Intro to Tick-borne Illnesses

19/21July2022

**Case 1**

A 30 year-old friend from IM residency with no prior PMH texts you a picture during lunch of a rash on his leg. He is originally from Pennsylvania and was last there 10 days ago visiting friends. They went hiking and reports that they also did some skeet shooting in a grassy field. He did not notice any insect bites. He states that 3 days ago (7 days after returning from PA) he noted the appearance of a red, non-tender, mildly pruritic, macular lesion on his mid-left thigh (photo). The lesion has expanded any now measures well over 6 cm in diameter. He has no other symptoms, takes no medications, and has no medication allergies.



1. What is the diagnosis? What is the specific underlying pathogen?
2. What is the other primary differential consideration for this rash, and how can you (generally) distinguish between them?
3. What is the epidemiology of this infection? What is the primary vector?
4. What other important infections can be transmitted by this vector?
5. What is your next step in evaluation and/or treatment of this patient?

Later, you are called to the ER to see a patient with “headache and difficulty closing his eye”. You say that this sounds more like a Neuro patient, but they add that there’s “a weird rash too”. On exam, the patient complains of a global headache and neck stiffness. The ER has already performed a lumbar puncture, and the CSF formula is as follows: protein 83, glucose 50, WBC 75, RBC 2, N 19%, L 75%, Gram stain and M/E PCR negative. On exam, you note the following findings:



1. What is this patient’s diagnosis, and how does it differ from your friend?
2. What are the stages of this infection, and what manifestations can be seen with each stage?
3. When is testing indicated, what is the best test for diagnosis? What algorithms are available, and which one do we use currently at WR?
4. How could you diagnosis CNS Lyme disease? Lyme arthritis?
5. The above patient abruptly becomes lightheaded and syncopizes in the ER. You ask the ER staff to obtain an EKG, and see the following finding. Aside from appropriate antibiotics, how do you recommend that this condition be managed?



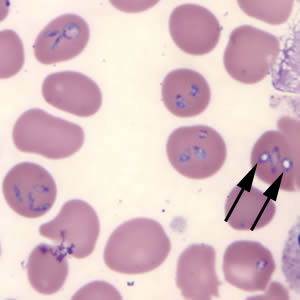
1. The ER staff curbside you as you attempt to escape about a pregnant woman in the next room over with a history of severe photosensitivity to multiple medications presenting with a classic EM rash. What alternative oral treatment options are available?
2. When should you consider IV therapy for Lyme disease?
3. One week later your friend again waltzes back into your clinic, and this time states that he found another tick on him after yet another skeet shooting trip. There is no rash and he is afebrile. He brought the tick with him but says he “sat on it on the way over, so it might be a little squished”. He is asking about post-exposure prophylaxis for Lyme disease. What are the indications for post-exposure Lyme prophylaxis, and assuming that he meets them, what would you prescribe?

**Case 2**

A 50 year-old a woman presents to the ER with complaints of ongoing fever, chills, fatigue, headache, and malaise. She is asplenic, having required a splenectomy following a tragic hot dog eating contest accident. Current symptoms began 7 days ago and have occurred at least daily. She is from Massachusetts and 3 weeks ago went hiking, where she found a tick attached to her abdomen at the belt line. Around the time her current symptoms began, the following rash appeared on her leg.



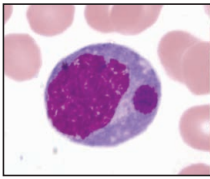
Her primary care physician prescribed her 10 days of doxycycline, which she has taken as instructed, however her symptoms have remained unchanged. On exam, she is febrile and tachycardic. Scleral icterus is noted. Labs reveal WBC 3.0, Plt 90, Hgb 8.5, Tbili 3.5 with previously normal baselines. Other adjunctive lab studies are ordered which return abnormal, prompting a peripheral blood smear for microscopy, which shows the following:



1. What is the diagnosis? Why was doxycycline ineffective?
2. What is the vector and epidemiology of this infection?
3. What is another major differential consideration, and how might these diseases be distinguished at the bedside?
4. What is the typical clinical and laboratory presentation? What can be seen with severe disease?
5. What are some risk factors for severe disease with this pathogen?
6. What diagnostic modalities are available for diagnosis? What is the classic microscopic finding seen above?
7. Aside from a tick bite, what is another major avenue for human infection with this organism?
8. What is the primary treatment? What is the secondary treatment? What adjunctive therapy could be considered in severely ill patients?

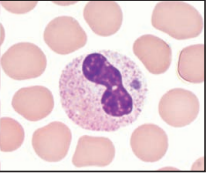
**Case 3**

A 55 yo immunocompetent woman from Missouri is in DC visiting family when she develops the acute onset of fever, headache, malaise, myalgia, and fatigue. There is no rash or eschar and she does not recall a tick bite. She comes from a rural area of MO and was recently viewing property on an area of overgrown farmland. There is no confusion or neck stiffness. Vitals are notable for a fever to 103 F and mild tachycardia. Labs reveal a WBC count of 2500, Hgb 13, Plt 80,000. AST/ALT are 80/100 respectively, with no other LFT abnormalities and no kidney injury. CXR and UA are normal. The night resident requested a peripheral blood smear, which reveals the following:



1. What is the diagnosis? What is the above finding on peripheral smear called?
2. What other differential diagnoses should be considered?
3. What is the vector of this pathogen, and what other infections might it carry?

The above patient’s sister has flown in from Wisconsin, and while visiting her sister in the hospital develops the acute onset of the same symptoms. Lab testing in the ER reveals identical abnormalities (leukopenia, thrombocytopenia, elevated AST/ALT). She also lives in a rural area but does not recall a tick bite and has no rash. Having gotten a feel for this sort of thing, you order another peripheral blood smear and see the following:



1. What is the diagnosis in this patient, and how were you able to discriminate it from that of her sister?
2. What are the key historical, clinical, and laboratory findings seen in infections caused by these organisms?
3. What diagnostic modalities are available for these conditions?
4. What is the treatment? Are there any alternative treatment options for these infections?

Bonus:

A previously healthy 40 yo M from Tennessee presents to the hospital with 2 days of high fever, severe headache, chills, and malaise. His labs show a mild leukocytosis and thrombocytopenia. He recalls removing a tick 1 week ago, and being an amateur entomologist, he tells you that it was a *Dermacentor variabilis* tick. On day 4 of illness, a maculopapular rash appears on his wrists and ankles that progresses both proximally and distally to involve his palms/soles.

What diagnosis cannot be missed in this patient? How is it diagnosed and treated?

Case 1 Answers.

1. Early localized Lyme disease (erythema migrans) due to *Borrelia burgdorferi.*
2. Southern tick-associated rash illness (STARI). If tick is identified, could be used to distinguish (STARI transmitted by the Lone Star tick, Ambylomma americanum). Otherwise, location is a clue though there is overlap (Lyme in northeast and upper central US; STARI more south/south-east).
3. Northeast (ME down to NC); northern Midwest (WI, MN, MI). New infections peak in summer. Ticks of the genus *Ixodes* (ie, *Ixodes scapularis*, aka blacklegged or deer tick). Primarily transmitted by nymphal stage. Lives in reservoirs of white-footed mouse and white-tailed deer.
4. Besides *B. burgdorferi: Babesia microti, Anaplasma phagocytophilum, Borrelia miyamotoi,* Powassan fever virus.
5. Doxycycline 100mg BID x10 days. No serologic testing should be performed, only 30% are positive in early localized disease.
6. Early disseminated Lyme disease, w/ meningitis, facial nerve palsy, and multiple EM rashes.
   1. Stage 1 – early localized disease. Erythema migrans.
   2. Stage 2 – early disseminated disease. Weeks later. Multiple EM lesions, meningitis, CN palsies (esp CN VII), radiculoneuropathy, encephalitis, fluctuating heart block (any degree).
   3. Stage 3 – late disseminated disease. Months-years later. Most commonly as arthritis characterized by large effusions, relatively painless, most common joint is knee but can be any joint. Rarely causes late neurologic manifestations such as polyneuropathy and encephalomyelitis.
7. Testing could be done in later disseminated stages of Lyme disease if the diagnosis is in question. The best test is a two-tiered serum serology, performed by running one serological assay first followed by a second confirmatory assay. Classically, this was done with an ELISA followed by Western blot (done here at WR until recently). Positive Western blots require at least 2 positive IgM bands and/or at least 5 positive IgG bands. Newer test design uses two sequential ELISA assays (what we do now).
8. These are special situations. Consult ID.

Neuroborreliosis requires comparative antibody titers between CSF and serum, called a CSF:serum Ab index. PCR or culture not recommended. Not performed here, must be sent to reference lab.

For Lyme arthritis, begin by performing routine Lyme serology. If positive and clinical diagnosis is unclear, arthrocentesis with Lyme PCR sent on synovial fluid can be considered. This is the only true use (currently) for Lyme PCR.

1. Temporary pacer. Avoid placement of permanent pacemaker, AV block should resolve with treatment of underlying infection.
2. Doxycycline is the drug of choice. When there is a contraindication to doxycycline, the primary alternative agents are amoxicillin 500mg TID and cefuroxime 500mg BID, both x14 days. Azithromycin is third line.
3. For initial treatment of symptomatic Lyme carditis, as well as serious neurological manifestations such as encephalomyelitis. Arthritis and less severe neurological manifestations can typically be treated with doxy. The IV agent of choice is ceftriaxone.
4. All of the following should usually be met:
   1. High risk tick bite: Tick identified as nymph or adult *I. scapularis* in a highly endemic region
   2. Tick engorged or estimated to be attached for at least 36 hours
   3. Prophy started within 72 hours of removal
   4. Able to take oral doxycycline
      * Give one dose of doxycycline 200mg PO.

Case 2 Answers.

1. Babesiosis, caused by *Babesia microti*. Amongst the infections commonly transmitted by ticks, doxycycline does not cover *Babesia* infection.
2. *Ixodes scapularis,* same tick as Lyme. It is endemic in essentially the same regions as Lyme (NE US and upper Midwest), though the areas of very high endemicity are slightly more restricted (MA, CT, RI).
3. Malaria. Both will result in ring-stage trophozoites that appear very similar (although there are very subtle differences, such as lack of hemozoin production in babesiosis). Generally speaking (and definitely in the US), the areas of endemicity of these infections do not overlap. Patients may or may not recall the tick bite. Thus, a good travel and exposure history is key!
4. Fever, chills, headache, sweats, anorexia, myalgia. On labs, hemolytic anemia with thrombocytopenia. WBC often low but is variable. High indirect bili/LDH/reticulocytes, low haptoglobin. Finding tetrads of merozoites (the “Maltese cross”, seen above) is pathognomonic.

With severe disease, pulmonary edema, ARDS, DIC, splenic rupture, and shock can occur.

1. Age >50, asplenia (either anatomic or function), immunocompromise including HIV/AIDS or organ transplant.
2. Visualization of parasites on blood microscopy (thick/thin blood smears) is definitive. PCR is also available, but may not result in clinically relevant timeframe. Serology is also available but even less likely to be of clinical utility (may be negative in acute infection, persists after infection resolves). Maltese cross appearance is rare but pathognomonic, more often ring stage trophozoites are seen.
3. Blood product transfusion, primarily pRBCs. Rarely platelets, which are contaminated by residual infected RBCs. Organ transplant possible but very rare; same is true of transplacental (vertical) transmission.
4. Atovaquone 750mg BID + azithromycin 500mg daily for 7 – 10 days is the first line therapy. Atovaquone is oral; azithro can be oral in milder disease, or IV in more severe infection. The alternative, older therapy for severe infection is clindamycin 600mg IV q6hr + quinine 650mg PO q6hr. This latter regimen is associated with greater risk of adverse effects, primarily due to the quinine (cinchonism).

In the setting of immunosuppression or asplenia, therapy may need to be extended up to 6 weeks.

In very severe, life-threatening infection with severe hemolysis (Hgb <10) and high parasitemia (parasite burden >10%), exchange transfusion may be of benefit.

Case 3 Answers:

1. Human monocytic (monocytotropic) ehrlichiosis, caused by *Ehrlichia chaffeensis.* Ehrlichiosis can produce inclusions within monocytes called morulae. These are uncommonly seen in ehrlichiosis (<10%), but are much more common in anaplasmosis.
2. Acute viral syndromes including HIV, RMSF, tick-borne relapsing fever, tularemia, Heartland virus. Rash may be present, though not as commonly as with RMSF; if present, also consider meningococcemia, secondary syphilis, rat bite fever, typhus.
3. Ehrlichiosis is transmitted by the *Amblyomma americanum* (Lone Star) tick. This tick can also transmit *Ehrlichia ewingii* (rarer form of ehrlichiosis), Heartland virus (looks like ehrlichiosis but does not respond to doxy), tularemia, Bourbon virus, and STARI.
4. Human granulocytic (granulocytotropic) anaplasmosis caused by *Anaplasma phagocytophilum*, also from the *I. scapularis* tick. Patient is coming from an endemic area and the morula here is in a neutrophil, not a monocyte/macrophage.
5. History and location of tick bite are helpful, as is identification of tick if available. Fever, headache, myalgia, malaise all extremely common. Rash in about 26% of ehrlichiosis, only 5% of anaplasmosis, no eschar. Leukopenia and thrombocytopenia with elevated AST/ALT are typical findings.
6. Peripheral blood smear may show morulae, better chance with anaplasmosis. PCR available for both. Culture difficult and not typically done. Traditional gold standard has been four-fold rise in IgG serology (compare acute vs convalescent titers).
7. Doxycycline (and tetracycline) is essentially the only accepted treatment for ehrlichia and rickettsial infections. Typical duration is 5 – 10 days. It should be used (even in children and pregnant women) unless absolutely contraindicated (history of documented anaphylaxis, SJS/TEN, etc). Rifampin also active against erlichiosis and anaplasmosis, may be alternative. It is not active against RMSF. Alternative RMSF agent used to be chloramphenicol, which is essentially not available in US anymore. Consult ID!

Bonus:

Rocky Mountain Spotted Fever caused by *Rickettsia rickettsii.* Do NOT delay treatment if this is suspected clinically or by history, just give the doxy! It is clear that early treatment given within the first 5 days of illness correlates with survival, and mortality is high in untreated patients. Can be diagnosed by blood PCR, PCR of rash biopsy, or acute/convalescent IgG serology.

