RMSF and Serious Tick-Borne Illnesses (Lyme, Ehrlichiosis, Babesiosis and Tick Paralysis)

16

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Background

Tick-borne illnesses plague large parts of North America especially in the warm summer months when vector burden is higher and exposure is more frequent due to outdoor activities. Rocky Mountain spotted fever (RMSF) along with other serious tick-borne illnesses found in the United States (US) such as Lyme disease, ehrlichiosis, babesiosis, and tick paralysis will be the focus of this chapter.

Tick-borne diseases include rickettsiae organisms such as intracellular gram-negative coccobacilli (e.g., *Rickettsia*, *Ehrlichia*, and *Anaplasma*), spirochetes (e.g., *Borrelia*), other bacteria (e.g., *Francisella tularensis*), protozoa (e.g., *Babesia*), and viruses.

Tick paralysis, or *tick toxicosis*, is unique to the "tick-borne illnesses"; in the fact it is not caused by an infectious organism. Tick paralysis is caused by a neurotoxin that is produced in the tick's salivary gland. Once the tick is fully engorged and still attached to the host, the tick transmits the toxin to its host.

The life cycle of tick-borne disease organisms includes ticks as the "vector" and vertebrates such as dogs, deer, or mice as "hosts." Humans are considered "accidental hosts" [1].

Table 16.1 shows organism, vector, and geographic distribution of Rocky Mountain spotted fever and other selected serious tick-borne illnesses.

According to the Centers for Disease Control and Prevention (CDC), tick-borne rickettsial diseases are on the increase in the United States (US) and continue to cause morbidity and mortality despite the availability of effective antibiotics [1].

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Table 16.1 Serious tick-borne illnesses demographics in the United States

Disease	Organism	US vector	US location (predominant)
RMSF *R. Rickettsii*	Spirochete *Rickettsia rickettsia*	*Dermacentor variabilis* (American dog tick) most commonly (Fig. 16.1 dog tick)	Most prevalent in southeastern and south Central United States
Lyme disease	Bacteria *Borrelia burgdorferi*	*Ixodes ricinus*	Northeastern and upper Midwestern states; some presence in Pacific Northwest
Ehrlichiosis, *E. chaffeensis*	Bacteria *Ehrlichia chaffeensis*	Lone star tick (*Amblyomma americanum*)	Southeastern United States, also Midwest and New England states
Babesiosis	Protozoa *Babesia*	*Ixodes* species	Northeast and Midwest areas
Tick paralysis	Toxin (not organism)	*Dermacentor andersoni* and *variabilis* (wood tick) most common	Pacific Northwest

Ten percent of children living in the Southeastern region of the United States have been found to be seropositive for prior rickettsial infections [2]. The lower incidence of clinically apparent cases is likely due to rickettsial infections with unknown or subclinical findings.

Increase in tick replication and increase in human outdoor activities in the warmer months result in a predominance of tick-borne infections occurring from April to October. Colder months are not immune with the CDC reporting 3% of RMSF and 3% of ehrlichiosis cases occurring in 2000–2007 from December to February. Almost 10% of RMSF cases in New York, New Jersey, and Pennsylvania occur in these winter months [3, 4].

Tick-borne infections are often not considered when the patient or parent of a child does not reveal or is unaware of exposure. Especially in summer months when tick illnesses are more prevalent, a thorough clinical history should include questions regarding tick exposure, work or recreational exposure to tick-infested areas, travel to areas where tick illness is endemic, and similar illness in family members, coworkers, or pet dogs [1]. Dogs can act as a transport for ticks into human dwellings and can transfer ticks directly to humans during human-dog interactions such as petting or bathing. A history of recent tick removal from a family pet might be useful in evaluating the potential for human tick exposure. Pets are susceptible to the same tick-borne illnesses as humans such as *R. rickettsia*, *E. chaffeensis*, *E. ewingii*, and *A. phagocytophilum*.

Ticks are small especially early on in their life cycle (nymphs are 1–2 mm) and will often attach themselves, usually painlessly, to less visible areas such as the hair or groin (Fig. 16.1). Ticks may remain on the skin feeding for several days without being noticed by the host. Data shows at least one-third of seropositive RMSF or ehrlichiosis patients do not remember being bitten [1, 5]. Patients may attribute a bite to other insects such as mosquitos, spiders, chiggers, or fleas which may be

Fig. 16.1 Dog tick *Dermacentor variabilis*. (Image appears with permission from Centers for Disease Control and Prevention (CDC))

indistinguishable from a tick bite. Transmission of the tick-borne infection from the tick to the host occurs while the tick is feeding and has been attached to the host for about 6–10 h. Additionally, infection can be transmitted due to crushing of the tick during removal.

Ticks can attach and feed anywhere on the body but are most commonly found in the scalp, behind the ear, or in the groin, axilla, or perineum [6]. A thorough examination of the skin is imperative on any patient who presents with signs or symptoms in which the differential includes a tick-borne illness. Ticks have been found, after admission to the hospital, by parents, residents in training, nurses, or technicians [7]**.** When one tick is found, continued search for other ticks is recommended. Because tick paralysis is more common in girls, a very thorough search of what is often very thick, long hair is crucial. A fine-tooth comb can often aid in the search.

Risk factors for tick-borne illnesses include living in endemic areas and outdoor activities such as camping, hiking, gardening, walking dogs, golfing, or simply playing the backyard.

Prevention of tick-borne illness is mainly based on avoiding areas where ticks and their hosts are known to thrive in the late spring, summer, and early fall months. Light-colored clothing that covers the arms and lower legs is required including long-sleeved shirts buttoned at the cuffs and long pants tucked into socks or boots.

Clothing can be sprayed with permethrin (Permanone). Pretreated clothing with permethrin can be purchased and is considered safe for use by adults and children [5]. DEET-containing products (N,N-diethyl-meta-toluamide) can be applied to the skin as protection against tick bites. Both the Environmental Protection Agency (EPA) and the American Academy of Pediatrics (AAP) have concluded that, when

used properly, DEET products are safe for both adults and children with the AAP recommending a 10–30% concentration for children older than 2 months old. Picaridin, 5–10% concentration, is also now available in the United States and safe for children [5, 8].

If time is spent outdoors, the body should be thoroughly searched for ticks. High-risk areas include the head, neck, axilla, and scrotum. Any ticks found should be removed as soon as possible with fine-tipped tweezers using steady pressure to gently pull back- and upward to remove the tick from the skin. If tweezers are not available, then fingers with gloves or tissues can be used. Alternative removal methods such as application of isopropyl alcohol, petroleum jelly, or a hot extinguished match are not recommended and are more likely to result in transmission of organisms [5].

Keeping grass mowed and avoiding plants or shrubberies that attract hosts such as deer are important. Fencing to deter deer and walls to deter mice can help keep these hosts away from property [9].

Vaccines are not available and prophylactic antibiotic treatment after known tick exposure is not recommended [5].

Spotted fever group rickettsiosis, ehrlichiosis, and anaplasmosis are all reportable conditions in the United States. It is important that providers check with their local health departments for an accurate list of reportable conditions. A brief summary of Rocky Mountain spotted fever and some of the more serious tick-borne illnesses mentioned in this chapter can be found in Table 16.2.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is caused by the organism *Rickettsia rickettsia*, the most common rickettsial infection in the United States [10]. Transmitted by the dog tick *Dermacentor variabilis* (Fig. 16.1), *R. rickettsia* is an intracellular pathogen that infects vascular endothelial cells and, less often, underlying smooth muscle cells of small and medium vessels. This infection causes direct vascular injury, prostaglandin production that may cause increase vascular permeability, and perivascular lymphocytic infiltrate. Clotting factor activation results but rarely disseminated intravascular coagulation (DIC). Infection leads to this systemic vasculitis that is characterized by petechial skin lesions. Untreated RMSF can have potentially fatal consequences.

Although RMSF has been reported in all areas of the contiguous United States, predominance is in the Southern and Eastern regions [11, 12]. According to the CDC, the incidence of RMSF is now reported under a new category called spotted fever group (SFG) rickettsiosis that captures other spotted fever group *Rickettsia* species. The number of SFG cases has been steadily increasing since 2000, peaking in 2012 to 14.2 cases per million persons [1]. Whether this is truly an increase in disease or just improved reporting is controversial. Transmission of *R. rickettsia* has been seen after blood products transfusions [1].

Table 16.2 Tick-borne illnesses clinical and laboratory findings

Disease	Incubation period	Clinical characteristics	Laboratory findings
RMSF *R. Rickettsii*	Symptoms appear 3–12 days after initial tick bite	Diffuse macular or papular rash starting on wrists and ankles (often palms/soles) spreading to arms, legs, trunk, associated with systemic symptoms such as fever, headache, myalgias, and malaise	Thrombocytopenia, increased hepatic transaminase levels, normal or increased white blood cell count with increased immature neutrophils, hyponatremia, increased serum urea nitrogen, creatinine, and bilirubin
Lyme disease	Symptoms appear 7–14 days after initial tick bite but may be as long as 30 days	Erythema migrans, solitary erythematous lesion, at site of tick bite followed weeks to months later by multiple erythema migrans, neurological, or cardiac sequelae, followed months to years later by arthritis	Mild thrombocytopenia, mild leukopenia, increased hepatic transaminase levels
Ehrlichiosis, *E. Chaffeensis*	Symptoms appear 1–2 weeks after tick bite, but shorter periods have been reported	Maculopapular rash, not as common as the RMSF rash and less often on palms and soles; leukopenia and thrombocytopenia	Leukopenia, thrombocytopenia, increased hepatic transaminase levels, hyponatremia, anemia
Babesiosis	Symptoms appear 1–6 weeks after tick bite	Fever, fatigue, weakness	Hemolysis of RBCs
Tick paralysis	Symptoms may not appear for several days after tick bite	Acute symmetric ascending paralysis eventually effecting the upper extremities and respiratory muscles; mental status not affected unless hypoxia from respiratory failure ensues	No laboratory abnormalities define tick paralysis

Classic Clinical Presentation

Although clinical symptoms and signs vary somewhat between the tick-borne illnesses, most cases present with nonspecific features such as fever, nausea, and headache. Because of these nonspecific features early on, practitioners will often attribute the illness to more common viral processes such as acute gastroenteritis or bacterial processes such as streptococcal pharyngitis.

RMSF presents classically in approximately 90% of patients with a macular and then maculopapular rash (small 1–5 mm lesions) 2–4 days after onset of fever [13]

Fig. 16.2 RMSF rash
adult (Image appears with
permission from VisualDx)

Fig. 16.3 RMSF rash
child (Image appears with
permission from VisualDx)

(Fig. 16.2). The rash may soon become petechial or purpuric in about 50% of cases. Classically beginning on the wrists and ankles, and often involving palms and soles, the rash soon spreads to the arms, legs, and trunk. The rash may be transient or localized to one region of the body [5]. The rash is typically not pruritic. Darker skin may make the rash less noticeable. Children develop the rash more often than adults and develop the rash earlier in the course of the illness [1, 11] (Fig. 16.3). The rash may even be absent in up to 10% of cases making the diagnosis more difficult and a fatal outcome more likely [1, 14]. In severe cases, distal areas such as fingers and toes may develop necrosis due pathogen-induced damage to the small vessels.

Atypical Presentation

An atypical presentation would be late onset or absence of rash, significant gastro-intestinal symptoms early in the disease, or lack of headache [1].

Associated Systemic Symptoms

RMSF clinical presentation includes fever, headache, chills, myalgias, and fatigue. Nausea, vomiting, abdominal pain, anorexia, and photophobia have also been noted [1]. Headache is usually more present in adults. Especially in children, abdominal pain may be a prominent complaint, and an erroneous diagnosis of gastroenteritis can occur early on before the rash is present. Pedal edema is especially noticeable in children. The classic triad of RMSF (fever, rash, and headache) is present in only 5% of patients in the first few days but up to 60–70% of patients by the second week [5, 15, 16]. Rash, fever, and a history of a tick bite are equally insensitive [5]. Other less common symptoms include diarrhea, conjunctival suffusion, peripheral edema (more often in children), calf pain, transient hearing loss, hepatomegaly, or splenomegaly [1].

Time Course of Disease (Incubation Period After Exposure to Infectious Agent or Drug Exposure)

Symptoms of RMSF typically present 3–12 days after an infected tick bite. Patients who go on to develop severe disease generally present with symptoms sooner [1].

Common Mimics and Differential Diagnosis

Early RMSF has similar symptoms to many common disorders. Headache and fever may be attributed to viral syndrome, meningitis, or encephalitis. The maculopapular rash may be thought due to drug reaction, viral syndrome, scarlet fever, or Kawasaki disease. Abdominal pain associated with RMSF has been mistaken for appendicitis, cholecystitis, or gastroenteritis [1]. Significant cutaneous necrosis or vasculitis of RMSF may be mistaken for meningococcemia or an idiopathic vasculitis such as Kawasaki disease in children.

Key Physical Exam Findings and Diagnostic Features

The key physical exam finding of RMSF is the maculopapular, and then often vasculitic, rash starting on the distal extremities.

Laboratory tests are generally not revealing with the total leukocyte count usually normal or slightly elevated with increased numbers of immature neutrophils. Mild thrombocytopenia (<150,000/mm^3) occurs in about 60% of patients, and half of patients may have mild hyponatremia (<135 mEq/L) or transaminitis. Thrombocytopenia is thought due to increased destruction at the areas of pathogen-induced vascular injury. Other laboratory abnormalities include increases in serum urea nitrogen or creatinine and bilirubin. A prolonged prothrombin or partial thromboplastin time can also be seen. If analyzed, cerebrospinal fluid (CSF) may show a predominance of lymphocyte or monocyte pleocytosis (usually <100 cells/microL)

and increased protein concentration (100–200 mg/dL) [1, 11]. Azotemia can be present and is likely due to hypovolemia.

Serology testing using indirect fluorescent antibody (IFA) testing to RMSF *Rickettsia* can be performed. Typically IgG and IgM antibodies do not appear until 7–10 days after the onset of symptoms, and therefore IFA testing cannot be used in the decision to treat in the first few days of the illness.

Management

Treatment for RMSF should be started as soon as possible. In several studies, patients, ultimately diagnosed with RMSF, were shown to seek care early on in the illness when the diagnosis was not as obvious [5]. Mortality due to RMSF has been shown to be linked in delays to antimicrobial treatment [5]. Treatment therefore may need to be started when clinical suspicion of RMSF is high and not wait for definitive diagnosis. Serum antibodies to *Rickettsia* causing RMSF may not be positive for 7–10 days into the illness, and therefore serology testing may be negative when the patients present early in the course of the illness. If the decision is made to test for disease, then antimicrobial therapy should probably be started.

Doxycycline is the drug of choice for the treatment of RMSF for both adults and children. Five- to 7-day duration of therapy is usually curative [16, 17] (Table 16.3). Chloramphenicol had been the treatment of choice because of the perceived risk of permanent teeth staining by doxycycline but has now fallen out of favor and is not available orally in the United States. Chloramphenicol is less effective, does not provide treatment for ehrlichiosis which can be difficult to differentiate from RMSF, and has its own toxicity including aplastic anemia. Concerns over a short course use of doxycycline and its effects on teeth also appear unfounded. The CDC and the American Academy of Pediatrics (AAP) have recommended doxycycline as the treatment of choice for all children with suspected rickettsial disease [1, 5].

Other antibiotics such as beta-lactams, macrolides, aminoglycosides, and sulfonamides are not effective against RMSF. Severe doxycycline allergy such as anaphylaxis or Stevens-Johnson may require the use of an alternative antibiotic, inpatient desensitization, and/or consultation with an infectious disease expert.

The use of doxycycline during pregnancy remains inconclusive as controlled studies regarding teeth staining or teratogenicity have not been reported [1].

More severe presentation or inability to take oral antibiotics should prompt inpatient treatment. Fever should typically subside within 24–48 h after treatment if antibiotics are started in the first 4–5 days of illness.

Complications

Complications include end-stage manifestations such as meningoencephalitis, cerebral edema, acute renal failure, cutaneous necrosis, non-cardiogenic pulmonary edema (acute respiratory distress syndrome, ARDS), arrhythmia, shock, and seizures.

Table 16.3 Antibiotic treatment of tick-borne illnesses

Tick-borne illness	Adults	Children
RMSF, *R. rickettsii*	Doxycycline 100 mg PO or IV BID for 5–7 days	Doxycycline 2 mg/kg PO or IV BID for 5–7 days (for children <45 kg)
Lyme disease	Doxycycline 100 mg PO BID for 10–21 days Amoxicillin 500 mg PO TID for 14–21 days Cefuroxime axetil 500 mg PO BID for 14–21 days	Doxycycline 2 mg/kg PO BID (max dose 100 mg) for 10–21 days Amoxicillin 50 mg/kg PO divided TID (max dose 500 mg) for 14–21 days Cefuroxime 30 mg/kg PO per day divided BID (max dose 500 mg) for 14–21 days
Ehrlichiosis	Doxycycline 100 mg PO BID for 10 days Rifampin 300 mg PO BID for 10 days	Doxycycline 2 mg/kg PO BID (max dose 100 mg) for 10 days Rifampin 10 mg/kg PO BID (max dose 300 mg) for 10 days
Babesiosis, *B. microti*	(1) Atovaquone 750 mg orally every 12 h plus azithromycin 500 mg/d orally on day 1 and then 250 mg/d from day 2 onward for 7–10 days (2) Quinine 650 mg orally every 6–8 h plus clindamycin 600 mg orally every 8 h for 7–10 days#* For severe disease, consider clindamycin 300–600 mg IV every 6–8 h or 600 mg PO every 6–8 h plus quinine 650 mg PO every 6–8 h # Regiment (2) better tolerated *Treatment of choice during pregnancy	(1) Atovaquone 20 mg/kg orally every 12 h (max 750 mg/dose) plus azithromycin 10 mg/kg orally on day 1 (max 500 mg) and then 5 mg/kg (max 250 mg/d) orally from day 2 onward for 7–10 days@ (2) Quinine 8 mg/kg orally every 8 h (max 650 mg/d) plus clindamycin 7–10 mg/kg orally every 6–8 h (max 600 mg/dose) for 7–10 days# For severe disease, consider clindamycin 7–10 mg/kg IV every 6–8 h (max 600 mg/dose) or 7–10 mg/kg PO every 6–8 h (max 600 mg/dose) @ Used safely in kids >5 kg # Regiment (2) better tolerated
Tick paralysis	Removal of the tick Given that tick paralysis is not an infectious process, no specific antibiotic treatment is warranted unless evidence of an infectious process exists	Removal of the tick Given that tick paralysis is not an infectious process, no specific antibiotic treatment is warranted unless evidence of an infectious process exists

A small portion of patients with severe RMSF may suffer long-term sequelae such as peripheral neuropathy, hemiparesis, or deafness [16].

Mortality due to RMSF has significantly decreased as a result of antimicrobial therapy. Prior to antibiotics, mortality generally ranged from 20% to 30% [10]. Recent data from the CDC shows a case fatality rate of less than 1% since 2001 [1]. Mortality is highest in the very young (<4 years old), 3–4%, and the elderly (>60 years old), 4–9% [1, 10]. Other risk factors for complications include male gender, black race, chronic alcohol abuse, and G6PD (glucose-6-phosphate dehydrogenase) deficiency. Treatment for RMSF should ideally begin within 5 days of the start of symptoms; delay in treatment has also been shown to contribute to mortality [10, 13].

Lyme Disease

Lyme disease, caused primarily by the bacterial spirochete *Borrelia burgdorferi*, is endemic to the Northeastern and Upper Midwestern states with some presence in the Pacific Northwest. Illnesses in travelers to endemic areas and false-positive testing can account for reports of Lyme disease in non-endemic areas. The tick vector is *Ixodes ricinus.*

Classic Clinical Presentation

Clinical manifestations of Lyme disease present classically in three stages: early localized, early disseminated, and late disease; some patients may initially present with a later stage symptomatology.

The *early localized stage* presents with an erythematous expanding patch often with central clearing located at the site of the tick bite. The rash, known as erythema migrans (EM), is usually nonpruritic and nontender and may have purpuric, vesicular, or pustular components (Figs. 16.4 and 16.5). In adults, EM lesions are often found in or near the axilla, inguinal region, popliteal fossa, or belt line. In children, the EM lesions are more often found in the head and neck, arms and legs, and back areas [18]. Eighty percent of adult and pediatric patients manifest the rash [19, 20].

If the early localized stage is not treated, the spirochete will then enter the blood stream resulting in the *early disseminated stage*, manifesting as disseminated erythema migrans lesions. Neurological sequelae include lymphocytic meningitis, cranial nerve palsies (especially facial nerve), radiculopathy (Bannwarth syndrome), peripheral neuropathy, or rarely cerebellar ataxia or encephalomyelitis. Lyme disease is one of the few causes of bilateral facial nerve palsies. Lyme meningitis will present similarly to other viral meningitis in addition to erythema migrans, possible

Fig. 16.4 Lyme disease, erythema migrans (Image appears with permission from VisualDx)

Fig. 16.5 Lyme disease, erythema migrans. Image appears with permission from Centers for Disease Control and Prevention (CDC)

cranial nerve palsy or palsies, papilledema, prolonged duration of symptoms, and minimal polymorphonuclear cells in the CSF. Facial nerve palsy without signs of central nervous system infection (e.g., severe headache, vomiting, nuchal rigidity, or papilledema) does not necessarily require a lumbar puncture.

Cardiac sequelae can include atrioventricular heart block or sometimes myoperi-carditis. Early disseminated stage can occur weeks to months after the tick bite. Ocular findings include conjunctivitis, keratitis, and uveitis.

Late disease stage results in intermittent or persistent arthritis involving usually one or more large joints especially the knees (Fig. 16.6). Rarely, neurological symptoms such as mild encephalopathy ("Lyme encephalopathy") or polyneuropathy may persist. Late disease presents months to a few years after the tick bite and may be the presenting sign of Lyme disease.

Patients with Lyme disease almost always also present with classic signs and symptoms such as erythema migrans, facial nerve palsy, or arthritis of larger joints. If these classic signs or symptoms are not present in the setting of nonspecific consti-tutional signs and symptoms, then Lyme disease is not the likely diagnosis [1, 5, 11].

Fig. 16.6 Lyme disease arthritis (Image appears with permission from Emily Rose MD)

Atypical Presentation

Not all Lyme disease cases manifest all three stages. In some cases, disseminated erythema migrans, arthritis, or neurological symptoms may be the first presentation.

Associated Systemic Symptoms

Constitutional symptoms such as fatigue, headache, myalgias, and arthralgias are seen in close to half of affected patients. Fever may not be as common [21]. Respiratory or gastrointestinal symptoms are not common with Lyme disease.

Time Course of Disease (Incubation Period After Exposure to Infectious Agent or Drug Exposure)

Early localized signs of erythema migrans appears usually within 7–14 days after the tick bite but as long as 30 days. Early disseminated may take weeks to months with late Lyme disease presenting, sometimes, years later.

Common Mimics and Differential Diagnosis

Hypersensitivity to a tick bite can mimic Lyme disease. Hypersensitivity will result in a small lesion, <5 cm, which will defervesce by 24–48 h. Erythema migrans lesion will continue to grow in size.

STARI (southern tick-associated rash illness) has an erythema migrans-like rash, similar to the rash of Lyme disease. Found in the Southeastern and South Central areas of the United States, STARI does not appear to progress to disseminated illness as Lyme disease does if left untreated.

Nummular eczema results in multiple circular lesions, 2–10 cm in diameter, located on the trunk and extremities that are intensely pruritic.

Tinea corporis (ringworm), a dermatophytic infection, manifests as an enlarging pruritic circular or oval erythematous patch or plaque with central clearing and erythematous border.

Erythema multiforme manifests as distinctive target lesions.

Key Physical Exam Findings and Diagnostic Features

The key physical exam finding is the classic rash of erythema migrans.

Laboratory findings include erythrocyte sedimentation rate more than twice normal. Other laboratory abnormalities such as elevated serum creatine phosphokinase, leukocytosis, leukopenia, or anemia are seen much less frequently. Serological testing is not sensitive enough during early localized disease and so is not helpful in making the diagnosis. Blood cultures for *B. burgdorferi* are not commercially available.

Management

Treatment for early Lyme disease (erythema migrans) is the same whether the patient has the initial erythema migrans lesion or multiple from more disseminated disease without evidence of neurological or cardiac involvement. The goal is to reduce the risk of development of late Lyme disease. Amoxicillin, doxycycline, or cefuroxime axetil are considered first-line therapy for patients with Lyme disease (Table 16.3). Doxycycline is often used because of its effectiveness against *Anaplasma phagocytophilum*, a potential coinfecting organism. Although doxycycline's effect on the teeth of young children appears unfounded [5], amoxicillin is a viable alternative.

In the United States, macrolides such as azithromycin or erythromycin are not recommended as first-line therapy for erythema migrans. Macrolides may be used in patients who are intolerant of the first-line therapy antibiotics, but patients should be closely monitored for inadequate response to treatment. First-generation cephalosporins such as cephalexin are not effective against Lyme disease. Early Lyme disease (erythema migrans) may be mistaken for cellulitis. In endemic areas, it's important for providers to consider treatment of "cellulitis" with an antibiotic that also treats erythema migrans, such as amoxicillin-clavulanate or cefuroxime.

Early disseminated Lyme disease presenting with acute neurological findings such as meningitis, facial nerve palsy, and/or motor or sensory neuropathies often requires intravenous antibiotic treatment. Studies are limited but it appears high-dose penicillin is effective, as is ceftriaxone or cefotaxime. Facial nerve palsy even meningitis has been treated successfully in Europe using oral doxycycline. Guidelines from the American Academy of Neurology (2007) and the Infectious Diseases Society of America (2006) both still recommend parenteral therapy. Consultation with an infectious disease specialist is recommended [21].

Up to 15% of patients with early Lyme disease, especially those with multiple skin lesions, may experience a worsening of symptoms during the first 24 h of treatment. What is thought to be a Jarisch-Herxheimer reaction is due to the immune response to antigens released by the treated organisms [21].

From 4% to 28% of Lyme disease patients will also be infected with other organisms transmitted by *Ixodes* ticks. In the United States, these include *A. phagocytophilum* (causes human granulocytic anaplasmosis) and *Babesia microti* (causes babesosis) [22, 23]. Because of this, doxycycline is considered the drug of choice in areas where coinfection is high.

Complications

Coinfection with another tick-borne illness may occur. In the Unites States, other organisms transmitted by the *Ixodes* tick include *Anaplasma phagocytophilum* and *Babesia microti*. Patients with Lyme disease who are persistently febrile after 48 h of antimicrobial treatment warrant a search for a coinfection. Anemia, leukopenia, and/or thrombocytopenia may occur with these other coinfections.

Unlike syphilis, another spirochete disease, current evidence shows that Lyme disease occurring during pregnancy poses no threat for a congenital abnormality or fetal demise [21].

Some patients treated for Lyme disease may experience persistent nonspecific symptoms such as fatigue or musculoskeletal pain. The Infectious Diseases Society of America (IDSA) defines this post-Lyme disease syndrome as requiring a prior history of Lyme disease treated with an accepted regimen and resolution or stabilization of initial symptoms. Later, subjective symptoms such as fatigue, musculoskeletal pain, or cognitive difficulties occur within 6 months of the Lyme disease diagnosis and persist for at least 6 months [24]. Other diagnoses such autoimmune, malignancy, or psychiatric illnesses must be excluded. There is no evidence that these patients have persistent *Borrelia burgdorferi* infections [5, 24]. Prolonged courses of antibiotics to treat these persistent symptoms have not been shown to be helpful. The Infectious Diseases Society of America (IDSA) specifically recommends against treating persistent Lyme disease symptoms with prolonged courses of antibiotics [5, 24].

Ehrlichiosis

The most important ehrlichial disease is human monocytic ehrlichiosis (HME) caused by *Ehrlichia chaffeensis*. Two other *Ehrlichia* species also cause human disease but less frequently – *E. ewingii* and EML agent ehrlichiosis. Human granulocytic anaplasmosis (HGA), previously known as human granulocytic ehrlichiosis, is caused by *Anaplasma phagocytophilum*. In some references, HGA and HME are

both considered ehrlichial diseases; in other references the diseases are separated as anaplasmosis and ehrlichiosis. Although these are considered separate diseases, their clinical and laboratory presentations are similar. This section will focus mainly on HME caused by *E. chaffeensis*.

Incidence of ehrlichiosis has been on the rise over time in the United States [1, 25]. In 2012, the annual incidence of ehrlichiosis was 3.2 cases per million persons with wide variation by state [1]. In some states, ehrlichiosis may be more common than RMSF.

E. chaffeensis (causing HME) is most commonly transmitted by the lone star tick (*Amblyomma americanum*). *A. phagocytophilum* (causing HGA) is most commonly transmitted by the *Ixodes* tick species, *I. scapularis* (black-legged tick) in the Eastern United States and *I. pacificus* (Western black-legged tick) in the Western United States [1].

Ehrlichiosis cases have been reported in the Southeastern United States and extending into the Midwest and New England states. Highest reported rates include Arkansas, Delaware, Missouri, Oklahoma, Tennessee, and Virginia.

White-tailed deer appears to be an important host for a number of *Ehrlichia* species. It has been reported that ehrlichiosis can be transmitted via maternal-child transmission, blood transfusion, or direct contact with a slaughtered deer [26].

Ehrlichia are obligate intracellular bacteria that grow in animal and human leukocytes. The organisms multiply in cytoplasmic membrane-bound vacuoles and form clusters of bacteria called morulae. In fatal cases, the greatest burden of bacteria has been found in the spleen, lymph nodes, and bone marrow [1]. The patient's systemic inflammatory response is likely responsible for most of the clinical findings of ehrlichiosis [1].

Classic Clinical Presentation

The clinical presentation of ehrlichiosis is similar to RMSF and can run the spectrum from subclinical to acute to chronic infection.

Compared with RMSF, the rash associated with HME is present less often occurring in only one-third of adults and two-thirds of children. The rash varies ranging from maculopapular or petechial to diffuse erythema (Fig. 16.7). The rash appears a few days later than in RMSF and is less often petechial. The ehrlichial rash is typically on the extremities and trunk less commonly involving the palms and soles. The rash occurs more often in children than in adults [1].

Atypical Presentation

Subclinical infections of ehrlichiosis may go unrecognized.

Fig. 16.7 Ehrlichiosis
(Image appears with
permission from VisualDx)

Associated Systemic Symptoms

Most patients with ehrlichiosis are febrile but many may be low grade. Nonspecific symptoms such as headache, myalgias, and malaise may occur in up to two-thirds of patients; cough, vomiting, and arthralgias can occur in up to 50% of patients [26]. Children have a similar presentation to adults. Neurological symptoms such as altered mental status, stiff neck, and clonus can happen but are not common. When CSF is evaluated, lymphocytic pleocytosis and elevated protein levels may be found [27].

Time Course of Disease (Incubation Period After Exposure to Infectious Agent or Drug Exposure)

The incubation period for ehrlichial diseases appears to be 1–2 weeks but shorter time frames have been seen.

Common Mimics and Differential Diagnosis

Ehrlichiosis has often been called "spotless" RMSF but *R. rickettsii* may also result in a spotless infection. The combination of leukopenia and no rash in the setting of tick-borne illness makes ehrlichiosis more likely. The differential diagnoses also include viral infections such as mononucleosis or *West Nile virus*, thrombotic thrombocytopenic purpura, malignancies, or liver disorders such as viral hepatitis or cholangitis.

Key Physical Exam Findings and Diagnostic Features

Laboratory results include leukopenia (<4000/mm^3) occurring in 60% of patients and up to 90% of patients showing thrombocytopenia, elevated transaminases,

Fig. 16.8 Peripheral blood smear of *E. chaffeensis* (ehrlichiosis) morulae (Image appears with permission from Centers for Disease Control and Prevention (CDC))
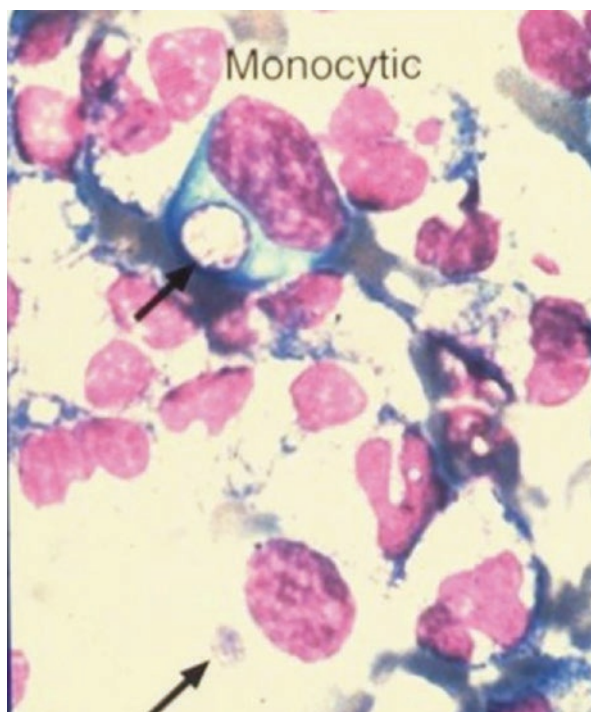
lactate dehydrogenase, and alkaline phosphatase. Anemia and elevated creatinine may also be seen [1, 11, 28]. CSF evaluation may show a lymphocytic pleocytosis with CSF white blood cells typically <250 cells/microL (higher in children) and elevated protein.

In some patients, morulae may be observed in monocytes in peripheral blood or in CSF (Fig. 16.8). Visualization of morulae still requires confirmatory testing. Culture of the *Ehrlichia* bacteria is very difficult. The preferred method is the indirect fluorescent antibody (IFA) test. Antibodies, however, are not detectable for the first 2–3 weeks of the illness.

Management

When ehrlichiosis is the most reasonable diagnosis (history of tick bite or tick exposure during spring or summer months in an endemic area with a fever, leukopenia, and/or thrombocytopenia), then doxycycline is the treatment of choice. As stated in the section on RMSF, doxycycline has not been shown to have the risk of staining permanent teeth like tetracycline and therefore is safe to use in both adults and children (Table 16.3). Currently, no guidelines exist for the treatment of ehrlichiosis in pregnant women, but doxycycline has been used to treat severe ehrlichiosis in pregnant women [10].

Complications

Mortality rate for ehrlichiosis is estimated to 3% with highest rates among children less than 10 years old and older individuals greater than 70 years old [1]. Patients who are immunocompromised or have chronic illnesses are also at higher risk for death [1]. Complications include seizures, coma, and respiratory renal or hepatic failure. A septic or toxic shock-like illness as a sequelae of ehrlichiosis has also been reported [26]. Due to a limited number of cases, it is unclear of the real effects of ehrlichiosis on pregnant women or the fetus. There is no evidence currently that untreated ehrlichiosis results in persistent symptoms.

Babesiosis

Background

Babesiosis is caused by protozoa of the genus *Babesia* and is endemic to geographic areas similar to Lyme disease typically in the Northeast and Midwest parts of the United States.

Most cases of babesiosis in the Northern Hemisphere occur from May to September with predominance in July and August [29]. In 2014, over 1700 cases of babesiosis were reported to the CDC [30].

Babesia are obligate parasites of red blood cells (RBCs) causing a febrile hemolysis and renal failure. Babesiosis (or Babesia infection) was first described in cattle in the days of the Pharaohs but was only found to cause human disease in the 1950s. *B. microti* is the most common species in the Unites States with organisms. Organisms similar to *B. microti* have been found in Europe, Asia, and Australia. *B. divergens* is predominantly found in Europe with organisms similar to *B. divergens* found in the Midwest and West Coast of the Unites States. *B. duncani* has also been found on the West Coast [29].

The tick vector of babesiosis is the *Ixodes scapularis* tick species (also known as the deer tick or black-legged tick) which also transmits Lyme disease.

Classic Clinical Presentation

Babesiosis classic clinical presentation ranges from asymptomatic to severe illness and can be fatal. Twenty-five percent of seropositive adults and 50% of seropositive children are asymptomatic in certain endemic areas [11].

Classic symptoms can range from mild to severe symptoms. Mild symptoms include gradual onset of fever, fatigue, and weakness due to the parasite-mediated hemolysis of RBCs. Severe illness may show signs of severe hemolysis such as jaundice or hemoglobinuria.

Nearly all *B. divergens* found in Europe and *B. divergens*-like organism illnesses found in the Midwest and Washington state appear to cause symptomatic disease, usually severe, in asplenic patients [29].

Patients with babesiosis infections are often coinfected with other tick-borne illnesses. Reports show two-thirds of babesiosis patients also suffer from concurrent Lyme disease and one-third concurrent human granulocytic anaplasmosis [31]. Studies vary but it appears babesiosis patients with coinfections will remain symptomatic for longer duration than patients without a coinfection of another tick-borne illness [29].

Atypical Presentation

Asymptomatic infections can occur and generally self-resolve in immunocompetent patients without treatment.

Associated Systemic Symptoms

Fever and nonspecific symptoms are typically present. Fever can wax and wane ranging from low 38 °C to over 40 °C. Fatigue, weakness, chills, and myalgias are common. Other less common symptoms include sore throat, dry cough, vomiting, and diarrhea.

Time Course of Disease (Incubation Period After Exposure to Infectious Agent or Drug Exposure)

Symptoms typically develop 1–6 weeks after the patient has been bitten by the tick. Symptoms may first appear or recur many months after exposure in patients who are or become immunocompromised. Subclinical cases that became more apparent have been reported when the patient underwent a splenectomy for an unrelated illness or developed a malignancy [9, 29].

Common Mimics and Differential Diagnosis

Differential diagnosis of babesiosis includes malaria which also presents with fever, anemia, and associated symptoms such as headache, fatigue, and myalgias. Malaria should be considered in a patient who has traveled to or lived in an endemic area. Diagnosis is made by visualizing parasites on peripheral smear or the use of a rapid diagnostic test for malaria. Other tick-borne illnesses transmitted by the *B. microti* tick vector can have similar presentations to babesiosis. These include human

granulocytic anaplasmosis (*A. phagocytophilum*) and *B. miyamotoi* (*B. miyamotoi*) diseases. Diagnosis again would be made via microscopy, polymerase chain reaction, or serology. Rickettsial infections such as Rocky Mountain spotted fever can present with similar nonspecific symptoms, but also a petechial or purpuric rash may develop. Viral hepatitis infections will typically show a significantly elevated transaminitis and positive viral serologies.

Key Physical Exam Findings and Diagnostic Features

Hepatosplenomegaly may be present. Lymphadenopathy is not present. Lab results classically show anemia and thrombocytopenia. Hemolysis results in increased reticulocyte count, increased bilirubin, decreased haptoglobin, and increased lactate dehydrogenase. White blood cell counts (WBCs) can range from decreased to increased. Liver function tests are typically increased [9, 11, 28, 29].

Definitive diagnosis of babesiosis is made by manual microscopy of thin blood smears using Wright or Giemsa staining. Early on in the disease, microscopy results may be negative as red blood cells with parasites are few. Repeat microscopy is recommended if concern for babesiosis is still high. Expertise by lab technicians is typically required. Automated cell readers can often miss the parasitemia and are generally not recommended to be used [29].

Polymerase chain reaction (PCR) assay can be used to detect low levels of parasitemia in cases such as early disease or convalescent phase. Serology testing using indirect immunofluorescent antibody test may be positive when microscopy and PCR are both negative. This may occur in cases of asymptomatic carriers or patients who cleared the infection with or without antibiotics [29].

In one review, severe babesiosis was associated with a parasitemia >4%, alkaline phosphatase >125 units/L, and WBC >5 × 10(9)/L. Risk factors for severe illness include asplenism (or decreased function of the spleen), HIV/AIDS with low CD4 cell count, and immunosuppression due to other causes such as cancer treatment.

Parasite serum levels (or parasitemia) range from 1% to 20% with mild cases having levels less than 4% [29].

Management

Asymptomatic patients generally do not require any treatment. Mild symptomatic cases of babesiosis usually self-resolve or respond to a short course 7–10 days of antibiotics. Treatment should be reserved for symptomatic patients with babesial parasites on blood smear or babesial DNA detected by PCR. Treatment is also recommended for asymptomatic patients with babesial parasites on blood smear or babesial DNA detected by PCR for greater than 3 months [29].

Antimicrobial recommendations for *B. microti* infections include two options: (1) atovaquone plus azithromycin or (2) quinine plus clindamycin (Table 16.3). The second regiment is generally better tolerated. Intravenous quinine and clindamycin

are recommended for those patients who cannot tolerate oral medications. Higher oral dosages and/or prolonged treatment course up to 6 weeks may be needed in immunocompromised patients [29, 32]. The Centers for Disease Control recommends quinine plus clindamycin for the treatment of babesiosis in pregnant patients. Atovaquone has been used safely in kids >5 kg [33].

Treatment for other babesiosis infections such as *B. divergens* or *B. duncani* also includes the use of quinine/quinidine plus clindamycin [29].

Adverse effects of the atovaquone plus azithromycin treatment include diarrhea and rash. Quinine plus clindamycin can result in diarrhea and symptoms of cinchonism (tinnitus, decreased hearing, and vertigo). QT prolongation can be seen with quinine and quinidine and less often, azithromycin [29].

Patients with evidence of severe babesiosis require hospitalization. The 2006 Infectious Diseases Society of America (IDSA) guidelines recommend oral quinine plus intravenous clindamycin for cases of severe disease [32]. Due to quinine toxicity, some have recommended a three-drug regimen (atovaquone plus azithromycin plus clindamycin), but this regimen has not been clinically studied [29]. Intravenous quinidine, if required, can result in ventricular arrhythmias, hypotension, hypoglycemia, and QT prolongation or torsades de pointe on cardiac monitoring.

Red blood cell (RBC) exchange transfusion can be useful for clearing the body of infected RBCs, removing inflammatory mediators and toxic results of RBC lysis. RBC exchange transfusion should be considered for patients with evidence of severe disease such as severe anemia (hemoglobin <10 g/dL) with high counts of parasitemia ($\geq$10%). Exchange transfusion is also recommended for those patients with high parasitemia and risk for severe complications such pulmonary, renal, or hepatic. It can be also considered in those with severe disease even if parasitemia is not high (<10%). RBC transfusion can be considered in moderately ill patient cases with milder parasitemia but hemoglobin $\leq$10 mg/dL [29].

Infections caused by *B. divergens* are usually severe and therefore RBC exchange transfusion is recommended. For all severe cases, consultation with experts in hematology is recommended.

Complications

Although babesiosis resolves without sequelae in most patients, infections can be life threatening especially in asplenic or other immunocompromised states [9, 11, 28]. Serious complications include splenic infarct, acute respiratory distress syndrome, disseminated intravascular coagulation, congestive heart failure, and liver or renal failure. In one study, 5% of patients infected with *B. microti* died [9]. Severe disease is more likely in older patients or those with splenectomies, malignancies, or other immunocompromised conditions. Nausea and vomiting with hyperbilirubinemia appear to be predictive of severe disease [9, 34]. Babesiosis has been known to be recurrent or relapsing [29].

Tick Paralysis

Tick paralysis occurs worldwide with a predominance of cases in the Pacific Northwest of the United States and Southwest Canada [7]. Australia has also reported cases of tick paralysis. As stated earlier, tick paralysis is caused by a neurotoxin that is produced in the tick's salivary gland. While fully engorged and still attached to the host, the tick transmits the toxin to the host (Fig. 16.9). The true incidence of tick paralysis in the United States remains unclear as reporting is not mandatory, and many cases are likely attributed to other causes of flaccid paralysis such as Guillain-Barré syndrome.

Although tick bites are very common, tick paralysis is extremely rare. Even when reporting was mandatory, the Department of Health in the state of Washington only reported 33 cases from 1946 to 1996 [6]. Most cases of tick paralysis are in children with a predominance of cases in females. This may be due to long hair in young girls that allows the ticks' camouflage [7].

Classic Clinical Presentation

Tick paralysis in North America presents as an acute symmetric ascending paralysis, beginning in the lower extremities, evolving over hours to days. Deep tendon reflexes are usually diminished or absent. Pain is typically rare. If the tick is not removed, the paralysis will continue on to the upper extremities and then cranial nerves. Respiratory muscles will eventually weaken and the patient will be at risk for respiratory failure and death. Patients will remain alert and only become altered as respiratory failure with hypoxia and hypercarbia ensues [7].

Laboratory studies are typically normal in tick paralysis with CSF showing classically normal WBCs and protein. MRI imaging of the brain will be normal.

Fig. 16.9 Tick engorged with blood (Image appears with permission from Centers for Disease Control and Prevention (CDC))

Atypical Presentation

Scattered cases of focal weakness have been reported with almost all of them occurring in Australia. A tick or group of ticks is usually found near the site of weakness such as unilateral facial or upper extremity weakness. Pupillary dilation has been seen in the Australian version of tick paralysis. Flaccid paralysis with pupillary dilation in North America should suggest botulism or possibly diphtheria [7].

Associated Systemic Symptoms

Prodromic symptoms can occur that include paresthesias, myalgias, irritability, and fatigue. Patients are typically afebrile. These symptoms are followed often within hours by the flaccid paralysis.

Time Course of Disease (Incubation Period After Exposure to Infectious Agent or Drug Exposure)

Ticks associated with tick paralysis only begin to secret toxin once they have become engorged with blood. Symptoms and signs of tick paralysis may not present for several days after a patient is first bitten as it takes time for the tick to become finally engorged and start to secrete the toxin. Once the tick has been removed from the patient's body, North American cases (*Dermacentor* spp.) will typically see remission of symptoms. Australian cases (*Ixodes* sp.*)* will typically still see progression of symptoms for an additional 24–48 h.

Common Mimics and Differential Diagnosis

Guillain-Barré syndrome (GBS) is typically the most common cause of a flaccid paralysis. Just as with tick paralysis, GBS will present rarely with fever or pain. Unlike tick paralysis, sensory findings are frequently seen as a prodrome in GBS. The ascending paralysis associated with GBS is usually slower onset than with tick paralysis. Both tick paralysis and GBS can involve the cranial nerves with GBS most often involving cranial nerve VII but also III, IV, and VI. Pupils are rarely dilated in GBS. And CSF will show elevated protein in GBS. MRI imaging is usually normal. Miller-Fischer variant of GBS typically presents with ophthalmoplegia, ataxia, and areflexia without muscular weakness.

Transverse myelitis may also present with flaccid paralysis and may present with fever depending upon the cause. Pain and sensory complaints are common. Dilated pupils are absent. CSF evaluation in transverse myelitis will show an elevated WBC and often protein. MRI imaging is typically abnormal showing variable areas of enhancement indicating inflammation.

Spinal cord compression can also present with flaccid paralysis. Fever is usually absent except in some cases of epidural abscesses. Pain and sensory complaints are also common. Pupil dilation is absent. CSF results will be variable depending upon the cause. MRI imaging will be abnormal. Spinal cord ischemia or infarction should also be considered with many similar findings.

Botulism can also be mistaken for tick paralysis. Botulism also presents without fever, pain, or sensory complaints. Dilated pupils are present. CSF evaluation will be normal. And MRI imaging will also be normal.

Poliomyelitis was once a common cause of acute paralysis but is now only seen in Afghanistan, Pakistan, and Nigeria. A viral encephalomyelitis can also present with a flaccid paralysis but, unlike tick paralysis, will present with fever and often altered mental status or pain. Sensory complaints are not common and dilated pupils are absent. CSF evaluation in a patient with encephalomyelitis will be abnormal with elevated WBC and protein. MRI imaging will also be abnormal. Other enteroviruses, *West Nile* and *Powassan virus*, have all both been identified as causes of encephalomyelitis [7, 35, 36].

Key Physical Exam Findings and Diagnostic Features

Key physical exam findings include a painless symmetric ascending flaccid paralysis without fever or sensory findings. CSF evaluation is normal. Finding an engorged tick on the patient's body with improvement of the symptoms (24–48 h later in Australian cases) after removal is diagnostic. If evaluated, electrophysiologic tests in patients with tick paralysis show a diffuse reduction in the compound muscle action potentials. GBS will show similar results. North American tick paralysis cases may show reduced sensory and motor nerve conduction studies, but Australian cases will typically be normal [7].

Management

Any patient diagnosed with an ascending flaccid paralysis is at risk for respiratory complications and therefore requires cardiac and pulmonary monitoring. A thorough search for and then removal of the tick is imperative and is the definitive treatment. Symptoms can progress even after tick removal. North American cases generally improve faster than Australian cases. Once the tick (or ticks) are found and removed, symptoms generally begin to improve rapidly and are usually completely resolved by 24 h. Australian cases can continue to progress for some time. Until symptoms have resolved, supportive care is typically all that is required.

Complications

If an ascending paralysis is unrecognized, the patient is at risk for respiratory failure, hypoxia, and death. Even though tick paralysis is potentially fatal, today in the era of critical care, death is rare [6].

> **Bottom Line: Clinical Pearls**
> 1. For many tick-borne illnesses, decision to treat should be based on clinical symptoms rather than waiting for confirmatory testing.
> 2. Early empiric antimicrobial treatment can prevent severe disease and death.
> 3. Doxycycline is the treatment of choice for rickettsial infections in both adults and children.
> 4. Coinfections by two or more tick-borne illnesses are not uncommon.
> 5. Providers should be aware of the reportable diseases in their area.

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