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Tick-Borne Illnesses: Identification and Management in the Emergency Department

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Abstract

Tick-borne illnesses are increasing in prevalence and geographic reach. Because the presentation of these illnesses is sometimes nonspecific, they can often be misdiagnosed, especially in the early stages of illness. A detailed history with questions involving recent activities and travel and a thorough physical examination will help narrow the diagnosis. While some illnesses can be diagnosed on clinical findings alone, others require confirmatory testing, which may take days to weeks to result. This issue reviews the emergency department presentation of 9 common tick-borne illnesses and evidence-based recommendations for identification, testing, and treatment.

Authors

Jennifer Bellis, MD, MPH
Instructor, Department of Pediatrics, Section of Emergency Medicine, University of Colorado, Aurora, CO

Ee Tay, MD
Clinical Assistant Professor, Ronald O. Perelman Department of Emergency Medicine, Clinical Site Chief, Pediatric Emergency Medicine, Bellevue Hospital Center, New York, NY

Peer Reviewers

Michael Gottlieb, MD, RDMS
Director of Emergency Ultrasound, Department of Emergency Medicine, Rush University Medical Center, Chicago, IL

Lise Nigrovic, MD, MPH
Associate Professor of Pediatrics and Emergency Medicine, Harvard Medical School, Boston Children's Hospital, Boston, MA

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Case Presentations

A 10-year-old girl presents to the ED with left knee swelling and pain. She has been able to walk, but the swelling and pain have become worse over the last 3 to 4 days. The girl says she has not had a fever or chills, and there is no known trauma. The girl's mother states that her daughter spent 3 weeks at summer camp in Connecticut a few months ago, but otherwise has not traveled recently. On examination, the girl's knee is swollen, but without erythema or warmth. The girl is able to bear weight, but she is unable to fully flex her knee. X-rays of her knee are significant only for a joint effusion. Should you perform an arthrocentesis of the girl's knee? What lab work would help in making the diagnosis? What are the best treatment options for this patient?

A 5-year-old girl with no past medical history presents to your ED. Her mother noticed that the girl was having difficulty walking today, so she brought her in. She states that her daughter has been complaining that she's tired, and has been saying that her legs feel "weird" after playing in the park yesterday. The mother also mentions that they have a new dog that likes to run in the woods behind their house. On examination, the girl is afebrile with a normal heart rate and respiratory rate. The examination is significant for 3/5 strength in her legs bilaterally, with normal sensation. The girl has had no fever, cough, or congestion. As you consider the possible diagnoses, you begin to wonder whether a lumbar puncture or head imaging is necessary...

An otherwise-healthy 8-year-old boy is brought in by paramedics for altered mental status. He is lethargic, responds only to painful stimuli, and has incomprehensible speech. The child has had fevers, headache, and vomiting for the last 5 days. The boy's vital signs are as follows: heart rate, 150 beats/min; temperature, 39°C (102.2°F); respiratory rate, 30 breaths/min; oxygen saturation, 98%; and blood pressure, 75/40 mm Hg. On examination, you note a diffuse petechial rash on his trunk, arms, legs, palms, and soles. The boy's mother tells you the rash has been spreading from his extremities to his abdomen over the last few days. What initial laboratory studies would help you make a diagnosis? What additional complications could arise? Is doxycycline safe for this patient?

Introduction

Tick-borne illnesses often present a diagnostic challenge for the emergency clinician. Tick bites are usually not painful, and patients are often unaware of the bite[1] because the initial local reaction to a tick bite may be similar to the bite of another insect, such as a mosquito or a chigger. Tick-borne illnesses can be easily overlooked on a patient's initial presentation to the emergency department (ED), because the risk and exposure may seem minimal, such as simply playing in the backyard or having a pet that may bring ticks into the house. Nonetheless, many tick-borne illnesses can lead to serious or life-threatening sequelae if left untreated. This issue of *Pediatric Emergency Medicine Practice* discusses the presentation of 9 tick-borne illnesses, reviews the differential diagnosis for each illness, and provides recommendations for the diagnosis and management of these illnesses in the ED.

Critical Appraisal of the Literature

A literature search was performed on PubMed using the search terms: *pediatric tick*, *tick-borne illness*, *tick-borne disease*, *pediatric Lyme*, *pediatric Rocky Mountain spotted fever*, *pediatric tick paralysis*, *pediatric babesiosis*, *pediatric ehrlichiosis*, *Rocky Mountain spotted fever*, *tick paralysis*, *babesiosis*, *ehrlichiosis*, *anaplasmosis*, *tularemia*, *meat allergy tick bite*, and *red meat tick bite*. A total of 177 articles published between 1998 and 2018 were reviewed. The Cochrane Database of Systematic Reviews was searched using the key terms: *tick-borne*, *Lyme*, *Rocky Mountain spotted fever*, *tick paralysis*, *babesiosis*, *ehrlichiosis*, *anaplasmosis*, *tularemia*, and *tick-borne relapsing fever*. This search identified 1 review on the treatment of neurologic manifestations of Lyme disease.

According to standard evidence-level scales, the majority of evidence for tick-borne illnesses falls into the weaker and moderately strong categories. Tick-borne illnesses are relatively rare diseases, particularly in the pediatric population. Currently, there are few randomized controlled trials evaluating treatments for tick-borne illnesses. The majority of studies are based on retrospective and prospective observational studies. There are a number of review articles with recommendations based on observational studies, expert consensus, and case reports on rare complications of tick-borne illnesses. Many of the pediatric recommendations for the diagnosis and management of children with suspected tick-borne illness are based on adult literature.

Etiology and Pathophysiology

Most patients with tick-borne illnesses present in the late-spring and summer months, due to the activity of the tick vectors.[2,3] However, because of varying climate patterns and incubation periods, tick-borne illness cannot be excluded based solely on the time of year of the presentation. **Figure 1, page 3** shows the distribution of reported cases of tick-borne illnesses in the United States in 2015, based on reporting to the United States Centers for Disease Control and Prevention (CDC).

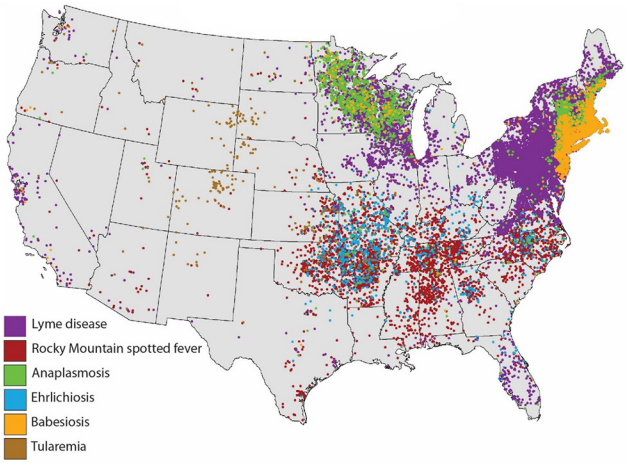
Lyme Disease

Lyme disease is caused by *Borrelia* spirochete species, with *Borrelia burgdorferi* being the major pathogen in North America.[4] The spirochete is transmitted by the bite of an *Ixodes* tick, a type of deer tick that is found most commonly in wooded areas or fields.[4,5] **(See Figure 2.)** Deer, mice, dogs, and birds are common hosts for *Ixodes* ticks.[5] The ticks that transmit *Borrelia* are found in various regions throughout the United States, including the Northeast, mid-Atlantic, Upper Midwest, Pacific Northwest, Northern California, and Oregon, as well as in Europe.[4] In 2016, the incidence of Lyme disease in the United States was 8.1 cases per 100,000 persons, with the highest rates among boys aged 5 to 9 years.[6]

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsia*, a gram-negative obligate intracellular bacterium.[2] It is transmitted by several different types of tick, including *Dermacentor*, *Amblyomma*, and *Rhipicephalus*.[2] The bacterium is transmitted after 6 to 10 hours of feeding, with a higher risk of transmission if the tick is crushed while being removed.[7] All states in the continental United States have reported cases of RMSF.[7-9] RMSF is grouped with other rickettsial diseases for the purposes of disease reporting. In 2014, the incidence of rickettsial diseases in the United States was 11 cases per 1 million persons.[9] There is a slight male predominance for contracting RMSF, and it is more common in elderly adults; however, children aged < 10 years have a higher case fatality rate.[9]

Figure 1. Distribution of Key Tick-Borne Diseases in the United States, Based on Reported Data From 2015



United States Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/media/dpk/diseases-and-conditions/lyme-disease/images/distribution-of-key-tickborne-diseases-lg.jpg.

Ehrlichiosis

Ehrlichiosis, also called human monocytic ehrlichiosis, is caused by a gram-negative obligate intracellular bacterium that infects leukocytes, in particular, macrophages and monocytes.[10] This pathogen is transmitted primarily by the *Amblyomma americanum* tick.[11] It is most commonly found in the Upper Midwest, Southeast, Northeast, and South Central United States.[12,13] In 2016, 1377 cases of ehrlichiosis were reported in the United States, with an incidence of 6.4 cases per 1 million persons in the highest-risk areas.[14] The elderly and patients who are immunocompromised are at the highest risk for ehrlichiosis.[14]

Anaplasmosis

Anaplasmosis, previously called human granulocytic ehrlichiosis, is caused by obligate intracellular bacteria that live primarily in granulocytes.[10] The bacterium alters the function of neutrophils and produces a systemic inflammatory response-like reaction.[15] The bacterium is transmitted by *Ixodes* ticks, which are primarily located in the Northeast, Pacific Northwest, and Upper Midwest regions of the United States.[16] In 2016, the reported incidence in the United States was 6.1 cases per 1 million persons.[17] Children aged 5 to 9 years are at the highest risk of fatal disease.[18]

Babesiosis

Babesiosis is a protozoal infection caused by *Babesia microti*, which infect circulating erythrocytes.[19] *B microti* is primarily transmitted by *Ixodes* ticks, but cases of babesiosis have also been transmitted in

Figure 2. *Ixodes scapularis* Tick

Photo credit: Jim Gathany. Content providers: Centers for Disease Control and Prevention/Michael L. Levin, PhD. Available at: https://phil.cdc.gov/Details.aspx?pid=1669.

blood transfusions and perinatally.[20-22] The distribution of the transmitting vector is similar to Lyme disease. In 2016, the incidence of babesiosis in the United States was 0.8 cases per 100,000 persons.[23] Symptomatic infections are more common in adults and immunocompromised patients.[3]

Tularemia

Tularemia is caused by *Francisella tularensis*, an aerobic gram-negative coccobacillus that can be transmitted by inhalation, tick vectors, and other insect and mammalian vectors.[24] The most common tick vectors are: *A americanum*, *Dermacentor andersoni*, and *Dermacentor variabilis*.[25] Tularemia is found all over North America, with the highest concentrations in the Southern and Central United States.[26] The incidence of tularemia in the United States in 2016 was 0.07 cases per 100,000 persons.[27] The largest number of cases in 2016 was reported in boys aged 5 to 9 years.[27]

Tick-Borne Relapsing Fever

Tick-borne relapsing fever is caused by a *Borrelia* spirochete and transmitted by *Ornithodoros* ticks.[28] It is found most commonly in the states west of the Mississippi River, in mountainous regions, particularly in log cabins infested by rodents.[3,24] It is a rare disease, with only 483 cases reported in the United States from 1990 to 2011.[29] The pathophysiology responsible for the recurrent fevers is not well delineated, but is thought to be related to the interplay of host cytokines and antigenic variation.[28] The *Borrelia* species responsible for tick-borne relapsing fever can undergo multiple genetic conversions to produce antigenic variation, which is potentially responsible for the relapsing nature of the disease.[28]

Colorado Tick Fever

Colorado tick fever is caused by *Orbivirus*, an RNA viral infection transmitted by the *D andersoni* tick.[3] It can also be transmitted by blood transfusion, but this is rare.[3] Colorado tick fever is most frequently seen in Southwest Canada and in the Rocky Mountains, at high elevations (4000-10,000 feet).[3] It is a rare disease, with 83 cases reported to the CDC from 2002 to 2012, though it is a reportable condition in only 6 states.[30] Some studies indicate that the actual case rate may be higher, at 200 to 400 cases per year.[31]

Tick Paralysis

Tick paralysis is an uncommon but potentially lethal disease that can be caused by several different ticks. Unlike other tick-borne illnesses, tick paralysis is not caused by a bacterium or parasite, but by a neurotoxin produced in the salivary glands of adult female ticks.[32] In the United States, it is usually caused by the bite of *Dermacentor*, *Amblyomma*, and *Ixodes* ticks, which are most commonly found in the Pacific Northwest and Rocky Mountain regions.[32] Young children are affected more than adults; the mechanism for this difference is unclear, but may be related to the smaller body size of children.[32] Females are more affected than males, which is thought to be related to their longer hair concealing the ticks.[32] Tick paralysis is a very rare disease, and is currently not a reportable illness, so reliable incidence data are not available.

Differential Diagnosis

Lyme Disease

Lyme disease is often divided into early localized, early disseminated, and late manifestations.

Early Localized Lyme Disease

Early localized Lyme disease classically presents with an erythema migrans (EM) lesion.[33] The rash often begins at the site of the tick bite and transforms from a small papule to a blanching erythematous patch with central or paracentral clearing over the course of several days to weeks.[33] **(See Figure 3.)** The EM rash is typically > 5 cm in diameter, with a median diameter of 10 to 16 cm.[33] The incubation period from tick bite to the onset of the rash can

Figure 3. Classic Erythema Migrans Rash

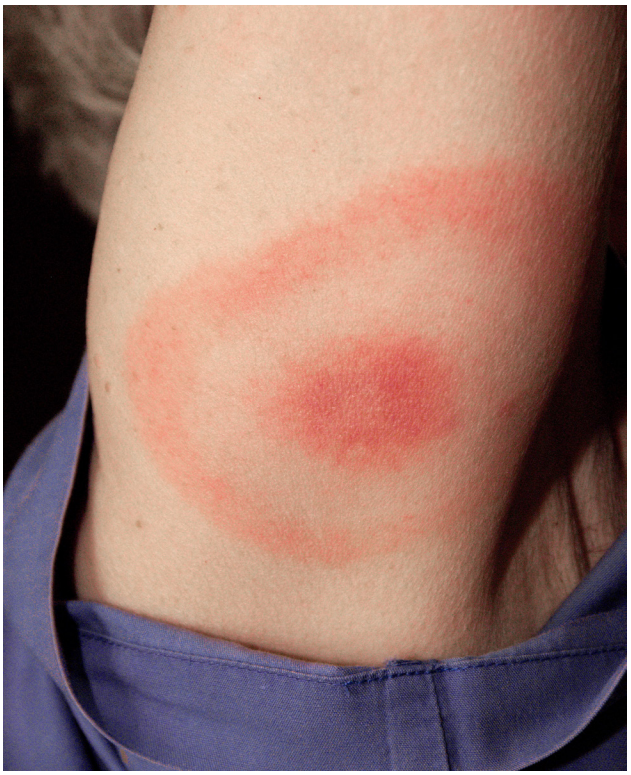


Photo credit: James Gathany. Content providers: Centers for Disease Control and Prevention/James Gathany.
Available at: https://phil.cdc.gov/Details.aspx?pid=9875.

range from 1 to 30 days, with most presenting 7 to 14 days after a tick bite.[34] Early localized Lyme disease is commonly associated with low-grade fever, myalgias, arthralgias, headache, and fatigue.[35]

Early Disseminated Lyme Disease

In early disseminated Lyme disease, patients can have multiple EM lesions.[35] Peripheral facial nerve palsy (cranial nerve VII), meningitis, and carditis are also symptoms of early disseminated disease.[35] Lyme disease is responsible for approximately 30% of cases of peripheral facial nerve palsy.[36] Lyme meningitis may present similarly to bacterial meningitis, with moderate neck stiffness and fever.[36-38] The Rule of 7s is a validated clinical prediction rule to distinguish viral meningitis from Lyme meningitis.[37] Children who do not have any of the following findings are at low risk for Lyme meningitis: > 70% cerebrospinal fluid (CSF) mononuclear cells; VII facial or other cranial nerve palsy; or 7 or more days of symptoms.[37] Some children with early disseminated Lyme disease may develop papilledema, most commonly associated with CSF infection.[37]

Cardiac involvement is uncommon in children with Lyme disease, occurring in about 4% to 8% of cases.[34] Lyme pericarditis, myocarditis, or atrioventricular block may present as fatigue, palpitations, chest pain, or syncope.[34] Atrioventricular block is the most common cardiac manifestation of Lyme disease.[39,40]

An MDCalc online tool for the Rule of 7s, distinguishing Lyme meningitis from aseptic meningitis, is available at: https://www.mdcalc.com/rule-7s-lyme-meningitis

Late Lyme Disease

If untreated, hematogenous spread of the spirochete causes late-stage manifestations[4] of monoarthritis or oligoarthritis.[41,42] The knee is the most common joint involved.[41] Joints may be swollen but are less likely to be erythematous than in patients with a bacterial septic joint.[39] Lyme arthritis is more common in children than adults.[43] Patients with Lyme arthritis were typically asymptomatic or had mild early symptoms prior to the onset of Lyme arthritis, and thus may not have presented for care prior to the development of the arthritis.[43,44] There have been no known cases of Lyme arthritis developing in patients who were previously treated for localized or early disseminated infections.[44]

Rocky Mountain Spotted Fever

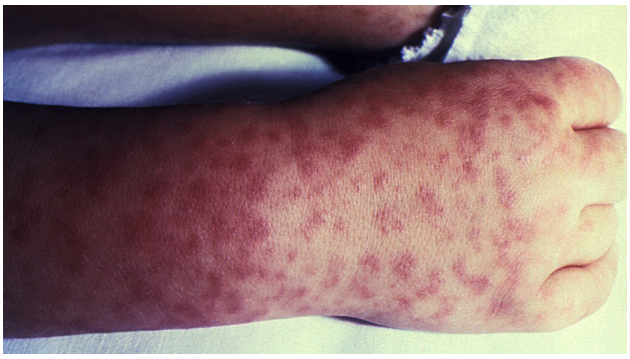
RMSF is a potentially fatal tick-borne illness. Symptoms usually begin 2 to 14 days after a tick bite.[45] RMSF causes a systemic, small-vessel vasculitis and procoagulant state.[8] However, early manifestations can be nonspecific, including fever, headache, fatigue, and anorexia.[45] Early RMSF can also present with gastrointestinal symptoms including nausea, vomiting, diarrhea, and abdominal pain. RMSF may be confused with gastroenteritis, cholecystitis, and appendicitis.[7] Ophthalmologic involvement may include iritis, uveitis, retinal inflammation, optic disc edema, and cotton wool spots.[46] RMSF frequently presents with a rash that may not be present until after day 3 of the illness.[3] The rash associated with RMSF varies, depending on the stage, beginning with small macules on the palms, soles, wrists, forearms, and ankles, and then spreading centripetally.[3] The lesions then become petechial or purpuric; occasionally they may also become ecchymotic and necrotic at the fingertips, nose, and toes.[3,25] **(See Figure 4.)** Case studies have also reported the presence of an eschar at the site of the tick bite.[47,48]

If left untreated, RMSF may progress to more severe infection. Late-stage manifestations are due to microvascular leakage from endothelial damage.[8] Late-stage RMSF can be confused with sepsis, meningococcemia, and thrombotic thrombocytopenic purpura. One-third of RMSF cases may present with altered mental status or meningismus.[45] Delayed diagnosis of RMSF can present with seizures.[45] Case reports have also described patients with acute demyelinating encephalomyelitis, bilateral sixth nerve palsies, and increased intracranial pressure with tonsillar herniation.[49-51]

Ehrlichiosis

Similar to other tick-borne illnesses, early symptoms of ehrlichiosis are nonspecific. Ehrlichiosis may appear similarly to early RMSF, viral illness, or viral gastroenteritis. Fever, headache, myalgias, arthralgias, and malaise are commonly reported.[52,53] These symptoms usually present 5 to 10 days after a tick bite.[52] Nausea, vomiting, pharyngitis, and cervical lymphadenopathy are also common. While abdominal pain is not usually a prominent feature, abdominal pain is

Figure 4. Rash Associated With Late-Stage Rocky Mountain Spotted Fever



Content Provider: Centers for Disease Control and Prevention. Available at: https://phil.cdc.gov/Details.aspx?pid=1962.

described in case reports and may mimic appendicitis in rare cases.[54,55] On examination, approximately two-thirds of patients will have a rash, usually a nonspecific, maculopapular rash.[52,56] Patients with ehrlichiosis may also have conjunctivitis and optic nerve atrophy.[46] Strawberry tongue, oral or genital ulcers, hepatosplenomegaly, meningitic symptoms, or neurologic symptoms, including foot drop and speech problems, can also be found on examination.[53,57,58]

Severe cases may also present as hemophagocytic lymphohistiocytosis, even in patients without a genetic predisposition.[59,60] Hemophagocytic lymphohistiocytosis is a rare, potentially lethal condition that results from uncontrolled activation of the immune system, primarily T cells and macrophages.[60] Excess inflammatory cytokines can cause multiorgan dysfunction and irreversible tissue damage.[60] Other complications of ehrlichiosis may necessitate admission to the intensive care unit in up to 25% of cases; these complications include respiratory failure, renal failure, disseminated intravascular coagulation, and opportunistic infections.[56,61] Immunocompromised patients are at higher risk of having more severe presentation or delayed diagnosis, though a case series of bone marrow transplant patients showed good recovery with doxycycline treatment.[62]

Anaplasmosis

Anaplasmosis presents similarly to ehrlichiosis and can often be difficult to distinguish.[63] Anaplasmosis is usually less severe; however, hospitalization rates of 36% to 50% have been reported.[16,64,65]

Patients with anaplasmosis typically present with fever, headache, and myalgias.[16] Rash is less common in anaplasmosis as compared to other tick-borne illnesses.[3] Neurologic manifestations are rare, occurring in about 1% of patients.[16] Neurologic manifestations of anaplasmosis have more peripheral nerve involvement; however, case reports have also described meningitic symptoms with focal neurologic findings.[64,66] Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and abdominal pain are less common; however, in a Chinese study of patients with anaplasmosis, these symptoms were present in up to 50% of cases.[67]

More severe anaplasmosis has been described as resembling macrophage activation syndrome.[68] Patients with severe anaplasmosis may have elevated ferritin, triglyceride, and interleukin levels,[68] which is thought to be caused by a proinflammatory response with impairment of neutrophil functioning by the bacterium.[68]

Babesiosis

Babesiosis infection is a rare disease in pediatric patients, and most infections in immunocompetent children are subclinical.[69] Symptoms present 1 to 4 weeks after a tick bite, though transfusion-acquired babesiosis can occur up to 6 months after exposure.[70]

Children with severe *Babesia* infection may present with high fevers, chills, malaise, myalgias, arthralgias, nonproductive cough, and anorexia.[69] Less common symptoms include conjunctival injection, vomiting, abdominal pain, photophobia, emotional lability, weight loss, and hyperesthesia.[69,71,72] Children may have fever and relative bradycardia.[73] In a retrospective study of 17 patients, 89% of the patients had a relative bradycardia while febrile.[73] Hepatosplenomegaly, jaundice, and retinopathy may also be noted on examination.[69] Severe babesiosis can progress to respiratory failure, disseminated intravascular coagulation, renal failure, coma, and congestive heart failure.[74] Case reports have described splenic infarction and splenic rupture with babesiosis.[75-79] These complications are more common in patients with a high parasite burden and severe anemia.[80] Patients may develop a nonimmune hemolytic anemia, and there have also been case reports of patients presenting with a warm antibody autoimmune hemolytic anemia after recovery from *Babesia* infection.[81]

Tularemia

Tularemia often presents with fever, chills, vomiting, anorexia, fatigue, and myalgias.[24] Symptoms present 3 to 5 days after exposure to a tick.[25] Tick-borne tularemia is more commonly associated with ulceroglandular disease, which is characterized by an ulcerated lesion at the site of the tick bite and regional lymphadenopathy.[24] There may be a pulse-temperature dissociation similar to babesiosis.[24,25] Ocular manifestations include conjunctivitis, chalazion, acute angle-closure glaucoma, optic nerve atrophy, corneal ulceration or edema, and dacrocystitis.[46] Patients can also develop pleural effusions, pericarditis, pneumonia, and acute respiratory distress syndrome, though these are more likely in inhalational tularemia compared to tick-borne tularemia.[3]

Tick-Borne Relapsing Fever

Tick-borne relapsing fever often presents with high fever (> 40°C/104°F).[82] Symptoms begin within about 7 days of exposure.[82] The fever can be associated with arthralgias, myalgias, headache, nausea, vomiting, and dizziness.[3,24] Conjunctivitis, iritis, keratic precipitates, choroiditis, cranial nerve palsy, and papillitis can also be seen.[46] Hepatosplenomegaly and a nonspecific maculopapular rash also may be found on examination.[83] Urinary symptoms such as proteinuria and microscopic hematuria may be seen, due to high spirochete load disrupting the glomerulus or causing tubule-interstitial disease.[83] Fever may self-resolve after 3 days, then return after 7 days.[82,83] This pattern will continue for an average of 3 cycles but can occur up to 13 times.[25,82,83] More severe disease can present with coma, meningitis-like symptoms, pneumonitis, myocarditis, or cranial nerve palsy.[83]

Colorado Tick Fever

Colorado tick fever usually presents within 1 to 14 days after a tick bite.[3] Symptoms can be nonspecific and include fever, photophobia, conjunctival injection, nonspecific maculopapular rash, headache, and vomiting.[3,24,25,46] About 50% of cases are biphasic, with symptoms returning several days after resolution, with the second fever often being higher than the first.[24,84] Rarely, Colorado tick fever can present with meningitis, encephalitis, and hemorrhagic fever.[3,85] Neurologic manifestations are more common in children than adults, with rates of up to 5% to 10% of cases.[31]

Tick Paralysis

Most studies of tick paralysis are based on case reports and case series.[86-91] The mechanism of paralysis is largely unknown; however, animal studies suggest that the toxin may affect the release of acetylcholine.[89] Symptoms can often be confused with Guillain-Barré syndrome, botulism, and polio.[92] In North America, patients often present with a prodrome of lethargy, myalgias, fatigue, and irritability.[32] This is followed by ataxia and an ascending paralysis, often with accompanying facial nerve paralysis.[32] Patients with tick paralysis may have findings of lower extremity weakness that ascends, decreased deep tendon reflexes, and intact sensation.[93,94] Ophthalmoplegia is also observed in some cases.[32] If the tick is not removed, progression of the paralysis can involve the respiratory muscles, with a mortality rate of about 10% due to respiratory failure.[95]

Prehospital Care

Most patients with a tick-borne illness are stable on presentation to the ED. Critically ill patients, in particular those with RMSF, require rapid evaluation of airway, breathing, and circulation. Aggressive fluid resuscitation may be needed for patients with signs of shock. Patients with progressive tick paralysis may require respiratory support if respiratory muscles are involved.

Emergency Department Evaluation

History

The often-nonspecific complaints of tick-borne illnesses make them difficult to distinguish from other diseases and disease processes. However, there are several key points in the history that are common to tick-borne illnesses. Most tick-borne illnesses, with the exception of tick paralysis, present with fever, myalgias, and rash. Fatigue is also commonly associated with tick-borne illness; Lyme disease, in particular.[96] Neurologic complaints are also frequently seen in patients with a tick-borne illness. The most common complaint is headache, which is a feature of almost all tick-borne illnesses,[3] and the headache may be associated with photophobia. Gastrointestinal symptoms of vomiting and diarrhea may also be present in patients with tick-borne illnesses, but these are usually not the only presenting symptoms.

A history of tick exposure or a tick bite may be elicited. However, small case studies have reported that only a minority of patients with a tick-borne illness report a history of a tick bite, as the bites may be small or in locations that are not easily visible.[1,2,26,97,98] A history of recreational or occupational activities may increase suspicion for tick-borne illnesses. Recreational activity may include play in a backyard or park—even in urban settings—in endemic areas.[2] Pets may also be a vector for exposing children to ticks.[2]

Physical Examination

Clinical findings from examination of patients with a tick-borne illness may be nonspecific. A vital component of the physical examination is a thorough head-to-toe examination for the presence of a tick, particularly in the hair, axilla, and groin, where attached ticks can be easily missed. Patients with severe cases of RMSF, ehrlichiosis, and anaplasmosis may present in shock, with acute respiratory distress syndrome or have evidence of bleeding or coagulopathy on examination.[10,99] A rash is a classic finding in many tick-borne illnesses; however, the rash characteristics can vary depending on the infectious etiology. A description of the rash, the location of the rash, and a detailed history of the development and changes in the rash may help to differentiate between the various etiologies. Examination of the joints may be normal, but in cases of Lyme arthritis, the affected joint may be swollen and stiff with or without erythema and warmth.[39] A detailed neurologic examination may also reveal evidence of meningeal or neurologic involvement. Findings of a bilateral peripheral cranial nerve VII palsy are highly suggestive of Lyme disease.[38]

Diagnostic Studies

A classic EM lesion that is > 5 cm is diagnostic of Lyme disease, and no further testing is required prior to treatment.[35] Other tick-borne illnesses have suggestive laboratory findings in the right clinical context. Often, diagnostic studies must be sent to specialized laboratories for processing and may take several days to result. A summary of relevant diagnostic testing for tick-borne illnesses is presented in **Table 1, page 8**.

Laboratory Studies

Patients with RMSF will classically have thrombocytopenia, hyponatremia (due to inappropriate antidiuretic hormone secretion), elevated aspartate

aminotransferase, anemia, and a normal or mildly elevated white blood cell count.[8] Patients with ehrlichiosis may also have thrombocytopenia, elevated aspartate aminotransferase, leukopenia, and anemia. Patients with anaplasmosis are more likely to have elevated C-reactive protein, thrombocytopenia, abnormal liver function tests, and a low white blood cell count compared to control patients without anaplasmosis.[100,101] Laboratory results for patients with babesiosis may show evidence of hemolysis (elevated lactate dehydrogenase, low haptoglobin, anemia, reticulocytosis), thrombocytopenia, and elevated liver enzymes.[25]

Peripheral Blood Smears

Peripheral smears may be diagnostic in some cases. A babesiosis smear may show ring forms in peripheral erythrocytes.[102] Tick-borne relapsing fever is diagnosed by a peripheral blood smear with either a Wright or Giemsa stain to visualize spirochetes.[24] Morulae (intravacuolar inclusions) in neutrophils are highly suggestive of anaplas-

Table 1. Diagnostic Testing for Tick-Borne Illnesses[3,19,24,25,104,105]

Disease	Suggestive Laboratory Results	Confirmatory Tests	Timing of Test	Other Considerations
Lyme disease	None	ELISA followed by immunoblot	IgM and IgG < 4 weeks; IgG only if > 4 weeks	CSF and synovial fluid testing are not diagnostic without concurrent serum testing
Rocky Mountain spotted fever	Hyponatremia, thrombocytopenia, elevated AST	PCR of blood (preferred) or biopsy sample; immunohistochemical staining of biopsy specimen; serum antibody testing or ELISA	PCR can be performed on presentation Antibodies develop 7-10 days after illness	PCR testing has a high false-negative rate in blood samples; convalescent antibody sample > 1:64 or more than 4x increase between acute and convalescent stage to confirm diagnosis
Ehrlichiosis	Pancytopenia, elevated AST, hyponatremia; morulae in monocytes	DNA PCR testing; serum antibody testing	PCR can be performed on presentation Convalescent sample needed for confirmation if using antibody testing	PCR preferred; convalescent antibody sample > 1:64 or more than 4x increase between acute and convalescent stage to confirm diagnosis
Anaplasmosis	Leukopenia, thrombocytopenia, elevated AST; morulae in granulocytes	DNA PCR testing; serum antibody testing	PCR can be performed on presentation Convalescent sample needed for confirmation if using antibody testing	PCR preferred; convalescent antibody sample > 1:64 or more than 4x increase between acute and convalescent stage to confirm diagnosis
Babesiosis	Giemsa staining showing parasite in red blood cells-maltese cross; evidence of hemolysis	PCR testing	Immediate	Repeat testing may be required if low levels of parasitemia
Tularemia	None	Serum antibody testing	Convalescent sample needed for confirmation	Single convalescent antibody sample > 1:160 or more than 4x increase between acute and convalescent stage to confirm diagnosis (**Caution:** culture can be infectious to laboratory personnel)
Tick-borne relapsing fever	Spirochetes in Wright or Giemsa stain of peripheral blood smear	Serologic testing has limited utility	Blood smear on presentation	High rate of cross-reaction and variation between causative species
Colorado tick fever	Leukopenia	PCR testing; serum antibody testing	IgM antibodies, 14-21 days to develop	IgM antibodies have limited clinical utility
Tick paralysis	None – presence of tick	None	N/A	N/A

Abbreviations: AST, aspartate aminotransferase; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; N/A, not applicable; PCR, polymerase chain reaction.

mosis and are most frequently found in the first week of illness (25%-75% of cases).[103] Morulae in monocytes are rare (3% of cases), but if found, are highly suggestive of ehrlichiosis.[11]

Confirmatory Diagnostic Testing

Further diagnostic testing may be useful to confirm the diagnosis of a tick-borne illness. Causative agents for tick-borne illnesses are often difficult or dangerous to culture, so most diagnostic testing relies on antibody testing or polymerase chain reaction (PCR) tests. However, serologic testing for tick-borne illnesses has a high false-negative rate early in the disease course. If initial serologic test results are negative in high-risk patients, begin empiric treatment or consider repeat testing. A recent study of modified testing protocols for Lyme disease may allow for earlier diagnosis without the need for Western blot confirmation;[106] however, these tests are not widely available and will need more evaluation before they are routinely recommended.

For patients with evidence of meningismus or neurologic involvement, but without a clear diagnosis based on history and physical examination, lumbar puncture is indicated to aid in diagnosis and to exclude bacterial meningitis in patients early in the disease course. The exception is for patients with classic tick paralysis in whom an attached tick is identified; these patients do not require CSF studies.[95] If a lumbar puncture is performed in these cases, CSF studies are usually normal.[32,89] RMSF often shows a moderate leukocytosis with lymphocytic predominance, mildly increased protein, and normal glucose.[107] Case reports of patients with neurologic manifestations of RMSF demonstrated a "starry sky" appearance on diffusion-weighted magnetic resonance imaging (MRI).[107,108] A recent retrospective review of 68 patients with central nervous system Lyme disease found that all but 1 patient had leukocytosis, with the majority having elevated protein with IgM and IgG antibodies to the bacteria.[102]

Clinically differentiating Lyme arthritis from septic arthritis can be a diagnostic challenge.[109] Given the poor reliability of PCR testing of joint fluid, Lyme arthritis is diagnosed based on a positive serum titer.[41,44] Synovial fluid can be sent for PCR testing to aid in establishing the diagnosis, but serum testing is required for diagnosis.[44] Given that serum testing for Lyme disease takes several days to result, several studies in Lyme-endemic areas have examined synovial fluid characteristics to determine whether there was a difference between fluid aspirated in septic arthritis and Lyme arthritis. These studies failed to show a difference in the synovial fluid cell counts to reliably differentiate septic arthritis from Lyme arthritis, though 1 study found a lower median white blood cell count in the synovial fluid of patients with Lyme arthritis compared to septic arthritis.[110,111] A study performed on children residing in Lyme-endemic areas developed and validated a clinical prediction rule to differentiate septic arthritis and Lyme arthritis. The study found that patients with an absolute neutrophil count ≤ 10×10^3 cells/mm^3 and an erythrocyte sediment rate ≤ 40 mm/hour had a low risk of having septic arthritis and may not require a joint aspiration, given the right clinical context.[109] However, this prediction rule needs to be studied on a larger scale before being used routinely.

Treatment

If a tick is found, it can be removed using tweezers or fine-tip forceps by grasping the head of the tick near where it enters the skin and pulling the tick straight out with gentle, even pressure.[24] Care should be taken to not leave the tick head embedded in the skin.[24] **Table 2, pages 12 and 13** summarizes the recommended treatment regimens for the respective tick-borne illnesses.

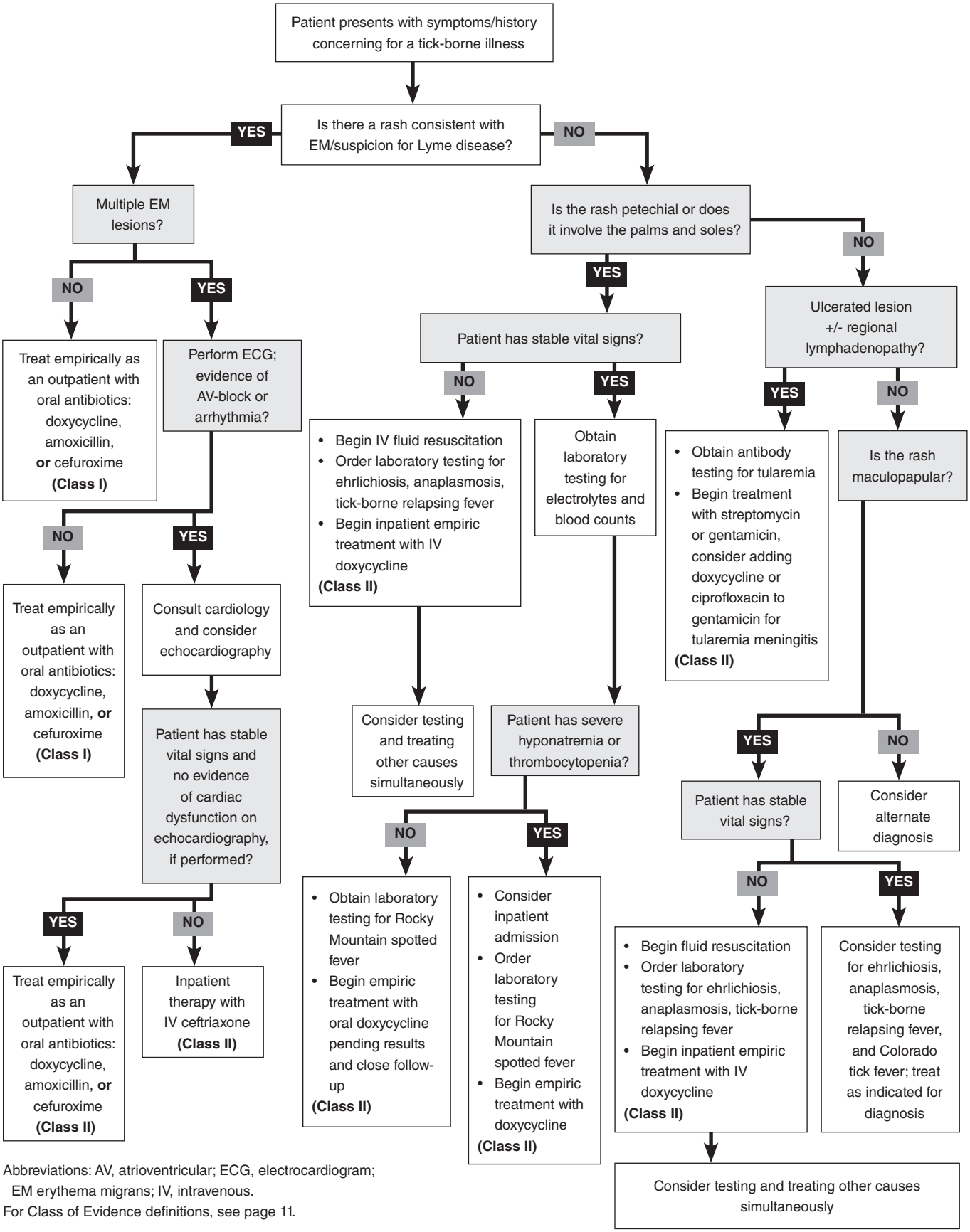
Lyme Disease

For patients with a classic EM lesion, treatment can be started based on the clinical findings alone. A study of 118 patients who had microbiologically confirmed EM showed resolution of symptoms and good outcomes for patients treated empirically with antibiotics.[117]

The updated 2018 guidelines from the American Academy of Pediatrics (AAP) that are based on Infectious Diseases Society of America recommendations have an updated treatment recommendation to allow use of doxycycline for patients of any age for treatment of Lyme disease.[42,44] Treatment with doxycycline, amoxicillin, or cefuroxime is now recommended for patients of any age, with treatment decision based on potential for co-infection, ability to avoid sun exposure, stage of disease, ease of dosing, and medication allergy.[44] A study of children in Arizona, where RMSF is prevalent, demonstrated lower rates of teeth-staining with doxycycline, compared to historical rates of older tetracyclines. This study also did not find evidence of teeth-staining in children treated with an average 1.8 courses of doxycycline (average of 7.3 days per course) when compared to children who did not receive doxycycline.[118]

Doxycycline is preferred over other oral regimens for facial palsy or Lyme meningitis, due to lack of efficacy studies with amoxicillin or cefuroxime.[44] Corticosteroids are not indicated for facial nerve palsy, and treatment with doxycycline is primarily to prevent late complications and does not improve time to recovery of facial palsy.[44] Carditis and meningitis can be treated with an oral regimen; however, if the patient requires hospitalization, a parenteral regimen should be started and transitioned to an oral regimen after the patient is stabilized.[44] Lyme

Clinical Pathway for the Management of a Pediatric Patient With a Suspected Tick-Borne Illness[3,19,115,119,129]



Abbreviations: AV, atrioventricular; ECG, electrocardiogram; EM erythema migrans; IV, intravenous.

For Class of Evidence definitions, see page 11.

arthritis is treated with a prolonged course of oral antibiotics. Given the limited safety data for prolonged courses of doxycycline in children aged < 8 years, amoxicillin or cefuroxime is preferred for children in this age group.[44] Persistent arthritis after treatment or recurrence shortly after antibiotics can be retreated with oral antibiotics or parenteral antibiotics, if symptoms are worsening.[44]

Rocky Mountain Spotted Fever

The treatment of choice for children of all ages with RMSF is doxycycline, given orally or parenterally.[119] Treatment should be continued until the fever has resolved for at least 3 days, typically requiring a 5- to 7-day course.[112] In several retrospective studies, treatment with nontetracycline antibiotics and delay in treatment with doxycycline beyond day 5 of illness were independently associated an increased risk of mortality.[18,120,121] Sulfonamides should be avoided in patients with RMSF, as these have been shown to be associated with worse clinical outcomes, though the mechanism for this association is unclear.[8] For patients with RMSF with life-threatening anaphylaxis to doxycycline, chloramphenicol may be an alternative treatment.[119] However, it is associated with a decreased cure rate and a higher risk for complications.[2]

Ehrlichiosis

Doxycycline is the treatment of choice for children of all ages [113,122] Treatment should be continued until the fever has been resolved for at least 3 days, typically requiring a 7- to 14-day course.[113] Rifampin is an alternative for patients with life-threatening anaphylaxis to doxycycline or for pregnant patients.[10] There have been reports of sulfonamides being associated with more severe disease and worse disease outcomes.[2,113] A small retrospective review of cases in a highly endemic area did not show an association between sulfonamides and severity of illness; however, it is likely prudent to avoid sulfonamides, given the potential risk.[98]

Anaplasmosis

Mild cases of anaplasmosis may be self-limiting. For patients requiring treatment, the current recommendation for treatment of patients of all ages is doxycycline.[122] Treatment should be continued until the fever has been resolved for at least 3 days, typically requiring a 7- to 14-day course.[113,122] Rifampin is an alternative for patients with life-threatening anaphylaxis to doxycycline or for pregnant patients.[10,16] Due to impairment of neutrophil functioning, patients (particularly those who were immunocompromised prior to the infection) may also require treatment for concurrent bacterial or fungal infection.[15,16,65] Sulfonamide medications should be avoided in patients with anaplasmosis, as they have been associated with worse outcomes and more severe complications.[2,64,122]

Babesiosis

In immune-competent patients, babesiosis is often a self-limiting illness. In patients requiring treatment, a regimen of azithromycin plus atovaquone or clindamycin plus quinine is recommended.[114,123] The combination of azithromycin and atovaquone has been associated with fewer side effects and equivalent rates of cure.[124] Malaise and fatigue may persist for several months.[125] European babesiosis may require treatment with clindamycin, quinine, and atovaquone.[123] Patients with asplenia (either anatomic or functional), high-grade parasitemia, or who do not improve on antibiotic therapy, may require additional treatment with exchange transfusion or plasma apheresis.[21,126,127]

Tularemia

Tularemia may be a self-limited disease. In patients in whom the diagnosis is made or in those with more severe symptoms, the treatment of choice is gentamicin or streptomycin.[115] Gentamicin is preferred in children due to fewer side effects and because it is more readily available than streptomycin.[115] There may be an increased risk of relapse with oral monotherapy with doxycycline, so this is no longer recommended for treatment of tularemia.[24,115]

Class of Evidence Definitions

Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Table 2. Recommended Treatment Regimens for Tick-Borne Illnesses[3,10,16,19,28,31,32,44,112-116]

Indication	Medication/ Intervention[a, b]	Dosage	Route	Duration
Lyme Disease				
Single or multiple erythema migrans lesions: first-line agents	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO	10 days
	Amoxicillin	50 mg/kg/day (max 1.5 g/day), divided into 3 doses	PO	14 days
	Cefuroxime	30 mg/kg/day (max 1 g/day), divided into 2 doses	PO	14 days
Single or multiple erythema migrans lesions: second-line agent (if patient is unable to take a first-line agent)	Azithromycin	10 mg/kg/day (max 500 mg/day), once a day	PO	7 days
Facial palsy, isolated	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO	14 days
Meningitis	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO	14 days
	Ceftriaxone	50-75 mg/kg (max 2g/day), once a day	IV	14 days
Carditis (including heart block)	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO	14-21 days
	Amoxicillin	50 mg/kg/day (max 1.5 g/day), divided into 3 doses	PO	14-21 days
	Cefuroxime	30 mg/kg/day (max 1 g/day), divided into 2 doses	PO	14-21 days
	Ceftriaxone	50-75 mg/kg (max 2g/day), once a day	IV	14-21 days
Arthritis[c]	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO	28 days
	Amoxicillin	50 mg/kg/day (max 1.5 g/day), divided into 3 doses	PO	28 days
	Cefuroxime	30 mg/kg/day (max 1 g/day), divided into 2 doses	PO	28 days
Persistent arthritis (after oral antibiotics) or recurrence after initial episode	Retreat with same oral regimen as initial episode[c]			
	Ceftriaxone	50-75 mg/kg (max 2 g/day), once a day	IV	14-28 days
Rocky Mountain Spotted Fever				
	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO, IV	Continue until patient is afebrile for at least 3 days (typically, 5-7 day course)
Ehrlichiosis				
First-line agent	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO, IV	Continue until patient is afebrile for at least 3 days (typically 7-14 day course)
Second-line agent	Rifampin	20 mg/kg/day (max 600 mg/day), divided into 2 doses	PO	5-7 days

Continued on page 13.

Abbreviations: IV, intravenous; PO, by mouth.

[a]Unless otherwise specified, the medications listed are options for treatment, not to be used in combination.

[b]Unless otherwise specified, the medications listed are options for first-line treatments.

[c]For children aged < 8 years, amoxicillin or cefuroxime is preferred, given the prolonged treatment.

Table 2. Recommended Treatment Regimens for Tick-Borne Illnesses (Continued)

Indication	Medication/ Intervention[a, b]	Dosage	Route	Duration
Anaplasmosis				
First-line agent	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO, IV	Continue until patient is afebrile for at least 3 days (typically 7-14 day course)
Second-line agent	Rifampin	20 mg/kg/day (max 600 mg/day), divided into 2 doses	PO	5-7 days
Babesiosis				
Mild disease	Atovaquone **PLUS** azithromycin	Atovaquone 40 mg/kg/day (max 750 mg/dose), divided into 2 doses **PLUS** azithromycin 10 mg/kg/day (max dose 500 mg), once on day 1, then 5 mg/kg/day (max dose 250 mg), once a day	PO	7-10 days
Severe disease	Clindamycin **PLUS** quinine	Clindamycin 20-40 mg/kg/day (max 600 mg/dose), divided into 3 doses **PLUS** quinine 30 mg/kg/day (max 650 mg/dose), divided into 3 doses	Clindamycin: IV Quinine: PO	7-10 days
Tularemia				
First-line agent	Gentamicin	5-7.5 mg/kg/day divided 3 times a day; dose adjusted to maintain peak serum levels ≥ 5 µg/mL	IV, IM	10 days
Second-line agent	Streptomycin	30-40 mg/kg/day (max 2 g/day), divided into 2 doses	IM	10 days
Tularemia meningitis (ciprofloxacin or doxycycline should be added to the gentamicin regimen, not used as monotherapy)	Ciprofloxacin	20 mg/kg/day (max 500 mg/dose), divided into 2 doses	PO	10 days
	Doxycycline	4.4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO	10 days
Tick-Borne Relapsing Fever				
Without central nervous system involvement/meningitis: first-line agents	Doxycycline	4 mg/kg/day (max 200 mg/day), divided into 2 doses	PO, IV	7-10 days
	Ceftriaxone	50-75 mg/kg (max 2 g/day), once a day	IV, IM	7-10 days
	Aqueous penicillin G	400,000 units/kg/day (max 24,000,000 units/day), divided into 6 doses	IV, IM	7-10 days
Without central nervous system involvement/meningitis: second-line agents	Erythromycin	50 mg/kg/day (max 2 g/day), divided into 4 doses	PO	7-10 days
	Tetracycline (children aged ≥ 8 years)	25 mg/kg/day (max 2 g/day), divided into 4 doses	PO	7-10 days
Central nervous system involvement/ meningitis	Ceftriaxone	50-75 mg/kg (max 2 g/day), once a day	IV	10-14 days
	Aqueous penicillin G	400,000 units/kg/day (max 24,000,000 units/day), divided into 6 doses	IV	10-14 days
Colorado Tick Fever				
	Supportive care	N/A	N/A	N/A
Tick Paralysis				
	Tick removal	N/A	N/A	N/A

Abbreviations: IM, intramuscular; IV, intravenous; PO, by mouth.

[a]Unless otherwise specified, the medications listed are options for treatment, not to be used in combination.

[b]Unless otherwise specified, the medications listed are options for first-line treatments.

Tick-Borne Relapsing Fever

There are many different treatment regimens for patients with tick-borne relapsing fever. Patients with tick-borne relapsing fever can be treated with doxycycline, erythromycin, aqueous penicillin G, or ceftriaxone.[3,23,83] Patients aged ≥ 8 years can also be treated with tetracyline.[28,83] Patients requiring parenteral therapy can be transitioned to oral therapy once there is an improvement in symptoms.[83] Patients with evidence of meningitis or central nervous system involvement should be treated with intravenous antibiotics, either ceftriaxone (preferred) or aqueous penicillin G for 10 to 14 days.[3,28]

Colorado Tick Fever

Symptoms of Colorado tick fever usually self-resolve in 7 to 8 days.[25] Treatment is primarily supportive care, though older patients should be counseled against donating blood or bone marrow for 6 months after the illness resolves.[3]

Tick Paralysis

Removal of the tick is the mainstay of treatment for tick paralysis. A thorough search for a tick is important for patients with symptoms of ascending paralysis. Once removed, patients in North America have a rapid recovery, often showing improvement in several hours. Complete resolution of these patients occurred over the course of 1 to 2 days. In Australia, recovery is often slower, taking several weeks for complete resolution, though the mechanism responsible for this difference is unknown.[95]

Risk Management Pitfalls for Management of Pediatric Patients With Tick-Borne Illnesses (Continued on page 15)

1. **"There was no history of a tick bite, so I don't have to worry about tick-borne illnesses."**
   Tick bites are often painless and may be in locations that are not easily visible. Patients may not give a history of a tick bite; therefore, a careful history to elicit risk factors for tick exposure is necessary, particularly in endemic areas. In studies of tick-borne illnesses, a history of a tick bite was not reported in 30% to 40% of confirmed cases.[1,2,26,97,98]

2. **"It's not the summer, so this patient cannot have a tick-borne illness."**
   Most tick-borne illnesses have a seasonal variation, with most cases presenting in the summer months. However, due to variable incubation periods and weather pattern variations, seasonal exclusion alone is not reliable to exclude a tick-borne illness. Cases of RMSF, anaplasmosis, and ehrlichiosis have been reported during all months of the year, particularly in milder southern climates.[2,13,142]

3. **"I did not examine the skin on my patient with ascending paralysis, as the history was most consistent with Guillain-Barré."**
   Ticks may often be hidden in difficult-to-find places, including the hair and groin. Neglecting to complete a thorough skin examination, particularly in endemic areas during high tick season, may subject patients to unnecessary and invasive testing and treatments, in addition to the potential for respiratory failure.[86]

4. **"I had a strong suspicion that my patient had a tick-borne illness, but I wanted to be sure, so I waited for the confirmatory tests to result before starting her on an antimicrobial."**
   For most tick-borne illnesses, confirmatory testing may take days or weeks to result. In patients with a consistent history, examination, and preliminary laboratory findings, empiric treatment may be started while test results are pending. In particular, delayed treatment with doxycycline is associated with a higher mortality rate for RMSF.[143] Untreated, RMSF has a case fatality rate of 10% to 25%.[144]

5. **"I treated my 5-year-old patient with Rocky Mountain spotted fever with chloramphenicol because of the risk of teeth-staining with doxycycline."**
   Unless a patient has an anaphylactic reaction to doxycycline, the treatment of choice for patients with a rickettsial disease is doxycycline, regardless of age. In a survey study of clinical practitioners, 80% of practitioners correctly identified doxycycline as treatment for RMSF in children aged > 8 years, while only 35% chose doxycycline for children aged < 8 years.[145] This is similar to findings from other studies.[146,147]

Special Circumstances

Pregnancy

Some tick-borne infections can result in pregnancy-specific complications, and choosing the appropriate treatment regimens can be challenging. Pregnant patients with tick-borne relapsing fever may experience abortion, preterm delivery, or neonatal infection.[83] Some tick-borne illnesses, such as babesiosis, can be transmitted perinatally.[22] A case series of 6 pregnant patients with anaplasmosis during pregnancy showed perinatal transmission in 1 case; however, no long-term complications from the infection or treatment with rifampin or doxycycline were observed.[128] Patients who are pregnant and contract Lyme disease should avoid treatment with doxycycline unless no clear alternative is available.[129] For pregnant patients with rickettsial illness (RMSF, ehrlichiosis, anaplasmosis), the United States Food and Drug Administration (FDA) released a consensus statement, based on a review of available data, that states that doxycycline is unlikely to have a significant teratogenic risk, though no controlled trials exist and there are insufficient data to conclude that there is no risk.[130] The AAP also recommends considering the use of chloramphenicol, though this is associated with potentially worse outcomes and side effects, such as aplastic anemia and gray baby syndrome.[119] The FDA also concluded that doxycycline is considered safe at therapeutic doses for a short duration in women who are breastfeeding.[130]

Co-Infection

For patients with a tick-borne illness who fail to improve within the expected time frame, a co-infection with another tick-borne illness should be considered,

Risk Management Pitfalls for Management of Pediatric Patients With Tick-Borne Illnesses (Continued from page 14)

6. **"I strongly suspected my patient had Lyme arthritis, so I didn't need to cover for other etiologies."**
Tick-borne illnesses often mimic other serious diseases. Of these, bacterial meningitis, septic joint, and sepsis are among the diseases with higher morbidity. Given that the testing for tick-borne diseases takes time to result, in severely ill patients, treatment for both tick-borne illnesses and other bacterial infections should be started until confirmatory testing is completed.

7. **"Most patients already know how to prevent tick bites, so I don't need to counsel them."**
Preventive behaviors can be effective means to decrease the incidence of tick-borne diseases. Checking for ticks within 36 hours of potential exposure and bathing within 2 hours of spending time outdoors have been shown to be protective against Lyme disease.[148] Other recommendations include wearing protective clothing and applying tick repellent, though the studies are mixed on the effectiveness of these preventive measures.[149]

8. **"I suspect my patient has Rocky Mountain spotted fever, but he doesn't have a petechial rash, so that can't be the diagnosis."**
Petechial rash may not develop in all patients, and a small percentage of patients will not develop a rash. Some studies report as many as 95% of patients will develop a rash, though a retrospective study in Arizona reported lower rates, with only 68% of confirmed cases having had a rash.[25,150] Of those that do develop a rash, up to 60% may not become petechial.[151]

9. **"The patient has a dog, but no other risk factors, so a tick-borne illness is unlikely."**
Household pets, and dogs in particular, can be a significant risk factor for tick exposure in endemic areas. Dogs may pick up ticks more easily or be more likely to play in areas with tall grass, bringing ticks into the home as a source of exposure. Contact with dogs is associated with exposure to ticks and cases of tick-borne illness.[143,144,150,152] Preventive measures, such as frequently examining dogs for ticks and use of tick repellent on pets, are recommended to decrease this exposure.[152,153]

10. **"I'm not in a high-risk area, so I don't need to consider tick-borne illnesses in my differential."**
While there are areas that are highly endemic for certain diseases, tick-borne illnesses have been reported in all of the contiguous 48 states.[154] A thorough travel history is critical to identifying possible tick exposures, as cases acquired during travel to endemic areas may be easily missed.[155] Patients may also be exposed during international travel.[156,157] Excluding a specific disease based solely on geographic location may delay diagnosis and increase the risk of developing complications.

in addition to alternate diagnoses. A 2018 study of 187 children with anaplasmosis found that approximately one-fourth of the children were co-infected with Lyme disease. These patients had a higher risk of hospitalization and complications from both diseases.[101] Amoxicillin alone may be insufficient for patients co-infected with Lyme disease and anaplasmosis.[41] Patients treated with rifampin for anaplasmosis will also require separate treatment for Lyme disease.[41]

Jarisch-Herxheimer Reaction

Jarisch-Herxheimer reaction can occur with treatment of *Borrelia*-caused tick-borne illnesses, such as Lyme disease or tick-borne relapsing fever. The reaction is seen, on average, in about 15% of cases, but a case series of patients treated for tick-borne relapsing fever reported a rate of 54%.[83] Jarisch-Herxheimer reaction occurs within a few hours to a few days of starting treatment, due to the release of cytokines and phagocytosis from the spirochetes.[83] It presents with fever, chills, hypotension, flushing, sweating, and tachycardia. Treatment is supportive, with close monitoring, antipyretics, and fluids.[3]

Controversies and Cutting Edge

Meat Allergy After a Tick Bite

In both adults and pediatric patients, development of anaphylaxis to mammalian meat products has been increasingly reported over the last few years.[131,132] The association was first described in Australia in 2009; since then, cases have been reported from all continents in which ticks are present.[131-133] In the United States, the bite of a lone star tick (*A americanum*), found in the Southeast and Eastern United States, has been implicated in development of a meat allergy.[132,134] Other tick species have been implicated around the world.[132,135] Patients who were bitten develop an allergy to galactose-alpha-1,3-galactose (alpha-gal), which is a sugar found in mammalian red meat such as pork, beef, and lamb.[131] This is thought to be due to type 2 helper T cells in genetically susceptible people, triggering B cells to switch from making IgG antibodies to IgE antibodies in response to tick alpha-gal proteins causing a cross-reaction with meat alpha-gal proteins.[131,136,137]

Patients present with "middle of the night" anaphylaxis, with symptoms ranging from true anaphylaxis to delayed urticaria, delayed angioedema, or gastrointestinal symptoms.[132] Unlike other food hypersensitivities that typically present shortly after ingestion, allergy to alpha-gal occurs on average 3 to 6 hours after ingestion (range 2-10 hours).[131,134] This is due to factors that delay uptake of the allergen and presentation to the immune system.[131]

Treatment in the ED is similar to that for other patients with anaphylaxis or allergic reactions.[138] Patients with a meat allergy will have alpha-gal IgE antibodies in their serum or test positive in a skin test to raw meat, but serum titers must be correlated with clinical symptoms for diagnosis.[131,138] Boiling milk destroys the alpha-gal protein, so pasteurized milk is generally tolerated, but patients may react to unpasteurized milk.[131] Some patients may also need to avoid gelatins (found in many medications, capsules, and tablets), some vaccines (eg, measles, mumps, rubella, and varicella), certain antivenoms, porcine heart valves, and cetuximab.[131] It is unclear whether this allergy is life-long or whether people can become desensitized.[132] Some patients are, at times, able to consume meat without a reaction, while having a reaction other times.[132] The effect of co-ingestions is still unclear.[131]

Prophylaxis After a Tick Bite

Prophylaxis after a tick bite for disease prevention has been a controversial topic. A 2010 meta-analysis of patients treated with doxycycline demonstrated that these patients had a reduced risk of developing Lyme disease, with a number needed to treat of 50.[139] However, the risk of Lyme transmission after a tick bite is estimated to be about 3%, with low rates of transmission associated with a short time of attachment and nonengorgement of the tick.[44] The AAP Redbook recommends treatment if the tick is engorged and if treatment is begun within 72 hours for patients of any age in a Lyme-endemic area.[44,129] Prophylaxis is a single dose of 200 mg (or 4.4 mg/kg) of oral doxycycline.[44] Prophylaxis has not been demonstrated to be beneficial for other tick-borne illnesses.[44] However, a randomized controlled trial of 93 patients in Israel showed benefit in preventing tick-borne relapsing fever in a highly endemic area.[140] Testing the tick for *Borrelia* or other tick-borne pathogens is not currently recommended.[44]

Disposition

Generally, most stable patients in whom a tick-borne illness is suspected can be discharged with close follow-up with their pediatrician either with or without empiric treatment, depending on the disease and level of clinical suspicion. Close follow-up is essential if empiric treatment is not begun, as disease progression can be severe in some cases. Clinically ill-appearing patients or patients with severe symptoms should be admitted for monitoring and workup. Patients with suspected RMSF, even if stable, should be considered for admission, given the high risk of clinical deterioration and the difficulty in distinguishing between RMSF and early meningococcemia. Similarly, patients with suspected central nervous system involvement should be considered for admission for intravenous antibiotics and monitoring pending test results to rule out other causes of the patient's symptoms.[44] Patients with

Lyme arthritis can be treated as outpatients, provided there is a low suspicion for septic arthritis.[44,111] Most patients with tick paralysis should be admitted for monitoring and resolution of symptoms.[32]

Summary

The symptoms of tick-borne illnesses are often nonspecific and are easily misdiagnosed early in the course of illness. Emergency clinicians, particularly those in endemic areas, need to maintain a high level of suspicion to correctly identify, diagnose, and treat patients with suspected tick-borne illnesses. Clinical characteristics can vary greatly between the 9 tick-borne illnesses discussed in this review; however, most of these illnesses will present with a fever and rash. The diagnosis of many tick-borne illnesses can be time-consuming. Treatment is often based on clinical characteristic and clinical suspicion, as many confirmatory tests take days to weeks to result. The recommendations on the use of doxycycline have recently been expanded to include patients of all ages who have Lyme disease. Early identification and treatment of tick-borne illnesses may prevent severe complications or mortality from these diseases.

Time- and Cost-Effective Strategies

- For patients with clear symptoms that are indicative of a tick-borne illness, such as a classic EM rash or an attached tick for a patient with tick paralysis, laboratory testing and further workup is often unnecessary. In one study, about 40% of patients with a single EM rash had negative testing during the first week of the rash.[141] Empiric treatment can be started for patients with a classic EM rash.
- For patients with Lyme arthritis, serology testing may be sufficient for diagnosis in the right clinical context. Joint aspiration is indicated to rule out bacterial septic arthritis, if suspected.
- Lumbar puncture may assist in distinguishing between viral and Lyme meningitis, when used in combination with the Rule of 7s.
- For patients suspected of having RMSF, treatment with doxycycline should begin immediately.
- For patients with tick paralysis, removal of the tick and admission for monitoring is sufficient in the right clinical context.

Case Conclusions

The patient with left knee swelling and pain had an absolute neutrophil count that was 8 x 10^3 cells/mm^3 and an erythrocyte sedimentation rate of 10. Two-tier Lyme disease testing was sent and resulted as positive. The girl was started on oral doxycycline and was discharged on a 28-day course of doxycycline and follow-up with her pediatrician.

On detailed examination, you found a tick in the 5-year-old girl's hair, and you suspected tick paralysis. You explained that there is no diagnostic test for tick paralysis, but the treatment is removal of the tick. The tick was removed, and the patient was admitted to the ICU for further monitoring. Over the course of the next 24 hours, the patient's symptoms resolved and she was discharged with a normal neurologic examination.

The 8-year-old boy was resuscitated with IV isotonic crystalloid fluids for shock, with improvement in his blood pressure after 2 boluses. His initial lab results showed hyponatremia, thrombocytopenia, and a mild leukocytosis. Blood was drawn for bacterial cultures. He was treated for bacterial sepsis with IV vancomycin and IV ceftriaxone. Given your concern for RMSF, titers were sent, and IV doxycycline was added to the treatment regimen. The boy was admitted to the ICU and his symptoms improved after treatment. The blood cultures were negative, and the titers for RMSF were elevated. The boy was discharged home to complete a course of oral doxycycline. Repeat titers 4 weeks later confirmed the diagnosis of RMSF.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of patients. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study is included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. **A 10-year-old boy presents with bilateral facial nerve palsy. He was at summer camp in Rhode Island a few months prior, but otherwise has not had any recent travel. He is afebrile. The boy has mild fatigue but no headache, weakness, or other related complaints. Except for the bilateral peripheral facial nerve palsy, the rest of his neurologic examination is normal. What is the best next step in the management of this patient?**
   a. Perform a lumbar puncture.
   b. Begin a high-dose corticosteroid course with a 2-week taper.
   c. Begin doxycycline 4.4 mg/kg (maximum, 200 mg/day) for 14 days.
   d. Obtain head imaging.

2. **A 12-year-old boy is brought in by his mother for fever. The mother reports that he had a high fever that ranged from 40°C to 40.6°C (104°F-105°F) last week for 4 to 5 days. The fever went away for 2 to 3 days but is now back. The boy has also had body aches, nausea, and vomiting. On examination, you note hepatosplenomegaly and a maculopapular rash. The boy's mother states that they were hiking a few weeks ago, and that she removed several ticks from both herself and the patient. The boy has had no foreign travel outside of the United States. What is the most likely diagnosis?**
   a. Malaria
   b. Tick-borne relapsing fever
   c. Dengue fever
   d. Tularemia

3. **A 17-year-old adolescent boy has been diagnosed with Colorado tick fever. Which of the following is TRUE for this patient?**
   a. Treatment with doxycycline should begin immediately.
   b. The patient should avoid contact sports for 6 months after symptoms resolve.
   c. The patient can donate blood at his school's blood drive next week.
   d. The disease may be biphasic and return several days after it initially resolves.

4. **A 5-year-old girl presents with fever and headache for 3 days. Her mother states that the girl was at a camp in Tennessee 2 weeks ago. On examination, the girl has a petechial rash on her palms and the soles of her feet. What laboratory results would support the most likely diagnosis?**
   a. Hypernatremia, thrombocytopenia, elevated creatinine
   b. Hyponatremia, thrombocytosis, elevated liver function tests
   c. Hypernatremia, thrombocytopenia, elevated liver function tests
   d. Hyponatremia, thrombocytopenia, elevated liver function tests

5. **A 9-year-old girl with a history of acute lymphoblastic leukemia on chemotherapy presents to the ED with high fever, myalgias, arthralgias, and a nonproductive cough. She has received multiple blood transfusions since she was diagnosed 1.5 years ago. Laboratory tests are sent and a peripheral blood smear demonstrates ring forms in her peripheral red blood cells. Which of the following is not one of the standard oral treatment regimens for this illness?**
   a. Azithromycin
   b. Atovaquone
   c. Doxycycline
   d. Quinine

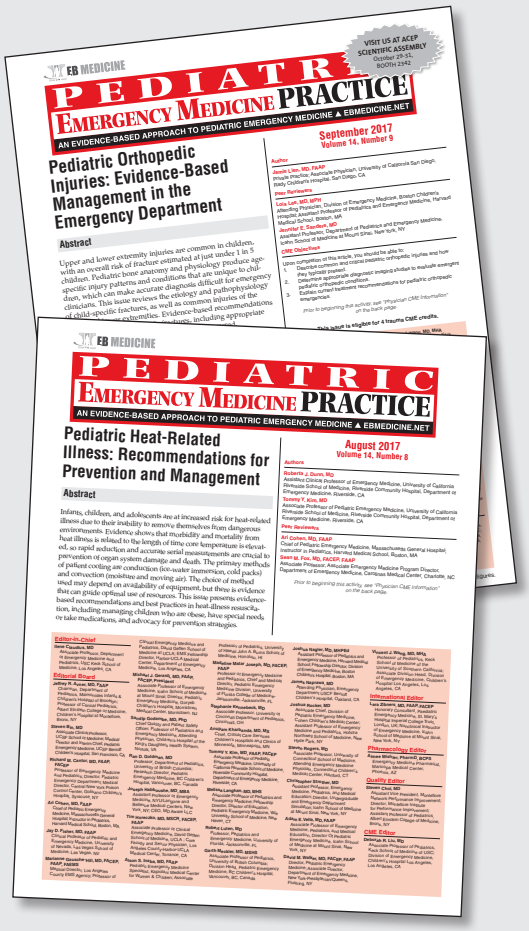
6. **A 15-year-old adolescent boy presents with abdominal pain, fever, headache, and oral ulcers for the last 4 to 5 days. His examination is significant for diffuse tenderness, oral ulcers, and a maculopapular rash. Which of the following laboratory findings, if present, would be most suspicious for ehrlichiosis?**
   a. Leukopenia
   b. Thrombocytopenia
   c. Inclusion bodies in monocytes
   d. Inclusion bodies in neutrophils

7. **A 13-year-old girl reports that she has been having difficulty walking in the last 24 hours, and that she is feeling progressively weaker. The day before her symptoms started, she was hiking in the woods with her friends, without problems. The girl needs to be supported by her mother when walking, and she is noted to have 3/5 strength in her lower extremities, with normal upper extremity strength. Which of the following will help aid in the diagnosis?**
   a. Inspect her hair and body carefully for the presence of a tick.
   b. Order a lumbar puncture.
   c. Send the patient for an MRI.
   d. Order electromyography studies.

8. **A 3-year-old girl has been diagnosed with Rocky Mountain spotted fever. What is the most appropriate treatment to start for a patient this age?**
   a. Amoxicillin
   b. Doxycycline
   c. Sulfamethoxazole-trimethoprim
   d. Chloramphenicol

9. **An 8-year-old girl presents to your ED. The girl's father reports that she has had a rash on her abdomen for 4 days, it started as a "red bump" on her trunk, but then changed, so he brought her in. The girl has had a low-grade fever for 2 days, but is otherwise well. On examination, you note a blanching erythematous patch with central clearing. What is the best next step in the management of this patient?**
   a. Start oral doxycycline (4.4 mg/kg/day, max 200 mg/day) for 10 days.
   b. Offer reassurance and recommend follow-up with her pediatrician.
   c. Send titers for Lyme disease and have her follow up with her pediatrician for treatment if positive.
   d. Treat the rash with topical hydrocortisone.

10. **An 8-year-old girl presents with fevers, chills, and malaise for the last 3 days. On examination, you note that she has lymphadenopathy in her axilla and an ulceration on her upper back. The patient returned from camp 3 days ago and reports that she had multiple ticks removed while she was away. What is the first-line treatment for her illness?**
   a. Supportive care and monitoring
   b. Intramuscular streptomycin
   c. Oral amoxicillin
   d. Oral doxycycline



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- Genital Injuries
- Bacterial Meningitis
- Hypothermia
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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

CME Objectives: Upon completion of this article, you should be able to: (1) Describe presenting signs and symptoms in children with common tick-borne illnesses; (2) determine appropriate workups and manage children with tick-borne illnesses and related complications; and (3) discuss complications that can arise from undiagnosed or late presentation of tick-borne illnesses.

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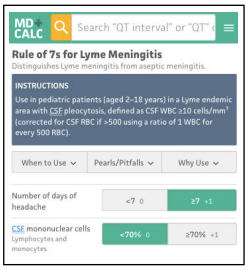

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Rule of 7s for Lyme Meningitis

Introduction: The Rule of 7s for Lyme Meningitis is a validated clinical prediction rule to distinguish Lyme meningitis from aseptic meningitis.

Points & Pearls

- The Rule of 7s should not be used in settings in which patients do not have access to close follow-up care by a medical provider.
- If the cerebrospinal fluid (CSF) red blood cell count is > 500 cells/mm³, the CSF white blood cell count must be corrected using a ratio of 1 white blood cell for every 500 red blood cells in the CSF cell count.

Advice

This tool should be used to assist clinicians in decision-making, not to replace clinical evaluation of a patient. Patients with scores of 1 to 3 points are not at low risk for Lyme meningitis, and antibiotic therapy for Lyme meningitis should be considered for these patients. Patients with a score of 0 are at low risk for Lyme meningitis; their symptoms may be due to aseptic meningitis or another etiology. Clinicians should use clinical judgment and consider whether the patient has access to adequate follow-up care before initiating antibiotic therapy.

Critical Actions

The Rule of 7s is meant to aid in the decision to begin antibiotic therapy for suspected Lyme meningitis. It should not replace clinical judgement and clinician assessment of patients.

CALCULATOR REVIEW AUTHOR

Matthew Lecuyer, MD
Department of Emergency Medicine (Pediatrics)
Warren Alpert Medical School of Brown University
Providence, RI

Why to Use

The Rule of 7s has been validated by a retrospective cohort study of 423 children in Lyme-endemic areas. It can help guide clinicians in assessing the need to initiate antibiotic therapy for Lyme meningitis, versus observation and close follow-up care.

When to Use

Use the Rule of 7s in Lyme-endemic areas when considering antibiotic treatment for pediatric patients who:

- Are aged 2 to 18 years, AND
- Have undergone a lumbar puncture and the CSF demonstrates pleocytosis (CSF WBC count ≥ 10 cells/mm³, corrected for CSF RBC count if > 500 cells/mm³ by using a ratio of 1 WBC for every 500 RBCs).

Next Steps

- If the patient is at low risk for Lyme meningitis, consider discharging the patient after stressing the importance of follow up with a primary care provider.
- If the patient is not at low risk for Lyme meningitis, consider treatment with an antibiotic that covers *Borrelia burgdorferi*, using an age-appropriate dosage.

Abbreviations: CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

Evidence Appraisal

Avery et al (2006) first derived a clinical prediction model to calculate the probability of Lyme meningitis in children from Lyme-endemic regions, using a statistical analysis of history, physical examination, and laboratory findings. Their model was prospectively validated by Garro et al (2009) in a study of 50 children aged 2 to 18 years who lived in a Lyme-endemic region. Fourteen of the children had Lyme meningitis, 6 had possible Lyme meningitis, and 30 were ultimately diagnosed with aseptic meningitis. Categories of low (< 10%), indeterminate (10%-50%), and high (> 50%) probabilities of Lyme meningitis were derived based on the percentage of CSF mononuclear cells, duration of headache, and presence of cranial nerve neuropathy.

The positive predictive value with a cutoff of > 50% probability of Lyme meningitis was 100% (95% confidence interval [CI]: 66%-100%). The negative predictive value with a cutoff of < 10% probability of Lyme meningitis was 100% (95% CI: 82%-100%). The authors noted that when patients had < 7 days of headache, < 70% CSF mononuclear cells, and no seventh or other cranial nerve palsy, the probability of Lyme meningitis was always < 10%, indicating that those patients were at low risk for Lyme meningitis. The authors termed this the Rule of 7s.

The Garro et al study was validated in a large retrospective cohort study by Cohn et al (2012) using electronic medical record data from 3 pediatric emergency departments in Lyme-endemic areas. The sample of 423 children, aged 90 days to 19 years, included 117 children who were diagnosed with Lyme meningitis and 306 who were diagnosed with aseptic meningitis. The specificity of the Rule of 7s for low risk was 41% (95% CI: 36%-47%), and the sensitivity was 96% (95% CI: 90%-99%).

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Aris Garro, MD, MPH
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Validation Reference

- Cohn KA, Thompson AD, Shah SS, et al. Validation of a clinical prediction rule to distinguish Lyme meningitis from aseptic meningitis. *Pediatrics.* 2012;129(1):e46-e53.
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