Other Potentially Life-Threatening Conditions with Mucocutaneous Findings (Leptospirosis, Typhoid Fever, Dengue, Diphtheria, Murine Typhus)

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Leptospirosis

Background

Leptospirosis is a potentially fatal zoonotic infection seen in both temperate and tropical regions exposed to heavy rainfall and flooding. Rodents are the most important reservoir for transmission. Commonly carried by the brown rat (Rattus norvegicus), the virus is excreted through urine of the rat or other infected animal and contracted by contact with mucosal surfaces or skin breaks [1]. It is most commonly seen in tropical areas subject to poverty, large rainfall, and flooding; however, cases do occur within the United States, particularly the South Pacific coastal states and Hawaii [2]. The organism can infect many types of mammals which can be either asymptomatic or fatal. Spontaneous abortion is a common complication in animals and frequently described in cattle, swine, sheep, and goats. Risk factors for acquiring leptospirosis infection include activities with exposure to infected animals or water. Farmers and animal caretakers are at particular risk. Sporadic outbreaks commonly occur and have been described in athletes participating in triathlons who swam in infected water [3–6].
Clinical Presentation

Symptoms are largely nonspecific, and patients often present with flu-like illness including fever, myalgias, and headache. However, there are several distinguishing features that herald a diagnosis of leptospirosis (see Table 23.1). Ocular findings are quite common and may be present in up to 90% of cases. In particular, conjunctival suffusion, a dilatation of conjunctival vessels, is a common presentation in leptospirosis but rarely seen in other infectious diseases (see Fig. 23.1). Other ocular findings may include subconjunctival hemorrhage, icterus (seen in severe disease), and hypopyon [7].

Rash is less common and may lead one to consider other diagnoses such as dengue, hantavirus, chikungunya, and others; however, other cutaneous findings such as jaundice with intense pruritus (secondary to liver and renal failure) as well as petechiae or ecchymosis from hemorrhagic complications may be present [7].

Table 23.1 Classic features of leptospirosis

| Typical presentation          |
|-----------------------------|
| Flu-like illness            |

Conjunctival suffusion

- Myalgias (especially calf pain)
- Headache with retro-orbital pain

*Distinguishing clinical feature*

![Fig. 23.1 Conjunctival suffusion with subconjunctival hemorrhage in a patient with leptospirosis. (From Lin et al. [57]. (Link to image: (may be better quality via the link) https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=3269263_tropmed-86-187-g003.jpg)](https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=3269263_tropmed-86-187-g003.jpg)
Atypical Presentation

There have been documented cases of a pretibial rash with leptospiral infection; however, this is uncommon, as the majority of leptospiral diseases are without cutaneous findings. Other atypical findings include pharyngeal injection, maculopapular skin rashes, and cutaneous hyperesthesias [8, 9].

Associated Symptoms

Systemic symptoms are common, predominantly fever, myalgias, and headache. The headache is frequently described as a throbbing, bitemporal, frontal headache often accompanied by retro-orbital pain and photophobia. Myalgias with back and calf tenderness are commonly described. Cough, nausea, vomiting, diarrhea, and abdominal pain are also not infrequent [9].

Disease Progression

With leptospirosis, the disease course may vary significantly from patient to patient. Following exposure, the average incubation period is 10 days (see Fig. 23.2). In typical cases, patients then proceed to a biphasic illness. In the first phase, patients experience rapid onset of fever, rigors, myalgias, and headache that lasts 4–9 days. Patients then experience an afebrile phase for up to 3 days, followed by a recurrence of fever and possible complications such as meningitis and uveitis [9].

Common Mimics and Differential Diagnosis

Differential diagnosis includes malaria, dengue, chikungunya, typhus, rickettsial disease, and hantavirus. See Table 23.2 for distinguishing features of the differential diagnoses.

Complications

Severe leptospiral infections can lead to significant and potentially lethal complications (see Table 23.3). Weil’s syndrome is characterized by liver and renal failure usually in association with altered level of consciousness, hemorrhage, and anemia. Advanced age and jaundice are associated with a higher mortality rate. Severe infections may also be complicated by progression to ARDS and circulatory collapse [9, 10].

Fig. 23.2  Leptospirosis disease timeline
Hemorrhagic complications may also occur, secondary to coagulopathy and thrombocytopenia. Pulmonary hemorrhage is one of the most severe complications with a demonstrated fatality rate over 50%. GI bleeding, severe epistaxis, and hemolytic anemia are other hemorrhagic complications that may be present [1, 11].

Myocarditis, although rare, is another well documented complication of leptospirosis [9].
Patients may also experience a myriad of neurologic complications including aseptic meningitis (relatively common) and transverse myelitis [9].

Management

Diagnosis
Definitive diagnosis is made from PCR, antibody titers, or culture. However, as these diagnostic measures take time, empiric treatment should be initiated if there is a high clinical suspicion of the disease [12].

Treatment
While the majority of leptospirosis cases are mild and will resolve without intervention, early antibiotic therapy may prevent disease progression (see Table 23.4). Outpatient therapy is indicated for mild disease and consists of either doxycycline or azithromycin, with azithromycin being the preferred treatment for pregnant women and children. If rickettsial infection is a possible diagnosis, doxycycline should be given (see Chap. 16 for further discussion on rickettsial infections). Patients with evidence of complications, hemodynamic instability, or severe dehydration should be admitted for supportive care, targeted treatment of the specific complication and intravenous antibiotics [1, 13]. Inpatient treatment includes IV penicillin, ampicillin, ceftriaxone, or cefotaxime. A Jarisch-Herxheimer reaction may occur following treatment, which should be managed supportively [14].

Table 23.4 Treatment of leptospirosis

| Treatment regimen | Outpatient | Inpatient |
|-------------------|------------|-----------|
| Doxycycline       | 100 mg orally twice daily for 7 days | IV penicillin 1.5 million units every 6 h for 7 days |
| Azithromycin      | 500 mg orally daily for 3 days | Doxycycline 100 mg IV twice daily for 7 days |
| Amoxicillin       | 50 mg/kg in 3 equally divided oral doses for 7 days | Ceftriaxone 1–2 g IV once daily for 7 days |

Bottom Line: Leptospirosis Clinical Pearls
- Leptospirosis can range from mild flu-like illness to multi-organ dysfunction.
- Patients typically present with flu-like illness, headache, and myalgias, predominantly in the back and calves.
- Ocular findings are a key diagnostic clue to leptospirosis.
- Conjunctival suffusion is the most common ocular finding in leptospirosis.
- Other ocular findings include subconjunctival hemorrhage, scleral icterus, and scattered petechiae.
Typhoid Fever

Background

Typhoid fever is a febrile illness common among travelers endemic to Asia, Africa, Latin America, and the Caribbean. It is caused by Salmonella enterica serotypes (Typhi and Paratyphi) and is commonly spread through urine and feces. Humans are the only reservoir and it is endemic in areas with poor sanitation [15].

Clinical Presentation and Disease Progression

Typhoid fever is a febrile illness that often develops mucocutaneous findings. Classically, typhoid fever is known for its “rose-spot” rash, which is characterized as a blanching salmon-colored maculopapular rash that appears across the trunk in groupings of 5–15 papules (Fig. 23.3). These lesions may extend across the back and to proximal extremities as well [16].

Atypical Presentation

One notable atypical finding that appears to be specific to typhoid fever is “furry tongue” (see Fig. 23.4). There are well-documented cases of white-yellow-coated tongues following infection with a reported specificity up to 94% [17, 18].

Associated Symptoms

In addition to fever and rash, patients commonly present with abdominal pain. This abdominal pain may be associated with either constipation or diarrhea which occur with similar frequency. In addition, relative bradycardia (Faget’s sign/sphygmothermic dissociation) is a well-described phenomenon as are headache, sleep disturbance, cough, arthralgias, and myalgias (see Table 23.5) [19].

- Diagnosis should be made clinically and is confirmed with serology, PCR, and culture.
- Outpatient treatment includes doxycycline, azithromycin, or amoxicillin.
- Inpatient regimens include IV penicillin, doxycycline, ceftriaxone, and cefotaxime.
- Complications may affect nearly any organ system and include hemorrhagic complications, liver failure, myocarditis, neurologic manifestations, ARDS, and renal failure.
Fig. 23.3  Patient with a rose-colored rash on chest and shoulders with acute typhoid fever. (Photo courtesy: https://phil.cdc.gov/details.aspx?pid=2215)

Fig. 23.4  Coated tongue in a patient with typhoid fever. (From Bal and Czarnowski [18]. Open access https://www.ncbi.nlm.nih.gov/pmc/articles/PMC374215/bin/21FF1.jpg)
Classically, typhoid fever presents in stages (see Fig. 23.5). The incubation period lasts roughly 5–21 days after ingestion of the microorganism. In the first week of clinical symptoms, patients often develop fever which classically rises in a stepwise fashion and, if left untreated, may persist for weeks. In the second week of infection, the classic “rose-spot” rash appears with lesions usually lasting 3–5 days before remitting. Patients commonly complain of abdominal pain at this time and may suffer from a myriad of GI symptoms. In the third week, patients may develop complications of ongoing illness as discussed below [15].

Common Mimics and Differential Diagnosis

Findings in typhoid fever are largely nonspecific, and therefore a wide differential needs to be maintained. The differential diagnosis includes malaria, tuberculosis, brucellosis, tularemia, leptospirosis, rickettsial infections, dengue fever, hepatitis, and infectious mononucleosis.

Complications

Left untreated, typhoid fever can lead to a number of significant complications, which commonly present as GI complaints in the later weeks of infection (see Table 23.6). These include small bowel ulceration, intestinal perforation, and subsequent septic shock. Other complications are also possible, including psychosis, neurologic deficits, and “typhoid encephalopathy” which can be described as altered level of consciousness or delirium. The bacteria can also seed nearly every other organ system so there may potentially be cardiac, respiratory, genitourinary, musculoskeletal, and central nervous system abnormalities. Finally, patients if untreated, may become chronic carriers causing autoinoculation and or transmission to other contacts [19–21].
The diagnosis of typhoid fever should largely be clinical with high suspicion in patients exposed to endemic areas. Diagnosis can be confirmed with cultures from blood, stool, urine, rose spots, and bone marrow; however, these diagnostic methods are imperfect. Serology is of limited utility as a positive result may indicate a prior infection rather than an ongoing one. Other developing modalities include ELISA and PCR [22].

Treatment

Historically, chloramphenicol or amoxicillin were the drugs of choice for treatment of typhoid fever; however, drug resistance has become a significant problem (see Table 23.7). Treatment should be directed by local resistance patterns and severity of illness. In severe disease with systemic signs, IV ceftriaxone or fluoroquinolones should be initiated if there is local susceptibility. Glucocorticoid therapy has been shown to reduce severity of illness and mortality in patients with severe disease based on a randomized, double-blind placebo-controlled trial out of Indonesia with a relatively low side effect profile. Therefore, if patients develop delirium, coma, shock, or DIC, glucocorticoid therapy should be considered with dexamethasone loading at 3 mg/kg IV followed by 1 mg/kg IV every 6 h for eight doses. Steroid treatment beyond this is contraindicated as it may increase relapse rate [23–26].

In uncomplicated disease, oral agent therapy with ciprofloxacin 500–750 mg PO BID for 14 days should be initiated. In quinolone-resistant regions, azithromycin 1 g PO may be taken daily for 5 days [23].
**Dengue Fever**

**Background**

Dengue fever, caused by several serotypes of Flaviviridae, is one of the most common etiologies of arthropod-borne viral disease in the world. While often asymptomatic and self-limited, dengue fever can vary significantly in severity and is a significant public health concern in developing nations [27].

**Clinical Presentation**

Dengue fever classically presents with high fever, headache, abdominal pain, myalgias, and arthralgias as well as mucocutaneous findings (see Tables 23.8 and 23.9). During the febrile portion of the illness, conjunctival injection and oropharynx hyperemia are commonly present (see Fig. 23.6). Facial flushing or erythematous mottling may occur at the beginning of fever or just before, usually resolving within 2 days after onset of symptoms (Fig. 23.7). Rash can occur in up to 50% of patients, occurring either early or late. The rash is typically described as maculopapular and can occur diffusely across face, throat, abdomen, and extremities. Patients may endorse pruritus as well. With defervescence, a late cutaneous eruption develops, characterized by confluent and erythematous islands, which are often pruritic in nature (Figs. 23.8 and 23.9). The rash often resolves within 2–3 days but may last up to as many as 5 days. In addition, as the disease resolves, puritic desquamation of the palms and soles may occur. Other cutaneous manifestations occur secondarily to hemorrhagic complications, as discussed below, and include petechiae, purpura, and ecchymosis (see Fig. 23.10) [28].
Associated Symptoms

As above, patients may experience a myriad of symptoms consistent with viral illness. Patients commonly complain of frontal headache with retro-orbital pain, myalgias, arthralgias, nausea, and vomiting. During the febrile phase of the illness, patients commonly have a relative bradycardia to the degree of fever. Less common associated symptoms include anorexia, altered taste sensation, and mild sore throat. Other symptoms may occur secondarily to complications and will be discussed below [28].

Physical Exam

Patients may have conjunctival injection and pharyngeal erythema. Given propensity for hemorrhagic complications, patients commonly develop petechiae, purpura, and ecchymosis. Additionally, lymphadenopathy, hepatomegaly, facial plethora, or signs of overload secondarily to vascular leak may be present [28].

Time Course of Disease

Dengue virus is typically transmitted by the Aedes mosquito and is typically found in densely forested areas. The viral incubation period is 3–14 days after inoculation. Dengue fever is divided into three phases: the febrile phase, the critical phase, and the convalescent phase [28].
Fig. 23.6  Scleral injection in a patient with dengue fever. (From Thomas et al. [58] (open access))

Fig. 23.7  Erythematous blanching rash of a patient with dengue infection. (From Thomas et al. [58] (open access))

Fig. 23.8  Confluent erythematous rash with islands of sparing in a patient with dengue fever. (From Thomas et al. [58] (open access))
In the febrile phase, patients experience fever that waxes and wanes, lasting from 2 to 7 days, as well as many of the symptoms above [28].

The critical phase occurs around the time of defervescence, often 3–7 days after fever onset. This phase usually lasts 24–48 h and may be complicated by systemic vascular leak syndrome. This syndrome is characterized by plasma leak, bleeding, shock, and organ dysfunction [29].

The convalescent phase, often occurring 1–2 days after defervescence, is characterized by resolution of plasma leakage and hemorrhage. A pruritic confluent erythematous rash often is present during this phase as seen above [28].

Fig. 23.9 Early erythematous mottling and secondary maculopapular rash. (Used with permission from Kenzaka and Kumabe [59])
Common Mimics and Differential Diagnosis

Differential diagnosis should include malaria, dengue, chikungunya, typhus, rickettsial disease, and hantavirus. See Table 23.2 for distinguishing features of the differential diagnoses.

Complications

The complications of dengue are many and involve multiple organ systems with potential organ failure. Table 23.10 outlines many of the common complications [28–33].

Management

Diagnosis

Early diagnosis of dengue fever is usually clinical and should be suspected in patients with the signs and symptoms above and exposure to endemic regions. Although neither sensitive nor specific, providers may perform a tourniquet test to
help in diagnosis (Figs. 23.11 and 23.12). In this test, a blood pressure cuff is inflated midway between systolic and diastolic pressures and left for 5 min. A positive test is characterized by ten or more new petechiae in 1 square inch. Diagnosis may be confirmed by detection of viral components in serum or PCR, although these methods are labor intensive and costly. Serology is also available but is of lower specificity. Viral culture is also available but of limited utility given time needed for test to result [34–36].

**Management**

Management is largely supportive because there is no antiviral therapy for dengue fever. Outpatient management may be appropriate in patients without systemic complications or comorbid conditions such as pregnancy, infancy, advanced age, renal failure, underlying hemolytic disease, or poor social support/access to follow-up care [37].

Inpatient management should be considered for any patient with comorbid conditions or for those with signs of severe infection. Signs of severe infection include abdominal pain, persistent nausea and vomiting, fluid accumulation (ascites, pleural effusion), mucosal bleeding, lethargy or altered mental status, hepatomegaly, increased hematocrit with rapid decrease in platelet count, and signs of shock or end-organ dysfunction. Aggressive IV fluid supplementation is warranted in those with signs of dehydration. FEVER, myalgias, and arthralgias can be managed with acetaminophen. NSAIDs and aspirin should be avoided, given the potential hemorrhagic complications. During the disease course, hemoglobin and platelets should be monitored. Transfusion with packed red blood cells is indicated for worsening anemia and suspected bleeding. Platelet transfusion is indicated for severe thrombocytopenia (<10,000/mm³) but should not be pursued prophylactically. Vitamin K may be indicated if the prothrombin time is prolonged which may occur as a result of liver dysfunction or DIC [37–39].
Fig. 23.11 Positive tourniquet test in dengue. (Used with permission from Kenzaka and Kumabe [59])
Diphtheria

Background

Caused by the gram-positive rod *Corynebacterium diphtheriae*, diphtheria is a disease that can cause a myriad of symptoms, ranging from asymptomatic infection to respiratory distress. It is often associated with mucocutaneous symptoms. Diphtheria
was a significant cause of morbidity and mortality in the pre-vaccine era; however, since the advent of the diphtheria vaccine, the disease has largely been eliminated in developed countries but may sporadically occur [40].

**Clinical Presentation**

Patients infected with *C. diphtheria* usually present in one of two fashions: respiratory diphtheria or cutaneous diphtheria. Respiratory diphtheria is often caused by toxigenic strains, whereas cutaneous diphtheria may be caused by both toxigenic and non-toxigenic strains.

Respiratory diphtheria often presents with sore throat, malaise, cervical lymphadenopathy, and low-grade fever. Early in the disease course, only pharyngeal erythema may be present, which then progresses to isolated areas of gray and white exudate (see Figs. 23.13 and 23.14; Table 23.11). Although known as the hallmark of this disease, pseudomembranes form in only one third of cases. Pseudomembranes

![Fig. 23.13](image-url) Early diphtheria in a 26-year-old female. Note the membrane on the right tonsil. (Used with permission from Kadirova et al. [61])

**Table 23.11** Mucocutaneous findings in diphtheria

| Classic presentations                                      | Respiratory diphtheria                                                                 | Cutaneous diphtheria                        |
|-----------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------|
| Pharyngeal erythema                                       | Gray-white exudate                                                                     | Blisters or pustules that progress to shallow ulcers |
| Gray-white exudate                                        | Pseudomembrane                                                                        | Gray membranes                            |
| Pseudomembrane                                            | *note that these findings can occur anywhere along respiratory tract*                  | Hemorrhagic or violaceous base             |
|                                                            |                                                                                       | Painful lesion that becomes anesthetic     |
|                                                            |                                                                                       | Heals poorly                              |

are easily friable gray tissue adhering to underlying tissue, composed of necrotic fibrin, leukocytes, epithelial cells, and organisms. These membranes can spread anywhere along the respiratory tract; however, the majority of cases are found along tonsils and oropharynx. Extensive spreading of these membranes can lead to respiratory compromise which will be discussed below [41].

Cutaneous diphtheria is often the more benign of the two conditions as systemic toxicity is rare. Early, patients may experience a small blister or pustule, often over a site of minor skin trauma, with straw-colored fluid that ruptures early forming a punched-out ulcer. These shallow ulcers usually become chronic, poorly healing lesions (taking from 6 weeks to up to a year to heal) that become covered by gray membrane. While initially painful during the first 2 weeks, these lesions often become anesthetic and develop a hemorrhagic or purple base (see Fig. 23.15). In addition, this variant of the disease tends to predominate affect the impoverished and intravenous drug users. Patients with cutaneous diphtheria rarely develop the respiratory variant of the disease but commonly serve as a reservoir of infection for others [42–44].
Cutaneous Diphtheria

Associated Symptoms

Respiratory diphtheria often presents similar to streptococcal pharyngitis with sore throat, malaise, lymphadenopathy, and low-grade fever; however, patients may also experience cough as areas of the respiratory tract become involved. Symptoms may become significantly more severe in cases of systemic toxicity as discussed below. Symptoms are not solely limited to cutaneous and respiratory systems, however, and further manifestations will be discussed below [45, 46].
Physical Exam

As above, findings consistent with diphtheria are posterior oropharynx erythema and pseudomembrane formation. In cases of nasal diphtheria, the clinician may find serosanguineous to purulent nasal discharge. In laryngeal diphtheria, hoarseness and cough may be present. In severe cases, the pseudomembranes may be extensive causing massive swelling of the tonsils, uvula, cervical lymph nodes, submandibular region, and neck. This presentation is colloquially known as the “bull neck” of diphtheria, and such swelling may cause stridor and respiratory distress (see Fig. 23.16) [41].

Time Course of Disease

Humans are the only known reservoir of disease, with spread primarily occurring via respiratory secretions or direct contact with mucocutaneous manifestations. Symptoms often appear 2–5 days postexposure. After symptoms begin, in untreated patients, the disease often lasts up to 2 weeks but can last up to 6 weeks. In appropriately treated patients, the infection is often cleared within 4 days [41, 47].
Common Mimics and Differential Diagnosis

Differential diagnosis should include infectious mononucleosis, group A streptococcal pharyngitis, epiglottitis, viral pharyngitis, acute necrotizing ulcerative gingivitis, oral candidiasis, and viral pharyngitis.

Complications

See Table 23.12 for a summary of complications associated with diphtheria. The primary and most feared complication is severe membranous pharyngitis which can lead to thickening of the neck, narrowing of the airway, and resultant respiratory distress. Airway management is of the utmost importance in the emergent management of these patients [41].

Another well-described complication of diphtheria is myocarditis, which is more common in severe infections. Cardiac manifestations of diphtheria have been noted in up to 10 to 25 percent of patients with diphtheria, often occurring 1–2 weeks after symptom onset. Patients may experience heart blocks, arrhythmia, heart failure, and, in severe cases, circulatory collapse. These potential complications mandate cardiac monitoring in patients with potential systemic disease [41, 48].

Neurologic toxicity is another well-known complication of severe diphtheria infection. As with cardiac complications, neurologic symptoms are more common with worsening systemic illness. Manifestations of neurologic involvement often include paralysis of the soft palate and posterior pharyngeal wall. These neuropathies can progress to cranial neuropathies and peripheral neuritis ranging from mild weakness to total paralysis [49].

Management

Diagnosis

A diagnosis of diphtheria should first be suspected clinically in the unvaccinated or exposed population in the setting of above findings, particularly with friable pseudomembrane formation. Culture from respiratory tract or cutaneous lesions is

| Complications       | Respiratory                        | Cardiovascular       | Neurologic                        |
|---------------------|------------------------------------|----------------------|----------------------------------|
| Respiratory         | Airway narrowing                   | Myocarditis          | Cranial nerve palsies            |
|                     | Respiratory failure                | Heart blocks         | Soft palate and posterior pharynx |
| Cardiovascular      |                                    | Arrhythmia           | paralysis                         |
|                     |                                    | Heart failure        | Peripheral neuropathies          |
| Neurologic          |                                    |                      |                                  |
required for definitive diagnosis; however, a presumptive diagnosis can be made in the setting of gram-positive rods on gram stain with the above findings. PCR and toxin assay are also available to help distinguish whether a toxigenic form of diphtheria is causing the patient symptoms [50].

**Treatment**

The most important aspect of treatment of treatment in diphtheria is airway management given risk for obstruction. Patients should also be monitored for dysrhythmias and hypotension secondary to cardiac involvement with supportive management as needed [41].

In cases of early suspected or confirmed respiratory diphtheria, antitoxin should be administered. Of note, antitoxin is only effective before the toxin enters the cell. In addition, there is a 5–20% risk of hypersensitivity or serum sickness; therefore, ideally a scratch test can be performed before IV administration, and epinephrine should be readily available in cases of anaphylaxis [51].

Antibiotic therapy also plays a role in the treatment of diphtheria, with the antibiotics of choice being erythromycin or penicillin. Benefits of antibiotic therapy are threefold: killing of bacteria preventing further toxin formation, slowing spread of local infection, and reducing of transmission. Treatment with these antibiotic regimens is for 2 weeks followed by a repeat culture to ensure eradication [47, 51]. See Table 23.13 for antibiotic treatment regimens.

**Table 23.13** Antibiotic treatment regimens for diphtheria

| Treatment   | NOTE                                                                 | dose                          |
|-------------|----------------------------------------------------------------------|-------------------------------|
| Erythromycin| 500 mg four times daily for 2 weeks                                  |                               |
| Penicillin  | PO intolerant                                                        | Penicillin G IM injections 600,000 units every 12 h |
|             | PO tolerant:                                                         | Oral penicillin V 250 mg four times daily for 2 weeks |

**Bottom Line: Diphtheria Clinical Pearls**

- Diphtheria is a potentially life-threatening illness of two variations: Respiratory and cutaneous.
- Respiratory diphtheria classically causes pseudomembrane formation which may be diffuse and can lead to airway obstruction.
- Cutaneous findings are generally nonspecific, characterized by grayish non-healing ulcers.
- Diphtheria may affect multiple organ systems with cardiac and neurologic manifestations being the most common in severe systemic illness.
- Diagnosis is initially clinical and confirmed with cultures and PCR.
- Treatment includes antibiotics and antitoxin (if early in the disease course).
Murine Typhus

Background

Murine or endemic typhus is a flea-borne infectious disease caused by *Rickettsia typhi*. The infection is often mild and self-limited and likely frequently remained undiagnosed as a nonspecific febrile illness with rash. As with other rickettsial disease, infection induces a widespread vasculitis [51, 52].

Murine typhus is primarily transmitted via the rat flea, particularly in the developing world and in locations with large rat populations. However, any type of flea may carry and transmit the disease. In suburban United States, cats, opossums, mice, and shrews may host infected fleas. Humans are infected via infected flea bite. Most cases of murine typhus in the United States are reported in people from California, Hawaii, and Texas [51, 52].

Classic Clinical Presentation

Murine typhus is typically a mild illness of nonspecific viral-type symptoms (see Table 23.14). Typically, the onset of illness is abrupt with fever, headache, chills, and myalgias. A rash is present in 20–50 percent of patients. The classic rash is a fine, maculopapular rash that begins on the abdomen and spreads centripetally to the extremities (see Fig. 23.17). Classically, the palms, soles, and face are spared. The rash is frequently faint and less apparent in dark-skinned individuals [51, 53].

Atypical Presentation

Children are more likely to additionally have abdominal pain, vomiting, and diarrhea [54]. In approximately 10 percent of patients, the rash may be petechial. In contrast to the typical mild disease course, severe complications may potentially occur, particularly in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) and the elderly (see Complications below).

| Table 23.14  Classic murine typhus presentation |
|------------------------------------------------|
| **Classic presentation**                        |
| Flu-like illness                                |
| Fevers                                         |
| Headache                                       |
| Myalgias                                       |
| Fine maculopapular rash                        |
| *Spreads from trunk to extremities*            |
| *No palms or soles involvement*                |
Time Course of Disease

After inoculation, there is a 7–14-day incubation period prior to symptom onset. Low-grade fever generally occurs within the first 1–2 days and resolves within 2 days. Rash onset classically occurs 5 days after onset of symptoms and usually resolves spontaneously within 4 days. Total resolution of symptoms generally occurs within 14 days (see Fig. 23.18) [55].

Common Mimics and Differential Diagnosis

There is a wide differential diagnosis to the nonspecific symptoms of murine typhus. Important diagnoses to consider include viral infections, rubella, measles (see Chap. 6), mononucleosis, and classically tropical infections such as dengue and Zika.

Key Physical Exam Findings and Diagnostic Features

Diagnosis typically occurs with initial clinical suspicion in a patient with fever, headache, rash, and possible exposure to infected fleas. Similar to other rickettsial infections, there is no reliable diagnostic test early in the disease course. Serologic confirmation may occur with an indirect fluorescent antibody testing which is
typically only available at a health department laboratory. Other laboratory findings are nonspecific and also nondiagnostic. Thrombocytopenia occurs in approximately half of all patients with murine typhus [51, 55].

**Management**

Treatment of murine typhus rapidly improves clinical symptoms and decreases complication rates; therefore, empiric treatment should be initiated in those with a high enough index of suspicion (see Table 23.15). While tetracyclines and chloramphenicol are effective treatments, doxycycline is the antibiotic of choice for rickettsial infections (see Chap. 16), and adults should receive 100 mg twice daily. In children, doxycycline is still the recommended agent of choice regardless of age. The recommended dosing of doxycycline in children is 4 mg/kg daily divided into two doses to be received every 12 h. Of note, fluoroquinolones and chloramphenicol may also be used but appear to be less efficacious. In addition, fluoroquinolones should not be used in children under the age of 18 years. While duration of therapy is controversial, some sources recommend treatment until 3 days after defervescence, and evidence of clinical improvement is documented. In addition, it should be noted that most individuals will recover from illness within 2 weeks without treatment [51, 52, 56].

**Complications**

While complications are rare, nearly any organ system may be affected by murine typhus. Notable complications include renal dysfunction, pulmonary edema, respiratory failure, aseptic meningitis, splenomegaly, and rarely septic shock and multi-organ system failure. Severe disease is more likely to occur in patients with G6PD deficiency and advanced age [52].

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**Fig. 23.18** Murine typhus disease timeline

**Table 23.15** Treatment regimens for murine typhus

| Treatment | Adults        | Doxycycline 100 mg twice daily\(^a\) |
|-----------|---------------|--------------------------------------|
| Children  | Doxycycline 4 mg/kg/day divided into two doses every 12 h\(^b\) |

\(^a\)Treatment duration is controversial and not clearly outlined
\(^b\)Tetracyclines and chloramphenicol can be used as alternatives, but are generally less effective
Bottom Line: Murine Typhus Clinical Pearls

- Murine typhus is a flea-borne illness that causes an abrupt onset of symptoms including fever, headache, and myalgias.
- It is often generally a mild, self-limited disease.
- A faint maculopapular rash begins on the trunk and spreads peripherally, sparing the palms and soles.
- Patients with G6PD deficiency and advanced age are at risk for life-threatening complications.
- Treatment is with doxycycline.

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