

# Tick-Borne-Associated Illnesses in the Pediatric Intensive Care Unit

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## Abstract

When unrecognized and antibiotic delay occurs, Lyme disease, Rocky Mountain–spotted fever, babesiosis, and human ehrlichiosis and anaplasmosis can result in multiorgan system dysfunction and potentially death. This review focuses on the early recognition, evaluation, and stabilization of the rare life-threatening sequelae seen in tick-borne illnesses that require admission in the pediatric intensive care unit.

## Keywords

- ▶ Rocky Mountain–spotted fever
- ▶ Lyme disease
- ▶ human ehrlichiosis and anaplasmosis
- ▶ babesiosis

## Introduction

In the United States, the reported number of tick-borne diseases each year is increasing.<sup>1</sup> This is at least partly due to the rising average temperatures caused by global warming which is elongating the season of tick activity and enhances their survival in the environment.<sup>2</sup> Studies have shown that increased temperatures influence the life cycle of ticks, as well as the ecosystem overall, creating an environment more prone to the spread of tick borne illnesses.<sup>3,4</sup> Because of this, tick-borne illnesses have now begun to appear in the fall, winter, and spring months, in addition to the summer due to changes in the epidemiology of these diseases from rising temperatures.<sup>5</sup> Environmental conditions that are suitable for tick survival (i.e., persistence of shrubs), increased tick activity, and a reported lack of recognition of the occurrence of a tick bite place children at risk of exposure.<sup>2,3,6,7</sup>

The Centers of Disease Control and Prevention (CDC) recognizes the threat of many diseases worldwide, including old diseases which have evolved, mutated, and gained new features.<sup>2</sup> If unrecognized, these tick-borne–associated illnesses (–Table 1) can have life-threatening sequelae.<sup>8</sup> Clinicians must quickly identify and treat the tick-borne illness

and any complications to ensure the best possible outcome. This article focuses on the most common tick-borne illnesses, their rare life-threatening sequelae, and therapeutic options that allow prompt stabilization.

## Tick-Borne Illnesses

### Lyme Disease

#### Key Points

- The clinical manifestations of Lyme disease vary depending on the stage of illness, thus a careful history and objective clinical findings is required to identify this condition.
- When a pediatric intensivist is faced with a patient with carditis, heart block, or myopericarditis, early Lyme disease should be considered.
- Diagnose via a two-tier method with enzyme-linked immunosorbent assay (ELISA) and immunoglobulin (Ig)-M and IgG immunoblots.
- For neurologic or cardiac sequelae, intravenous ceftriaxone, cefotaxime, or penicillin should be administered.

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- Because of an increased risk of coinfection, empiric therapy with doxycycline should be administered in endemic areas.

### Brief Background

Lyme disease is commonly seen in the northeast and mid-Atlantic regions.<sup>9,10</sup> Expansion of this disease has been recently noted in the Midwest.<sup>9,11</sup> It is transmitted via an *Ixodes* tick bite infected with *Borrelia burgdorferi* with an average incubation period of approximately 2 to 3 weeks.<sup>12,13</sup>

### Life-Threatening Clinical Presentation

Lyme disease develops in three stages. First, the typical erythema chronicum migrans rash and nonspecific symptoms develop, followed by wide hematogenous dissemination resulting in preferential involvement of specific organs, leading to joint pain, neurological complications, *Borrelia* lymphocytoma or Lyme carditis.<sup>11,14–16</sup> A late manifestation of this disease includes arthritis and acrodermatitis chronica atrophicans.<sup>15</sup>

Patients with early Lyme disease may develop Lyme carditis, leading to atrioventricular (AV) heart block, myocarditis or first, second, or third degree heart block.<sup>15</sup> Heart block most commonly occurs above the bundle of His, including the AV node. Symptoms include syncope, dyspnea, or chest pain.<sup>16</sup>

Patients with Lyme meningitis are less likely to be febrile but are often sicker for a longer duration than those with viral meningitis. These patients often have erythema migrans, cranial nerve palsy, or papilledema.<sup>16</sup>

### Diagnosis

The diagnosis of early localized Lyme disease can be made clinically (presence of characteristic erythema migrans lesion in a patient who resides in an endemic area).<sup>17</sup> All other manifestations of Lyme disease require serologic testing.<sup>18</sup> Testing is typically two-tiered, involving a polyvalent ELISA then IgM and IgG immunoblots.<sup>14,16</sup> A positive or equivocal ELISA with a positive IgM Western immunoblot ( $\geq 2$  of 3 bands) and positive IgG result ( $\geq 5$  of 10 bands) has a sensitivity of approximately 70 to 100% and a specificity of  $>95\%$  for disseminated Lyme disease.<sup>18</sup>

Lumbar puncture is indicated for patients with a strong clinical suspicion of cerebral nervous system involvement. This may have a lower negative predictive value and the cerebrospinal fluid (CSF) results may be difficult to differentiate from aseptic meningitis.<sup>14,16,19</sup> A high index of suspicion for Lyme meningitis should occur if the patient is older (greater than 10 years of age), has a CSF specimen with a predominance of mononuclear cells (fewer white blood cells), longer duration of symptoms (more than 12 days), presence of cranial nerve palsy, and presence of papilledema.<sup>19–22</sup>

Echocardiogram and cardiac magnetic resonance imaging (MRI) can determine if there is pericardial involvement or left ventricular dysfunction.<sup>15</sup> The presence of transmural inflammatory infiltrates with characteristic band-like endo-

cardial lymphocytic infiltration on endomyocardial biopsy is gold standard for diagnosing myocarditis.<sup>15</sup>

### Stabilization

The first-line treatment is doxycycline (oral 2 mg/kg/dose twice daily for 10 to 21 days depending on clinical manifestation type).<sup>16</sup> Amoxicillin or cefuroxime axetil are alternatives for erythema migrans for children under 8 years. Macrolides and first-generation cephalosporins should not be used.<sup>16</sup>

In cases of Lyme meningitis and carditis, intravenous ceftriaxone (50 to 75 mg/kg/dose once daily) is recommended.<sup>15,16</sup> Alternatives include cefotaxime or penicillin.<sup>15,16</sup>

For symptoms of increased intracranial pressure, serial lumbar punctures, acetazolamide, or shunting may be required.<sup>23</sup>

Patients with Lyme carditis should be hospitalized for monitoring due to possible decompensation and need for a temporary pacemaker.<sup>15</sup> Due to a direct effect on the atrioventricular node rather than an indirect vagotonic effect, most patients do not respond to atropine administration.<sup>24</sup>

There is an increased risk of coinfection with other infections that can be transmitted by *Ixodes* ticks, particularly babesiosis.<sup>11,16</sup> Empiric antibiotic therapy with doxycycline should be administered.<sup>11,16</sup>

### Rocky Mountain–Spotted Fever

#### Key Points

- When an intensivist is faced with a patient with nonspecific flu-like symptoms and shock, Rocky Mountain–spotted fever (RMSF) should be considered as the classic triad of fever, rash, and headache is not always initially present.
- The best diagnostic test are immunofluorescent antibody assays.
- Common laboratory abnormalities include thrombocytopenia and hyponatremia.
- Empiric treatment with doxycycline is recommended in suspected cases of RMSF to reduce the risk of mortality.

### Brief Background

In the United States, cases of RMSF were reported with an incidence of 2 to 4 per million among 1- to 19-year-old children between 2000 and 2008 in the southeastern and southcentral region.<sup>25</sup> Most cases occur between April and September and rates are increasing.<sup>25</sup> After inoculation from a feeding tick (*Dermacentor variabilis* [the American dog tick], *Dermacentor andersoni* (the Rocky Mountain wood tick), or *Rhipicephalus sanguineus* (common brown dog tick)], the *Rickettsia rickettsii* bacteria infect the endothelial and vascular smooth muscle cells in the brain, skin, liver, lungs, kidneys, and gastrointestinal tract with patients becoming symptomatic 5 to 7 days after exposure.<sup>26–28</sup> Many possible disease manifestations result from the small- to medium-sized vessel vasculitis produced.<sup>27</sup> A delay of antibiotic treatment of more than 5 days can result in the mortality risk increasing more than three folds.<sup>8,29,30</sup>

**Table 1** Tick-borne-associated illnesses in the pediatric intensive care unit

	Lyme disease	Rocky Mountain–spotted fever	Babesiosis	Human granulocytotropic anaplasmosis	Human monocytotropic ehrlichiosis
Epidemiology in the United States	Northeast and mid-Atlantic region	Southeastern, south-central region	Northeast and upper Midwest region	Midwest, Northeast region	Southeastern, Southcentral, mid-Atlantic region
Microbiology	<i>Borrelia burgdorferi</i>	<i>Rickettsia rickettsi</i>	<i>Babesia microti</i>	<i>Anaplasma phagocytophilum</i>	<i>Ehrlichia chaffeensis</i>
Clinical presentation	EM rash	Nonspecific viral-like symptoms, petechial rash often a late presentation	Nonspecific viral-like symptoms, evidence of hemolysis	Nonspecific viral-like symptoms	Nonspecific viral-like symptoms
Laboratory features	Nonspecific	Thrombocytopenia, hyponatremia	Hemolytic anemia, reticulocytosis	Lymphopenia, neutropenia	Leukopenia, thrombocytopenia, elevated transaminases
Diagnosis	Clinical in presence of EM rash and other manifestations, two-tiered: <ul style="list-style-type: none"> <li>• ELISA</li> <li>• Western immunoblot</li> </ul>	Immunofluorescent antibody assay confirmed by four-fold or greater rise in antibody titers between acute and convalescent sera	Identification of babesial parasites determined by blood smear (Giemsa's stain), deoxyribonucleic acid polymerase chain reaction ( <i>Babesia</i> DNA PCR) or isolation of <i>Babesia</i> parasites from a whole blood specimen	Elevated Immunofluorescent antibody (seroconversion or four-fold rise in IgG titers of at least two serum samples collected 2 to 4 weeks apart), positive PCR, detection of morulae in mononuclear cells ("buffy coat examination"), or a positive biopsy or culture	Elevated Immunofluorescent Antibody (seroconversion or four-fold rise in IgG titers of at least two serum samples collected 2 to 4 weeks apart), positive PCR, detection of morulae in mononuclear cells ("buffy coat examination"), or a positive biopsy or culture
Treatment	Doxycycline (EM) Ceftriaxone (meningitis or carditis)	Doxycycline	Atovaquone plus azithromycin or clindamycin plus quinine	Doxycycline	Doxycycline

Abbreviations: ELISA, enzyme-linked immunosorbent assay; EM, erythema migrans; Ig, immunoglobulin; PCR, polymerase chain reaction.

### Life-Threatening Clinical Presentation

The classic triad of fever, rash, and headache is rarely present early in the course.<sup>8,25,31</sup> Nonspecific symptoms, such as myalgia, abdominal pain, nausea, vomiting, and conjunctival injection can be mistaken for common viral or bacterial infections, leading to a delayed diagnosis.<sup>29,32</sup> The rash may present as petechial on the ankles, progressing centrally or as a maculopapular rash.<sup>25</sup> The intensivist should be aware that petechial rashes often manifest later in the disease course (day 5 or 6), may be difficult to distinguish from meningococemia, and is a sign of severe disease.<sup>30</sup> Thus, a high clinical suspicion is required (especially in an immunocompetent patient), and every attempt should be made to treat the patient before petechiae develop.<sup>33</sup> The rash can, however, be completely absent.<sup>34</sup>

Critically ill patients can develop hypotension, shock, renal failure, seizure, stupor, coma, encephalitis, hemorrhagic manifestations, noncardiogenic pulmonary edema, or acute respiratory distress syndrome.<sup>35</sup> When this occurs, they are five times more likely to succumb to this illness due to airway compromise, hypoxemia, and hemodynamic instability.<sup>35</sup>

### Diagnosis

The gold standard for diagnosis is immunofluorescent antibody assays (IFA) confirmed by a four-fold or greater rise in serum antibody titers between acute (as IgM and IgG antibodies against *Rickettsia* are not detectable during the first 7 days of illness) and convalescent sera.<sup>25</sup>

Laboratory features include thrombocytopenia and hyponatremia.<sup>28</sup> The white blood cell count is typically normal, with an increased number of immature bands.<sup>28</sup> Other laboratory abnormalities include elevated transaminases, elevated blood urea nitrogen (BUN) level, and creatinine, hyperbilirubinemia, low-serum albumin, leukocytosis, and leukopenia.<sup>25</sup> CSF studies often shows a lymphocytic pleocytosis (<100 cells/ $\mu$ L).<sup>28</sup>

MRI findings in RMSF encephalitis may show a starry sky pattern on T1, T2, and diffusion-weighted imaging.<sup>27</sup>

### Stabilization

Patients requiring intravascular volume support warrant hospital admission.<sup>25</sup> If antimicrobial administration is delayed, multiorgan system dysfunction can occur. Thus, treatment with oral or intravenous doxycycline (2.2-mg/kg/dose every 12 hours for minimum of 5–7 days and continue for at least 3 days after fever resolution and clinical improvement) should be initiated without waiting for confirmation.<sup>28</sup> In this disease (and any severe presentation of suspected tick-borne diseases), the American Academy of Pediatrics supports the use doxycycline in all age groups for less than 21 days.<sup>32</sup> Dental staining is a minor concern but the risk is outweighed by the potential life-threatening sequelae.<sup>32</sup>

Children with severe RMSF are at risk for multiorgan system dysfunction. Neurologically, the patient may develop acute encephalopathy due to cerebral edema, sepsis, or increased intracranial pressure.<sup>36</sup> The clinician must be

prepared to provide supportive care including airway, fluid, and electrolytes, and intracranial pressure monitoring. Children with severe RMSF can develop acute respiratory failure due to loss of airway, pulmonary edema, or acute respiratory distress syndrome.<sup>28</sup> Thus, these patients often require invasive mechanical ventilation. If shock develops, inotropic and vasopressor support is routinely required.<sup>25</sup> Clinicians should be aware of the risk of peripheral vasoconstriction resulting in skin necrosis, gangrene, and the risk of amputation that may be potentiated by vasopressor therapy.<sup>37</sup> In some cases, renal insufficiency can develop, thus, the clinician should be prepared to provide hemodialysis.<sup>25</sup>

### Babesiosis

#### Key Points

- When an intensivist is faced with a patient with fever, viral-like illness, and evidence of hemolysis, babesiosis should be considered.
- High-grade parasitemia ( $\geq 10\%$ ) indicates severe babesiosis.
- Laboratory abnormalities include hemolytic anemia with elevated reticulocyte count.
- Diagnose with identification of babesial parasites in Giemsa's stains or DNA polymerase chain reaction (PCR).
- Severe cases may require exchange transfusion and should be performed at centers with expertise in apheresis.
- Treat with atovaquone and azithromycin if mild or moderate; clindamycin and quinine in severe cases and when requiring exchange transfusion.

#### Brief Background

Babesiosis is caused by intraerythrocytic protozoa.<sup>38</sup> The parasite causes proinflammatory cytokines that stimulate the production of nitric oxide, which results in erythrocytic cellular damage.<sup>38</sup> It is endemic to parts of New England, New York, New Jersey, Minnesota, and Wisconsin.<sup>16</sup> Babesiosis is transmitted by *Ixodes scapularis* ticks with an incubation period of 1 to 4 weeks.<sup>39,40</sup> Because it shares a vector with other tick-borne diseases, it often occurs as a coinfection most commonly with *Borrelia burgdorferi* and *Anaplasma phagocytophilum*.<sup>28</sup>

### Life-Threatening Clinical Presentation

Babesiosis can go undiagnosed in healthy patients.<sup>38</sup> Patients experience a viral-like illness, with fever, chills, sweats, myalgia, arthralgia, anorexia, nausea, vomiting, fatigue, and dark urine.<sup>16</sup>

Severe babesiosis is indicated by high-grade parasitemia ( $\geq 10\%$ ), significant hemolysis or renal, hepatic or pulmonary compromise.<sup>16</sup> Patients may experience acute respiratory failure, disseminated intravascular coagulation, congestive heart failure, coma, and renal failure.<sup>16,41,42</sup>

There have been case reports of splenic rupture.<sup>43</sup> Symptoms include left upper quadrant abdominal pain, hypotension, and anemia.<sup>43</sup>

## Diagnosis

Diagnostic criteria includes the presence of viral-like symptoms and identification of babesial parasites. The presence of parasites can be determined by blood smear (Giemsa's stains), deoxyribonucleic acid PCR (*Babesia* DNA PCR) or isolation of *Babesia* parasites from a whole blood specimen.<sup>44</sup>

Laboratory abnormalities include hemolytic anemia with elevated reticulocyte count, thrombocytopenia, proteinuria and elevated liver enzyme, BUN, and creatinine levels.<sup>16</sup>

## Stabilization

Initial therapy includes atovaquone (20 mg/kg every 12 hours) plus azithromycin (10 mg/kg/day on day 1 followed by 5 mg/kg/day from day 2) or intravenous clindamycin (7–10 mg/kg every 6 to 8 hours) plus quinine (8 mg/kg in every 8 hours) for 7 to 10 days.<sup>14,16,45</sup> Hematocrit and percentage of parasitized erythrocytes should be monitored daily until the level of parasitemia has decreased to <5% of erythrocytes.<sup>16</sup>

According to the Infectious Disease Society of America Guidelines, exchange transfusion and quinine plus clindamycin should be used for all patients with severe babesiosis, defined as high grade parasitemia ( $\geq 10\%$ ), significant hemolysis, or renal, hepatic, or pulmonary compromise.<sup>14,45</sup>

The clinician must be prepared to provide supportive care for severe illness, such as antipyretics, vasopressors, blood transfusions, exchange transfusions, mechanical ventilation, or dialysis.<sup>38</sup>

## Human Ehrlichiosis and Anaplasmosis

### Key Points

- Human granulocytotropic anaplasmosis (HGA) and human monocytotropic ehrlichiosis (HME) typically manifest as a self-limiting, flu-like illness. The intensivist should be aware; however, that severe complications can occur especially in the immunocompromised for HGA.
- Neurological complications are often severe in HME.
- Diagnosis requires clinical symptoms and positive laboratory results.
- Treat with doxycycline.

### Brief Background

HGA and HME are rickettsial infections.<sup>46,47</sup> HGA infects the neutrophils while HME infects monocytes and macrophages.<sup>48</sup> HGA is endemically found within the Midwest and northeastern areas and its principal tick vector is *Ixodes scapularis* with an incubation period of 5 to 14 days.<sup>28,46</sup> HME is mainly in the southcentral, southeastern, and mid-Atlantic regions and its tick vector is the lone star tick (*Amblyomma americanum*) with an incubation period of 5 to 14 days.<sup>47,49</sup> Most cases are diagnosed between April and September.<sup>32,46,47</sup> While reportedly rare, their prevalence is likely underreported in children due to mild infections that do not require medical care.<sup>46</sup>

## Life-Threatening Clinical Presentation

Clinical manifestations of HGA and HME are often nonspecific, including rash, fever, malaise, chills, headache, myalgias, and abdominal pain.<sup>34,46,47,50</sup> Neurologic manifestations are most commonly seen with HME.<sup>47</sup>

Life-threatening clinical signs seen in HGA and HME include encephalopathy, seizures, respiratory failure, shock, cardiac failure, myocarditis, and acute renal failure.<sup>34,47</sup>

## Diagnosis

Diagnosis requires presence clinical findings and any of the following diagnostic tests: an elevated IFA (seroconversion or four-fold rise in IgG titers of at least two serum samples collected 2–4 weeks apart), positive PCR, detection of morulae in neutrophils (HGA) or mononuclear cells (HME; “buffy coat examination”), or a positive biopsy or culture.<sup>46,47,51</sup> Laboratory abnormalities include thrombocytopenia, leukopenia, increased liver enzymes, elevated C-reactive protein, and hyponatremia.<sup>16,46,47,52</sup>

## Stabilization

Doxycycline (2.2 mg/kg/dose every 12 hours for 7–14 days) is the treatment of choice for both conditions.<sup>28</sup> If contraindicated, rifampin (10 mg/kg/dose twice per day 7–10 days) may be used.<sup>16</sup>

HGA can have significant morbidity and mortality, especially in immunocompromised patients or cases of delayed treatment.<sup>16,52</sup> The clinician should be prepared to provide neurologic, airway, respiratory, and hemodynamic support.

## Conclusion

Tick-borne illnesses are associated with rare but life-threatening sequelae. Many cases present initially with unspecific, viral-like symptoms, and no known history of a tick bite. Early recognition, stabilization, and prompt referral to a tertiary center is recommended to reduce the risk of morbidity and mortality in pediatric patients who acquire these diseases.

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### Conflict of Interest

None declared.

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