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.

E. Stamell, M.D. (✉)
Department of Medicine, Division of Dermatology, Albert Einstein College of Medicine, Bronx, NY, USA
e-mail: estamell@gmail.com

K. Krishnamurthy, D.O
Dermatology, Jacobi Medical Center, Cosmetic Dermatology Clinic, Montefiore Medical Center, Albert Einstien College of Medicine, Bronx, NY, USA
e-mail: kkderm@gmail.com

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

B. Buka et al. (eds.), *Buka's Emergencies in Dermatology*,
DOI 10.1007/978-1-4614-5031-3_2, © Springer Science+Business Media, LLC 2013

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.

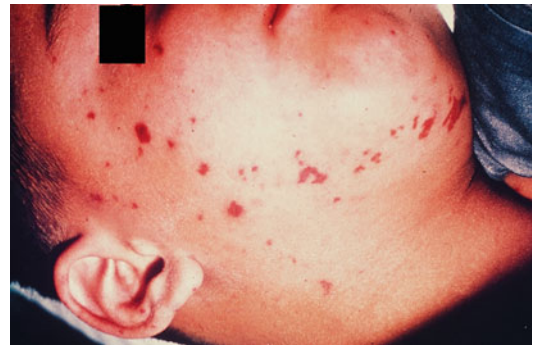

Fig. 2.1 Meningococcemia

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

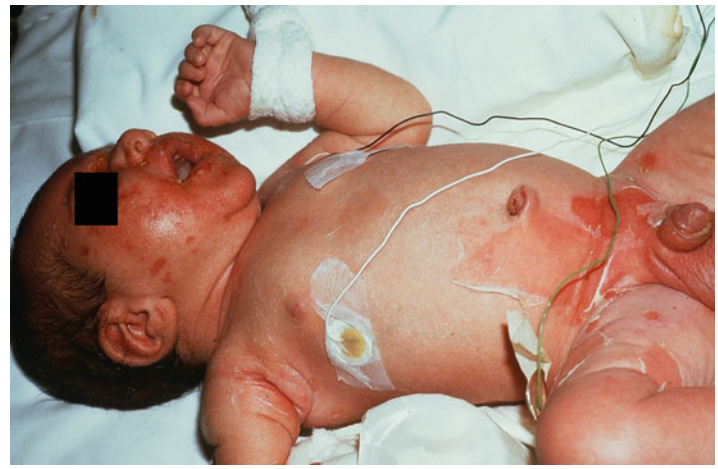

Fig. 2.2 Ritter's disease

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].

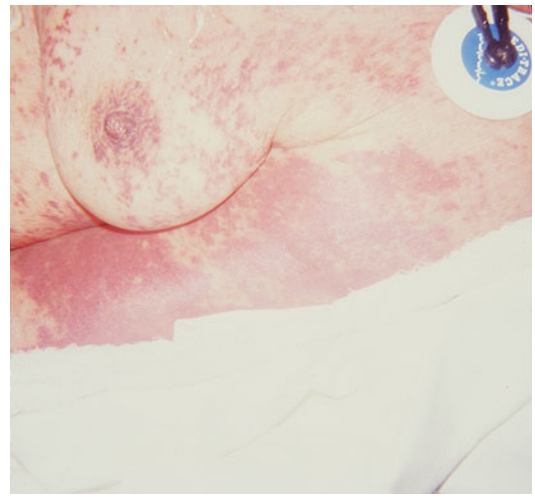

Fig. 2.3 Purpura fulminans

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

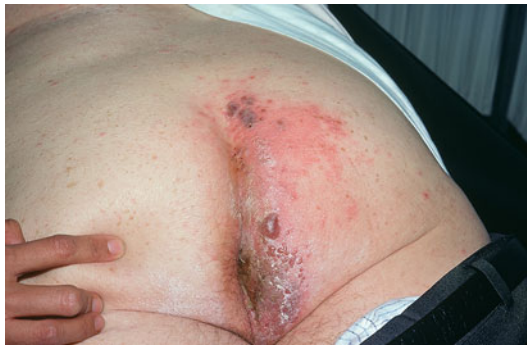

Fig. 2.4 Herpes simplex virus

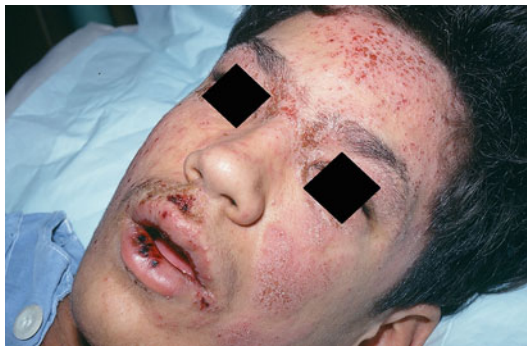

Fig. 2.5 Kaposi varicelliform eruption

[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

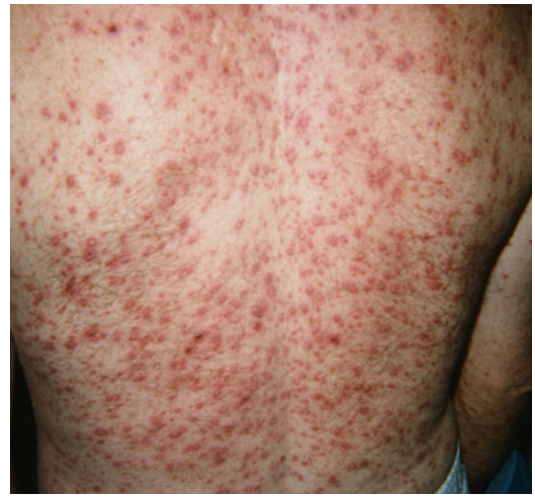

Fig. 2.6 Varicella virus

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

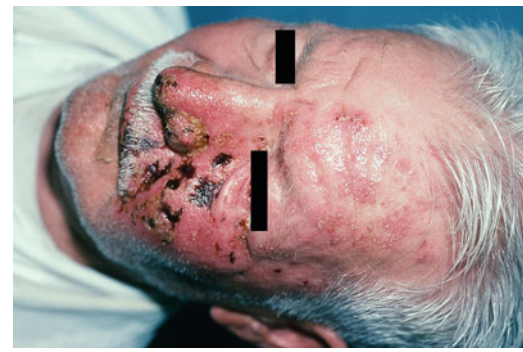

Fig. 2.7 Zoster virus

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].

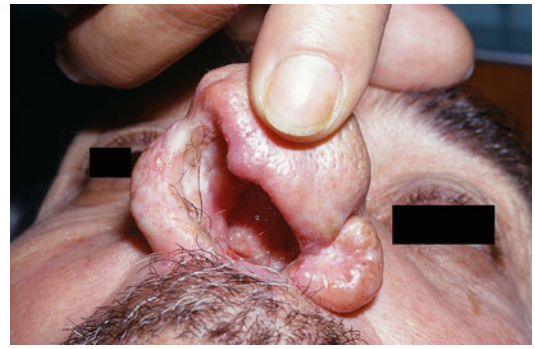

Fig. 2.8 Mucocutaneous leishmaniasis

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

All photographs used in this chapter are with permission and courtesy of Michael Fisher, M.D.

References

1. Singh G, Sinha SK, Adhikary S, Babu KS, Ray P, Khanna SK. Necrotising infections of soft tissues—a clinical profile. Eur J Surg. 2002;168(6):366–71.
2. Hasham S, Matteucci P, Stanley PR, Hart NB. Necrotising fasciitis. BMJ. 2005;330(7495):830–3.
3. Wolf R, Davidovici BB, Parish JL, Parish LC. Emergency dermatology. New York: Cambridge University Press; 2010.
4. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg. 1996;224(5):672–83.
5. Bolognia J, Jorizzo JL, Rapini RP. Dermatology. St. Louis, MO: Mosby Elsevier; 2008.
6. Jallali N, Withey S, Butler PE. Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. Am J Surg. 2005;189(4):462–6.
7. Kaul R, McGeer A, Norrby-Teglund A, Kotb M, Schwartz B, O'Rourke K, Talbot J, Low DE. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome—a comparative observational study. The Canadian Streptococcal Study Group. Clin Infect Dis. 1999;28(4):800–7.
8. Darenberg J, Ihendyane N, Sjolin J, Aufwerber E, Haidl S, Follin P, Andersson J, Norrby-Teglund A. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2003;37(3):333–40.

9. Huang KF, Hung MH, Lin YS, Lu CL, Liu C, Chen CC, Lee YH. Independent predictors of mortality for necrotizing fasciitis: a retrospective analysis in a single institution. J Trauma. 2011;71(2):467–73.
10. Givner LB. Periorbital versus orbital cellulitis. Pediatr Infect Dis J. 2002;21(12):1157–8.
11. Rudloe TF, Harper MB, Prabhu SP, Rahbar R, Vanderveen D, Kimia AA. Acute periorbital infections: who needs emergent imaging? Pediatrics. 2010;125(4):e719–26.
12. Mahalingam-Dhingra A, Lander L, Preciado DA, Taylormoore J, Shah RK. Orbital and periorbital infections: a national perspective. Arch Otolaryngol Head Neck Surg. 2011;137(8):769–73.
13. Hasanee K, Sharma S. Ophthaproblem. Orbital cellulitis. Can Fam Physician. 2004;50(359):365–7.
14. Carfrae MJ, Kesser BW. Malignant otitis externa. Otolaryngol Clin North Am. 2008;41(3):537–49. viii–ix.
15. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. N Engl J Med. 2001;344(18):1378–88.
16. Milonovich LM. Meningococcemia: epidemiology, pathophysiology, and management. J Pediatr Health Care. 2007;21(2):75–80.
17. Sexton K, Lennon D, Oster P, Aaberge I, Martin D, Reid S, Wong S, O'Hallahan J. Proceedings of the Meningococcal Vaccine Strategy World Health Organization satellite meeting, 10 March 2004, Auckland, New Zealand. N Z Med J. 2004;117(1200):1. p preceding U1027.
18. Ramos-e-Silva M, Pereira AL. Life-threatening eruptions due to infectious agents. Clin Dermatol. 2005;23(2):148–56.
19. James WD, Elston DM, Berger TG, Andrews GC. Andrews' diseases of the skin: clinical dermatology. London: Saunders Elsevier; 2011.
20. Healy CM, Baker CJ. The future of meningococcal vaccines. Pediatr Infect Dis J. 2005;24(2):175–6.
21. Usatine RP, Sandy N. Dermatologic emergencies. Am Fam Physician. 2010;82(7):773–80.
22. Dumler JS, Walker DH. Rocky Mountain spotted fever–changing ecology and persisting virulence. N Engl J Med. 2005;353(6):551–3.
23. Dantas-Torres F. Rocky Mountain spotted fever. Lancet Infect Dis. 2007;7(11):724–32.
24. Spach DH, Liles WC, Campbell GL, Quick RE, Anderson Jr DE, Fritsche TR. Tick-borne diseases in the United States. N Engl J Med. 1993;329(13):936–47.
25. Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis. 1984;150(4):480–8.
26. Parola P, Paddock CD, Raoult D. Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. Clin Microbiol Rev. 2005;18(4):719–56.
27. Gammons M, Salam G. Tick removal. Am Fam Physician. 2002;66(4):643–5.
28. Lacz NL, Schwartz RA, Kapila R. Rocky Mountain spotted fever. J Eur Acad Dermatol Venereol. 2006;20(4):411–7.
29. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2011;379(9814):461–73.
30. des Vignes F, Piesman J, Heffernan R, Schulze TL, Stafford 3rd KC, Fish D. Effect of tick removal on transmission of Borrelia burgdorferi and Ehrlichia phagocytophila by Ixodes scapularis nymphs. J Infect Dis. 2001;183(5):773–8.
31. Huppertz HI, Bohme M, Standaert SM, Karch H, Plotkin SA. Incidence of Lyme borreliosis in the Wurzburg region of Germany. Eur J Clin Microbiol Infect Dis. 1999;18(10):697–703.
32. Stanek G, Fingerle V, Hunfeld KP, Jaulhac B, Kaiser R, Krause A, Kristoferitsch W, O'Connell S, Ornstein K, Strle F, Gray J. Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. Clin Microbiol Infect. 2011;17(1):69–79.
33. Halperin JJ. Nervous system Lyme disease. Infect Dis Clin North Am. 2008;22(2):261–74. vi.
34. Bhate C, Schwartz RA. Lyme disease: Part II. Management and prevention. J Am Acad Dermatol. 2011;64(4):639–53. quiz 654, 653.
35. Brown SL, Hansen SL, Langone JJ. Role of serology in the diagnosis of Lyme disease. JAMA. 1999;282(1):62–6.
36. Branda JA, Aguero-Rosenfeld ME, Ferraro MJ, Johnson BJ, Wormser GP, Steere AC. 2-tiered antibody testing for early and late Lyme disease using only an immunoglobulin G blot with the addition of a VlsE band as the second-tier test. Clin Infect Dis. 2010;50(1):20–6.
37. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(9):1089–134.
38. Katz TM, Miller JH, Hebert AA. Insect repellents: historical perspectives and new developments. J Am Acad Dermatol. 2008;58(5):865–71.
39. Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D, Welch P, Marcus R, Aguero-Rosenfeld ME, Dennis DT, Wormser GP. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. N Engl J Med. 2001;345(2):79–84.
40. Vazquez M, Muehlenbein C, Cartter M, Hayes EB, Ertel S, Shapiro ED. Effectiveness of personal protective measures to prevent Lyme disease. Emerg Infect Dis. 2008;14(2):210–6.
41. Moayeri M, Leppla SH. The roles of anthrax toxin in pathogenesis. Curr Opin Microbiol. 2004;7(1):19–24.
42. Wenner KA, Kenner JR. Anthrax. Dermatol Clin. 2004;22(3):247–56. v.
43. Swartz MN. Recognition and management of anthrax–an update. N Engl J Med. 2001;345(22): 1621–6.

44. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Gerberding J, Hauer J, Hughes J, McDade J, Osterholm MT, Parker G, Perl TM, Russell PK, Tonat K. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA. 2002;287(17):2236–52.
45. Dixon TC, Meselson M, Guillemin J, Hanna PC. Anthrax. N Engl J Med. 1999;341(11):815–26.
46. Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Hauer J, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Tonat K. Anthrax as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA. 1999;281(18):1735–45.
47. Evans ME, Gregory DW, Schaffner W, McGee ZA. Tularemia: a 30-year experience with 88 cases. Medicine (Baltimore). 1985;64(4):251–69.
48. McGinley-Smith DE, Tsao SS. Dermatoses from ticks. J Am Acad Dermatol. 2003;49(3):363–92. quiz 393–6.
49. Choi E. Tularemia and Q fever. Med Clin North Am. 2002;86(2):393–416.
50. Dana AN. Diagnosis and treatment of tick infestation and tick-borne diseases with cutaneous manifestations. Dermatol Ther. 2009;22(4):293–326.
51. Amagai M, Matsuyoshi N, Wang ZH, Andl C, Stanley JR. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. Nat Med. 2000;6(11):1275–7.
52. Odom RB, James WD, Berger TG. Andrews' diseases of the skin: clinical dermatology. St. Louis, MO: Mosby; 2000.
53. Cribier B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults. A clinical review illustrated with a new case. J Am Acad Dermatol. 1994;30(2 Pt 2):319–24.
54. Murray RJ. Recognition and management of Staphylococcus aureus toxin-mediated disease. Intern Med J. 2005;35 Suppl 2:S106–19.
55. Gemmell CG. Staphylococcal scalded skin syndrome. J Med Microbiol. 1995;43(5):318–27.
56. Macias ES, Pereira FA, Rietkerk W, Safai B. Superantigens in dermatology. J Am Acad Dermatol. 2011;64(3):455–72. quiz 473–4.
57. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. Lancet Infect Dis. 2009;9(5):281–90.
58. Schlievert PM, Blomster DA. Production of staphylococcal pyrogenic exotoxin type C: influence of physical and chemical factors. J Infect Dis. 1983;147(2):236–42.
59. Bohach GA, Fast DJ, Nelson RD, Schlievert PM. Staphylococcal and streptococcal pyrogenic toxins involved in toxic shock syndrome and related illnesses. Crit Rev Microbiol. 1990;17(4):251–72.
60. Fraser JD, Proft T. The bacterial superantigen and superantigen-like proteins. Immunol Rev. 2008;225:226–43.
61. Stevens DL. Streptococcal toxic shock syndrome. Clin Microbiol Infect. 2002;8(3):133–6.
62. McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. Annu Rev Microbiol. 2001;55:77–104.
63. Kato K, Sakamoto T, Ito K. Gamma-globulin inhibits superantigen-induced lymphocyte proliferation and cytokine production. Allergol Int. 2007;56(4): 439–44.
64. Adcock DM, Brozna J, Marlar RA. Proposed classification and pathologic mechanisms of purpura fulminans and skin necrosis. Semin Thromb Hemost. 1990;16(4):333–40.
65. Carpenter CT, Kaiser AB. Purpura fulminans in pneumococcal sepsis: case report and review. Scand J Infect Dis. 1997;29(5):479–83.
66. Adcock DM, Hicks MJ. Dermatopathology of skin necrosis associated with purpura fulminans. Semin Thromb Hemost. 1990;16(4):283–92.
67. Betrosian AP, Berlet T, Agarwal B. Purpura fulminans in sepsis. Am J Med Sci. 2006;332(6):339–45.
68. Varon J, Chen K, Sternbach GL. Rupert Waterhouse and Carl Friderichsen: adrenal apoplexy. J Emerg Med. 1998;16(4):643–7.
69. Zomorrodi A, Wald ER. Ecthyma gangrenosum: considerations in a previously healthy child. Pediatr Infect Dis J. 2002;21(12):1161–4.
70. Baro M, Marin MA, Ruiz-Contreras J, de Miguel SF, Sanchez-Diaz I. Pseudomonas aeruginosa sepsis and ecthyma gangrenosum as initial manifestations of primary immunodeficiency. Eur J Pediatr. 2004;163(3):173–4.
71. Wong SN, Tam AY, Yung RW, Kwan EY, Tsoi NN. Pseudomonas septicaemia in apparently healthy children. Acta Paediatr Scand. 1991;80(5):515–20.
72. Bettens S, Delaere B, Glupczynski Y, Schoevaerdts D, Swine C. Ecthyma gangrenosum in a non-neutropaenic, elderly patient: case report and review of the literature. Acta Clin Belg. 2008;63(6):394–7.
73. Gucluer H, Ergun T, Demircay Z. Ecthyma gangrenosum. Int J Dermatol. 1999;38(4):299–302.
74. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA. 2003;289(2): 203–9.
75. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev. 2004;17(1):1–13.
76. Yeager AS, Arvin AM. Reasons for the absence of a history of recurrent genital infections in mothers of neonates infected with herpes simplex virus. Pediatrics. 1984;73(2):188–93.
77. Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL, Watts DH, Berry S, Herd M, Corey L. The acquisition of herpes simplex virus during pregnancy. N Engl J Med. 1997;337(8):509–15.
78. Whitley RJ, Corey L, Arvin A, Lakeman FD, Sumaya CV, Wright PF, Dunkle LM, Steele RW, Soong SJ, Nahmias AJ, et al. Changing presentation of herpes simplex virus infection in neonates. J Infect Dis. 1988;158(1):109–16.

79. Arvin AM, Yeager AS, Bruhn FW, Grossman M. Neonatal herpes simplex infection in the absence of mucocutaneous lesions. J Pediatr. 1982;100(5):715–21.
80. Rebora A. Life-threatening cutaneous viral diseases. Clin Dermatol. 2005;23(2):157–63.
81. Kusuhara T, Nakajima M, Inoue H, Takahashi M, Yamada T. Parainfectious encephalomyeloradiculitis associated with herpes simplex virus 1 DNA in cerebrospinal fluid. Clin Infect Dis. 2002;34(9): 1199–205.
82. Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. J Am Acad Dermatol. 2007;57(5):737–63. quiz 764–6.
83. Marcus B, Lipozencic J, Matz H, Orion E, Wolf R. Herpes simplex: autoinoculation versus dissemination. Acta Dermatovenerol Croat. 2005;13(4): 237–41.
84. Sanderson IR, Brueton LA, Savage MO, Harper JI. Eczema herpeticum: a potentially fatal disease. Br Med J (Clin Res Ed). 1987;294(6573):693–4.
85. Enders G, Miller E, Cradock-Watson J, Bolley I, Ridehalgh M. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Lancet. 1994;343(8912):1548–51.
86. Smith CK, Arvin AM. Varicella in the fetus and newborn. Semin Fetal Neonatal Med. 2009;14(4): 209–17.
87. Chapman SJ. Varicella in pregnancy. Semin Perinatol. 1998;22(4):339–46.
88. Selleger C. [Fatal varicella pneumonia in adults. Report of two cases and review of literature (author's transl)]. Rev Fr Mal Respir. 1979;7(1):9–18.
89. Grose C. Varicella vaccination of children in the United States: assessment after the first decade 1995–2005. J Clin Virol. 2005;33(2):89–95. discussion 96–8.
90. Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. Pediatrics. 2008;122(3):e744–51.
91. Gnann Jr JW. Varicella-zoster virus: atypical presentations and unusual complications. J Infect Dis. 2002;186 Suppl 1:S91–8.
92. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med. 2000;342(9):635–45.
93. Sweeney CJ, Gilden DH. Ramsay Hunt syndrome. J Neurol Neurosurg Psychiatry. 2001;71(2):149–54.
94. Murakami S, Hato N, Horiuchi J, Honda N, Gyo K, Yanagihara N. Treatment of Ramsay Hunt syndrome with acyclovir-prednisone: significance of early diagnosis and treatment. Ann Neurol. 1997;41(3): 353–7.
95. Uscategui T, Doree C, Chamberlain IJ, Burton MJ. Corticosteroids as adjuvant to antiviral treatment in Ramsay Hunt syndrome (herpes zoster oticus with facial palsy) in adults. Cochrane Database Syst Rev.2008;CD006852.
96. Sanjay S, Huang P, Lavanya R. Herpes zoster ophthalmicus. Curr Treat Options Neurol. 2011;13(1):79–91.
97. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. Ophthalmology. 2008;115(2 Suppl):S3–12.
98. Zaal MJ, Volker-Dieben HJ, D'Amaro J. Prognostic value of Hutchinson's sign in acute herpes zoster ophthalmicus. Graefes Arch Clin Exp Ophthalmol. 2003;241(3):187–91.
99. Harding SP. Management of ophthalmic zoster. J Med Virol. 1993;(Suppl 1):97–101.
100. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, Betts RF, Gershon AA, Haanpaa ML, McKendrick MW, Nurmikko TJ, Oaklander AL, Oxman MN, Pavan-Langston D, Petersen KL, Rowbotham MC, Schmader KE, Stacey BR, Tyring SK, van Wijck AJ, Wallace MS, Wassilew SW, Whitley RJ. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1–26.
101. Arnou R, Fiquet A, Thomas S, Sadorge C. Immunogenicity and safety of ZOSTAVAX(R) approaching expiry potency in individuals aged >/=50 years. Hum Vaccin. 2011;7(10):1060–5.
102. Sanford M, Keating GM. Zoster vaccine (Zostavax): a review of its use in preventing herpes zoster and postherpetic neuralgia in older adults. Drugs Aging. 2010;27(2):159–76.
103. Thomas B, Farquhar-Smith P. Extended-release gabapentin in post-herpetic neuralgia. Expert Opin Pharmacother. 2011;12(16):2565–71.
104. Adler SP, Marshall B. Cytomegalovirus infections. Pediatr Rev. 2007;28(3):92–100.
105. Cutts FT, Henao-Restrepo A, Olive JM. Measles elimination: progress and challenges. Vaccine. 1999;17 Suppl 3:S47–52.
106. Epidemiology of measles—United States, 2001–2003. MMWR Morb Mortal Wkly Rep. 2004;53(31):713–716.
107. Scott LA, Stone MS. Viral exanthems. Dermatol Online J. 2003;9(3):4.
108. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. N Engl J Med. 1990;323(3):160–4.
109. Balkhy HH, Sabella C, Goldfarb J. Parvovirus: a review. Bull Rheum Dis. 1998;47(3):4–9.
110. Norbeck O, Papadogiannakis N, Petersson K, Hirbod T, Broliden K, Tolfvenstam T. Revised clinical presentation of parvovirus B19-associated intrauterine fetal death. Clin Infect Dis. 2002;35(9):1032–8.
111. Katta R. Parvovirus B19: a review. Dermatol Clin. 2002;20(2):333–42.
112. Rex JH, Walsh TJ, Sobel JD, Filler SG, Pappas PG, Dismukes WE, Edwards JE. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. Clin Infect Dis. 2000;30(4): 662–78.
113. Pedraz J, Delgado-Jimenez Y, Perez-Gala S, Nam-Cha S, Fernandez-Herrera J, Garcia-Diez A. Cutaneous expression of systemic candidiasis. Clin Exp Dermatol. 2009;34(1):106–10.
114. Pagano L, Mele L, Fianchi L, Melillo L, Martino B, D'Antonio D, Tosti ME, Posteraro B, Sanguinetti M,

Trape G, Equitani F, Carotenuto M, Leone G. Chronic disseminated candidiasis in patients with hematologic malignancies. Clinical features and outcome of 29 episodes. Haematologica. 2002;87(5): 535–41.
115. Ratip S, Odabasi Z, Karti S, Cetiner M, Yegen C, Cerikcioglu N, Bayik M, Korten V. Clinical microbiological case: chronic disseminated candidiasis unresponsive to treatment. Clin Microbiol Infect. 2002;8(7):435–6. 442–34.
116. Uzun O, Ascioglu S, Anaissie EJ, Rex JH. Risk factors and predictors of outcome in patients with cancer and breakthrough candidemia. Clin Infect Dis. 2001;32(12):1713–7.
117. Sun HY, Singh N. Mucormycosis: its contemporary face and management strategies. Lancet Infect Dis. 2011;11(4):301–11.
118. Reyes HM, Tingle EJ, Fenves AZ, Spiegel J, Burton EC. Pulmonary invasive mucormycosis in a patient with secondary iron overload following deferoxamine therapy. Proc (Bayl Univ Med Cent). 2008;21(4):378–81.
119. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634–53.
120. Van Cutsem J, Boelaert JR. Effects of deferoxamine, feroxamine and iron on experimental mucormycosis (zygomycosis). Kidney Int. 1989;36(6):1061–8.
121. Almyroudis NG, Sutton DA, Linden P, Rinaldi MG, Fung J, Kusne S. Zygomycosis in solid organ transplant recipients in a tertiary transplant center and review of the literature. Am J Transplant. 2006;6(10):2365–74.
122. Liang KP, Tleyjeh IM, Wilson WR, Roberts GD, Temesgen Z. Rhino-orbitocerebral mucormycosis caused by Apophysomyces elegans. J Clin Microbiol. 2006;44(3):892–8.
123. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards Jr J, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis. 2009;48(12):1743–51.
124. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis. 2008;47(4):503–9.
125. Goodwin Jr RA, Shapiro JL, Thurman GH, Thurman SS, Des Prez RM. Disseminated histoplasmosis: clinical and pathologic correlations. Medicine (Baltimore). 1980;59(1):1–33.
126. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev. 2007;20(1): 115–32.
127. Reddy P, Gorelick DF, Brasher CA, Larsh H. Progressive disseminated histoplasmosis as seen in adults. Am J Med. 1970;48(5):629–36.
128. Smith JW, Utz JP. Progressive disseminated histoplasmosis. A prospective study of 26 patients. Ann Intern Med. 1972;76(4):557–65.
129. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, Kauffman CA. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807–25.
130. Rassi Jr A, Rassi A, Marin-Neto JA. Chagas disease. Lancet. 2010;375(9723):1388–402.
131. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. N Engl J Med. 2011;364(26): 2527–34.
132. Lescure FX, Le Loup G, Freilij H, Develoux M, Paris L, Brutus L, Pialoux G. Chagas disease: changes in knowledge and management. Lancet Infect Dis. 2010;10(8):556–70.
133. Rassi Jr A, Rassi A, Little WC. Chagas' heart disease. Clin Cardiol. 2000;23(12):883–9.
134. Rassi Jr A, Rassi SG, Rassi A. Sudden death in Chagas' disease. Arq Bras Cardiol. 2001;76(1): 75–96.
135. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. Am J Gastroenterol. 1998;93(6): 884–9.
136. Marin-Neto JA, Rassi Jr A, Avezum Jr A, Mattos AC, Rassi A, Morillo CA, Sosa-Estani S, Yusuf S. The BENEFIT trial: testing the hypothesis that trypanocidal therapy is beneficial for patients with chronic Chagas heart disease. Mem Inst Oswaldo Cruz. 2009;104 Suppl 1:319–24.
137. David CV, Craft N. Cutaneous and mucocutaneous leishmaniasis. Dermatol Ther. 2009;22(6):491–502.
138. Murray HW, Berman JD, Davies CR, Saravia NG. Advances in leishmaniasis. Lancet. 2005;366(9496): 1561–77.
139. Solbach W, Laskay T. The host response to Leishmania infection. Adv Immunol. 2000;74: 275–317.
140. Weigle K, Saravia NG. Natural history, clinical evolution, and the host-parasite interaction in New World cutaneous Leishmaniasis. Clin Dermatol. 1996;14(5):433–50.
141. Ahluwalia S, Lawn SD, Kanagalingam J, Grant H, Lockwood DN. Mucocutaneous leishmaniasis: an imported infection among travellers to central and South America. BMJ. 2004;329(7470): 842–4.
142. Scope A, Trau H, Bakon M, Yarom N, Nasereddin A, Schwartz E. Imported mucosal leishmaniasis in a traveler. Clin Infect Dis. 2003;37(6):e83–7.
143. Amato VS, Tuon FF, Siqueira AM, Nicodemo AC, Neto VA. Treatment of mucosal leishmaniasis in Latin America: systematic review. Am J Trop Med Hyg. 2007;77(2):266–74.