Tick-borne illnesses

June 6, 2019 by Josh Farkas

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overview

rationale for this chapter

- Tick-borne illnesses are spreading into a wider geographic distribution due to global warming.
- These illnesses are difficult to diagnose (often mimicking more common bacterial pathogens).
- Immediate initiation of treatment may be critical for a good outcome.

focus of this chapter:

- When to suspect possible tick-borne illness.

https://emcrit.org/ibcc/tick/
• Investigation of the patient with possible tick-borne illness.
• Use of empiric therapy while awaiting advanced testing.
• Four diseases are included as these will constitute the vast majority of tick-borne illness encountered in ICU: anaplasmosis, ehrlichiosis, babesiosis, and Rocky Mountain Spotted Fever (RMSF).
  • (Although Lyme disease is more common, it is not often seen in the ICU.)

**Pathophysiology**

Tickborne illnesses are somewhat unique in that they cause *intracellular* infection.

**Babesiosis**

- Causes infection & hemolysis of erythrocytes by a protozoan organism (similar to malaria).
- Among tick-borne illnesses, babesiosis is unique in its ability to cause *hemolysis*.

**Anaplasmosis & Ehrlichiosis**

- Obligate intracellular bacteria which infect *leukocytes*.
  - Anaplasmosis: predominantly infects *neutrophils*.
  - Ehrlichiosis chaffeensis (the most likely strain to be encountered in ICU) infects mostly monocytes and macrophages.
- Bacteria don’t damage host tissues directly, but instead most organ dysfunction results from an exuberant inflammatory response.
  - In severe cases, this overzealous inflammatory response may lead to full-blown hemophagocytic lymphohistiocytosis (HLH).
- In anaplasmosis, infection of neutrophils may lead to secondary opportunistic infections.

**Rocky Mountain Spotted Fever (RMSF)**

- Obligate intracellular bacteria which infect *endothelial cells*, leading to inflammation of the blood vessels. This may have the following consequences:
  - Systemic capillary leak
  - Occlusive thrombosis
  - Disseminated intravascular coagulation with consumption of platelets and fibrinogen

**Epidemiology**

**General Epidemiology of Tick-Borne Illnesses**

- Tend to peak between April and October. However, transmission can occur year-round in the southern United States.
- The vast majority of patients won’t require ICU admission. Risk factors for severe illness are listed below.

**Key Points in Exposure History**

- (1) History of tick bite is reported in roughly half of patients. Therefore, this cannot be relied upon as a diagnostic clue.
- (2) Exposure to environments with ticks.
  - Rural exposure may be highest risk (e.g. hiking). However, tick exposure can occur in suburban locations and even urban parks.
- (3) Clusters of illness may occur among family members, coworkers, or dogs (may resemble influenza, but during the *summer*).
- (4) Travel history (incubation may be weeks for some pathogens, so recent travel is relevant).
co-infection

- Ticks may harbor multiple pathogens, leading to several simultaneous infections.
- Anaplasmosis, Babesiosis, Lyme, and Powassan virus may occur together (because they may be harbored by the Ixodes scapularis tick).
  - Among patients with anaplasmosis, ~10% have co-infection with Lyme disease or babesiosis ([28457353](https://www.ncbi.nlm.nih.gov/pubmed/28457353)).

babesiosis

- Incubation is 1 to ~6 weeks.
- Risk factors for severe illness:
  - Age
  - Splenectomy
  - Malignancy, HIV, or immunosuppressive therapy (e.g. TNF-inhibitors or rituximab)
- Especially endemic within islands off the coast of New England (including Nantucket, Martha's Vineyard, Block Island, Long Island).
- Increasingly common in the northeastern United States, due to milder winters and an increasing deer population.
**anaplasmosis**

- Incubation is 5-14 days.
- Most cases occur June-November.
- Risk factors for severe illness:
  - Age
  - Immunosuppressive therapy
  - Chronic inflammatory illness
  - Underlying malignancy
- Distributed worldwide, including Europe (especially in Slovenia, Sweden, and Norway) and Asia (including China, Korea, and Japan).

**ehrlichiosis**

- Incubation 5-14 days.
- Risk factors for severe illness:
  - Age (however, fatal disease can occur in previously healthy young adults)
  - Immunosuppression, HIV, organ transplantation
  - Splenectomy
- Beyond the United States, ehrlichial infections are reported in South America, Africa, and eastern Asia.

**rocky mountain spotted fever**

- Incubation is 3-12 days.
- Reported in all 48 contiguous states of the United States (including a city park in the Bronx!)(3130574)
- Endemic to some American Indian communities in Arizona, with transmission year-round.
- Risk factors for severe illness: older age, alcoholism, glucose-6-phosphate dehydrogenase deficiency, immunocompromise.
- Beyond the United States, RMSF may be seen in Central and South America (including Argentina, Brazil, Columbia, Panama, Costa Rica, and Mexico).

### presentation: signs & symptoms

### initial flu-like syndrome:

- All of these infections will often begin with a a nonspecific “flu-like” illness including fever, myalgia, headache, malaise, and gastrointestinal symptoms (nausea, vomiting, diarrhea).
- The symptoms below focus on more unique features, which may assist with diagnosis.

**babesiosis**

- Initial symptoms nonspecific (e.g., fatigue, weakness, fever, headache, myalgia, anorexia, nausea, dry cough, arthralgia).
- Intravascular hemolysis
  - Hemoglobinuria (pink/dark urine)
  - Jaundice
- Conjunctivitis, petechiae, or ecchymosis may be seen (28696196)
  (https://www.ncbi.nlm.nih.gov/pubmed/28696196).)
- Multi-organ failure can occur:
  - Confusion, coma
  - ARDS
  - Shock/CHF
  - Splenic rupture
  - Renal failure
  - Disseminated intravascular coagulation

**anaplasmosis**

https://emcrit.org/ibcc/tick/
Overall, causes severe disease less often, compared to ehrlichiosis.

- Erythema migrans rash seen in ~2-10% (this may reflect co-infection with Lyme disease).
- Confusion (20%), neck stiffness (45%)
- Rarely causes severe organ dysfunction
  - ARDS
  - Rhabdomyolysis
  - Renal failure
  - Carditis
  - Pancreatitits
  - DIC with hemorrhagic manifestations
  - Hemophagocytic lymphohistiocytosis (HLH)
- Invasive opportunistic infections with viral and fungal pathogens may occur following anaplasmosis.

**ehrlichiosis**

- Commonly manifests with nonspecific findings: fever (>90%), headache, malaise, myalgia.
- Gastrointestinal symptoms may be prominent (nausea, vomiting, diarrhea).
- Rash seen in ~20% of patients; may be petechial, maculopapular, or diffuse erythroderma (28457353
- Major end-organs which can be affected are brain and lungs:
  1. Meningitis or meningoencephalitis occur in ~20% of patients, may progress to seizure and coma.
  2. Cough or respiratory symptoms occur in about a third of patients, occasionally progressing to ARDS.
- Can evolve into multi-organ failure, including hepatic and renal failure.
- May trigger hemophagocytic lymphohistiocytosis (HLH), resembling bacterial septic shock.

**rocky mountain spotted fever (RMSF)**

**early (1-4 days)**

- Fever (>90%), headache, malaise, myalgia.
- **Early rash** (~2-5 days)
  1. Starts at wrists and ankles, later spreads to trunk (sometimes on palms and soles)
  2. Begins as blanching pink macules, which eventually become maculopapular.
  3. Absent in 10% of patients (“spotless” fever is seen more often in the elderly and in patients with dark skin). Furthermore, in fulminant RMSF, the rash may appear only shortly prior to death.
- **Nondependent edema** around eyes and on backs of hands (*endothelial dysfunction*).
- Gastrointestinal symptoms (nausea, vomiting, anorexia, abdominal pain).
- Photophobia, meningismus, and conjunctival suffusion may occur.

**late (day 5+)**

- Neurologic
  1. Altered mental status
  2. Coma, cerebral edema
- **Late rash**
  1. Petechial rash appears ~ day 6.
  2. Coalescence of rash may lead to areas of ulceration or gangrene (potentially requiring amputation).
- Multiorgan failure including renal failure and ARDS

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**synthesis: six clues for diagnosis**

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To synthesize the above sections on epidemiology and presentation, there are six key clues to consider the presence of tick-borne illness.

**Reported tick bite**
- Present in perhaps half of patients.
- Obvious red-flag to tick-borne illness. However, lack of a tick-bite history cannot exclude tick-borne illness.

**Travel or residence in an endemic region**
- Tick-borne illnesses are widespread, but there are some regions which are notoriously endemic (e.g. babesiosis in Nantucket and Block Island).
- Among areas with low a low burden of tick-borne illnesses, recent travel to an endemic region may be a red flag.
  - Note that incubation periods may last for weeks, so travel may have occurred a while previously.

**Rash or Conjunctivitis**
- Most commonly seen in Rocky Mountain Spotted Fever (although it may be entirely absent in 10% of such patients).
- Rash may also be seen in ehrlichiosis (various forms) or anaplasmosis (usually Erythema Migrans rash).
- Conjunctivitis may also be a useful clue, as this is typically not seen with bacterial sepsis.

**Immunocompromise**
- Whenever you are thinking about overwhelming post-splenectomy sepsis (OPSS), also consider babesiosis or ehrlichiosis.

**Thrombocytopenia**
- Mild thrombocytopenia is often seen in septic shock, but unusually severe thrombocytopenia may suggest a tick-borne illness.
- The combination of thrombocytopenia plus leukopenia may be even more suggestive.

**Hemolysis**
- Hemolysis is a hallmark of babesiosis.
- This manifests with clinically with anemia, hemoglobinuria, and elevated indirect bilirubin.
Tick-borne illnesses tend to cause relatively nonspecific abnormalities within commonly obtained labs (table below). Perhaps the most notable finding is thrombocytopenia (combined with leukopenia in anaplasmosis or ehrlichiosis).

<table>
<thead>
<tr>
<th>Babesiosis</th>
<th>Anaplasmosis</th>
<th>Ehrlichiosis</th>
<th>RMSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>Thrombocytopenia (75%)</td>
<td>Thrombocytopenia (75%)</td>
<td>Thrombocytopenia (~40%, mild initially)</td>
</tr>
<tr>
<td>WBC</td>
<td>Anything (low, normal, or high)</td>
<td>Leukopenia (55%) - Lymphopenia</td>
<td>Leukopenia (60%) - Lymphopenia</td>
</tr>
<tr>
<td>RBCs</td>
<td>Hemolytic anemia is a major diagnostic feature.</td>
<td>Anemia can occur later on in disease course</td>
<td>Anemia can occur later on in disease course</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Elevated indirect bilirubin from hemolysis - Transaminitis</td>
<td>Mild-moderate transaminitis</td>
<td>Slight transaminitis</td>
</tr>
<tr>
<td>Coagulation</td>
<td>DIC may occur</td>
<td>DIC is rare</td>
<td>DIC is rare (e.g. with reduced fibrinogen)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>May be elevated in secondary HUH</td>
<td>May be elevated in secondary HUH</td>
<td></td>
</tr>
<tr>
<td>Blood smear</td>
<td>Often will see parasites within erythrocytes (especially with repeat smears)</td>
<td>Commonly see intraleukocytic organisms (morulae)</td>
<td>Rarely see intraleukocytic organisms (morulae)</td>
</tr>
<tr>
<td>CSF analysis</td>
<td>If performed, it may show a pleocytosis (usually lymphocytic) and an elevated protein.</td>
<td>Glucose levels will generally be normal.</td>
<td></td>
</tr>
</tbody>
</table>

Common lab abnormalities caused by tick-borne illnesses encountered in critical care. Anaplasmosis and ehrlichiosis are similar, in that both cause intracellular infection of leukocytes. As such, they seem to cause a very similar pattern of lab abnormalities (red box).

A first-pass lab panel to investigate for tick-borne illness:

- Complete blood count with differential
- Liver function tests
- Babesiosis-specific labs (depending on index of suspicion)
  - Lactate dehydrogenase (LDH) & haptoglobin
  - Thin blood smear
- Ferritin may be considered if there are features of hemophagocytic lymphohistiocytosis.

CBC results obtained in anaplasma PCR-positive patients, among all patients tested for anaplasmosis within a large hospital. WBC >11 or platelets >300 strongly argues against anaplasmosis (especially among the context of critically ill patients).

**Babesiosis**

- Hemolytic anemia is a key diagnostic feature:
  - Lactate dehydrogenase (LDH) should be markedly elevated (absence of hemolysis excludes babesiosis).
  - Urinalysis may suggest the presence of cell-free hemoglobin (heme-positive dipstick, but no erythrocytes seen on microscopy).
- Thin blood smears may identify parasites.
Will generally be positive in severe cases, but multiple smears may be needed.
Level of parasitemia varies from 1-80%; usually low early in the disease course. Parasitemia > 10% may be an indication for exchange transfusion (see treatment section below).
Thick blood smears not recommended (organism is small and may be missed) (https://www.ncbi.nlm.nih.gov/pubmed/27115378).
PCR is more sensitive, but turn-around time is longer. PCR may remain positive for over a year after infection, so positive PCR doesn't prove acute infection.

**anaplasmosis**

- Blood smear in almost half of patients may reveal bacterial inclusion bodies (morulae) inside neutrophils (figure above from CDC (https://wwwnc.cdc.gov/eid/article/24/8/17-2048-f1)).
- This cannot be relied upon, as sensitivity will vary depending on expertise of the laboratory.
- PCR is the test of choice.

**ehrlichiosis**

- PCR is the test of choice.

**rocky mountain spotted fever (RMSF)**

- PCR or serology may be used. However, either test may be negative early in the course of infection.
doxycycline hits everything other than babesiosis

- Doxycycline is treatment of choice for anaplasmosis, ehrlichiosis, and RMSF.
- Empiric doxycycline should be initiated if there is suspicion for any of these diseases (don't delay treatment while awaiting confirmatory testing).
- The usual dosing is 100 mg doxycycline PO/IV q12hr.
- Clinical response should be brisk (e.g. defervescence within 24-48 hours). Persistent fever or clinical deterioration suggests an additional or alternative process.
- Doxycycline allergy:
  - Rifampin may be used as a 2nd line agent, but only for anaplasmosis or ehrlichiosis.
  - Chloramphenicol may be used as a second-line agent for RMSF (28696196).
  - Depending on the allergy history, doxycycline may be considered using either a graded challenge or supervised desensitization protocol.

babesiosis

- Unlike other tick-borne illnesses:
  - (1) Babesiosis isn't covered by doxycycline.
  - (2) Treatment should be initiated only following confirmation of the diagnosis. Fortunately, definitive diagnosis is usually possible rapidly, using blood smears.
- Traditional antibiotic regimens for babesiosis:
  - Severe disease: combination of clindamycin (600 mg IV Q6hr) plus oral quinine (650 mg PO Q6-8hr).
  - Less severe disease: combination of atovaquone 750 mg PO q12hr plus azithromycin 500-1000 mg PO daily.
  - There is relatively little evidence regarding these regimens.
- Exchange transfusion can achieve 90% reduction in parasitemia. Potential indications for exchange transfusion may include the following (28696196).
  - Parasitemia >10%
  - Severe hemolysis (e.g., hemoglobin <10 mg/dL)
  - Pulmonary, liver, or renal impairment
  - The level of parasitemia should be monitored daily until it falls below 5% (28696196).

treat other organ-system complications
- Anaplasmosis may cause rhabdomyolysis: check creatine kinase and treat as described in the chapter on rhabdomyolysis.
- Support other organ failures as necessary (e.g. renal failure, ARDS).

**ehrlichiosis & anaplasmosis: treatment for intercurrent hemophagocytic lymphohistiocytosis (HLH)?**

- Ehrlichiosis and anaplasmosis are established infectious triggers of hemophagocytic lymphohistiocytosis (HLH), a "cytokine storm" state which resembles septic shock.
- The front-line therapy here is doxycycline. By treating the cause of HLH, doxycycline alone may be sufficient to cause clinical improvement (28584460).
- Additional treatments directed towards HLH may be considered as well. The literature contains reports of therapies ranging from corticosteroid alone to the entire HLH-2004 regimen (a chemotherapeutic protocol that includes etoposide, cyclosporine, and dexamethasone)(26227842, 30524954).
  - It's unclear whether the entire HLH-2004 regimen is required here (probably not).
  - A reasonable approach to severe disease with HLH might be to initiate dual therapy with doxycycline and corticosteroid, with further escalation if needed. Emerging data might eventually suggest that ruxolitinib could be a safer option here (29417621).
**Antibiotic selection for severe tickborne illness**

**Critically ill patient with suspected tickborne illness**
- Don’t delay empiric treatment for anaerobiosis, ehrlichiosis, and/or rocky mountain spotted fever while awaiting definitive diagnosis (e.g. PCR tests)

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**Is babesiosis possible?**
- Consider epidemiology
- Lack of hemolysis (e.g. normal haptoglobin or LDH) excludes babesiosis
- If initial labs & epidemiology consistent with babesiosis:
  - STAT thin & thick blood smears should be obtained

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**Babesiosis excluded**
- Doxycycline 100 mg BID empirically (Covers every tick-borne illness other than Babesiosis!)
- Follow up confirmatory test results for various tickborne illnesses (e.g. PCR studies)
- Follow up other studies for alternative diagnoses (e.g. bacterial blood cultures)
- Consult with infectious disease specialist if available

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**Definite/probable Babesiosis**
- Treatment for babesiosis
- Consider doxycycline as well (may have coinfection with anaplasmosis)

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**Simplified algorithm:**
- Suspect tick-borne illness
- Doxycycline 100 mg BID

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**Approach to antibiotic selection in patients with suspected tick-borne illness.** If you’re in a rush and have only a moderate index of suspicion for tick-borne illness, then simply starting empiric doxycycline will generally be fine:

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**The Podcast Episode**

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**questions & discussion**

To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/tick/).

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**Pitfalls**

- Don’t forget that the incubation of these diseases may be weeks, so patients may be at risk long after they went to a trip to an endemic area.

[https://emcrit.org/ibcc/tick/](https://emcrit.org/ibcc/tick/)
For a critically ill patient, don’t withhold therapy while awaiting a definitive diagnosis (instead, consider initiation of empiric doxycycline).

Patients may be co-infected with numerous tick-borne illnesses. Therefore, diagnosing one tick-borne illness should prompt consideration and testing for others (e.g. Lyme disease).

Absence of a known tick bite doesn’t exclude these diseases.

Going further:

- Diagnosis and treatment of Rocky Mountain Spotted Fever in the ED (Brit Long, emDocs)
- Tick-borne illness (Anand Swaminathan and Jenny Beck-Esmay, CoreEM)
- Rocky Mountain Spotted Fever (WikiEM)

Key references

- Diagnosis and Management of Tickborne Rickettsial Diseases: RMSF, Ehrlichioses, and Anaplasmosis – Practical guide for healthcare professionals by CDC (MMWR 2016)

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.