by four and then by the total body surface area of second- and third-degree burns in percentage points. One-half the calculated volume is given over the first 8 h from the time of injury (not from the time of evaluation). The second half is given over the next 16 h (Table 12.2). Regardless of the formula used, the clinician should bear in mind that any mathematical calculation of fluid requirements is merely an estimate. Close monitoring of the response to fluid administration and physiologic tolerance of the patient is crucial. Fluid management in the pediatric population can be challenging, especially in infants where lack of renal maturation and reduced GFR makes resuscitation more delicate. Adequacy of resuscitation should be carefully monitored in multiple ways via heart rate, blood pressure, mental status, acid–base balance, etc. Among these methods, urine output is the most accurate. A urine output of 0.5–1.0 ml/kg/h indicates that hydration is appropriate. Higher urine outputs may be desired in patients with crush or high-voltage electrical injuries where myoglobinuria can damage the renal tubules.

12.3.2 Burn Wound Infections

Diagnosing burn wound infections by regular monitoring of vital signs and frequent wound inspection prevents delays in wound healing and potential systemic sequelae such as bacteremia, sepsis, and multi-organ dysfunction syndrome. Minimizing exposure to pathogens and treating infections early are critical to successful burn management as infection remains responsible for the majority of mortalities. Although wound infections are common, many burn patients are also at risk for pneumonia if they are intubated, immobile, or septic, or if they have suffered an inhalation injury or chest wall injury that limits thoracic cage excursion.

Although burn wounds are initially sterile, gram-positive bacteria may survive within the sweat glands and hair follicles and will quickly colonize the wound within 24–48 h if no antimicrobial agent is used. At approximately 1 week post-injury, the wound may be colonized by an assortment of gram-positive bacteria, gram-negative bacteria, and yeast or fungi. Microbes that colonize the wound may arise from the host's own gastrointestinal or respiratory flora, or they may originate from the hospital environment.

Staphylococcus aureus is a common etiologic agent of burn wound infections, particularly ones arising soon after injury. However, *Pseudomonas aeruginosa* has become the predominant agent overall in a number of burn centers. It is often characterized by a greenish-blue discharge and a characteristic grape-like odor. Gram-negative bacteria have become a more frequent cause of invasive infections as a result of their numerous virulent factors and antimicrobial resistance traits. Anaerobes are a less common source of infection and typically occur in the setting of electrical injury or when open wound dressings are used [6].

Fungi and yeast tend to colonize wounds later, and patients on broad-spectrum antibiotics may be at increased risk. Fungal wound infections are associated with a high mortality and their resistance to topical antimicrobials highlights the importance of aggressive wound debridement.

12.3.3 Topical Burn Care

Burn care is largely dependent on the depth, size, and location of the burn sustained. It is imperative

that the treating clinician be mindful of the fact that each burn may vary in depth and, therefore, require different treatment. Initial treatment for all but superficial burns remains the same. Clothing, jewelry, and debris should be gently removed. Mineral oil can be applied to painlessly remove charred clothing adherent to a burn. Wounds should be cleansed with soap and water to remove smaller debris and loose tissue. Intact bullae are best left alone, whereas burst, flaccid blisters, and frankly necrotic tissue should be scraped off or debrided sharply to prevent infection and accurately assess burn depth. A minimally adherent dressing such as Vaseline-impregnated gauze should be applied to minimize contamination and evaporative loss.

Topical agents play an important role in burn care by their ability to augment wound healing and prevent infection. Given the variety of agents available, one needs to understand their subtle nuances in order to maximize their potential. Superficial, partial thickness burns that should heal without surgical intervention should be dressed with an easy-to-apply, topical antimicrobial agent. It is important to keep in mind that although burn wounds can be initially considered sterile they are typically colonized quickly by both gram-positive and gram-negative bacteria, necessitating the need for broad-spectrum topical antimicrobial coverage. Parenteral agents are not recommended in the absence of multi-organ system involvement. Deeper, partial thickness burns should generally be treated by tangential excision and grafting. In a similar fashion, full-thickness burns should be treated with an antimicrobial topical agent capable of eschar penetration until excision is appropriate.

12.3.3.1 Silver Sulfadiazine

Silver sulfadiazine (*Silvadene*®) remains one of the most popular agents. It is formulated as a white, water-soluble cream with broad-spectrum antimicrobial coverage (including *Pseudomonas*). Its application is painless and often found to be soothing. However, silver sulfadiazine is not able to penetrate a burn eschar, limiting its use in such wounds. A transient, self-limiting leukopenia develops in 3–5% of patients and should not require discontinuation. A small test dose on normal skin should be applied first only in patients with a known sulfa allergy.

12.3.3.2 Mafenide Sodium

Mafenide sodium (*Sulfamylon*®) is available as a water-soluble cream or solution. Like silver sulfadiazine, it has broad-spectrum antimicrobial coverage but unlike other topical agents, mafenide has excellent penetration, making it the "gold standard" for burns of the ear or in the presence of a burn eschar. In such cases, twice daily application is necessary. Application tends to be painful, potentially limiting its use. Mafenide is a potent carbonic anhydrase inhibitor that can cause metabolic acidosis, in addition to osmotic diuresis and electrolyte abnormalities [5].

12.3.3.3 Silver Nitrate

Silver nitrate is available as a solution-soaked dressing, and as such, dressings need to be changed frequently (3–6 times per day) to keep the wound moist. Application is painless although care must be taken as silver nitrate stains clothing and linens black. It too has broad-spectrum antimicrobial coverage. Silver nitrate is prepared as a hypotonic solution, which can result in electrolyte abnormalities, most commonly hyponatremia or hypochloremia, requiring frequent monitoring for those with large wounds. The silver ions in both silver nitrate and silver sulfadiazine can rarely cause methemoglobinemia. Should this develop, any silver containing agents should be immediately discontinued.

12.3.3.4 Other Topical Antimicrobial Agents

Over-the-counter ointments, such as bacitracin, neomycin, and polymyxin, are commonly used for superficial partial-thickness burns, especially on the face, as mentioned previously. These products carry a low risk of allergic dermatitis. Of note, mupirocin (Bactroban®) is the only agent in this class to be bactericidal against methicillin-resistant *staphylococcus aureus* (MRSA).

12.3.3.5 Topical Debriding Agents

Ointments containing collagenase or papain-urea stand apart from the previously mentioned agents

due to their ability to enzymatically debride nonviable tissue. They are an excellent choice in burn wounds with mild necrotic or fibrinous material. In these wounds, they can result in a clean dermis earlier, leading to faster re-epithelialization [5].

12.3.4 Systemic Derangements

Significant burn injury results in a large-volume fluid shifts and a systemic inflammatory response that affects nearly all organ systems. As a result, burn patients may present with or develop hypothermia during their hospital course. Forced-air warming blankets and gently heated intravenous fluids should be used to achieve or maintain normothermia. Hypothermia has been associated with increased mortality rates and a higher incidence of acute lung injury.

Severe burns results in a hypermetabolic state, which may last several months. The increase in energy expenditure is proportional to burn surface area and can lead to a doubling of the basal metabolic rate in severe burns. Enteral nutrition should be started early and is preferable as parenteral nutrition is associated with immunosuppression and higher mortality rates. Generally, patients with a total body burn surface area of greater than 20% should undergo tube feeding to ensure caloric needs are met. Close attention must be paid to changes in nutritional status as the patient recovers.

Basal energy expenditure (BEE) determines the required caloric intake and can be estimated using the Harris-Benedict equation (Table 12.3) [4]. BEE is then multiplied by a factor based upon the severity of the stress (i.e., in large burns this factor is 1.8–2.1). Indirect calorimetry is a more accurate way of measuring caloric expenditure by determining measured oxygen consumption and carbon dioxide production in ventilated patients.

Caloric intake should be appropriately balanced between lipids, carbohydrates, and proteins with the assistance of nutritionist. Highly stressed patients have higher protein needs, and may require up to 2 g/kg/day (assuming normal renal function) to prevent muscle breakdown. In addition, critically ill patients benefit from tight glucose control and therefore require regular monitoring of blood glucose levels. Adequate levels of vitamins and minerals are provided in most commercially available enteral feeding formulas. However, administering supernormal levels of certain nutrients (termed immunonutrition) may be beneficial. For example, omega-3-fatty acids can suppress proinflammtory cytokines, arginine can enhance lymphocyte function, and glutamine can improve gut barrier function [4].

Table 12.3 Figure 5. Harris-Benedict equation: used to estimate basal energy expenditure (BEE)

Harris-Benedict equation
For males: BEE = 66 + (13.7 × weight in kg) + (5 × height in cm) − (6.8 × age in years)
For females: BEE = 655 + (9.6 × weight in kg) + (1.8 × height in cm) − (4.7 × age in years)

Burn injury can cause renal failure from myoglobinuria secondary to muscle breakdown or hemolysis. Inadequate urine output despite adequate fluid resuscitation often heralds renal failure. Dialysis may be required and should not be delayed. In the presence of myoglobinuria, urine output must be kept high with intravenous fluids, and diuretic use should be considered.

Heart failure is a potential complication from circulating myocardial depressants (namely lipopolysaccharide) after a major burn. Diastolic dysfunction predominates and should be treated by administering an inotropic agent. Drugs should be chosen that minimize vasoconstriction so as to avoid worsening already hypoxic wounds.

12.3.5 Surgical Management

Distal perfusion after an extremity burn may be compromised by compartment syndrome, a condition characterized by increased compartment pressures secondary to edema. Pain out of proportion to the injury and aggravated by passively stretching muscles within the compartment is often reported early and nearly universal. Paresthesia and loss of pulses are much later findings. Although generally clinical examination is sufficient for diagnosis, intra-compartment

pressures of greater than 30 mmHg are confirmatory. Fasciotomies of the affected extremity are indicated to prevent muscle necrosis and limb loss.

Burn injury may also cause acute damage to regions distal to the injury as a result of circumferential compression to either the trunk and/or an extremity due to necrotic skin and soft tissue. Full-thickness injury can produce a tough eschar that may compromise distal perfusion of an extremity or ventilation by limiting thoracic cage excursion. In either situation, an escharotomy is indicated. This should be done soon after the initial assessment as fluid resuscitation may worsen the problem. Because the skin is insensate, this can often be done at the bedside with hand-held electrocautery through the eschar and into the subcutaneous adipose. The skin should subsequently spread restoring distal perfusion. Eventual coverage may be completed with autologous split and full thickness grafts, xenografts, cultured cells, or alloplastic dressings.

Following an adequate period of time to allow for fluid resuscitation and demarcation of areas of questionable depth, the patient may undergo tangential excision of those areas deemed too deep to heal within a reasonable period of time. Damage to the appendageal structures in these deep partial thickness burns limits their ability to reepithelialize. The skin is excised using a thin blade with an overlying guard until viable tissue is encountered. A tourniquet may or may not be used on an extremity since punctate bleeding determines adequate perfusion.

Skin is harvested from donor sites that are relatively flat and unnoticeable, such as the lateral thigh, lower back, or scalp. Split thickness skin is harvested at a depth of roughly 8 to 12/1,000 of an inch using an electric dermatome that moves a thin blade side to side between a guarded handle (Fig. 12.4). Firm, consistent pressure is used to harvest skin of suitable quality. Skin grafts may be placed through a mesher, which punches small holes in the graft at regularly spaced intervals in order to increase the total surface area. A graft that is meshed either 1½ or 3 times is valuable when larger amounts of skin are needed. Care must be taken with grafts meshed at a 3:1 ratio since the resultant skin bridges may rotate to the dermal side when the graft is placed on the recipient site. A meshed graft also minimizes fluid accumulation beneath the graft. Unmeshed grafts are preferred in cosmetically sensitive areas such as the face since meshed grafts have a hatched or waffle pattern once they heal. To prevent accumulation of fluid beneath unmeshed grafts, multiple incisions may be made to allow egress of serum or blood.

The skin graft may be affixed to the periphery of the debrided area using sutures, staples, or tape. Several sutures should also be placed centrally to minimize shearing forces. For added support, a tie-over bolster, circumferential dressing or negative pressure sponge should be used. If the latter is chosen, pressure should be low enough to allow for ingrowth of blood vessels. A splint is also helpful for burns on an extremity to limit movement and, therefore, shearing forces on the graft. The dressing is changed in 3–5 days to confirm take of the graft. Longer times until the first dressing change may be appropriate for meshed grafts with adequate postoperative compression since fluid accumulation is rarer. The first dressing change should occur earlier for unmeshed grafts which may not have ideal compression. At 3 days, fluid may be aspirated from beneath a skin graft without affecting its viability. Graft survival is much less likely if aspiration is delayed. Care should be exercised such that the graft is not inadvertently removed with the dressing. Failure of graft take is due to one or more complications, including an inadequately vascularized wound bed, infection, seroma or hematoma formation, and movement of the graft (i.e., shear forces).

For areas prone to complications due to secondary skin contraction with healing (e.g., the lower eyelid), full thickness grafts should be used. These are generally harvested by hand using a scalpel just above the level of the subcutaneous fat. Any remaining fat is then removed with a sharp, fine scissor from the undersurface of the graft prior to placement.

In the absence of sufficient healthy skin for grafting, a small amount of epithelial cells may be harvested from an unburned area such as the perineum or inner thigh and grown in a labora-

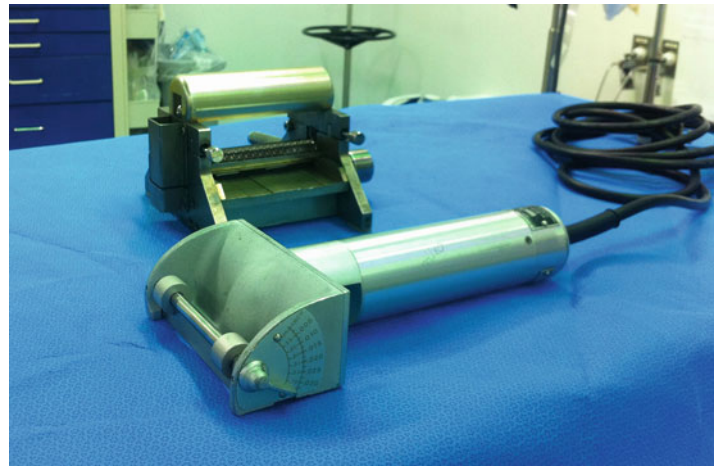

Fig. 12.4 A standard dermatome in the foreground with a control for skin graft thickness. A mesher in the background increases the surface of the skin graft. By changing the cutting roller, skin grafts can be meshed at a ratio from 1.5:1 to 3:1

tory as cultured sheets. Use of cultured epithelial cells is indicated for very large burns where donor area is limited. Unfortunately, high cost and lower strength are barriers to more widespread use.

Xenografts (tissues from other species) have held the promise of a natural replacement material in large supply. They have been used for years but still are complicated by immunologic rejection. Today, pig skin is used for large burns as a temporary occlusive dressing or as a test graft for wounds of questionable vascularity. If the xenograft fails to take, the wound bed is presumed to be inadequate for more valuable autogenous skin. However, if the xenograft successfully takes, it may be completely removed in favor of an autogenous skin graft. Another option is to remove the antigenic epidermis from the inert dermis by dermabrasion replacing it with a thinner skin graft. This allows the epidermis to regenerate more rapidly and subsequently becoming quickly available for repeat harvest.

Synthetic skin may also be used but is not able to completely obviate the need for an autogenous graft. Integra™ (Life Sciences) is composed of collagen fibrils bound to a silicone sheet replicating the dermal and epidermal elements of natural skin. The collagen fibrils are incorporated into the healing wound bed to recreate the dermis, while the silicone acts as a temporary barrier to fluid loss similar to a natural epidermis. In 2 or more weeks, the silicone sheet is removed and a thinner skin graft than normal may be applied.

12.3.6 Caring for Healed Wounds

Caring for a burn does not end once the wound has been successfully grafted or re-epithelialized (Fig. 12.5). Nutrition plays a large role in healing and adequate caloric intake following injury must be monitored. Healing wounds are sensitive to ultraviolet (UV) rays, and protection from the sun is critical. Patients must be reminded to use sunscreen or clothing that covers the wound when outdoors. Sun exposure can lead to hyperpigmentation of the graft or wound.

Pruritus is a common complaint since healed wounds lack adnexal structures needed to keep skin moist. A mild alcohol- and fragrance-free moisturizer should be applied daily and after washing. Despite liberal moisturizer use, many patients still complain of iprutitus. In these cases, an oral antihistamine may be beneficial.

Epidermal inclusion cysts can develop when skin grafts are placed over a wound bed that contains intact dermal structures or small, microscopic patches of epidermis that were not visible to the surgeon at the time of graft placement. Inclusion cysts may be treated by incision and drainage. Larger cysts may require excision [2].

Burn scar contractures are one of the most devastating sequelae of severe injuries. They result from prolonged healing, delayed re-epithelialization, or excessive immobility in a flexed position. Compression dressings, massage, silicone sheets, and active and passive range of motion activities

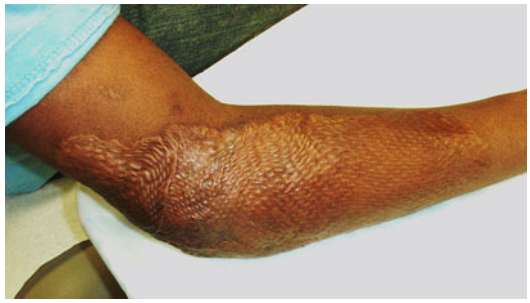

Fig. 12.5 Fully healed split thickness skin graft over the extensor surface of the elbow. A meshed graft was used in the case

can reduce long-term scar formation. Severe contractures are both physically and psychologically debilitating. Such patients should be referred to a plastic surgeon experienced in burn reconstruction for further management.

12.4 Electrical Burns

Electrical injuries represent an uncommon but potentially devastating event that can affect multiple organs outside of the area directly affected. It should be noted that tissue damage results from a combination of both thermal and nonthermal energy via protein denaturation and altering the permeability of the cell plasma membrane (i.e., electroporation). Electrical injuries are classically divided into low-voltage (less than 1,000 V) and high-voltage (greater than 1,000 V). Electrical injuries in the home are usually low-voltage, while high-voltage injuries typically occur at factory or construction sites. This distinction dictates subsequent management. Low-voltage injuries may generally be treated on an outpatient basis, assuming there are no significant injuries or arrhythmias.

High-voltage injuries are typically arc-mediated, meaning the patient is unlikely to have had direct contact with the electrical source. Since electrical energy travels along the path of least resistance, one should look carefully for entrance and exit sites on initial evaluation. Cutaneous burns do not necessarily reflect deep tissue damage, and, as a result, these patients may have extensive muscle and nerve injury. Electrical burns often do not fully declare themselves at first and the extent of soft tissue injury often extends beyond what is initially evident. Muscle injury and edema can result in increased compartment pressures and, ultimately, compartment syndrome. Consequently, patients at risk should have serial neurologic exams. Myoglobinuria from muscle necrosis results in tea-colored urine and necessitates maintaining a high urine output (approximately 100 cc/h) to prevent renal damage. If the urine does not clear despite adequate fluid resuscitation, mannitol can be administered. In addition, some advocate the alkalinization of urine to prevent precipitation of myoglobulin in kidney tubules.

Given the propensity of cardiac arrythmias as a result of electrical injuries, all patients should, at a minimum, have an electrocardiogram. Although not evidence-based, cardiac monitoring for 24 h is protocol at some institutions.

Electrical injuries can result in significant long-term sequelae. Most commonly, neurological deficits involving either the peripheral (i.e., peripheral neuropathy) or central nervous system (i.e., cognitive changes, poor motor skills) which can occur even months after the injury. In addition, cataracts occur in approximately 5% of electrical injury patients, with other ocular injuries occurring less frequently.

12.5 Chemical Burns

Chemical injuries constitute only 3% of cutaneous burns; however, they account for 30% of burn deaths [7]. They are broadly classified into acid or alkali (base) burns. Alkali burns have a more insidious course and generally cause more injury than acid burns as a result of liquefaction necrosis, allowing the alkali to penetrate deeper into the tissues. Acid burns, on the other hand, cause immediate, more-limited tissue damage. Coagulation necrosis results in eschar formation, which prevents further penetration of the acid.

The first step in treatment should be removal of the inciting agent. This includes discarding contaminated clothing. Healthcare workers must

take appropriate precautions as some chemicals can erode through standard protective equipment. The affected skin should be copiously irrigated for at least 30 min to an hour with room temperature water. Irrigation should be avoided in the presence of chemicals that ignite upon contact with water (e.g., elemental sodium, potassium, and lithium). Neutralizing the chemical agent should not be attempted, as an exothermic reaction often develops, potentially causing further injury. Depending on the inciting agent, patients should be monitored for systemic effects. For example, phenol causes central nervous system depression and cardiopulmonary collapse. Although hundreds of chemicals can cause burns, a few deserve specific mention for their unique treatments.

12.5.1 Hydrofluoric Acid

Hydrofluoric acid, commonly found in industrial cleaning solutions and frequently used in the glass and silicon chip industries, penetrates skin and tissue until its fluoride ion chelates with a calcium source, usually bone. Subsequent hypocalcemia may result in dysrhythmias. A topical calcium gluconate gel may prevent further damage and is most effective when applied soon after exposure. Subcutaneous injection of calcium gluconate can also be beneficial, although one must be cautious in its administration as it may cause skin necrosis. As a last resort, calcium gluconate can be injected intra-arterially. A marked decrease in pain signifies effective treatment [7].

12.5.2 Alkali

Alkali burns tend to penetrate deeper, causing more severe burns than acids. However, their course is more insidious, and treatment should assume that burns will progress significantly in depth during the 24 h after injury. Unlike acids, which result in coagulation necrosis, alkali burns are characterized by liquefaction necrosis and fat saponification. Prolonged vigorous water lavage for 60 min or more is necessary. Lye (found in drain cleaners and paint thinners) and cement are the most common agents causing alkali burns [7].

12.5.3 Tar and Grease

Tar and grease burns are two of the more commonly encountered chemical burns and should be initially treated by applying cold water to the hot, adherent material. In order to easily remove the tar, bacitracin, mineral oil, or Neosporin should be applied and washed off 12 h later.

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Dermatological Emergencies: Skin Manifestations of Abuse

13

Rachel Nazarian, Joy Checa, and Orit Markowitz

13.1 Overview

Abuse takes many forms, including physical abuse, sexual abuse, emotional abuse, and neglect. The definition of child abuse, by the Center for Prevention and Treatment of Child Abuse (USA), is stated as the mental and physical injury, sexual abuse, neglect, or mistreatment of individuals under 18 years of age, perpetrated by a caregiver, which indicates that the health of the child is threatened [1]. Physicians must always be alert for signs indicating any manifestation of abuse, looking for symptoms beyond skin lesions. The authors consider any form of abuse a medical emergency, recognizing that most children, or elderly, are unable to articulate their condition or alert authorities of any wrongdoing and rely nearly exclusively on the awareness of astute professionals. Many cases of abuse are left unrecognized by professionals, the findings being exceedingly subtle, often written off as innocuous lesions. Early recognition is crucial, not only to prevent subsequent injury which occurs in 30–70% of children, but reports have indicated that abuse tends to increase in severity with time [2], and early intervention may avert these avoidable events.

Advances in scientific analysis and medicine have allowed for objective evaluation and higher accuracy of garnering a correct diagnosis.

This chapter primarily addresses the skin manifestations of child abuse, including common conditions that mimic lesions of abuse, and those brought on cultural practices that are oftentimes misdiagnosed as child abuse. It is equally important that a physician does not wrongly accuse anyone of such a horrific crime as the repercussions of false accusations are grave; existing reports have included suicide of distraught parents mistakenly accused of abusing their child [3].

Reports of child abuse have been increasing significantly [4–6] and dermatologists are in a unique position to identify and prevent further abuse of children. The cutaneous signs of abuse, including bruises and burns, are the most frequent injury caused by physical abuse; all physicians, dermatologists especially, must remain vigilant

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in recognizing these signs despite little to no training or guidance. The challenge remains in distinguishing intentional from accidental injury, which occurs commonly in childhood, and recognizing even uncommon skin diseases that may mimic maltreatment [7].

Approximately 48 States, and the District of Columbia, among other regions, designate professionals who are mandated by law to report child abuse and maltreatment. Physicians and other health-care workers are included, as they typically have frequent contact with children, most especially dermatologists, pediatricians, and emergency room physicians, and are the first professionals to observe and hopefully recognize the signs of intentional injury.

13.2 Demographics

According to Child Protective Services, more than 700,000 children were abused or neglected in 2009. In reality, these cases likely represent only a fraction of all cases of abuse [8]. It is thought that many cases of abuse remain unreported, and abuse is rarely seen or acknowledged by individuals outside of the immediate family. Child maltreatment and abuse remains a concealed and hidden problem and despite the number of reported cases, some studies estimate that nearly 25% of the US children undergo some form of child abuse [9].

Although the short-term effects of physical abuse include lacerations, ecchymoses, burns, and bone fractures, recent studies have found that the effects of abuse are long-lasting and include physical and emotional health problems. Cardiac and pulmonary diseases in adulthood have been associated with childhood abuse [10, 11]; it is thought that prolonged mistreatment of children may lead to disruption of brain development and ultimately lead to dysfunctional immune and nervous systems [11].

Skin manifestations of abuse are the most visible of all injuries; however other forms of abuse including neglect may also beget continuing damage. Emotional effects of maltreatment include anxiety, depression, and the inability to form relationships with others. Studies have also shown that feeling of worthlessness continues into adulthood, causing some victims of abuse to consider or attempt suicide [12].

13.3 Workup

When initially facing a case of suspected abuse, the physician should approach the history like that of any other patient. Clues in the history that suggest abuse include an inconsistent or changing history with vague or absent details [13, 14]. A delay by the caretaker in seeking help, frequently defined as waiting more than 2 h before obtaining medical attention, without reasonable cause, or a child or a patient who has repeated visits for the treatment of injuries is suspicious for abuse. Subtle signs by the child, such as overly passive or withdrawn behavior, should also be noted by the physician and may be a strong indirect indication of abuse. The most common findings in the exam of a physically abused child include ecchymoses, burns (often cigarette burns), bites, lacerations, bites, and traumatic alopecia [15]; the common findings of maltreatment and how to recognize them are reviewed here.

13.4 Ecchymoses

Ecchymoses and contusions, recognized clinically as subcutaneous purpura, are the most frequently seen signs of abuse [16, 17] (Fig. 13.1), seen in about 80% of physical abuse cases [18]. Interpreting these findings can be difficult, as most children are exceedingly physically active and will sustain multiple ecchmyoses from routine play. More than three ecchymoses, larger than 1.0 cm or of varying stages of evolution, signal possible signs of abuse [7]. Contusions and ecchymoses on bony prominences, usual locations for accidental injury, such as the knees, forehead, anterior tibia, are common areas for nonviolent trauma in ambulatory children. Areas of the body that are normally protected and not routinely affected during day-to-day physical play include the posterior and medial thighs,

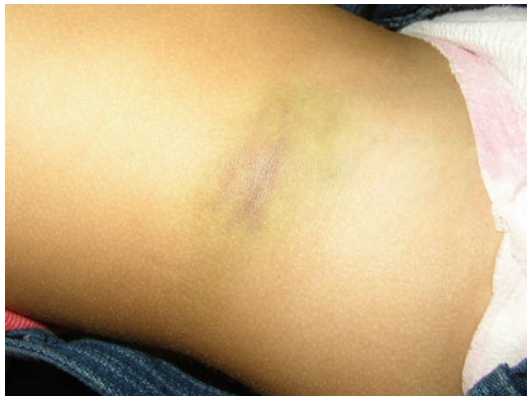

Fig. 13.1 Classic ecchymosis on flank (reprinted by permission, Dr. Pieter J. Offringa, M.D., Ph.D., Pediatrician Sint Maarten, Dutch West Indies pjosxm@yahoo.com)

hands, ears, buttocks, and genitals. The abdominal region is also rarely injured by accidental trauma, due to the protective layer of fat, and ecchymoses in this area require a large amount of force and may be accompanied by internal injury; these children should be examined fully and appropriate imaging and workup should be done to rule out internal organ damage [7]. When signs of trauma are seen in usually protected areas, the physician should consider them suspicious for abuse and conduct a thorough history and physical.

Ecchymoses seen on non-ambulatory or pre-ambulatory children should be noted with great concern. Contusions are typically sustained during ambulatory movement by physically active children; young children without mobility and with any soft tissue ecchymoses or signs of trauma should be regarded as likely abused. This is in contrast to children who are beginning in their attempts to walk and may suffer multiple ecchymoses, often on their legs and forehead, with their unstable movements [7].

Examination of each ecchymosis and its shape may also offer clues as to its etiology; Ropes, belt straps, and buckles leave ecchymoses behind that reflect their form. These specific patterns and shapes are not typically seen with accidental trauma and are suspicious, and often confirmatory, for abuse [7]. Spanking of children less than 2 years old is strongly discouraged by most experts in childcare, and has been associated with poor cognitive development in early childhood [19]. Although spanking is legal, and common, in the United States, many European countries have outlawed the practice [19]. Spanking will produce typical lesions on the skin, with parallel linear purpuric lesions and a small triangle at the base, corresponding to the interdigital space [7]. Objective measures have been developed to aid in the evaluation of ecchymoses. Using the fundamental pattern of color transformation undergone with time, bruises can be aged allowing differentiation between old and new lesions [20]. The timeline for color change, from red to blue/purple and then green/yellow, can be assessed by spectrophotometry to quantitatively determine age, and thus be used in the investigation of child abuse [20]. The practice of using spectrophotometry to analyze and age bruises based on color change over time has not been introduced into routine clinical practice, but may play a significant role in social cases of child abuse.

13.5 Burns

Burns are the third most frequent cause of injury resulting in death in the pediatric population after car accidents and drowning [21]. They comprise about 5–22% of all physical abuse cases, most commonly in children younger than 3 years old [7]. The typical age of children most likely to experience burn abuse ranges from 22 to 40 months [22]. When gathering the history of injury, the child's age and motor skills should be noted, and any discrepancy with the child's physical limitations and the history should be considered suspicious for abuse.

A recent review of 258 injury cases was conducted to determine distinguishing characteristics between intentional and unintentional injuries based on best evidence. Maguire et al. determined that the most common intentional scalds were immersion injuries and caused by hot tap water. Areas most frequently affected were the extremities, and buttocks (Fig. 13.2) and perineum, involved in 40–100% of cases while only involved

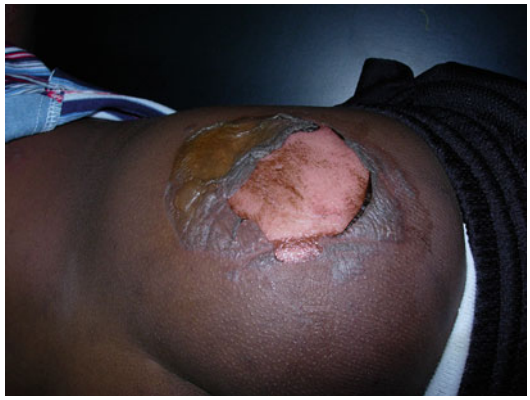

Fig. 13.2 Hot water burn on buttock (reprinted by permission, Dr. Pieter J. Offringa, M.D., Ph.D., Pediatrician Sint Maarten, Dutch West Indies pjosxm@yahoo.com)

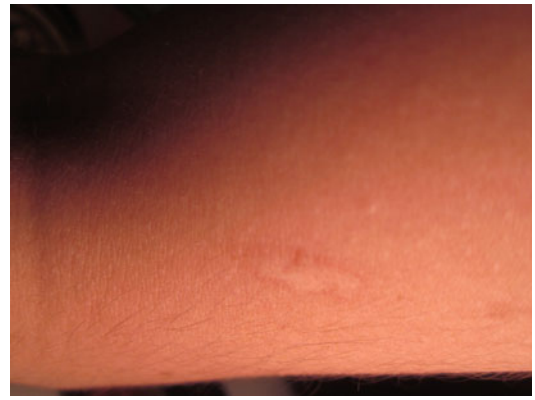

Fig. 13.3 Oval-shaped cigarette burn, accidental

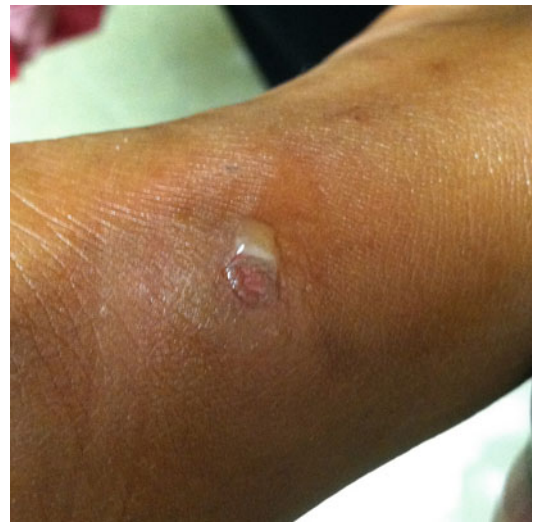

Fig. 13.4 Bullous arthropod bite

in less than 15% of accidental scalding cases [22, 23]. Distinguishing features of these burns were their symmetry and clear margins; cases were frequently associated with current or previous fractures and other injuries [23]. Forced immersion of a child in hot water will spare the folds and the resting point of the gluteal region. This type of abuse creates symmetric and accurate borders with uniform depth, while forced scalding of hands or feet will lead to "glove" or "sock" distribution burns. "Zebra stripes" and "doughnut hole" burns refer to two other presentations of abusive submersion in hot water. Forced submersion with flexed extremities will spare the flexural creases and create the striped "zebra" appearance [22]. Pressing a child's buttocks down along the cooler surface of a container of hot water spares the center giving the often-seen "doughnut hole" burn [22]. Intentional burns are usually found in multiplicity, and may be inflicted by hair curling or straightening irons, stoves, radiators, and commonly cigarettes. Cigarette burns, when intentional, are usually seen as multiple, often grouped, circular lesions of uniform size, typically 0.5–0.8 cm, with well-defined borders and a central crater; these lesions typically regress forming a scar [24]. Accidental cigarette burns are more superficial, and oval in shape (Fig. 13.3), as usually the child is able to quickly withdraw from the pain. Misdiagnosis of burns may occur with common mimickers, such as epidermolysis bullosa, impetigo, papular urticaria, and contact dermatitis [25]. Cigarette burns, especially when multiple, in various stages of healing, may be easily misdiagnosed as varicella or staphylococcal bullous impetigo. The authors have had experience with a case of suspected child abuse presenting as bullous lesions on the lower extremities of a young girl (Fig. 13.4). The suspicion that the lesions represented cigarette burns led to involvement of child protective services and the removal of the child from caretakers. This case emphasizes the utility of biopsy, which revealed a perivascular eosinophilic infiltrate in the superficial and deep dermis, consistent with bullous arthropod (blistering bug

bites) and undermining any suspicions of abuse. We recommend close communication with the dermatopathologist reading these particularly sensitive cases allowing for more specific commenting on pertinent positives or negatives of tissue section. If available, these biopsies should be sent for rush evaluation.

The features of intentional burn injury greatly contrast with those of unintentional injury, such as hot liquid spills, which are more likely to affect the head, neck, and anterior trunk, and have irregular margins and varied depth [23]. Any findings indicating abuse should be documented, with notation of location, size, and color, and a photograph taken as an objective record. It is also recommended that a skeletal survey be performed due to the frequent association with additional injuries in 20–33% of cases [2, 26, 27].

13.6 Sexual Abuse

Sexual abuse is defined as any sexual activity with a child below the age of legal consent. Sexual activity may be vaginal, oral, rectal, and viewing or fondling of any sexual anatomy. The sheer volume of children being sexual abused, currently about 1% of all children yearly, makes this diagnosis one that the physician should always remain especially vigilant, as it has reached epidemic proportions. According to community surveys, prevalence of sexual abuse in children ranges from 6 to 62% and 3 to 16% in girls and boys, respectively. It appears that cases of child abuse affect girls nearly 2.5 times more often than boys [28].

The most common offender of sexual abuse includes nonrelatives who are known to the child and family members [28]. The physician must try to illicit a thorough history from the child in question. The victim is frequently truthful, and the confirmatory history by the child is commonly the gold standard in cases of abuse. Unfortunately, there are rarely dermatologic findings in sexual abuse.

The physical examination for a sexually abuse child includes signs of penetrating anogenital trauma such as hymenal injury, lacerations and bruising around the genitals, or scarring. Sexually transmitted disease in children outside the perinatal period is highly suspicious for sexual abuse. Children more than 3 years old who are diagnosed with Chlamydia trachomatis, Trichomonas vaginalis, syphilis, Neisseria gonorrhoeae, HIV, HPV infections, and anogenital warts or HSV should have a thorough investigation to rule out abuse as these findings are strongly diagnostic. It must be noted that Chlamydia trachomatis infection when acquired perinatally may be seen until the second or third year of life [29].

Genital warts are most commonly diagnosed by dermatologists, and children beyond the perinatal period with these findings should be evaluated carefully. Genital warts have been reported in children with a history of sexual abuse, but it can also be seen in children without abuse, much like bacterial vaginosis, and is not sufficient to prove sexual abuse [30, 31]; vertical transmission should be excluded. The verification of sexually transmitted genital warts is made more difficult by the long latency period before clinical presentation. Specific serotypes of HPV, including HPV-2 and HPV-3, are typically associated with cutaneous warts, but have also been reported to cause anogenital HPV lesions in children as well [32]. Both inappropriate contact via sexual abuse and innocuous transmission through casual contact may present similarly as genital warts. Currently, detection of HPV DNA is not standard practice; HPV is diagnosed through clinical identification or through biopsy of lesions. Physicians must be cautious with their accusations of abuse. Multiple normal congenital variations may mimic the findings of abuse. Before declarations of abuse are made against caretakers, variations and conditions including periurethral bands, perineal grooves, lichen sclerosus et atrophicus, lichen planus, Beçhet's disease, perianal streptococcal dermatitis, and Kawasaki syndrome, among others, should be ruled out. Additional situational findings such as foreign body masturbation may also be mistaken for abuse. A child who is confirmed to have one sexually transmitted disease should undergo testing to look for additional diseases.

13.7 Additional Signs of Abuse

The oral cavity is an often overlooked aspect of the physical exam, but can identify many signs of abuse. Forced oral sex may cause petechiae or hematomas on the palate, specifically on the area of transition between the soft and hard palate. Signs of bruising, abrasions, or lip and lingual frenulum fissures can also be visualized in the mouth following aggressive forced feedings or forced oral sexual abuse. Clinical oral manifestations of HPV infection may also indicate signs of sexual abuse, but are difficult to support objectively. Condyloma acuminatum may be seen in the oral cavity, but HPV has also been correlated with other oral conditions, such as lichen planus, verrucous carcinoma, and pemphigus vulgaris. Oral HPV infection in healthy children has a prevalence varying from 12.3 to 48.1% [33]. Due to the varying routes of transmission of HPV, the role of subtyping has not yet been clarified. Sexual intercourse or direct contact with infected mucosa and skin is the predominant route of infection; however perinatal transmission, breast milk, autoinoculation, or heteroinoculation also remain other possible routes [33]. Further signs of child abuse include tooth loss or fractures in the mouth. These signs may indicate not only physical abuse but also abuse in the form of dental neglect. Neglect, usually chronic in nature, is defined by the failure of the caretaker to provide a child's basic needs and provisions, including nutritional needs, clothing, education, or healthcare. Chronic neglect may manifest dermatologically as scabies, pediculosis, or vitamin deficiencies. Hypovitaminosis A is seen most often in children aged 1–6 years; the role of vitamin A in maintaining epithelial integrity leads to many dermatologic signs of its deficiency. Children with hypovitaminosis A may present with generalized xerosis (dryness), often with scaling or fine wrinkling of the skin. Follicular hyperkeratosis, or phrynoderma, may be seen on thighs, arms, or bony prominences of the knees and elbows. Unlike other vitamin insufficiencies, vitamin D deficiency was not shown to be associated with the diagnosis of child abuse [34]. Although vitamin D insufficiency may lead to fractures, the most common cause of multiple fractures in young children is nonaccidental trauma [34]. A child with multiple fractures simultaneously, or one that is brought to the emergency room repeatedly for separate events of bone trauma, highly suggests abuse.

Bites illustrate another method of physical injury, but are unique in that they can be objectively used to identify the abuser. Typical human bite marks are 2–5 cm oval, semicircular or oval marks, occasionally with ecchymoses or with punctures caused by the canines; an intercanine distance less than 3.0 cm suggests a bite likely caused by a child, rather than an adult [35]. Unlike animal bites that usually tear flesh, human bites are more likely to compress flesh and may be a source of disease transmission, mainly hepatitis [35]. Dental characteristics, or salivary DNA, may ultimately expose the abuser and have been used in court cases to match perpetrators to bite marks on victims [36]. Forensic dentists may swab lesions for collection of DNA material, or make molds of the dental arch, and the physician should take accurate photographs of any suspected bites for documentation [35].

Traumatic or violent hair pulling, ultimately presenting as alopecia, petechiae, or hematomas of the scalp, may be an additional sign of child abuse. The child will show signs of tenderness on palpation of affected areas of scalp. An extensive subgaleal hematoma was documented to occur following severe sheer stress from forceful hair pulling of a young child; this phenomenon is referred to as "scalping" due to the distinctive radiologic findings [37]. Much like trichotillomania or traction alopecia, violent hair pulling of the scalp will show localized areas of hair loss with an irregular margin or outline; loose anagen syndrome, tinea capitis, and alopecia areata should be ruled out [7]. Tinea capitis, or kerion, when active or resolving, may present as uneven and patchy hair loss (Fig. 13.5).

13.8 Mistaken for Abuse

Many clinical findings may mimic those of abuse, and these must be identified and distinguished early by physicians to prevent erroneously

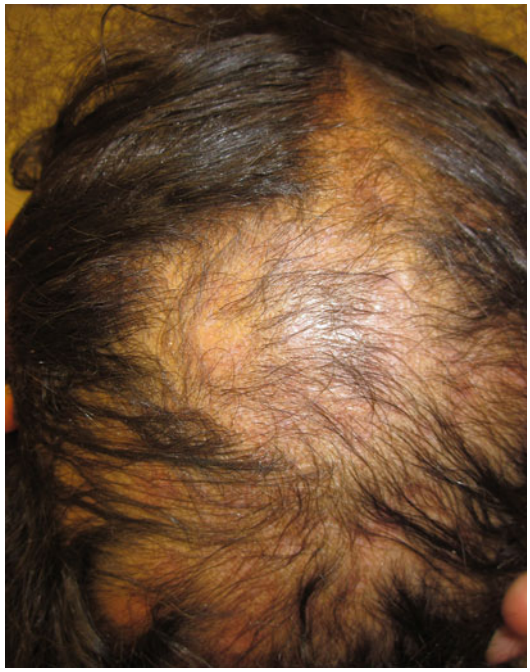

Fig. 13.5 Resolving kerion from *tinea capitis*

accusing caretakers and exposing them to unnecessary turmoil and possible prosecution. Several conditions ranging from congenital abnormalities to various cultural practices may present as clinical findings that are also similarly seen in cases of abuse.

Dermatologists often encounter mimickers of abuse, and can more readily identify these findings with accuracy. For physicians who only occasionally manage these somewhat rare dermatologic findings, the similarities between these conditions and those findings of abuse may lead to incorrect conclusions.

Anal fissures may result from forced sexual abuse and, when seen in a child with significant behavior changes of sexualized behaviors, may raise concerns for sexual abuse. More commonly, however, the child will confirm a history of constipation, or large bowl movements or hard stool, a more likely source of anal fissuring. Findings more specific for abuse include anal bruising, abrasions, and a history elicited by the child indicating sexual abuse.

Lichen sclerosus is a chronic inflammatory dermatosis that can present on young females and males and may mimic sexual abuse. Typically it presents as white papules, coalescing into plaques, with epidermal atrophy. Comedo-like plugs may be seen under dermoscopy which correspond to obliterated appendigeal ostia or follicular plugging, a feature also seen with discoid lupus or chronic cutaneous lupus [38]. Vulvar lichen sclerosus may cause symptoms of pruritus, dysuria, and even bleeding; penile lesions may present as new phimosis or urinary obstruction. Characteristic of lichen sclerosus is the figure-8 pattern, or butterfly lesions, typically on the perivaginal or perianal region, with sparing of the perineum between. Lesions found in the genital region may occasionally vesiculate secondary to excessive levels of inflammation, making trauma a consideration for the examining physician. The lesions of lichen sclerosus evolve into smooth, shiny white plaques, and although they can resemble lesions of trauma or sexual abuse if found on the anogenital, or vulvar, region, the physician must consider alternate conditions and evaluate the patient closely. Lichen sclerosus may ultimately lead to obliteration and stenosis of the introitus, and represents an additional dermatologic emergency, requiring correct identification to prevent grave, irreversible results. Skin biopsy, specifically punch or snip section, remains an additional tool for diagnosing equivocal cases of lichen sclerosus. The longest-standing lesion should be biopsied and evaluated by a dermatopathologist.

Congenital dermal melanocytosis, also referred to as Mongolian spots, are blue-gray patches or macules seen on the lumbosacral or buttock area of infants, often observed at birth or within the first few weeks of life. Occasionally these lesions can be found in the perineal area and, if multiple, may be mistaken for bruises or a sign of sexual abuse [39, 40]. The authors have also seen these blue-gray pigmented lesions on the face, one mimicking bruising around the eye of an infant (Fig. 13.6). Features that help differentiate these benign lesions from those of abuse include the classical fixed homogeneous blue-gray color, unlike the variable spectrum of colors experienced by bruising and ecchymoses. These melanocytic lesions typically appear at birth, or

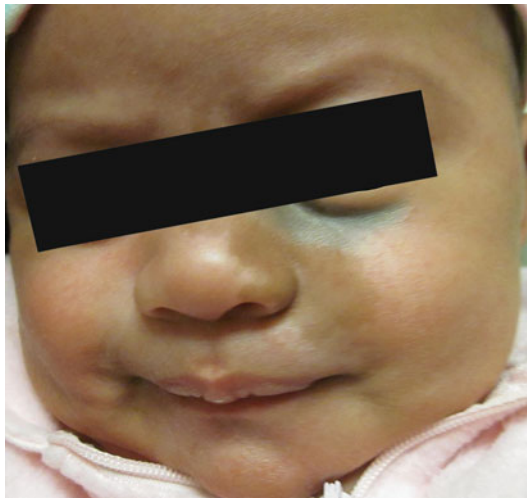

Fig. 13.6 Dermal melanocytosis (blue pigmentation)

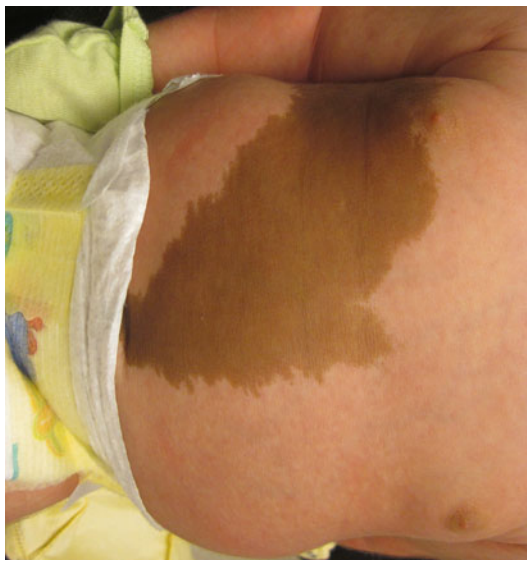

Fig. 13.7 Congenital nevus

within the first few weeks of life, and resolve by the fourth year of life, although occasionally will persist, more commonly in lesions found distal to the lumbosacral region. Histologic analysis of these lesions will show spindle-shaped melanocytes at the lower levels of the dermis [41]. Nevi, or birthmarks, may come in all shapes and sizes (Fig. 13.7), but their even pigmentation and history of long-standing presence make the diagnosis straightforward. Perianal streptococcal dermatitis represents another condition seen in children that can be misdiagnosed and misinterpreted as a sign of child abuse. It can be recognized as a well-demarcated brightly erythematous patch on perianal skin, and is caused by group A-beta hemolytic streptococci (Fig. 13.5). Children between the ages of 6 months and 10 years are commonly affected [42]. The affected child often complains of pain, pruritus, and may experience blood-streaked stool.

The literature contains multiple cases of suspected child abuse ultimately diagnosed as perianal streptococcal dermatitis, with a specific case involving skin beyond the perianal area and affecting penile skin [43, 44]. The condition may also involve vulvar skin, and the physician should be reminded of this disorder when examining children with pain and erythema in the genital area which may be suspicious of sexual abuse [45].

Diagnosis is easily and quickly confirmed with a rapid streptococcal test, and a skin culture can be sent for alternative affirmation. Amoxicillin or penicillin remains first-line treatment.

The pediatric population is subject to many cultural practices not well understood by western physicians. Without knowledge of many of these practices, the impulse to misdiagnose the cutaneous findings as those of abuse may be great, but physicians should be culturally aware and sensitive to these traditions.

The practice of "cupping" has been performed by a variety of cultures, including Middle-Eastern, Egyptian, Chinese, Greek, and European, and these practices are slowly gaining popularity in western culture [46]. Used for the treatment of various medical conditions, including polymyalgia rheumatica [46], cups of various shapes and sizes are placed on the skin and suction is created using low air pressure through heating of the cup or the air inside it. Lancing of the cup may allow the vacuum to draw blood into the cup, a practice known as "wet cupping." Clinically, circular erythema, ecchymoses, or hemorrhagic bullae may be seen, commonly on the back, shoulders, or thorax. Frequently, these lesions are erroneously thought to be due signs of abuse leading to regrettable social and legal consequences for the family involved [47–49].

Coin rubbing, also known as spooning or friction stroking, is a cultural practice seen in Chinese and Vietnamese cultures, and other Southeast Asian countries such as Cambodia and Laos [50]. A smooth-edged surface, such as the back of a coin, is placed against lubricated or pre-oiled skin and pressed deep while being dragged down the muscles along acupuncture meridians [50]; a symmetric, linear, "Christmas-tree" pattern on the back made up of linear ecchymotic or petechial streaks is commonly seen [50, 51].

Children who are subjected to practices based on cultural beliefs may be reluctant to discuss these traditions with their healthcare providers. Embarrassment over cultural differences or shame in un-American practices may prevent full-disclosure when these lesions are noticed by the practitioner. Physicians should remain sensitive to ethnic differences and consider these customs and cultural rituals when confronted with unusual cutaneous lesions suspicious for abuse, and yet are not considered harmful to the children affected.

When evaluating a patient for elder abuse, the same signs and findings as those with child abuse may be applied. Delay in seeking treatment, injuries in various stages of evolution, or injuries inconsistent with history are findings and observations strongly suspicious for abuse. Often signs of neglect, such as malnutrition, poor hygiene, or decubitus ulcers, are seen, and as most thorough exams require, the patient should be fully disrobed and evaluated in entirety. Although much of elder abuse lies beyond the scope of this chapter, the ubiquitous finding of multipharmacy in the geriatric population makes overdosing or underdosing of their medication another form of abuse.

13.9 Conclusion

Dermatologic emergencies are few in number, but represent significant clinical scenarios that require prompt attention and response by dermatologists and all health professionals. The high frequency and incidence of child abuse worldwide necessitate a level of suspicion by physicians in identifying this true dermatologic emergency and taking necessary action. There is a moral, ethical, and legal obligation to report any strong suspicion or confirmation of child abuse to child protective services or to make a referral to a child advocacy center. All healthcare workers should be able to identify signs of abuse with the level of confidence required to potentially set into action the removal of a child from its family. Any tests, imaging, or biopsies that may help in identifying lesions of abuse, or to rule out their presence, should be ordered and done quickly with results expedited.

The diagnosis of child abuse is a weighty one with severe and enduring consequences. With confirmation of abuse, and a systematic exclusion of any potential mimickers or dermatologic conditions, child protective services and the facility social worker should be alerted.

A missed diagnosis of child abuse may result in death of the child or continued violence and cruelty against the child. Scientific literature shows the statistically increased probability of behavioral, cognitive, and psychological disorders that emerge in adulthood of those abused in childhood, including depression, suicide, and addiction [52]; these and other consequences can be minimized or avoided with a vigilant and conscientious physician, alert to signs of abuse. However, the physician must always bear in mind that an erroneous charge of child abuse may cause undue anguish and distress and possible loss of reputation to the individual charged with simultaneous legal ramifications, and ultimately may lead to unnecessary separation of a child from its home and family.

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Dermatologic Surgery Complications

14

Amylynne J. Frankel and Ellen S. Marmur

14.1 Introduction

Dermatologic surgery is often performed in an outpatient surgical suite with local anesthesia, and moderate to advanced dermatologic procedures may be done without monitoring vital signs. A sound knowledge of the common dermatologic surgery complications is essential to a safe surgical practice. For example, identifying at-risk patients is key to preventing avoidable complications. Complications are to be expected in high volume practices. However, complications should be approached with well-rounded knowledge and managed accordingly. This chapter presents several of the most common surgical considerations for safe surgery and prevention and management of emergencies in dermatologic surgery.

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14.2 The Golden Rule: Prevention

The main approach in reducing complications is prevention. Prevention of complications requires an excellent informed consent which consists of

1. A clear definition of the procedure
2. A discussion of the key alternative therapeutic options
3. Education regarding the normal recovery time for different procedures
4. Education regarding the common and rare, major and minor side effects

Before any procedure in dermatologic surgery is performed, knowing how to treat the possible side effects is essential. An experienced dermatologic surgeon will take a moment to imagine the procedure from start to finish, including management of any and all potential side effects before actually starting the procedure. In this way, many side effects can be prevented. For example, if the patient is known to be on anticoagulation therapy and the possibility of a hematoma is anticipated, the intra-operative management of coagulation will be more conservative.

Finally, management of unforeseeable complications in dermatologic surgery also requires

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sensitivity regarding patients' expectations and emotions. For example, bruising, which is an accepted side effect in many procedures, is stressful for patients. Dermatologic surgeons should be readily available for follow-up appointments if only to offer reassurance while minor side effects and complications are resolving. When major side effects occur, the ability to discuss the potential cause and the management plan with the patient, while accepting appropriate responsibility for that complication, is essential for successful management of dermatologic surgical complications.

Four of the most common complications in dermatologic surgery include hemorrhage, infection, dehiscence, and necrosis of the skin. Each of these will be discussed below.

14.3 Hemorrhage

Even the most skilled surgeon will encounter bleeding at some point in his or her practice. To minimize the clinical sequelae of excessive bleeding, the astute surgeon anticipates the potential difficulties and recognizes and manages problems as they arise. However, much of the battle is to be won off of the operating table with a thorough preoperative assessment, familiarization with current guidelines for withholding blood thinners, knowledge of management of delayed bleeding, and excellent pressure bandaging for the postoperative period of time [1].

Beyond excessive bleeding intra-operatively, postoperative bleeding can be both distressing for the patient and have the potential for hematoma formation. A hematoma is a localized collection of blood outside of the blood vessel, usually in liquid form in the tissue. It appears as a deep purple, grape jelly-like nodule in or adjacent to the area of surgery. One common area for a hematoma is the infraorbital space occurring after surgery near or trauma to the infraorbital vessels. Another is the leg where superficial vessels may bleed or clot. A hematoma differs from an ecchymosis, or a bruise, which is due to the spread of blood under the skin—usually throughout the fat—in a thin layer. An ecchymosis may extend beyond the area of a hematoma, as in dependent areas or areas inferior to a surgical site, such as a wound on a cheek with an ecchymosis that extends around the jaw and submentally, or a wound on the forehead with periorbital bruising. Ecchymoses resolve after 5–14 days depending on the location. In contrast, a hematoma resolves much more slowly and often confers an increased risk of infection. The most common factor leading to hematomas in patients presenting for dermatologic surgery is concurrent anticoagulation therapy. Of the many types of anticoagulants, it is often aspirin, ibuprofen, or clopidogrel that contribute to increased risk of hemorrhage more than warfarin.

Assessing potential bleeding risk includes a thorough history of significant bleeding during prior low-risk surgical or dental procedures, common medical problems such as hypertension, alcoholism, and anxiety, and known medical conditions that contribute to abnormal coagulation, such as liver disease, renal dysfunction, and malignancies [2]. Finally, it is imperative to obtain a medication history that includes medications the patient takes both daily and as needed, as well as the last date the patient may have taken each of these medications. Several common over the counter medications may have anticoagulation effects, including Alka-Seltzer, which contains aspirin, and Advil Cold and Sinus, which contains ibuprofen. Gingko biloba, garlic, ginseng, ginger, feverfew, vitamin E, and saw palmetto have all been implicated in increased operative and postoperative bleeding. Many studies suggest waiting 3 days after the last dose of aspirin to reduce the risk of bleeding. However, the life span of a platelet is 12 days, the half life is 6 days, and one baby aspirin (81 mg) effects all of the platelets in circulation. Therefore, 1 week is the ideal time to request patients avoid non-medically necessary supplements or anticoagulants. Excessive bleeding secondary to acquired abnormalities in coagulation or platelet function from medications or ingested substances is surprisingly common (Table 14.1). For example, alcohol decreases vasoconstriction and impairs coagulation of platelets. Furthermore, various dietary supplements and alternative medicines

Table 14.1 Common anticoagulants

Warfarin	Dabigatran	Crataegues oxyacantha (Hawthorne)
Heparin	Aspirin	Ethanol
Clopidogrel	High salicylate containing foods[a]	Gingko biloba
Ticlodopine	Omega-3 fatty acids	Garlic
Enoxaparin	Vitamin E	Ginger

[a]Ex prunes, cherries, cranberries, blueberries, grapes, and strawberries

Table 14.2 Current recommendations regarding discontinuing and resumption of oral medicines and supplements to prevent complications due to bleeding[a]

Medicine/herbal	Preoperative	Postop
Vitamin supplement/herbal medications	10–14 days	1 week
NSAIDs	3 days	1 week
Aspirin (primary preventative)	10–14 days	1 week
Warfarin/aspirin (medically necessary)	Do not discontinue	N/A
Clopidogrel[b]	Do not discontinue	N/A

[a]Semin Cutan Med Surg 26:40–46 © 2007
[b]Further studies regarding this medication and complications are necessary

have the potential to alter the coagulation cascade and should therefore also be taken in to account when obtaining a medication history [3].

The decision to discontinue nonsteroidal anti-inflammatory medicines (NSAIDs) is important (Table 14.2). Many take NSAIDs for nonmedical but necessary reasons such as comfort. However, a significant proportion take NSAIDs or other anticoagulant/antiplatelet medications for medically necessary reasons such as prevention of cardiac and/or cerebrovascular events, making the decision to discontinue such medications moot. Studies comparing hemorrhagic complications have generally not shown an increased risk of severe hemorrhagic complications in patients on anticoagulants versus those who are not [2, 4–6]. This topic has been debated in the dermatologic surgery literature, specifically regarding warfarin, aspirin, and NSAID use, and there is a general consensus that *continuation* of these anticoagulants is associated with a very low risk of complications and is *not* statistically increased compared with patients in whom the same medications are discontinued [7–9].

Despite the current literature, the decision about whether to discontinue anticoagulation remains, and one must consider the real and increased risk of bleeding and hemorrhage with the lower but potentially life-threatening risk of a thrombotic event should an anticoagulant be temporarily discontinued [10–13]. For instance, the risk of a thrombotic event from discontinuing anti-thrombotic medications may outweigh the risks of intra-operative bleeding [11]. Kirkorian et al. surveyed current practice regarding perioperative management of anticoagulant therapy among dermatologic surgeons finding 87% discontinue prophylactic aspirin therapy, 37% discontinue medically necessary aspirin, 44% discontinue warfarin, 77% discontinue NSAIDs, and 77% discontinue vitamin E therapy perioperatively at least some of the time. Although clopidogrel was not surveyed in this article, 78 physicians included comments about the management of this agent [14]. Bordeaux et al. concluded that warfarin or clopidogrel increased bleeding risk, but these medications should be continued to avoid adverse thrombotic events [2, 15].

Should there be excessive bleeding during surgery, the use of proper bandages after surgery will help prevent hematoma formation. In our practice we use condensed cotton dental roles under 4×4 gauze followed by Hypafix™ paper tape which has an elastic property to create a pressure dressing that remains on the site for 24 h following Mohs or excisional surgery. In addition, we recommend that those on anticoagulant medications or who present with excessive bleeding during surgery employ ice packs for 20 min every hour for the first 6 h. Patients are given a detailed, written handout with instructions on how to manage excessive bleeding including application of ice and pressure for 20 min continuously without removing the pressure to examine the area. Patients are advised to call or return to the office promptly if they have concerns such as a warm, expanding and possibly painful mass, or especially if involving the periorbital or cervical spine areas.

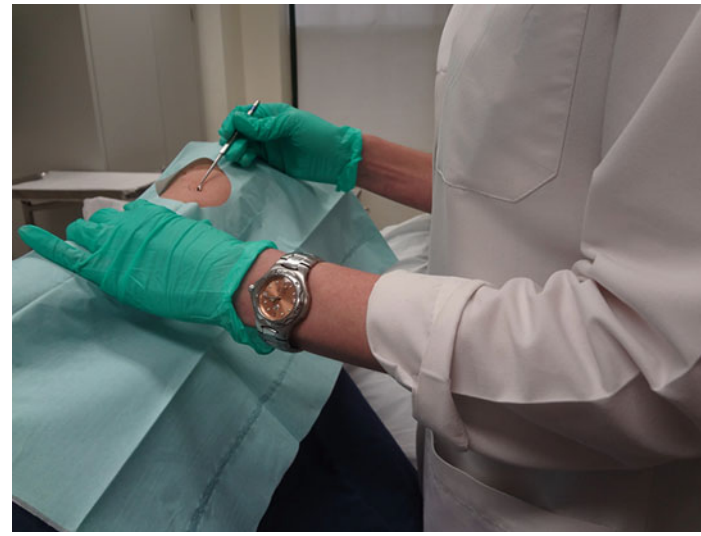

Fig. 14.1 Proper placement of a patient for surgery

Fig. 14.2 Proper placement of a patient for surgery

The primary method to treat an expanding hematoma is (1) partial or complete opening of the surgical wound, (2) identifying the culprit vessels and stopping bleeding by suture ligation or electrosurgery, (3) and either a full-layer reclosure of the wound or allowing the wound to heal by secondary intention [2]. The latter is considered if there is a high risk of more bleeding or the wound is contaminated.

Clinical Pearl: *To prevent a hematoma intra-operatively, take time to implement proper positioning of the patient, the surgeon, and the instrument tray. Something as simple as proper positioning may yield a better field for the dermatologic surgeon to visualize the source of bleeding, and ensure effective perioperative hemostasis* (Figs. 14.1, 14.2, 14.3, and 14.4).

Fig. 14.3 Improper placement of a patient for surgery, forcing the surgeon into a less than optimal position given the location of the surgery on the patient

Fig. 14.4 Improper placement of a patient for surgery, forcing the surgeon into a less than optimal position given the location of the surgery on the patient

14.4 Infection

Surgical site infections (SSIs) after dermatologic surgery cause pain, prolong healing, may result in altered cosmesis, and lead to excessive use of antibiotics [16]. Signs and symptoms of wound infection usually present 4–6 days postoperatively with erythema, pain, warmth, and swelling at the wound site. If cellulitis and fever are present, prompt institution of oral antibiotic therapy and close follow-up care are adequate. However, if the wound is fluctuant, if there is purulent exudate or inflammatory edema, or if systemic symptoms are present, the wound must be opened, lavaged with sterile sodium chloride solution and packed with iodoform gauze. Cultures and gram stains should be performed, and broad-spectrum antibiotics should be instituted while awaiting results. Patients should be closely monitored to evaluate clinical response.

Table 14.3 AHA guidelines for preventative antibiotics prior to certain dental procedures

Artificial heart valves
History of infective endocarditis
Cardiac transplant with known heart valve problem
Congenital heart conditions: • Unrepaired or incompletely repaired cyanotic congenital heart disease, including those with palliative shunts and conduits • A completely repaired congenital heart defect with prosthetic material or device during the first 6 months after the procedure • Any repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or a prosthetic device

Despite the potential for SSI, antimicrobial prophylaxis is rarely appropriate for dermatologic surgery. Reported infection rates for Mohs micrographic surgery (MMS) range from less than 0.7–3.5% and occur most frequently on the legs [17, 18]. Dermatologic procedures seldom cause bacteremia, and they have been implicated in only an extremely small fraction of cases of endocarditis or infections of vascular grafts or orthopedic prostheses. According to the newest guidelines, systemic prophylactic antibiotics are rarely indicated in patients undergoing dermatologic surgery, even those who would otherwise require prophylaxis for dental procedures (Table 14.3). Because wound infections following dermatologic surgery are uncommon, usually mild, and generally easily treatable, systemic antimicrobial prophylaxis is not indicated to prevent postoperative wound infections either. Topical antibiotic ointments for that purpose are also ineffective, yet often used regardless [19].

Although the overall trend in the literature supports decreased use of antimicrobials in dermatologic surgery as a whole, it is important to know which situations still warrant antibiotics [20]. Patients at high risk for wound infection should receive prophylactic antibiotics chosen to cover the organism most likely to cause infection [21]. *Staphylococcus aureus* is the most common agent of skin wound infections. However, *Streptococcus viridans* is commonly found in oral flora, and *Escherichia coli* is present near the gastrointestinal and genitourinary tracts. For legs with granulating wounds, common causes of postoperative infections are from *E. coli* from above. For this reason, this author instructs all patients to use Hibiclens surgical scrub from the groin down. *Pseudomonas* species are a common pathogen of the external ear. If the patient has chondritis of the ears postoperatively, it may not be a true infection. However, patients are often put on ciprofloxin 500 mg by mouth twice a day for 7 days to cover for *Pseudomonas*. Additionally, any time a patient has a laser procedure, photodynamic therapy or surgical procedure around the lips, it is important to get a full history of herpes infections—ask about fever blisters—and institute prophylaxis with acyclovir or a related medication. This author uses Famvir 500 mg by mouth twice daily for 3 days for anyone with a history of HSV, or for anyone receiving ablative procedures such as CO_2 laser resurfacing.

As mentioned in Table 14.2, dermatologic surgery is not considered in the AHA guidelines for endocarditis prophylaxis [22]. In one review, the authors did not recommend routine prophylaxis for high-risk patients undergoing procedures of less than 20 min duration on intact skin (Table 14.3). Patients at high risk for endocarditis should receive prophylaxis in cases where there is infected skin, breach of oral mucosa, or noninfected site at high risk for SSI [23]. This prophylaxis should be administered 30–60 min prior to performing the procedure to allow the antibiotic to be present in the blood at the time of the initial incision [24]. Appropriate specialists should be consulted—and documented for each procedure performed on patients with orthopedic prostheses, those with ventriculoatrial and peritoneal shunts, and in any case where the surgeon is not comfortable making the decision alone. A 2008 advisory statement on antibiotic prophylaxis is the most recent and widely used reference algorithm for dermatologic surgeons [25].

Clinical Pearl: *Three main factors are essential in the decision making process regarding antibiotic prophylaxis.*

- *How contaminated is the wound (or will it be)?*
- *Where is the lesion located and what kind of procedure is intended?*

- *Is the patient among the highest risk group for endocarditis?*

Infection control measures including active surveillance of SSI, implementation of a protocol for dealing with SSI, compliance observations and instruction/training of healthcare workers, clipping surrounding hair instead of shaving, and following the often-times confusing perioperative antibiotic prophylaxis guidelines are essential measures in the prevention of SSI. Though preoperative MRSA screening and implementation of a decontamination protocol appears to decrease postoperative MRSA wound infections after Mohs surgery, the clinical efficacy and cost effectiveness of this screening has yet to be determined [26]. Finally, infection control includes safety of the surgical team from exposure to HIV or Hepatitis C virus. Vigilant infection control for both the patient and the team is critical to surgical safety.

14.5 Necrosis

Necrosis of tissue occurs secondary to ischemia. Any condition that results in a decrease of oxygenated blood flow to the wound has the potential to cause necrosis. Too much tension on wound edges, excessive suturing and undermining, and superficial undermining all may result in tissue compromise and decreased blood flow to the distal wound margins. Hematomas may create excessive tension on the wound, increasing the risk of necrosis. Flaps and grafts with a length-to-base ratio of greater than 4:1 are at high risk of necrosis because of the tenuous circulation at the wound edges. Location of the wound is also an important consideration; high-risk areas include the lips, ears, nose, and skin grafts. Additionally, anesthesia type, amount, and addition of epinephrine all affect circulation around the wound and can contribute to ischemia [27].

Cigarette smoking results in vasoconstriction, increased blood viscosity, hypoxia, increased platelet aggregation, and clots. Smoking more than one pack of cigarettes per day increases the risk of necrosis by threefold compared to never smokers, ex-smokers, and smokers of less than one pack per day. When necrosis does occur, the area involved tends to be greater in smokers compared to those who have never smoked. Stopping or decreasing smoking for at least 2 days prior to surgery and for at least 1 week postoperatively can potentially reverse some of the negative effects of smoking on the microvasculature [28].

When necrosis occurs, treatment is conservative. Except in cases of hematoma formation and infection, the full extent of the necrosis should be allowed to manifest. Debriding the wound prior to this may injure viable tissue [27]. When the eschar is freely separable from the wound bed, careful and sharp debridement may be performed, and the wound may be allowed to granulate. Necrotic wounds are at higher risk for infection and the surgeon should observe the affected area carefully and frequently, and consider systemic antibiotics.

14.6 Dehiscence

Wound dehiscence is a surgical complication in which the layers of a wound unintentionally reopen. Wound dehiscence may be caused by anything that causes excessive tension on the wound edges. This includes inadequate undermining or putting undo strain on the wound after surgery. When wounds are located in highly mobile or high tension areas such as the back, shoulders, or legs, the risk of wound dehiscence is higher. Underlying conditions such as Ehlers-Danlos syndrome, allergic contact dermatitis to adhesive or topical antibiotics, infection, spitting sutures, or obesity can also increase risk for wound dehiscence. Other risk factors include smoking, previous scarring or radiation, cancer, recent use of Accutane, or chronic use of corticosteroids.

Dehiscence can be prevented by adequately undermining the tissue and using as much tissue reservoir as necessary to close the wound without tension. The patient should be instructed to avoid heavy lifting or extra activity, maintain adequate nutrition to speed wound healing, control underlying conditions that might alter wound healing (such as uncontrolled diabetes), and avoid prednisone use during the healing period. Because hematomas may also contribute to wound dehiscence,

appropriate postoperative bandaging is important, as is perioperative bleeding management.

If wound dehiscence occurs, the surgeon has several options, including allowing the wound to granulate on its own or recutting and re-suturing the wound edges [29]. For wound dehiscence on the face, there are several options based on the nature, time, and condition of the wound after dehiscence. For instance, if dehiscence is caused by trauma (e.g., a patient trips and falls and hits a graft site on the nose) or premature suture removal (e.g., the wound needs more than the standard 7-day period to heal), refreshing the wound edges and re-suturing is acceptable if there is no evidence of infection or the edges look intact. If signs of infection are present, appropriate antibiotic therapy is recommended. Areas such as the temple are known to heal poorly due to poor circulation. Allowing small dehiscent areas to granulate for 2–6 weeks is often the best course of action. The skin will heal, there will be less serous fluid, and the wound edges will be more amenable to refreshing and re-suturing. Too much intervention, or premature intervention, may worsen the cosmetic outcome. However, deeper dehiscence involving muscle, such as wedge reconstructions of the lip may require immediate intervention. One tip: if Vicryl™ sutures were rejected prematurely resulting in dehiscence, switch to Monocryl™ when reconstructing the wound. Because Monocryl is monofilament and less inflammatory, it has a longer duration and lower probability of spitting suture. In summary, for most cases of wound dehiscence, appropriately manage infection, excess moisture, and allow granulation to occur unless the dehiscence involves deeper layers where cosmesis will be difficult to achieve with a delayed intervention.

14.7 Other Dermatologic Procedural Emergencies

14.7.1 Laser Emergencies

Today in dermatology, hundreds of different laser and light devices exist for various indications, including excessive hair, superficial and deep vascular lesions, tattoos, lentigines, birthmarks, cutaneous aging and laxity, and psoriasis [30]. In many cases, laser complications result from collateral damage created when energy intended for the target chromophore is nonselectively diffused and absorbed by surrounding tissues. The theory of selective photothermolysis aims to reduce laser complications by selectively heating a target chromophore while sparing the nonintended but nearby targets. For example, melanin selectively absorbs photons in the 532 nm wavelength creating heat, resulting in pigment destruction, while sparing the surrounding cells. Mild, short-term complications of laser treatment include erythema, edema, urticaria, crusting or erosion, ecchymoses, blistering, and infection, such as reactivation of herpes simplex virus (HSV). More moderate, longer-lasting complications include pigmentary changes, visible lines of demarcation, burns, textural abnormalities, or delayed reepithelialization. Severe, long-term complications include permanent dyspigmentation, scarring, and ocular damage [31]. The complications noted above are devastating, but are not emergent [32]. Fortunately, there are few, emergencies from laser treatment other than ocular damage. All potential side effects of a particular device should be discussed and provided in writing ahead of time to a patient, along with instructions for appropriate cutaneous care following laser treatment. Additionally, if the patient has a history of HSV, prophylaxis should be instituted prior to the procedure. Close follow-up is essential in the management of these potentially upsetting but non-emergent problems.

14.7.2 Filler Emergencies

Inappropriate placement of filler such as superficial placement is one of the most frequent reasons for patient dissatisfaction. Some fillers, including hyaluronic acid, are reversible with hyaluronidase, and these complications can be easily corrected. Hypersensitivity to current FDA approved products is rare and can most often be managed with anti-inflammatory agents. Infection is also uncommon and is managed with antibiotics

or antivirals, depending on the etiology. The most concerning complication is necrosis [33].

The risk of skin necrosis following injection of filler is increased in certain potential danger zones, including the glabella, nasal skin, temple, alar groove, and even the lip [34, 35]. The most common of area for filler-related necrosis is the glabella. Major facial vessels of concern during soft tissue augmentation are the superior and inferior labial arteries, both branching off the facial artery at the angle of the mouth; the angular artery, the terminal branch of the facial artery; the lateral nasal artery, branch of the angular artery; the dorsal nasal artery, which forms an anastomosis with the angular artery; the supratrochlear artery, one of the terminal branches of the ophthalmic artery; and the superficial temporal artery, arising from the external carotid artery [36].

Several treatment algorithms for impending facial necrosis due to filler injection have been proposed in the literature [37–41]. If tissue blanching is observed, injection should be stopped immediately. Warm gauze (to facilitate vasodilation) and tapping (to potentially break up product) are then recommended. If the filler was an HA, immediate injection of hyaluronidase should be used. The authors recommend injection of a 1:1 volume of hyaluronidase to HA in the zone of ischemia or necroses. Typically, a range of 8–16 μL vitrase 0.5 mL of HA will dissolve the cosmetically imperfect swelling. For emergency situations when occlusion or ischemia is suspected, use more. No absolute maximum dose has been published but this author has used 50 μL hyaluronidase in the area of the alar crease to correct a 0.2 mL compression induced ischemia of the ipsilateral ala. Per the literature, it is exceedingly rare to dissolve native HA with hyaluronidase. Immediate use of nitroglycerin paste to facilitate vascular dilatation and blood flow to the area should be applied [42]. Additionally, anticoagulants such as aspirin and nonsteroidal anti-inflammatory agents, as well as vitamins that inhibit platelet aggregation, should be encouraged in any protocol to treat cutaneous tissue ischemia.

Given that hyperbaric oxygen has proven successful in healing of nasal tip grafting in cases of cancer or trauma reconstruction, this author suggests administration of oxygen via nasal cannula, face-mask or in the form of hyperbaric oxygen for ischemia secondary to cosmetic filler injection [43, 44]. For cases with severe, unremitting swelling, oral antihistamines may also be employed. Finally, treatment with low molecular weight heparin (5,000 IE daily) has been reported to treat impending necrosis after hyaluronic acid injection in the treatment of frown lines of the glabella due to occlusion or compression of the supratrochlear vessels [45].

14.7.3 Botox Emergencies

There are many neurotoxins approved by the FDA in use today. Botox acts via prevention of the release of acetylcholine at the presynaptic nerve terminal, thereby stopping the electrical impulse and blocking muscular movement. Complications of botox include

- Overcorrection
- Undercorrection
- Asymmetric result
- Upper eyelid ptosis
- Dysphagia
- Neck weakness
- Perioral droop
- Bruising
- Headache
- Intravascular injection
- Globe perforation
- Diplopia

Particularly distressing can be true eyelid ptosis, which occurs when botox is injected or diffuses into the levator palpebrae superiorus muscle. Though temporary, this effect can be distressing for the patient and can impact their quality of life. To avoid this complication, all injections should be at least 1 cm above the bony orbital rim. If this complication occurs, iopidine (apraclonidine) 0.5% drops may be used to stimulate Muller's muscle, providing some lid opening to partially alleviate the ptosis [46].

Similar to those complications encountered with laser treatment, the adverse effects of Botox can be distressing to the patient, but few, if any, represent a true emergency.

14.7.4 Chemical Peel Emergencies

Common chemical peel side effects include stinging, redness, and desquamation of the skin. These side effects should be expected by any patient who undergoes a chemical peel, as the mechanism of the peel is controlled skin injury in an attempt to remodel the epidermis [30, 47]. Chemical peels can target the superficial, medium or deep layers of the epidermis, depending on the type of chemical used and the desired outcome. Other complications of peels include contact dermatitis, milia formation, infection, acne or rosacea flare, and pigmentary changes [30]. It is important to discuss the common side effects prior to performing the procedure on any patient. Additionally, certain medications may potentiate the effects of the peel and are thus necessary to be aware of prior to performing the procedure.

The most superficial chemical peels include alpha-hydroxy acids (AHA), such as glycolic acid, and these peels are associated with minimal side effects. The two major side effects of AHA peels are irritation and sun sensitivity, which are transient. Medium depth peels include trichloroacetic acids (TCA). Side effects are similar to AHA peels but last longer. The deepest peels include phenols, and can be painful requiring local anesthetic or sedation. Healing time is longer—usually 2–3 weeks—and the most consistent side effect is pigmentary alteration (hypo- or hyperpigmentation). Other serious side effects of phenol include scarring, infection, as well as rare cardiac arrhythmias and temporary laryngeal edema [30]. Patients who have impaired liver or kidney function are most at risk of phenol toxicity, as phenol is absorbed through the skin and subsequently metabolized by the liver and excreted by the kidneys. In addition, the size of the treatment areas, rather than the concentration of the phenol, determines the extent of cutaneous absorption. To minimize these serious complications, cardiac monitoring during the procedure and in the immediate recovery period, as well as pausing treatment for 15 min between each cosmetic unit is recommended. Regarding laryngeal edema, heavy smokers seem to be most at risk for this rare but serious complication.

One very real emergency of any chemical peel is a burn of the eye from an accidental splash. Cover the eyes with proper protection such as tape or stickers. Arrange the procedure tray to avoid accidental spillage; always label of the peel container to ensure the proper product, and place the original bottle on the counter as opposed to the Mayo stand, where it can more easily spill. Additionally, a clearly marked eye wash station is essential should a splash occur. Furthermore, immediate evaluation by an ophthalmologist or transfer to the emergency department is warranted should an accident occur.

Clinical Pearl: *To avoid complications of chemical peels*:

- *Take a good medication history, including use of cosmeceuticals, retinoids, and glycolics, as well as a history of previous chemical peels or contact dermatitis.*
- *Consider performing a small patch test prior to the procedure.*

14.8 Conclusion

Dermatologic surgery is an art that involves complex procedures involving excisions, repairs, injections, and devices. Thorough understanding of the anatomy and pathophysiology of the skin, proper patient evaluation, appropriate selection of procedures based on each patient, and divulging potential complications of each procedure are essential to achieving optimal results and minimizing complications in cutaneous procedures [30].

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Bites and Stings

15

Annemarie Uliasz

15.1 Introduction

As travel increases and humans continue to expand their presence throughout the world, dermatologists must be familiar with a number of creatures capable of inflicting medically significant injury. This chapter describes those creatures which, when encountered by the unsuspecting human, may result in notable morbidity and mortality.

15.2 Insects

15.2.1 Hymenoptera

Hymenoptera are the most common cause of insect stings (Fig. 15.1). Most hymenoptera are social creatures that build nests or hives. Hymenoptera stings usually occur in self-defense, when the insect is swatted or stepped on. If the hive or colony is disturbed, hundreds to thousands of stings may follow. Medically significant hymenoptera are discussed below and include apidae (honey and bumble bees), vespidae (wasps, hornets, yellow jackets, paper wasps), and formicidae (imported fire ants).

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15.2.2 Apidae and Vespidae

The stinging apparatus of apidae and vespidae is connected to a venom-filled sac. In honey and bumble bees, the barbed stinger and venom sac detach following contact, resulting in death of the insect. The barbed stingers of bees should be removed immediately to prevent further release of venom and potential foreign body reaction [1]. Hornets and wasps, on the other hand, are able to sting multiple times as their stinger does not detach.

The resultant injury sustained by apidae and vespidae stings ranges from mild local reactions to systemic reactions including anaphylaxis. The venom of bees, hornets, and wasps contains phospholipase A which is thought to be responsible for IgE sensitization. Local reactions to bee, hornet, or wasp stings commonly manifest as painful, papular urticaria which develops within minutes and typically resolves within hours to days.

In large local reactions, the pruritus, erythema, edema may spread to encompass a more extensive area (over 10 cm), peaking at 24–48 h before resolving [2]. Those who experience large local reactions may develop similar reactions upon subsequent exposure to the same insect. Additionally, in these patients, there is an approximate 5–15% risk of anaphylaxis with subsequent

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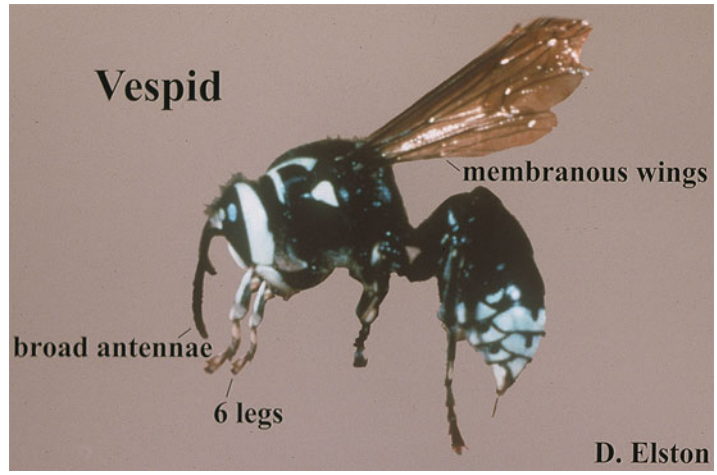

Fig. 15.1 Vespid (Courtesy of Dirk M. Elston, M.D.). Photograph in the public domain

stings. Reactions limited to the skin may be symptomatically treated with cold compresses, antihistamines, nonsteroidal anti-inflammatory drugs, and high potency topical corticosteroids. Oral corticosteroids may be required for large local reactions and immunotherapy may be considered to reduce the risk of future stings.

Toxic systemic reactions to vespids may result when a large number of stings is sustained. Although clinically similar to an allergic reaction, toxic systemic reactions due to multiple stings are caused by the vasoactive constituents of the venom rather than an allergic mechanism, and radioallergosorbent testing, which detects allergen-specific IgE antibodies in the serum suggesting an allergic reaction, is recommended to distinguish the etiology.

Anaphylaxis, a type I IgE-mediated hypersensitivity reaction, is estimated to occur in 1.5–34% of patients sustaining an insect sting [3]. Those at increased risk for severe systemic reactions include those with increased age, prior venom sensitization, underlying cardiovascular disease, and patients with mastocytosis. Symptoms of anaphylaxis may occur as early as 10 min or as late as 72 h after the sting. Early signs and symptoms include generalized urticaria, angioedema, and flushing, and may progress to bronchoconstriction, laryngeal edema manifesting as wheezing, hypotension, cardiovascular collapse, and, potentially, death. Elevated concentrations of serum histamine, tryptase, and mast cells support the diagnosis of anaphylaxis. Immediate intramuscular epinephrine is the initial acute treatment and patients should be discharged with a prescription for an epinephrine auto-injector and clear instructions for use as well as an allergy identification bracelet. Additionally, all patients with systemic reactions should be referred to an allergist for skin prick or serum immunoassays to confirm venom-specific IgE [4] as well as venom immunotherapy which is available for both honeybee and vespid allergies. Venom immunotherapy is highly effective and has been demonstrated to lower the risk of a subsequent systemic allergic reaction from 30 to 60% to less than 5% [5–11].

15.2.3 Formicidae

Imported fire ants (*Solenopsis invicta* and *Solenopsis richteri*) are believed to have been imported from South America via ship to Mobile, Alabama in the 1950s with subsequent spread throughout the southern USA. They are also found in regions of Mexico, the Caribbean, New Zealand, Australia, Taiwan, and China [12]. In endemic areas, they are the leading cause of hymenoptera hypersensitivity reactions [13]. Fire ants are notoriously difficult to avoid. In fact, one study revealed that more than 50% of people fall victim to the sting of this aggressive creature within 3 weeks of moving to an endemic area [14].

Fig. 15.2 Imported fire ant mound (Courtesy of Dirk M Elston, M.D.). Photograph in the public domain

Fire ants typically live in mounds proportional to the size of the colony (Fig. 15.2). When disturbed, the ants stream out of the mound in a swarm, stinging anything they encounter including both humans and animals. During times of flooding, these resourceful insects have been observed to self-assemble into waterproof rafts to avoid drowning. These "ant rafts" may float into houses where they may subsequently inflict stings on the inhabitants [15].

Equipped with a stinging apparatus located on the distal tip of the abdomen, fire ants are capable of inflicting multiple stings within a brief period of time. After grasping the skin with their mandibles, they sting while pivoting their body in a circular pattern (Fig. 15.3). They should be removed promptly to prevent further injury. In those who are immobile such as nursing home patients or infants, dramatic reports exist of massive attacks in which ants were found completely covering the victims resulting in death in some cases due to cardiovascular or respiratory collapse or anaphylaxis [16].

The venom of fire ants is composed of predominantly of water-insoluble piperidine alkaloids, responsible for the formation of sterile pustules. The remainder of the venom consists of allergenic proteins, Sol i I-IV, which may cross-react to the venoms of honeybees, yellow jackets, and the centipede *Centuroides vittacus* [17].

The sting of the fire ant results in varying clinical presentations ranging from local reactions to

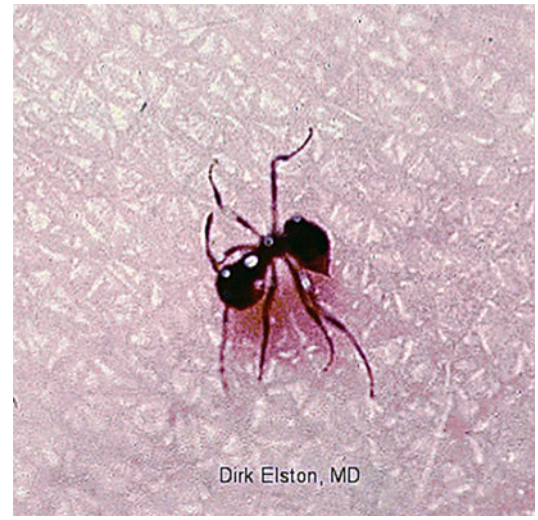

Fig. 15.3 Imported fire ant stinging (Courtesy of Dirk M Elston, M.D.). Photograph in the public domain

life-threatening anyphylaxis. Local reactions are characterized by a wheal and flare reaction with intense burning sensation. In the majority of cases, characteristic sterile pustules develop within 24 h (Fig. 15.4). Large local reactions are notable for expanding erythema and edema contiguous with the sting site which may persist for 2–3 days. The sequelae of a massive attack is due to a toxic reaction to the hemolytic, cytotoxic, neurotoxic properties of the venom [18]. Anaphylaxis may occur in up to 1% of those who are stung and may result from a single fire ant sting [19, 20].

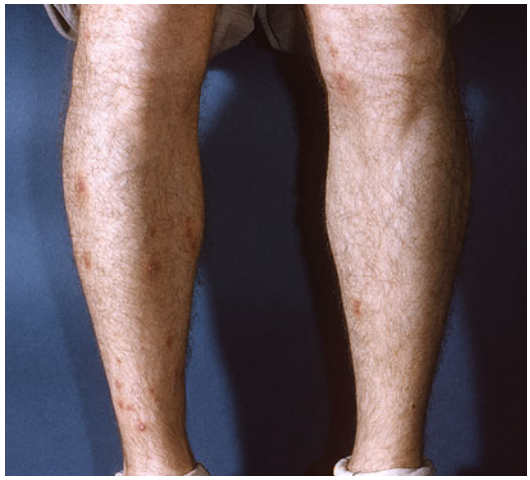

Fig. 15.4 Characteristic pustules resulting from imported fire ant sting (Courtesy of CDC/Dr. Harold G. Scott). Photograph in the public domain

Local reactions may be treated with topical corticosteroids and oral antihistamines. Allergic patients should be provided with an allergy identification bracelet and an epinephrine autoinjector and proper instructions for use. Furthermore, referral to an allergist for appropriate diagnostic studies and immunotherapy is vital to prevent another potentially life-threatening anaphylactic event. Confirmation of an allergy to fire ant venom may be accomplished by skin-prick testing or serum testing for the presence to venom-specific immunoglobulin E antibodies. Fire ant whole body extract is used for immunotherapy with conventional protocols that may last 3–6 months or more and comprise 25–28 injections to reach the maintenance dose. Recent studies have demonstrated the efficacy of rushed 1-day protocols in which ten injections are given during the course of 1 day with maintenance dosing commencing on day 8 [21].

15.3 Arachnids

15.3.1 Spiders

Armed with venom that is nontoxic to mammals and mouth parts too small or weak to pierce human skin, the vast majority of arachnids are harmless to humans. The spiders most likely to pose a medical risk to humans include the black widow (Fig. 15.5), the brown recluse (Fig. 15.6), the Australian funnel web spider, and the South American armed spider.

Fig. 15.5 Black widow spider (Courtesy of CDC/Paula Smith, photo credit: James Gathany). Photograph in the public domain

Fig. 15.6 Brown recluse spider (Courtesy of CDC). Photograph in the public domain

The black widow spider (*Latrodectus* species) is found throughout tropical and temperate latitudes worldwide [22]. In the USA, it is predominantly found in the southern and western states under stones, within woodpiles, or in outhouses. The black widow spider is characterized by a glossy, black body with a red hourglass on its abdomen. Although males may bite, it is only the female black widow that is capable of significant envenomation. A bite by a black widow spider may result in local erythema and pain. Black widow venom, alpha-latrotoxin, is a neurotoxin that causes the presynaptic release of autonomic neurotransmitters resulting in the rapid onset of systemic symptoms including nausea, vomiting,

diaphoresis, agitation, hypertension, and muscle cramping [23, 24]. Abdominal rigidity may mimic an acute abdomen. In rare cases, myositis [25, 26], priaprism [27], respiratory arrest, and death may occur.

Treatment includes local wound care, ice, elevation, and immobilization. Tetanus prophylaxis should be given following all envenoming spider bites as *Clostridium tetani* spores and bacteria are commonly found throughout the environment and may gain entrance to the body via abrasions and wounds [28]. Muscle relaxants and analgesics are often used for black widow bites. Equine-derived antivenom may be employed for severe systemic cases; however, symptoms may subside spontaneously within hours to days. Furthermore, antivenin has been associated with immediate hypersensitivity reactions anaphylaxis, and may produce serum sickness 1–2 weeks following administration in up to 75% of patients [29, 30]. Its use is recommended in those cases involving patients with marked systemic symptoms unresponsive to other measures. It should be used only in locations where anaphylaxis may be adequately treated [31, 32].

The brown recluse spider (*Loxosceles* spp.) is found in North and South America. In the USA, the brown recluse predominantly inhabits the south central USA. It is identified by its brown color, and in females, a characteristic darker brown violin-shaped marking on the dorsal cephalothorax. The bite of the brown recluse may result in necrotic skin lesions due to venom containing sphingomyelinase D and hyaluronidase [33, 34]. The platelet aggregation, dermatonecrosis, and hemolysis caused by sphingomyelinase D is felt to result in cutaneous ulceration and systemic effects. Hyaluronidase may increase the spread of the lesion. The bite itself may go unnoticed and commonly occurs when the spider is trapped between bedsheets or clothing and the skin of the victim. The majority of cases are self-limited with mild erythema and edema and heal spontaneously without supportive care. In cases of dermatonecrotic loxoscelism, initially, a dark macule with surrounding erythema may appear, progressing within hours to cyanosis with a central vesicle or bulla. During the following weeks, a thick eschar gradually forms and then falls off to reveal a necrotic ulcer. A small minority of patients may experience systemic reactions including hemolysis, renal failure, and disseminated intravascular coagulation [35–37].

Treatment includes cleaning the wound, compression, ice, elevation, analgesics, and tetanus prophylaxis. The use of dapsone has been demonstrated to be ineffective [38]. Furthermore, it carries the risk of methemoglobinemia, and in those who are glucose-6-phosphate dehydrogenase (G6PD) deficient severe hemolysis may occur due to oxidative denaturation of hemoglobin which G6PD normally prevents. Early excision and intralesional corticosteroids are contraindicated as these measures may result in more tissue damage than conservative treatment. Healing may take several weeks to occur and excision and grafting may be considered for chronic ulcers 6–8 weeks after the initial injury [28, 39].

Internationally, the Australian funnel web spider (*Atrax* and *Hadronyche* spp.) is considered the most lethal spider in the world. It resides in southeastern and coastal Australia. Although cases of envenomation are rare, the Australian funnel spider bite remains a relevant medical entity given its life-threatening nature and the availability of an effective antivenom. The spiders are large (4 cm long) and aggressive. The bite of the Australian funnel spider is remarkable for visible puncture wounds created by long, sturdy fangs up to 5 mm in length capable of piercing fingernails. Cases of mild envenomation with its venom, the neurotoxin δ-atracotoxin, may yield local paresthesias, numbness, and spasms while severe envenomation results in autonomic and neuromuscular excitability with initial hypertension, tachycardia, diaphoresis, and nausea progressing to bradycardia, hypotension, respiratory edema, and in some cases, coma. Deaths have been reported to occur within 15 min in children [39]. Treatment consists of application of a pressure immobilization dressing until the administration of antivenom, a purified IgG derived from rabbits hyperimmunized with *Atrax* venom.

The South American armed spider (*Phoneutria* spp.), as its name suggests, is found in South America as well as Central America. A large spider with a body reaching up to 5 cm in length, it often resides in banana clusters. When threatened, it raises its front legs, displays its fangs, and bristles its arm hairs. Armed spider venom, containing the neurotoxin, PhTx-3, targets both the peripheral and central nervous systems. In the majority of cases, the bite of the spider may result in local effects such as extreme pain, piloerection, and diaphoresis at the bite site. Systemic effects are less common and may include hypertension, tachycardia, nausea, vomiting, priaprism, increased salivation, vertigo, and in rare cases, death. The treatment of armed spider bites should include tetanus prophylaxis, elevation and immobilization of the involved extremity, and analgesics. Following antivenom skin testing, the equine-derived antivenom may be administered [40].

It is important to keep in mind that the majority of presumed spider bites are in fact caused by another etiology. A definitive diagnosis of a spider bite may be made only if the spider was observed inflicting the bite and then subsequently captured and positively identified by an expert entomologist [41]. The differential diagnosis includes infections (MRSA, herpes, erythema migrans), vasculitis, other arthropod bites, urticaria, and contact dermatitis. Multiple bites or bites simultaneously sustained by multiple members of the same household should cast in doubt the diagnosis of a spider bite.

15.3.2 Scorpions

Scorpions are characterized by their large claws, four pairs of legs, and segmented tail which ends in a venom-containing stinger (Fig. 15.7). Globally, scorpions are a significant cause of morbidity and mortality. Of the roughly 1,500 species of scorpions found worldwide, approximately 30 pose a health threat to humans [42]. The South American *Buthidae* is considered the most dangerous family of scorpions worldwide. Of the approximately 70 species of scorpion found in North America, only the genus *Centuroides* (Fig. 15.7), which resides in the southwest USA and Mexico, is considered to be medically important [43]. However, as international travel has increased, cases of envenomation by non-endemic scorpions inadvertently transported to the USA have been reported [44].

Fig. 15.7 Scorpion (Courtesy of Dirk M. Elston, M.D.). Photograph in the public domain

Stings occur when the victim encounters a scorpion hidden in shoes, under sleeping bags, in closets, cellars, or woodpiles. Neurotoxic peptides are the main active component of venom from dangerous scorpions occurring at varying levels depending on the species.

The severity of a scorpion sting hinges on the species involved and may range from a mild local reaction comparable to a bee sting to a life-threatening systemic reaction due to activation of both the sympathetic and parasympathetic nervous systems. Children and the elderly are at a higher risk of developing respiratory, cardiovascular, and neurologic complications. In severe envenomations, the evolution of symptoms is rapid. Following the initial sting, pain may be accompanied first by a cholinergic stage (bradycardia, hypotension, nausea, emesis, diaphoresis, increased salivation, nystagmus, and priapism), then followed by an adrenergic stage (hypertension, tachycardia, tachypnea, dyspnea, agitation). It has been noted that the presence of gastrointestinal symptoms may be a harbinger of a more severe course and vigilance is recommended. Potentially lethal envenomation may lead to cardiovascular collapse and pulmonary edema [42].

Management consists of local wound care and pain management as well as tetanus prophylaxis when indicated. Cases of systemic involvement may necessitate supportive therapy and immediate administration of antivenom where available. Anaphylaxis and serum sickness are potential complications of antivenom treatment. Studies have also demonstrated benefit of prazosin via blockade of alpha-1 receptors in reversing the cardiovascular manifestations [45, 46].

15.3.3 Centipedes

Chiropods, or centipedes, are fast-moving, aggressive arthropods. These nocturnal creatures are characterized by a long, segmented body with pairs of legs attached to all but the final segment (Fig. 15.8). Modified appendages which are attached to the first segment act as claws and are capable of releasing venom through specialized ducts. The most dangerous centipede is of the *Scolopendra* genus which may reach a length of 30 cm. They are found world-wide in temperate and tropical zones; in the USA, they are found predominantly in the southern states and Hawaii.

Centipede venom has been found to contain several enzymes including metalloproteinases and hyaluronidases, as well as nonenzymatic toxins (neurotoxins, cardiotoxins, and myotoxins) [47]. A bite may result in excruciating pain, pruritus, erythema, edema, and bleeding, but is generally self-resolving with no serious morbidity or mortality. However, there are case reports of centipede stings causing necrosis [48], myocardial infarction [49], proteinuria [50], rhabdomyolysis with renal failure [51], Well's syndrome [52], and toxicity following ingestion [53].

Treatment includes local wound care and pain management. Pain control may be achieved with ice packs, hot water immersion, local anesthetics, and oral analgesics [54, 55]. Antihistamines and topical and/or systemic corticosteroids may be employed, and antibiotics may be administered as needed for secondary bacterial infection. Tetanus prophylaxis is recommended.

Fig. 15.8 Centipede (Courtesy of Dirk M. Elston, M.D.). Photograph in the public domain

Fig. 15.9 Millipede (Courtesy of Dirk M. Elston, M.D.). Photograph in the public domain

15.3.4 Millipedes

Diplopods, or millipedes, differ from centipedes in that they have two pairs of legs attached to each segment of their bodies (Fig. 15.9). They are vegetarians and are not known to bite humans. When disturbed, they release noxious substances such as benzoquinone, hydroquinone, and hydrogen cyanide secreted by repugnatorial glands along the length of their body [56]. However, some species are capable of squirting the substance up to 25 cm [57].

Cutaneous exposure results in a prickling or burning sensation with or without paresthesias that may progress to vesiculation. A characteristic mahogany discoloration develops simulating cyanosis, necrosis, or gangrene. This discoloration occurs due to oxidation of quinones and may persist for months [58, 59]. Treatment includes profuse irrigation to remove the toxins, analgesics, and topical corticosteroids [60].

15.4 Snakes

Worldwide, it is estimated that almost 200,000 people die each year of snake bites [61]. However this may be an underestimate due to lack of reporting in much of the developing world. According to the 2010 American Association of Poison Control Centers, there were over 3,000 reports of venomous snake bites treated in medical facilities in the USA [62]. Snakes use their venom to immobilize their prey and as self-defense when threatened or provoked. Of the 3,000 species of snakes found globally, approximately 15% are venomous, all of which are found in four families: Atractaspididae, Colubridae, Elapidae, and Viperidae. The venomous snakes indigenous to North America are confined to the Elapidae and Viperidae families which are discussed below.

15.4.1 Viperidae

Rattlesnakes, copperheads, and water moccasins, members of the subclass Crotalinae of the family Viperidae, are responsible for the majority of venomous snake bites in the USA. This group of snakes is commonly referred to as pit vipers owing to the infrared heat-sensing pits located posterior to the nostrils. Other characteristic features include prominent fangs, elliptical pupils, and triangular-shaped heads (Fig. 15.10). With the exception of Maine, Alaska, and Hawaii, rattlesnakes inhabit all states of the continental USA. Copperheads are found predominantly in the eastern USA, and water moccasins are native to the southeastern USA.

The spectrum of clinical presentations due to crotalid envenomation may range from local reactions to fatal systemic reactions. Severity is dependent on the age and underlying health of the victim, the location of the bite, and the amount of venom injected. Interestingly, approximately 25% of crotalid bites are "dry," meaning that no venom was injected. Furthermore, the components of the venom may vary according to season, as well as the age and nutritional status of the snake [63]. Crotalid envenomation commonly

Fig. 15.10 Western diamondback rattlesnake, *Crotalus atrox* (Courtesy of CDC/Edward J. Wozniak D.V.M., Ph.D., Photo credit: Michael Smith). Photograph in the public domain

results in immediate pain and the appearance of one or two fang puncture marks. Within the hours, erythema, edema, bullae, eccchymosis, lymphangitis, and lymphadenopathy may develop. Associated nonspecific systemic symptoms may include nausea, emesis, lethargy, weakness, and diaphoresis.

Patients should be closely monitored for the development of more severe systemic manifestations including hypotension, tachycardia, compartment syndrome, rhabdomyolysis with renal toxicity, and disseminated intravascular coagulation. Neurotoxicity is rare in crotalid envenomation except in bites caused by the Mohave rattlesnake.

Treatment begins in the field and includes removing the victim from the vicinity of the snake and immediately transporting the victim to the nearest health care facility. An attempt to capture the snake for identification purposes is discouraged owing to the risk of creating another victim. Instead, a photo may be taken from a safe distance if possible. Due to the risk of increased morbidity, several dangerous practices should be avoided including incising and suctioning venom from the wound, cryotherapy, electrotherapy, and applying a tourniquet [64, 65].

Wound management includes thoroughly cleaning the area, repeated circumferential mea-

Fig. 15.11 Venomous "Texas coral" snake, *Micrurus tener tener* (Courtesy of CDC/Edward J. Wozniak D.V.M., Ph.D.). Photograph in the public domain

surement along the affected limb, gentle immobilization, elevation of the limb, and administration of analgesics and tetanus prophylaxis as needed. Serial neurologic exams should be performed hourly until the edema resolves. Laboratory studies should be performed to evaluate for the development of coagulopathy and rhabdomyolysis. Fasciotomy should be reserved for compartment syndrome that does not resolve after the administration of antivenom.

Candidates for antivenom therapy include those with progressive worsening of local injury, coagulopathy, or systemic manifestations. An ovine-derived antivenom, Crotalidae Polyvalent Immune Fab is currently available in the USA and is infused four times over a period of 18 h. It is associated with acute hypersensitivity reactions in 16% and serum sickness in 14.1% [66].

15.4.2 Elapidae

Elapidae, or coral snakes, are found primarily in Florida and Texas. Although coral snake envenomation is much less common that crotalid envenomation, deaths have been reported and neurotoxicity is characteristic [67]. Venomous coral snakes are notable for their distinctive red, yellow, and black stripes (Fig. 15.11). They can be distinguished from non-venomous species

Fig. 15.12 Harmless "milk" snake, *Lampropeltis triangulum annulata* (Courtesy of CDC/Edward J. Wozniak D.V.M., Ph.D.). Photograph in the public domain

which display alternating red and black banding (Fig. 15.12) recalled by the colloquialism: "Red and yellow, kill a fellow. Red and black, venom lack." Unlike crotalids, coral snakes lack long fangs. Instead, they have small rows of teeth, and upon biting a victim, must gnaw the skin in order to pierce it and deliver venom.

Unlike crotalid envenomation, significant local tissue injury and coagulopathy are not characteristic of coral snake envenomations. Instead, the site of the bite may be erythematous with mild edema and pain. In further contrast, the victim may demonstrate neurological manifestations ranging from mental status changes, tremors, and

hypersalivation to obtundation and respiratory paralysis necessitating ventilatory support. It is important to note that the onset of neurologic effects may be delayed for up to 24 h.

Field treatment is similar to that of crotalids with emphasis placed on transporting the victim immediately to the closest medical facility. Tetanus prophylaxis should be administered as appropriate. Serial neurologic and cardiorespiratory evaluation should be conducted with intubation and mechanical ventilation if needed. In confirmed coral snake envenomations, North American elapidae antivenom, if available, should be administered immediately. Derived from horse serum, North American antivenom may cause an acute hypersensitivity reaction and serum sickness. If antivenom is not available, respiratory support should result in complete recovery in the majority of patients. However, the duration of mechanical ventilation may be as long as 1 week.

15.5 Marine Creatures

15.5.1 Jellyfish

Jellyfish are members of the phylum Cnidaria. Of the approximately 9,000 species of Cnidaria, at least 100 pose a threat to humans. There are three classes of Cnidaria which are hazardous to humans. The first, the Scyphozoans, or "true" jellyfish, are characterized by tentacles which are arranged radially at regular intervals around and within the bell.

The second, and most deadly class, the Cubozoans, or "box" jellyfish, are distinguished by tentacles arising only from the corners of their box or cube-shaped bells. The Cubozoans comprise two subgroups containing the Carybdeids and the Chiropods. The Carybdeids include the Hawaiian box jelly fish and *Carukia barnesi*, the small jellyfish responsible for "Irukandji Syndrome." The Chiropods include *Chironex fleckeri*, the Australian sea wasp, considered the most dangerous animals in the world [68].

The third class, the Hydrozoa ("other" jellyfish), includes the Physalia species (Portuguese man-o'-war, Fig. 15.13) and the Gonionemus found in the Sea of Japan.

Fig. 15.13 The Portuguese man-of-war, *Physalia physalis* (Courtesy of Dirk M. Elston, M.D.). Photograph in the public domain

Jellyfish are armed with stinging cells, or nematocysts, which contain venom and are triggered upon chemical or physical stimuli. Nematocysts are capable of stinging even after the jellyfish is dead or when the tentacles are separated from the jellyfish. Venom is delivered to small dermal capillaries and dermal tissue, where it is thought to be absorbed systemically via the lymphatic system. The venom contains both toxic and antigenic properties that are dermatonecrotic, cardiopathic, hemolytic, or neurotoxic.

The majority of reactions to jellyfish are localized. However, systemic and fatal reactions may occur. The severity of the reaction is dependent on the size, age, and underlying health of the victim, the body surface area involved, the number of nematocysts discharged, and the toxicity of the venom.

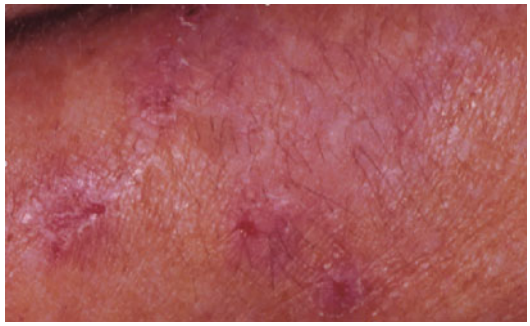

Fig. 15.14 Cutaneous reaction to jellyfish sting (Courtesy of Dirk M. Elston, M.D.). Photograph in the public domain

Localized cutaneous lesions appear as linear, urticarial erythema (Fig. 15.14) which may progress within minutes to hours to vesiculation and sometimes necrosis in the area of contact with tentacles. Pain, burning sensation, paresthesias, and hyperhidrosis may accompany the skin lesions. Cases of recurrent eruptions occurring at variable intervals after the initial injury have been reported [69–73].

Systemic symptoms may accompany the cutaneous manifestations of a jellyfish sting and include local cramping and muscle spasms, paresthesias, nausea and vomiting, weakness, dizziness, and malaise. The Irukandji syndrome, named after the aboriginal Australian tribe who inhabit Northeast Queensland, was first described in 1952. Jack Barnes positively identified the culpable jellyfish, which came to be known as *Carukia barnesi*, by envenomating himself, his 9-year-old son, and a local lifeguard in 1961 [74]. *Carukia barnesi* is a small jellyfish characterized by four tentacles and a bell of approximately 2 cm. Approximately 20–30 min after a relatively innocuous sting, victims experience severe, cramping pain, nausea, vomiting, diaphoresis, shortness of breath, and a sense of impending doom. Massive catecholamine release is thought to be responsible. The majority of envenomations resolve spontaneously [75]. However, cases of heart failure, pulmonary edema, and hypertensive stroke necessitating supportive therapy have been reported [76] as well as death [77, 78]. Various reports of Irukandji-like syndromes have been described in Thailand, Hawaii, and Florida [79–81].

Death due to jellyfish envenomation may occur from anaphylaxis or as a result of exposure to toxins. Potentially life-threatening envenomation may result from contact with *Chironex fleckeri* (the Australian box jellyfish or sea wasp) a large bell-shaped creature whose bell may span up to 30 cm and whose long tentacles may span up to several meters. Its potent venom contains dermatonecrotic factors and cardiotoxins. It is believed that approximately 10 cm of tentacles are sufficient to deliver a fatal dose. Contact with the Australian box jelly may results in whip or ladder-like cutaneous lesions, and in some cases, death from cardiovascular collapse within minutes.

Management of all jellyfish stings should include removing the victim from water to prevent drowning with assessment of the victim and initiation of basic life support as needed. Steps should be taken to prevent further stinging by non-discharged nematocysts. The sting should not be rubbed or rinsed with fresh water due to the danger of massive nematocyst discharge. Different species respond differently to various treatments [82], and it is important to note that vinegar (3–6% acetic acid) effectively inhibits nematocyst discharge in some jellyfish, but may trigger discharge in other species [83]. The Australian Resuscitation Council recommends vinegar use for the Australian box jellyfish and for cases of Irukandji syndrome [84]. If vinegar is not available, seawater may be used to rinse the sting. There is no evidence supporting the use of urine in the treatment of jellyfish stings. Once nematocysts are deactivated, all remaining tentacles should be removed from the victim.

Although inactivation of further nematocyst firing is critical, it does not provide pain relief for venom that has already been injected. Following removal of remaining tentacles, hot water may be applied to the area for pain relief and denaturing of venom [85, 86].

Localized reactions may then be symptomatically treated with antihistamines, topical corticosteroids, and local anesthetics. Tetanus prophylaxis should be administered, if indicated.

Systemic reactions secondary to Irukandji syndrome may require analgesics, oxygen, anti-

emetics, and supportive treatment as necessary. The toxic effects of envenomation by *Chironex fleckeri* may be neutralized by antivenom which is composed of immunoglobulins from hyperimmunized sheep serum. It should be administered in cases of severe pain, dyspnea, dysphagia, dysphonia, unconsciousness, cardiorespiratory arrest, hypotension, or dysrhythmia. Basic or advanced life support and intensive care measures should be taken as appropriate.

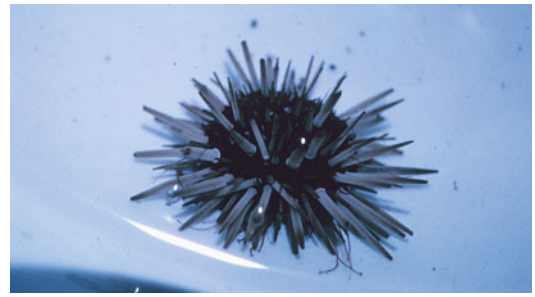

Fig. 15.15 Sea urchin (Courtesy of Dr. James P. McVey, NOAA Sea Grant Program). Photograph in the public domain

15.5.2 Sea Urchins

Found in all oceans, sea urchins belong to the phylum Echinodermata which also includes sea cucumbers and starfish. Sea urchins are slow-moving, coastal dwellers with numerous spines (Fig. 15.15). Depending on the species of sea urchin, the spines may be sharp or blunt, solid or hollow, and may or may not be venomous. Most venomous species are found in tropical and subtropical regions. The flower sea urchin (*Toxopneustes pileolus)*, found off the coast of Japan, is the most venomous sea urchin known.

Most injuries from sea urchins occur when the brittle calcium carbonate spines break off and become embedded in the skin when accidentally stepped on or handled. Penetration injury results in localized sharp pain, bleeding, erythema, and edema. Arthritis, synovitis, or tenosynovitis may occur if the injury is periarticular. The pigment of the implanted spines may leave behind a purple or black tattoo.

The affected area should be soaked in hot water (as hot as the patient can tolerate) to deactivate toxins and alleviate pain. Tetanus prophylaxis should be administered [87]. Although spine fragments may be absorbed by the body within 1–3 weeks, an attempt to remove all embedded fragments should be made as infections, granuloma formation, and arthritis may arise from retained spine fragments and the ensuing foreign body reaction [88–91]. Removal is often complicated by breakage of the delicate spines, and many techniques have been described using needles, forceps, punch biopsy [92], and erbium-YAG laser [93]. Imaging studies including plain radiographs, ultrasound, or MRI may be performed to confirm the complete removal of retained spines. Antibiotics are indicated for secondary infections.

15.5.3 Stingrays

Stingrays, members of the class Chondrichthyes, are flat bottom-dwellers that reside in shallow waters, hidden beneath a layer of sand with only their eyes visible (Fig. 15.16). Stingrays may be found in both saltwater (in temperate and tropical coastal regions throughout the world) and in fresh or brackish waters (in South America, Southeast Asia, and Africa) [94]. Injuries most frequently occur on the lower extremities when a swimmer or wader inadvertently startles the creature. Injury may be avoided by shuffling one's feet when walking in shallow water, alerting the stingray of human presence, and giving it ample time to swim away. When provoked, the stingray's whip-like tail swings forward impaling the victim with serrated spines which range in size from less than 2.5 cm to over 30 cm in length and release a heat-labile, vasoconstrictive venom [94]. The immediate effects are local, severe pain out of proportion to the injury and vasoconstriction progressing to necrosis of the involved area. Systemic effects may include myocardial infarction, cardiovascular arrhythmias, and bradycardia [95]. Rarely, death may occur from penetration injuries to the thorax or abdomen [96, 97].

Treatment consists of irrigating the area with hot water to inactivate the venom and administering

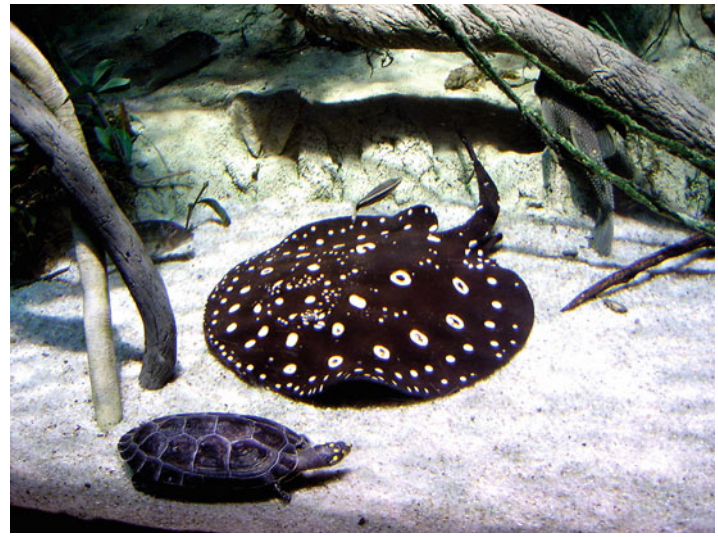

Fig. 15.16 The freshwater Polka Dot Stingray, *Potamotrygon leopoldi* (Courtesy of Dirk M. Elston, M.D.). Photograph in the public domain

local anesthetic or a nerve block without epinephrine as well as parenteral analgesics. Tetanus prophylaxis should be given. The wound should be debrided and explored for retained spines [98]. If superficially located, the spine should be removed. However, if the spine is found to be penetrating the neck, thorax, or abdomen, or completely though an extremity, it is best left in place until the patient is taken to a medical facility where this can be performed safely [94]. Radiographic studies may be employed to ensure complete removal. Secondary infections by gram-negative (*Vibrio*) and gram-positive (*Staphylococcus* and *Streptococcus*) bacteria are common and prophylactic antibiotics are recommended, most commonly a 5-day course of a quinolone or amoxicillin with clavulanic acid [99].

15.6 Further Resources

American Association of Poison Control Centers and Poison Help Hotline: http://www.aapcc.org/dnn/default.aspx.

World Health Organization World Directory of Poison Centers: http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/.

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Index

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