Rounding@IOWA: Tick-borne Illnesses

Transcript

[Upbeat theme music plays]

Dr. Clancy

Welcome to Rounding@IOWA, a continuing medical education podcast, developed by and for healthcare teams. I'm your host, Dr. Gerry Clancy, senior associate Dean of external affairs for the Carver College of Medicine here at the University of Iowa. Today we will learn about the increased risks of tick-borne illnesses across the US. Our objectives include, first, we want our participants and recognize the rising rates of tick-borne illnesses and the causes of those increases. Second, we hope our participants can cite the different tick-borne illnesses our patients may be at risk for and what the different sets of signs and symptoms that they can present with and third we will identify treatment measures and most importantly prevention measures. We have the great advantage today to host two guest experts, Dr. Benjamin Appenheimer and Dr. Jason Barker, to help us sort through all of this.

Dr. Appenheimer is a Clinical Associate Professor of Internal Medicine in the Infectious Diseases Division here at the University of Iowa. He is Assistant Director of the Infectious Diseases Fellowship program and the Associate Clinical Director of Infectious Diseases. He earned his MD at the University of Illinois College of Medicine in Peoria. He completed his Internal Medicine residency at the University of North Carolina and then came to the University of Iowa for his infectious diseases fellowship. Dr. Jason Barker is an Associate Professor of Internal Medicine in the Infectious Disease Division here at the University of Iowa, earned his MD degree from Baylor College of Medicine. He completed his Internal Medicine residency at University of Texas Southwestern in Dallas. He then also came to the University of Iowa for his fellowship in Infectious Disease. Dr. Appenheimer, Dr. Barker, welcome to Rounding@IOWA.

Dr. Barker

Thanks.

Dr. Appenheimer

Yeah. Thank you. Happy to be here.

Dr. Clancy

Well, I just provided our listeners a brief official description of your educational backgrounds and your current titles. I think it's important for everyone to know what kind of drew you to infectious diseases in the first place. And let's start with Ben.

Dr. Appenheimer

Yeah. So, I've been asked this question several times over the years and noticed that I've answered it in several different ways depending on how I'm feeling that day, which I think just goes to show that there were several aspects of ID that really drew me in. Thinking what initially drew me was an interest in microbiology and a fascination with the idea that these, you know, microscopic organisms that are all around can have such huge impacts on the human body. And then branching off of that, the fact that that there are different drugs that have been developed that can kill these microorganisms while leaving the host, you know, relatively unharmed. And so, I think that the scientific basis of that is really what interests me and part of that probably is my mom is a microbiologist and my dad is a family medicine physician. So, I just became kind of like, a combination of those two.

Dr. Clancy

What a great story, and I couldn't agree more with the interesting aspects of infectious diseases. Jason, how about you? What drew you to infectious diseases?

Dr. Barker

I remember two kinds of things. First thing is that I loved puzzles. If you wanted to think about the aspect of medicine, that is Sherlock Holmes noticing the detail, putting it together in a way that's you hadn't noticed at first. That's what I ended up loving and I figured out pretty quickly in med school that I was not going to be a proceduralist. I just figured it out. Think a lot of us do and we don't, you know, figure out which direction we're going to go. And then the other thing is when I was studying in Med school in the first year, year and a half, I just loved bugs and drugs. It was something I was good at, and I did a little bit of infectious diseases, pathogenesis research in my third and fourth year at Baylor with Dan Musher and that sort of put the hooks in me for wanting not just to practice ID, but also think about how infectious diseases happen.

Dr. Clancy

Great. Great. Well, I remember my favorite day in medical school first year was when we got to start doing unknowns in the microbiology lab, and I was just thrilled by how that whole flow diagram would actually work. And I think I was first in the class to come up with the unknown. So, I almost got there with infectious diseases as well. So, Jason, let's stick with you. What does a typical work week look like for you?

Dr. Barker

So, at this point in my career, I have a lot of educational oversight role, so I'm spending a lot of time as a course director for one of the preclinical medical school courses, but also a strand director overseeing the mechanisms of health and disease throughout the four years of the curriculum. So, a lot of my time is spent on that. And then the other time is clinical. It's the inpatient consult services or the outpatient consult services or outpatient HIV care.

Dr. Clancy

Got it. Ben, how about you? What's a what's a work week look like and I know there's a lot of variety.

Dr. Appenheimer

Yeah. So, I think this kind of goes back to the first question as well. One of the things that drew me also is just that no week is the same. Every week is a little bit different, a lot of what I do is similar to Jason, General ID consults and I also have a virology clinic that I spend some time in. I do consults both here at the university campus, the downtown campus and then also out in North Liberty and then have some medical education roles, usually around the fellowship, but also spend some time teaching the residents and medical students.

Dr. Clancy

And your consult service is one of the busiest in the hospital as well, I noticed that. Psychiatry is really busy too, so we cross a lot of paths. Before we talk about tick-borne illnesses, let's review ticks and their life cycle as it pertains to humans, because it's been a while since I learned that. What are ticks and how do humans play a role in their life cycle and their ability to exist in this environment.

Dr. Barker

So actually, for the ticks we're talking about now, humans are not part of the life cycle. We're sort of incidentally infected. They don't need us. And furthermore, the pathogens that we're gonna talk about that are spread by the ticks also don't need us. We're sort of the dead-end hosts, so to speak, for those pathogens. The life cycle that's really most important for us to think about is the one for the Black Leg tick because that life cycle affects how we think about Lyme disease. When we are infected and when the risk is highest, they have about a two-year life cycle and there's a sort of an initial first year period where they, you know, will feed as larvae. But then in that second year come out as nymphs and they're still quite small and it's that nymph stage. Because it's so small we can't see it. Because of their behavior because their interactions with humans, that tends to be where

we get most infections with Lyme, and it tends to be the late spring, early summer and there's a final feed in the fall later, it's less likely to get infected there, but that's the relevance and I think the take home point of this is that the tick that usually spreads disease can be extremely small. Really if you look at a picture, it's like the nymph is barely, you know, like visible is one of the letters on a dime kind of thing, meaning that you don't always see the one that gotcha. There's a common statistic that you know, 50% of people with tick-borne illnesses don't recall a tick bite. That's true. Now 100% were exposed to a tick of course. So, they were clearly in some setting where they could be exposed, but the point is we just don't see the one that got you.

Dr. Clancy

Ben, anything you want to add?

Dr. Appenheimer

No, I think that sums it up pretty well.

Dr. Clancy

So, as you mentioned, lyme but lyme isn't the only factor here. So, what different infectious organisms can ticks perform as really the carrier or the vector?

Dr. Appenheimer

Yeah. So, I think you know there's a variety of different organisms that can be transmitted from ticks. These include bacteria, parasites, and viruses. Some are obviously more common than others. When I think about clinically what we see in the United States, there's really five. I think that stands above the rest. And then there are a handful more that are either very rare in the United States or only seen in other countries. Five that we kind of think about clinically include Lyme disease, which Dr. Barker already mentioned, anaplasmosis, ehrlichia, rickettsia and then babesia. The Lyme disease is transmitted by a bacteria called Borrelia burgdorferi. It's a spirochete. Meet the three that will probably group together relatively frequently in this talk and anplasma, ehrlichia and rickettsia. Those are all obligate intracellular bacteria, and then the other one I haven't talked about is babesia, and that is a parasite that really kind of mimics malaria in addition to those, there's a handful of emerging viruses. That is rare and harder to diagnose. These are kind of case reports of things including the Heartland virus, Powassan virus, and bourbon virus. And then, you know, if you go outside of the US, you know, that opens up a whole other list of things that we have to. Think about.

Dr. Clancy

So, a little bit more on ticks. What makes them efficient as vectors for these infectious diseases? What makes it all? Work for them.

Dr. Barker

For one thing, we tend not to feel the bite. There are aspects of the saliva and their anatomy that make it so that we don't notice. The saliva turns out to be quite important, even on a species level. Turns out lyme and many of these organisms are very specific to which species of tick they'll be spread by. There are a lot of reasons for that. I think one sense that you can take away is that the ticks have evolved really specific sort of amazing mechanisms for the sort of adaptations they have to do? If you think about it. That the Organism, for instance, has to for Lyme has to get maintained in its reservoir of the mouse. But then it has to go to a tick and then. Back to. Other mammals, and it turns out the Organism actually regulates certain surface proteins in a way that are specific to the tick versus specific to being in a mammal. And those are required and that sort of results in a particular sort of distribution, a certain kind of vector and therefore a certain set of interactions with us. So, I think you can generally think about some, you know, anatomical and then maybe the tick saliva, but then it gets really complicated and specific to each Organism after that. Generally speaking, though, for everything we're talking about the reservoir in nature where these organisms have to be maintained. These pathogens we're talking about are tents, is rodents. So that's where we have to somehow. Be in contact with something that took the Organism from a rodent, ultimately to us.

Dr. Clancy

And you know, the climate is changing. What are we seeing regarding incidents and severity of tick-borne illnesses now because? You both have been practicing this for a while and it's in your wheelhouse as far as following this. What's happening as far as number of cases and severity of cases.

Dr. Appenheimer

Yeah, I think you know, overall, the numbers of tick borne illnesses that we're seeing has been increasing. I was looking at some reports that show that overall, they have more than doubled over the past 20. Years, I think some of that may be due to better diagnostics, but also, I do think we're seeing more and more true cases. You know, I wouldn't necessarily say that the severity is increasing on a per case basis, but just with more infections overall, we are seeing, you know, an increased number, absolute number of severe infections. What we're seeing. You know, I think you know what is associated with things like climate change and other factors. Is that the expanse of the ticks are spreading, so the geographic

distribution of the ticks is a really important thing. When we think about who's at risk for different tick-borne infection. And I think we are seeing that spread you know increase. So, for example the tick that spreads Lyme anaplasma and babesia has been spreading N into Canada. And actually, I would say some S into the Iowa as well. And then there are ticks that transmit things like ehrlichia and Rocky Mountain spotted fever that have. Basically, been South of us in Missouri and across to North Carolina. But we're seeing more of those cases in southern Iowa as well. So, kind of we're getting squeezed from both ends due to the increased distribution of ticks.

Dr. Clancy

Great. And how do changes in climate really benefit the tick? What happens? It allows them to spread like this.

Dr. Barker

I think one way to think about it is that there's sort of a chain of transmission and also a chain of or a certain set of factors that favor a tick being able to survive in an area. And they really have to come together for humans to get infections. What? I mean, it turns out if you look back over the last 100 years, a couple of factors have been important, particularly for the black leg tick, the that the deer tick that we're gonna talk a lot about, it turns out reforestation was a process because these ticks tend to prefer forested areas. Another issue is if we build out as our suburbs or towns or cities. Into areas humans are at this interface, and that's turns out to be very important. The deer population that maintains the tick does not seem to maintain the, for instance, the Borrelia or the other microorganisms, to my knowledge, but it does maintain tick population and the ticks overall life cycle that's changed a lot too. In fact, my understanding as we've seen an increase in many parts of the countries in deer populations. And then there's the fact that the traditional factors that just kind of quickly went through don't seem to explain the most recent changes that have Ben alluded to this sort of inexorable westward and southward move the black legged tick and the general spread. Of others, it does raise the issue that climate is having a role, but again the exact mediators of that aren't clear to me. It seems to be, though, yes, it's spreading. We don't understand exactly why the traditional factors don't seem to predict how it's spreading, but it is spreading. And as Ben mentioned in my career here, I've been here since 2002. We've gone from a situation where lyme was virtually always imported and HGA and and babesiosis which are also spread by that same black leg tick. Were also imported, but now we definitely see those acquired in, not just Northeast or eastern Iowa, but now into the Iowa City area for instance.

Dr. Clancy

I agree and you know I live right on the edge of town, and I feel like I'm experiencing a much wilder environment. For sure for sure.

Dr. Appenheimer

And I think that it kind of it goes without saying, I think, but as Dr. Barker alluded to, in order to get tick borne infections human have to come into contact with ticks. And so, whether that's because, you know, we're starting to expand out and housing into more forested or rural areas or even, you know, change in the recreational activities that people do, I think more people are going outside doing hiking kind of interacting with nature. And so, with that, I think also the increased risk is seeing.

Dr. Clancy

I'm going to put you in the position of both you know, a first presentation, primary care physician as well as you as infectious disease specialist. And you know, as these increases in tick-borne, illnesses recur. How might these illnesses present with our patients and what are the signs and symptoms to be on guard for?

Dr. Appenheimer

So, you know, I think when thinking about the clinical presentations and things that we look out for, I think it's important to distinguish between the different tick-borne infections that kind of I alluded to before because they present in very different ways. And of the five that I mentioned before, two of them have very distinct presentations. So, Lyme disease and Babesia have presentations that are separate from any of the others and you know relatively easily distinguishable. And then the other three ehrlichia, anaplasma and rocky mounted spotted fever have a lot of overlap in how they present. With Lyme disease, if you're thinking about first contact, you know there's a few different variations of Lyme. But for early lyme, we think of that targetoid rash, that classic kind of erythema migrans that that resembles that target lesion. And that's generally what you would see from a primary care physician's office for those patients who aren't recognized at that stage. There are more unique presentations that you can. See with early disseminated lyme and that can include things like carditis which can lead to a heart block that can cause a meningoencephalitis among several other things with Rocky Mountain spotted fever, ehrlichia, anplasma I think of those with a similar presentation, which is fever leukopenia. Elevated AST and Alt and thrombocytopenia along with oftentimes a rash. So, whenever you. That collection or that syndrome, so to speak, that should be on your mind as far as potential causes. You know there's a wide differential for those but definitely thinking about tick borne infections especially you know in the correct season in the correct geographic

location for the presentation of babesia. This is very unique and the way I kind of think of it as it mimics. Malaria. So, if I ever am thinking of malaria in a case where a patient has never traveled to a malaria endemic. Area then Babesia is on my mind and those are things like hemolytic anemia, fevers, hepatosplenomegaly and the way I kind of remember it as far as geographic location, I think of it as if I'm thinking of malaria and Martha's Vineyard, that's kind of the way I think about it. So, if I'm thinking of malaria, it's someone who has a lot of exposure to the Northeast. Or now, as Dr. Barker mentioned, expanding more into Wisconsin and Michigan and coming down into Iowa, you know, then I think of babesia.

Dr. Clancy

So, in your interview, you really do look at travel and geography. And absolutely, yeah, that's something we psychiatrists do near as much. So you've alluded to this, but let's just get back a little bit to the severity of this. You know the if you've kind of missed some of the hallmark symptoms, how sick can the patient get? And you mentioned before we started that sometimes the ICU is involved.

Dr. Barker

Yes, Ben and I, as practitioners at the university in a hospital, oftentimes we see the cases where people have ended up needing to be admitted or even in the ICU. So, one sort of way to progress is with those three that Ben mentioned together that have kind of a non localizing. Presentation at first, sometimes a rash, of course, Rocky Mountain spotted fever can have a rash. About 50% of the time on initial presentation, Monocytic Ehrlichiosis, says the rash rate is on the order of 25 to 30% and published series, but otherwise it's not really well localizing. And if someone doesn't think about tick borne disease. And let. Say I've seen cases call it like a community acquired pneumonia because maybe they had a lot like assist or something and they get on a standard regimen for that. If it progresses and the diagnosis is missed, some of those people will recover, but especially with Rocky Mountain spotted fever, which has an untreated mortality rate of about 25%. Those diseases can really progress and put you and make you sick and even cause mortality. So that's the sort of set of diseases that you can think about having that really high acuity kind of multi organ failure in the ICU setting. It's also. Why? I think we often talk about how there's this dictum or, you know, Ward lore, saying that you never let someone die without a trial of doxycycline because that is clinically kind of how you end there. You said wait a minute. I'm. I'm treating this person appropriate for X&Y, but wow, they sure are still sick. And if you can kind of. Go back to the beginning, reset your process a bit, and if you did miss the possibility of tick-borne disease. That's a way to then get back on track and then and to try the Doxy. Fortunately, Doxy is very well tolerated, treats a lot of the things we're going to be dealing with here in this talk and we could talk about treatment more later, but that's one way that

people end up progressing. Now the other way of course to progress and babesia by the way can also progress to very severe disease, especially in people. Again, analogous to malaria. Who don't have a spleen. It's also been regarded to be a more tenacious and more severe infection. People with various kinds of immune suppression. That's a little bit more of a specialized topic, but that's another one for babesia. And of course, for Lyme, it really does progress through different stages than I think the analogy we can use is to another spirochete illness. That can mimic a lot of things, and that's syphilis. And I find it useful when talking to students and to residents, fellows, colleagues, to think about, you know, the stages of Lyme. And I think that Ben alluded to this initially. It's kind of a generalized mild illness with the red classic, erythema migrans rash kind of a classic target lesion. Although of course, the Organism didn't read our textbook and doesn't know how it's supposed to look. But that's the classical appearance. But then when you get to sort of second stage presentations out three to six weeks ish, you get central nervous system, you get aseptic meningitis. You can get the bell's palsy, lyme carditis, so that can happen if you miss it. In one case. I do remember I think it's a very as a new faculty with someone who had been in Rhode Island because this is back before we had too much of our own lyme, we still had some, but this was an imported case and his local provider had thought about Lyme sent Serologies, which were negative. By the time I saw him though, he had not just one, you know, migrans rash, but he actually had multiple ones all over his body and he had a carditis of the heart block. So it was a situation where the provider did the appropriate thing, which was to think about lyme, but then it turns out that for the early stages of lyme, we have to understand how, first of all the delay in getting the diagnosis, but also the limitations of serology early really can bite you, so to speak, and really in that case with that person's presentation, they just should have received doxycycline. And they wouldn't have ended up in my office and in the in the hospital. So that's one. Pointy two we can get into diagnosis a little bit later, but it really is important to recognize those stages early because and then the third stage of the lyme I want to mention and I think Ben mentioned is you can get late arthritis, it's kind of an all like arthritis that can kind of resolve. Mostly. But then come back and move around and then there are very odd and unfortunately in this country, rare central nervous system syndromes you can get later, which can be quite thorny to diagnose, quite difficult. So really, it's distinct to the different organisms, the sort of first four we talked about. Again, those can progress to severe disease and then Lyme has its own kinda a story and I think about it in the three steps.

Dr. Clancy

I should have asked this earlier, but is it? Is it typical for these pathogens? Are they? Are they producing A toxin that is causing the trouble? Or is it the bacterial agent itself?

Dr. Barker

So, I'm a pathogenesis person. I used to think about this in quite a bit of detail, so I'm gonna. I'm gonna rein myself in here a little bit. It varies too. The different organisms. So, for the anaplasma and ehrlichiosis, they're called granulocytic anaplasmosis and monocytic ehrlichiosis because they're kind of telling you where they're infecting. They're infecting. Particular white cells that generate a lot of inflammation, and of course, we know that poorly regulated, you know, high levels of inflammation make us sick and can cause sepsis and organ failure and so forth. So, I think for those we. Think about how they infect the white cells and the consequences of that for immunity are really what make you sick. The other thing though, I think about for Rocky Mountain spotted fever, which is the most severe, most life threatening of what we're talking about here today. They infect endothelial cells well and there's some images I showed to students to sort of give them a powerful pneumonic for this. But if you think about it, you have endothelial cells everywhere, right? The rash that you see. You can think about it. Well, that's the endothelial damage associated with that rash. But of course, we have endothelial everywhere. And if those get damaged, they generate inflammation. And thrombosis all sorts of hallmark pathogenesis pathogenetic factors of sepsis, you get extremely sick. So that's what I think about for rickettsia then for Lyme. Oh, goodness. So, you got to think about it's got to go and persist in a human that's hard to do right. It's a microbial world and we just live here. So, when I think about it and but despite the fact that we're surrounded by all these organisms, it's really a very tiny list that can hack it in a human. So, to speak, and it turns out the Borrelia and there's not just lyme there's a bunch of different Borrelia, really have a bunch of interesting ways to vary their surface, to interfere with complement. There is some evidence to indicate that they really kind of spill a lot of their cell wall material called peptidoglycan. And that for some of the arthritis cases, that's particularly important to generating a lot of painful, persistent arthritis. So, I'm gonna stop there because you could go on. But there are particular stories, you know, for each Organism. I mean, one way to think about it is when I teach to the students and residents, you know, organisms. Diseases kind of have a story. Sometimes the story is that they have several stories or stages of their story, but there is a reason for each of those, and there are ways that these organisms have evolved to survive in a way they do. And we can see that.

Dr. Clancy

Fascinating. Ben what would you like to add to that?

Dr. Appenheimer

I was just going to add that questions like that are why I'm glad that Dr. Barker is on this podcast along with me because he answered that way more eloquently than I.

Dr. Clancy

Well, you know, even us as psychiatrists, our favorite question is why? So, you know, I sometimes just press, you know, why is it doing this? Why? And I mean, certainly COVID taught us this that that. You know, here's a coronavirus causing all these very complicated issues. And it all started with inflammation. Absolutely. You know, I was actually Speaking of code. It was really late to get COVID. I did not get COVID until 2024. And but post my post COVID experience I had a. Little bit of pots. Or orthostatic hypotension for a while, about six months out. And it was very strange. So, you know, you mentioned a lot of things that these. Pathogens can do as far as impact of white cells impact on endothelial cells. So, let's say you've come, you've come through a pretty serious episode of one of these tick borne illnesses. What can you see as far as some of? The long-term impacts.

Dr. Barker

Can I first say one thing really quickly and I think it's important because I want to give the good context for what's an excellent question. I do want to say that the vast majority of people that we treat for these infections do just fine. And I say that because I definitely see a lot of anxiety about some of the tick infections where people. Say they got doxycycline for Lyme or for Ehrlichiosis or something, and they immediately get referred. They think they're always going to have, like Lyme, particularly that there's they think it's a thing that you're sentenced with. And I should say, and this we have data for this that the first thing to say is that most people, especially when they're treated early and we'll talk about that, do just fine. And I want to sort of assuage, you know, our practitioners here and lay people listening that we can treat this stuff. It's all the more reason to get it early, but we can treat it. That said, certainly you can see, you know, persistent symptoms analogous, I think, to what we see with COVID. I don't know that it's identical, but it's certainly analogous.

Dr. Clancy

Yeah, I mean they it, it was for me with COVID, you know it lasted a little bit, but then it was gone. And you're right, I'm totally fine. So when do you guys get involved? You. Now tell me. Cause clearly this is a set of symptoms that's gonna present to most of the time. Primary care may be the emergency room, but when does Dr. Barker and Dr. Appenheimer get the consult?

Dr. Appenheimer

Yeah, I think there's a few different times and a few different ways that we get in. Involved, you know, the first way that I'm thinking of is during the diagnostic stage. So, this would be not as much, I guess mostly for things like our ehrlichia anaplasma that can be a little bit more indolent, but clear that something's going on. You know these patients sometimes

can come to us with, you know for outpatient consult for fever of unknown origin or I think the last one that I saw was a hospitalized patient who had had fever and weight loss for three weeks that they couldn't figure out what it was. And so, there's those situations where there's a little bit of diagnostic uncertainty and it's clear that there's something going on often associated with fever. So, people lean towards infection, so they reach out to us to help them get to the bottom of what it is and what's happening. And so that's one way that they come to us. A second way would be those really severe presentations. Things that require hospitalization, ICU's things like that. And so, a lot of times with that, it could be, as Dr. Barker alluded to before, but babesiosis usually in a patient without a spleen or who's immuno-compromised. Sometimes that can become very severe with DIC and a RDS and things like that. Lead to poor outcomes Rocky Mountain spotted fever, I think is the classic one that can progress the quickest. You know, I was looking at this a little bit in mortality rates. Even if the diagnosis is delayed just 8 or 9 days can be up to 50%. And so those are cases where patients are getting very sick very quickly. And so, we may get consulted there, there are certain. Stages of Lyme disease and in certain presentations of lyme that require IV antibiotics, you know specifically, like Lyme encephalitis and things like that, and severe Lyme carditis as well. So those are situations where we could get pulled in more for the management stage. Not that there's a diagnostic uncertainty. They know what's going on, but they just want our help kind of guiding to make sure that antibiotics are appropriate.

Dr. Clancy

You both mentioned you know that doxycycline is a is a common treatment, but what does treatment look like, particularly in the acute phase? And is it antibiotics plus other things? I really don't even know where to start, and obviously we have different agents. But what are your first recommendations? Usually when it's been made clear that we've got tick borne illness.

Dr. Barker

We give doxy, yeah, but that'll cover four of the five you think. Remember. So Babesia is a parasite if you remember from Med school or whenever you last were thinking about malaria. There are particular kinds of drugs we think of actually as anti malarials. Right. That's almost the mechanistic class. But there's of course diverse. But so Babesia will require its own sort of unusual regimen atovaquone azithromycin combination kind of thing. But for the other is, it's just given Doxy and you know give it the way that you think the patient will absorb it. Oftentimes it's still internal, but sometimes if you know in certain settings if you have possibility of nausea or perhaps, you're worried about sepsis and perfusion and stuff, you can give at least the first couple doses IV, but that's it. And as far as adjunctive measures, I'm going to say the vast majority of time, no, it's just get the

diagnosis right. I will note that there is an entity that probably requires its own episode. If you haven't done it already, which is. Kind of hemophagocytic lymphohistiocytosis or one called a variety of. Different things, but its kind of hyper inflammatory syndrome that has many different triggers. But one of the triggers that we know of is actually common ones or some of these tick-borne diseases especially the rickettsiosis and particularly the Monocytic Ehrlichiosis. So you can have a setting where the Organism was there, set-off tremendous illness you treat and in very rare cases you then have to invoke something more complex like that which does require different therapy, won't go into here. And that's actually a very difficult diagnosis to make. So that's its own story. But that's one thing to sort of be aware of that people can come in, for instance, with one of these syndromes and rarely when you get to the ICU kind of evolve to that hyper inflammatory syndrome with a very high mortality.

Dr. Clancy

But what I think you're saying is that if you can get ahead of the bug and start, you know, killing off the bug, the inflammatory. Stuff calms down pretty quickly.

Dr. Barker

That's right. Like we know for many problems in life, the earlier you get on it, the less of a problem you have that the rates of success of treatment are vastly better when you catch it early.

Dr. Clancy

And when do you get the diagnosis right and you get the cycline on board. How quickly does the patient turn around? Often. What does improvement look like with that really sick patient, but they finally get the antibiotic they need.

Dr. Appenheimer

Yeah, I would say most people we see improvement relatively quickly. I mean usually within a day or two, you at least have seen some improvement to where you know that you have the right drug on board.

Dr. Appenheimer

Sometimes it can take a little bit of time for patients to get back to their baseline, obviously, especially for those severely ill patients. You know, just like any other severe illness where it kind of takes a long time to get back to baseline. But overall, especially if caught relatively early, we start to see improvement, I would say within a few days.

Dr. Clancy

And what does testing look like? You know where we have a major pathology lab here and such. So how quickly does the lab testing help you with the diagnosis? Do you still have to wait several days sometimes? Or is it pretty quick?

Dr. Appenheimer

Yeah, I will. I guess I kind of attack this a few different ways, but the first point would be that most of the time we are treating this before we have a definitive diagnosis. So, most of the time based on the overall clinical presentation, we are starting empiric doxycycline while we're waiting for the testing to come back mainly to make sure that we have the right diagnosis. So, we don't have to keep thinking about other things. But oftentimes the patients are getting better by the time we get the testing back. And it's a little bit more complicated than that because each of the organisms we've talked about, the testing is a little bit different, but I can kind of walk through those a little bit 1st and just cause this is the easiest one for Rocky Mountain spotted fever. There's no good tests that will be back in time for the patient to still be alive if you don't treat it, you know there's the PCR that the Rocky Mountain spotted fever. Organism does not really doesn't have a tropism really, for the bloodstream, or doesn't stay in the bloodstream, and so even serum PCR's that come back, you know relatively quickly aren't great for the diagnosis of Rocky Mountain spotted fever. We're really reliant on serologies, which by the time we get the serologic testing back, you know the patients in that you know 8 to 9 days or whatever as I referenced before, you know could be severely ill and so I actually you know as you mentioned before, I did my residency in North Carolina where Rocky Mountain spotted fever is endemic. In the summer time, almost any hospitalized patient where we that we had a fever and we didn't have a diagnosis would receive doxycycline while we were kind of sorting things out just because it's a diagnosis, you don't want to miss, but there's no good testing that's back in a reliable amount of time. For ehrlichia, anaplasma, we do have PCR testing, but even those can take a few days to come back and because doxycycline is relatively well tolerated, safe, able to give you know orally a lot of times if we have a high enough suspicion to test you know we will start treatment and then we can monitor clinically it's important to. Send the testing before starting the doxycycline though because it doesn't take. Long for the doxycycline to, you know, decrease the sensitivity of that testing for Lyme disease. It's a little bit more complicated. We don't have a good lyme serum PCR and so it's we were reliant on serologic testing and the serologic testing isn't very specific. And so the recommendation is to do two tiered testing and there's different ways that different labs do this, but really, we send one serologic test, and if it's positive or suggestive of Lyme disease, then they send the second type of testing, either Western blot or another serologic test, to confirm the diagnosis. This and so that's one thing, and that's only good. You know that that

is not sensitive in the earliest lyme where we see erythema migrans. So, kind of similar to what I mentioned before with the clinical presentation is key for early lyme with erythema migrans. It's really you see the rash, you give them doxycycline. And the testing will likely be, you know, negative early on. And then kind of going on to babesia, there's a few different things that you can do there, but one of the best is probably PCR as well. You can also get a peripheral smear and you know we've kind of connected, babesia to malaria in several different ways throughout this podcast. And this is another way the peripheral smear, you can actually see the ring forms. And it looks very similar, almost indistinguishable from malaria. And so that's another way you can kind of get to the diagnosis is probably the fastest way to look for the diagnosis of babesia. But we'll often send serum PCR testing as well to try to, singe the diagnosis. And that has a little better sensitivity.

Dr. Clancy

Interesting. So, do you guys still do the smear yourself?

Dr. Barker

No, unfortunately it's not like the old days. One thing that is a clue that I think we should mention and that is thrombocytopenia and even a kind of relative leukopenia, something about particularly anaplasma, ehrlichiosis and Rocky Mountain spotted fever cause a certain kind of either consumption or. Margination or something that provides that clue and clinically that can be a really important one also, especially when they look sicker and then you get their white count. It's like, huh. Now of course, sepsis can cause low platelets. But when you see low platelets, you definitely use that as an additional sort of mark on the on your diagnostic process to think, OK cause you tick-borne infection and also the relative leukopenia despite the fact that someone can be unwell is another kind of clue. So, it's not just it's of course the red cell smear can be useful. For babesia, but you can sometimes actually catch the monocytic religiosas as a mom. Formula in the white and in the monocyte mononuclear phagocyte or in for granulocytic anaplasmosis you can actually see the Moria. The Organism in the neutrophil. So yeah. So, the, the CBC and the smear are going to be helpful in a lot of these conditions potentially.

Dr. Clancy

Very helpful. And I'm sure, Jason, as you know, work with the students on the ID. Service. You can go back to the first and second year medical school and highlight. You know, This is why we talked about this, yeah.

Dr. Barker

I have to be careful because I know where everything's taught right, so I. Have all this. And they, you know, sometimes it's just like, oh, you know, they didn't teach. Us that it's like, no.

Dr. Clancy

Yeah, we did.

(laughter)

Dr. Barker

Yeah, there's a lot to remember. I'm not. I'm not holding it against you. I certainly forgot a lot too. But let's talk about it again, you know, so, and of course, there's a lot we didn't have time to talk about, but no. So yes, we definitely try to sort of pull those useful concepts forward and show them how the foundational science helps you understand things.

Dr. Clancy

Yeah, you know, I love watching Dan McCabe and the toxicology service come back and, you know, teaching basic pathophysiology from this toxin did this to you. So yeah, it's one of the reasons why working in Med school is so great.

Dr. Appenheimer

And I think those kind of pattern recognition things that that Jason was referring to is how we kind of get the how do I want to say this, how we get tick borne illnesses honor differential to the point where we treat before the testing comes back is you see a patient you know in the hospital and they're febrile and they have you know leukopenia thrombocytopenia. And fevers, you know, to us, that's OK. This patient needs doxycyclin while we're considering other things as well. But that that's a high suspicion. And then when we're thinking about Babesia, it's the hemolytic anemia that kind of can point towards that direction along with the smear that we already talk. About but if you see someone with a, you know if you check an LDH, it's an elevated low haptoglobin lower hemoglobin in this. In this setting you know then that is what kind of triggers us to go down that route of Babesia. And then yeah, as we've talked about before, lyme is a little bit more complicated cause there's various different stages, various different organ systems that it can affect. And so that one there's not really that pattern recognition. Quite as much as there are with the others.

Dr. Clancy

Great, great answers. I love it. So, let's switch over. Prevention efforts and I'll tell a little story. I was about a decade ago, I was working with the World Health Organization, and I was headed to the Amazon. And went to the health department, County Health Department and the County Health Department. Nurse was so excited about all the different vaccines I was going to get. And then? Proceeded to tell me for about one-half an hour about how to coat my clothing with DEET and all sorts of high dose prevention methods. So, what guidance do you have for clinicians guiding patients on prevention and frankly, when you guys walk in the woods, what do you?

Dr. Barker

So one thing to sort of I think something you could picture to help you understand is that there are pictures out there, this footage out there of the how the ticks quest and they kind of you know crawl out on the edge of a leaf blade and then stick their arms out, they're sticky and they just wait for someone to come by and then crawl up and find a spot to nibble on. Yes. And so that is what you're sort of up against. So, I will, you know, I obviously it gets hot. I grew up in Houston, I know about dealing with hot weather, but like you know, I do try to sort of cover. It is important to know that DEET oil of lemon, eucalyptus and picaridin are all things you can wear to decrease mosquito bites that also have an ability probably not as potent. But some tick repellent properties. So, if you know you're going to be out, especially in uncut grass forested areas, the edge of forested areas. If you know that, especially if you know there's lyme in your area, then you can sort of cover up and you can use these products to and some of them are OK for clothes, others aren't. But you can use those to decrease the chances of tick by it. And then there's what to do if you find one and we can talk about that now. But the idea is that if you're in an area with very high prevalence. Of the borrelia burgdorferi. The Lyme disease agents in the black legged ticks. It's recommending that the arbitrary number that I've read is 20% and that's actually pretty high. Some, you know, counties. For instance, in Wisconsin, Minnesota, that's the number that there's just lyme everywhere. If you find a tick within 24 hours, then you can pull it off. And it's not complicated this, you know, you can. Use tweezers or something to sort of carefully get the mouth parts out to and remove it safely and decrease to zero. Essentially a chance of getting it. Unfortunately, once you get to 24 hours, especially to 48, we talked about how long you know that these agents you asked earlier about how they have to adapt to us, right? How do they do what they do, how are they good at this and what turns out that lyme has to do is go from one program, which is I'm sitting in the ticks gut turn on a different program, which is I'm going to go into the mammalian blood. And then just and then go into the mammal and that fortunately for us for lime takes at least 2024 hours plus. So, the point is if you have been out, you can check your legs, you can especially check your trunk.

That seems to be a spot where they can hide it and if you. Lucky you can catch it again as we talked about earlier, it's often the nymph for Lyme, for instance, that spreads it. And it's just really, really small. But there is a chance for you to remove it and then also if you're in a very high prevalence area, if you didn't get to it within 24 hours, you can take a higher dose of doxycycline once and that can reduce not to zero the chance of developing Lyme as far as we know, these just stay tuned. These recommendations could change a bit, especially with respect to where we do it. Generally speaking, in in our area here in central and central eastern Iowa, it's currently not technically that high that I know of that. Yeah, that could change. It might be that high in, in, in Wisconsin, it is that high in some parts of Wisconsin, Minnesota weather. That's true. Say on the bordering areas of Iowa, I'm honestly not sure. I don't think so. I haven't heard that, but that can change quickly. So yes, you can prevent the bite initially with the various measures, barriers, and those products. And then if you are bit there are things you can do to decrease the chance of the line we have, you know removal within 24 hours and maybe a dose of. Doxy big dose.

Dr. Clancy

Ben, anything you want to add?

Dr. Appenheimer

Yes, I can add a few things. I think some practical approaches that I take in order to prevent to being able to attach is 1 is you can wear bright colored clothing which then makes the ticks stand out more if it's on your clothes, you know, so something that you could really see that tiny black. Dot. So that's one thing. And the other thing, as long as you don't care how you look, which I'm past the age where I care that much, you can tuck your pants into your socks and then that, you know, cause a lot of times that you'll be walking through grass as the ticks will get on your boots or your socks, and then they can get up to your legs underneath. And then you don't find them because they're harder to look for. And so, if you tuck them in, then they stay on your clothing. Can't get to. Body and then you know if I'm in a really highly endemic area, you know, I'll even change clothes after I've been out hiking or things like that just to decrease the risk that they could migrate up the clothes to the spot where they could get to. So those are a few small, you know, practical things that you could do. I'll comment on the prophylactic a little bit. I looked at the guidelines for this recently. It's pretty, I guess, specific as far as who it's indicated. Before, and part of this was based on, you know, one of the studies they did that showed that while it is effective, most patients even in highly endemic areas that get tick bites don't get lime. And so, you know the study that led them to you know recommend this prophylaxis was done in a place where there were 50 to 100 cases of Lyme or 100,000. Patients and in order to into study, it had to be identified black legged tick. So, the known tick that will transmit line in that highly

endemic area and the tick had to be attached for greater than 36 hours or be engorged. And even with that, the number needed to treat was 40, so you'd give 40 doses of doxycycline to prevent one erythema migrans. And the argument that some people will make is that you know, as we mentioned before, if you catch Lyme early at the erythema migrant stage, the, you know, morbidity, mortality, those sorts of things are very low. And so, you know, usually when I when I've had people here in Iowa that have had concerns and they don't meet that. Criteria, I just say where the tick bite was is where you get the erythema migran. So, if you found the tick. Just keep an eye on that area, look for evidence of a rash. If you see any erythema or anything that's concerning, let me know and we'll give you a course of doxycycline. But because they don't meet the criteria for that prophylaxis for most of the places here in Iowa, that's the approach that I've taken.

Dr. Clancy

Really good advice, you know, to our listeners, they can't see the video here, but Ben is wearing neon orange, and his pants are tucked in. His socks. So.

(laughter)

Dr. Appenheimer

You never know where the ticks can get these days.

(laughter)

Dr. Clancy

That's right. You are both, you know, seasoned clinicians, but you still got a long way to go in in your career. What do you see as far as kind of future trends as far as tick borne illnesses? What do you see as far as needing to inform the public about the risks here and what do you see as far as some treatment options, anything that is on the horizon? That is helpful or anything that is worrisome.

Dr. Barker

I would say that we're probably going to learn the names of some new organisms. With an increase in molecular diagnostics and this has already happened to some extent, we found these organisms that are somewhat related to the ones we know about that cause similar syndromes, maybe not as severe, maybe not as frequent. So, you'll hear about some new ones. We've there's some we haven't mentioned today, we don't really need to. That can cause a Lyme like disease or can cause a. Say anaplasmosis like disease, but aren't that exact same agent again. The good news is Doxy works. So that's the bottom line as far as you know, there's really a need to as, I think, Ben alluded to earlier to improve our serologic

testing for Lyme because it leaves a lot to be desired false positives for false negatives early and there is work there to try to improve the serology by a variety of ways. It turns out that Organism does not cause a clinically or analytically significant bacteremia. Definitely disseminates, but for whatever reason it's just not something we tend to be able to even detect, even with molecular methods, so that may be a bridge too far, but we might get. I expect that we will get better algorithms. Things that we can use with sort of really much better optimized serologies that's my hope anyway.

Dr. Appenheimer

Yeah. When I was thinking about, you know, this question, I think the biggest thing I could think of was diagnostics and not that I know of anything down the pipeline, but I think that's where the biggest gap is right now is having rapid, accurate diagnostics that will help us determine. Or diagnose these more rapidly. I think as far as treatment goes, because doxycycline tends to be so effective, it's so safe, there's no resistance. You know, I don't think that there's been a big push to look for. Other therapeutics for these agents, but from a diagnostic perspective, there's a lot to be desired at this point.

Dr. Clancy

Well, you guys have been fantastic and the scientific nerd in me has really enjoyed this. So, as we close, what are some of the take home points you'd like to leave with our? Listeners and Ben, let's start with.

Dr. Appenheimer

Yeah. I mean, I think the biggest thing is just, you know, awareness that these are out there and learning the early diagnostic signs as we have kind of alluded to the things how these initially present, whether it's the subtle lab abnormalities like the thrombocytopenia and leukopenia or the erythema migrans, just kind of have these on your radar be thinking. Them and then just need to know that a lot of times we end up treating these with doxycycline empirically based on clinical presentations. The other thing I guess that I would mention mainly because we haven't touched on it yet is we have alluded. To the fact. That multiple of these organisms lyme, anaplasma, babesia are all transmitted via the same tick vector and that can lead to coinfection and so there can be times where, especially if they're Co infected with babesia, that doesn't respond to doxycycline, where you can get, you know, a clinical presentation that you think is classic for something like Lyme or anaplasma you give them doxycycline, they get better initially. And then there's this deterioration later. And so just remembering that those three. And we can go along together. And so, if there's a mixed presentation, you could have more than one Organism.

Dr. Clancy

Great point. Great point. Jason, how about you? Any particular highlights you want to leave with? Listeners.

Dr. Barker

Now I would just emphasize kind of what Ben had said about sort of having scripts or sort of you know the heuristics, the kind of pattern recognition to say, OK, for this pattern, let me at least add you know the tick-borne disease to the list. I think the non-specific non localizing infection and then you start to look at the skin then you start to look at the. Hematology and CBC and stuff really just having those again, just add them to the list because you often will not make the diagnosis, you won't start the doxy or the right treatment if you don't think of it. And that's really where it is. You got to think a bit.

Dr. Clancy

And as you guys both really highlighted the travel history really does. Play a role as well. Yeah, very much so.

Dr. Appenheimer

And I think too, you know, I would, I would add that I think here we think a lot about Lyme disease. We test a lot for Lyme disease. It's on a lot of our differentials. I don't know that they're ehrlichia anaplasma, those are at the forefront of people's minds. And so, so those because those don't localize, they are more nonspecific in their presentations. Those are things that I would just encourage people to keep on their mind and think about, especially given the trends that we've alluded to before where we're starting to see these, you know, more and more.

Dr. Clancy

Well, you both have been really great guests. And so, Dr. Appenheimer and Dr. Barker, thank you so much for joining us today. And thank you for your great work in preventing and fighting the really ever-changing world of infectious diseases.

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