

Newly Recognized Spotted Fever Group *Rickettsia* as Cause of Severe Rocky Mountain Spotted Fever–Like Illness, Northern California, USA

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[D. Peter Drotman] This podcast series is brought to you by *Emerging Infectious Diseases*, often referred to simply as EID. I'm Dr. D. Peter Drotman, Editor-in-Chief. EID is an open access, high impact, peer reviewed scientific journal published monthly by CDC. EID publishes articles on new and reemerging infectious diseases that occur anywhere around the world so as to improve the understanding of factors involved in disease emergence, control, and prevention.

[Candice Hoffmann] Hi, I'm Candice Hoffmann. On this episode of the *Emerging Infectious Diseases* podcast, we're discussing a newly recognized type of rickettsial bacteria called *Rickettsia* CA6269.

[Anne Kjemtrup] My name is Anne Kjemtrup. I'm a veterinary epidemiologist in the vectorborne disease section of the California Department of Health in the Center for Infectious Diseases. Here, I focus on tickborne disease epidemiology, and among these diseases are the rickettsial diseases, which we'll be discussing today.

[Candice Hoffmann] That was Dr. Anne Kjemtrup. She is one of the authors of an article in the July 2024 issue, titled, "A Newly Recognized Spotted Fever Group *Rickettsia* as the Cause of Severe Rocky Mountain Spotted Fever-like Illness in Northern California."

Many people have heard of Rocky Mountain spotted fever (also known as RMSF), but fewer are aware of how serious a disease it can be, with deaths occurring in several US states every year. RMSF is one of a group of diseases caused by closely related bacteria, called spotted fever group *Rickettsia*. It is one of the most severe of these diseases, which are primarily spread through the bite of an infected tick.

To set the stage for this episode, Dr. Kjemtrup will tell us about spotted fever group rickettsioses.

[Anne Kjemtrup] The symptoms of spotted fever group *Rickettsia* are varied in both the severity and the presentation.

Let's start with Rocky Mountain spotted fever, which you mentioned is one of the most severe diseases. So, people with Rocky Mountain spotted fever may first show symptoms that look like many other diseases. So, it includes a fever, a cough, chills, body aches. And then pediatric cases often present with really nonspecific stomach pain. In these initial few early days of disease, Rocky Mountain spotted fever can look like many other diseases—flu, appendicitis, or even in some endemic areas could look like dengue. So unfortunately, Rocky Mountain spotted fever can progress rapidly to a life-threatening disease as the organism wreaks havoc on the body.

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So, the spotted part of Rocky Mountain spotted fever often refers to the tiny red dots or bumps that form. These are often described as a macular or maculopapular rash, and that may appear around two to four days after the start of the disease. And then this rash may develop into what's called the petechial rash, and that implies that these small dots are in fact small breaks in blood vessels under the skin. And this is a very serious manifestation since similar breaking of small blood vessels is likely occurring throughout other organs, causing damage. The rash is said to spread from the hands and the feet to the trunk, though this pattern is variable. It may at first appear on the trunk, it may not appear at all, and in folks with dark skin it may be difficult to see. So, without prompt doxycycline treatment, patients with Rocky Mountain spotted fever can go on to develop some really serious disease which includes gangrene of the digits, pulmonary distress requiring ventilatory support, neurologic involvement, and kidney failure. And mortality estimates actually even in the face of treatment range anywhere from 4 to up to 40%. So that's why rapid treatment with doxycycline is so key to prevent these complications and death. And in fact, our two cases of *Rickettsia* California 6269 clinically looked like Rocky Mountain spotted fever.

Other spotted fever group *Rickettsia* do not have as dramatic a presentation. For instance, both the tickborne *Rickettsia parkeri* found in the Southwest US and the Pacific Coast tick fever caused by *Rickettsia* 364D in California produce a febrile illness accompanied by what is called an eschar, which is basically a scab. And that's usually at the tick bite site where the *Rickettsia* cause a necrotic lesion.

So, this is also treatable with doxycycline and in some cases, patients have been hospitalized for support. In other parts of the world, tickborne spotted fever group *Rickettsia* have similar eschar-like diseases, and these include things like African tick bite fever, Mediterranean spotted fever, and tick-borne lymphadenopathy or TIBOLA in Europe. And we actually see travel related cases of these each year.

[Candice Hoffmann] While rashes are a common symptom of spotted fever group rickettsioses, they don't always present the same way.

[Anne Kjemtrup] When we hear the word spotted fever group, we want to see a rash. We want to be able to say, "oh, fever and rash, therefore it's Rocky Mountain spotted fever." Unfortunately, the presence of the rash is variable. It can occur... estimates vary anywhere from half to more cases. But because it doesn't always present from hand to feet to central or it's on the trunk, it can look like a viral exanthema or a viral rash. So, it's something to be aware of. And, you know, when we talk about awareness to physicians about this disease, one of the things that we really emphasize is to have awareness, to get tick bite history, to get exposure information. Have you traveled? Have you been exposed to animals? That sort of thing, particularly in face when other diagnostic tests are not coming up what, you know, people would expect. It's really important to try to get that exposure information.

[Candice Hoffmann] Spotted fever group rickettsioses are on the rise and have tripled since 2010. The authors stressed the importance of identifying the specific pathogens that cause these illnesses.

[Anne Kjemtrup] It's really important to identify these specific pathogens precisely because these spotted fever group are on the rise. And this can help us...this test can help us identify and understand the disease better and start treatment sooner and can also help us understand the epidemiology. So, one of the reasons why spotted fever group *Rickettsia* are on the rise is that the commonly available serologic diagnostic tests, which is used to commonly test for spotted fever group *Rickettsia*, cross-react across so many *Rickettsia* species. And thus, we have some cases that we classify as probable in the official case definition established by the Council of State and Territorial Epidemiologists because they have compatible clinical signs and a single elevated titer. However, we can't necessarily say that that titer represents a clinical current condition, past infection, or an infection with a related organism. So, this molecular test can really specifically identify the organism, can help inform clinical decision making such as treatment choices, and help clarify if the patient is indeed infected with a *Rickettsia*. And knowing who and what is infected can also help us understand where the patient may have been infected.

Another reason why spotted fever group *Rickettsia* are on the rise is that we are actually detecting the presence of different species of *Rickettsia* in under-recognized tick vectors such as the brown dog tick or *Rhipicephalus sanguineus*, which is responsible for Rocky Mountain spotted fever transmission in our Mexico-California border region. So, a specific test, such as what we describe in the paper in the larger epidemiologic picture, can really help us guide in studies of other tick vectors, mammalian reservoirs, maybe exposure to people and animals—this is all information that's going to help us in the big picture to develop prevention messages.

[Candice Hoffmann] Testing and prompt treatment are important when patients have symptoms of Rocky Mountain spotted fever and other spotted fever rickettsioses. These diseases can be deadly, but they are treatable with doxycycline, a commonly prescribed antibiotic.

[Anne Kjemtrup] When a physician suspects a rickettsial disease, often they will administer doxycycline right away. And that's really our best-case scenario. And that way, that will really prevent progression to other diseases. Unfortunately, we have seen cases that present very confusingly in areas where physicians are not aware, *Rickettsia* is not known. And these are the cases that sometimes become the most tragic, where they can go on to develop gangrene, or, you know, even die actually. Really what we want to emphasize is getting an early diagnostic test, the molecular test, even if it's a *Rickettsia* species only. That is really important. We like to encourage testing for serology but because the antibodies don't develop for quite a while, the molecular test is a great early test. Then we can encourage sending that sample to reference laboratories such as ours or the CDC where we can characterize it further. And again, that's going to help us know how to develop more messaging for people. Where are you going to go and encounter this disease? What is that? How do you prevent it? All this is important information. It may not seem important right there in the moment for the person who is sick, but if we can get

that and the antibiotic in them, that's great. And then secondarily, we can, in the larger picture, prevent future disease.

[Candice Hoffmann] The authors of this article described two cases of *Rickettsia* CA6269, which is a newly discovered pathogen. Let's hear from another one of the authors.

[Kerry Padgett] Hi, I'm Dr. Kerry Padgett. I'm the chief of the high-risk pathogen section at the California Department of Public Health, and I've worked on tick-borne *Rickettsia* for decades, both in field and laboratory studies.

[Candice Hoffmann] That was Dr. Kerry Padgett. She described the two cases discussed in the article.

[Kerry Padgett] It was an exciting series of follow-up molecular tests after discordant initial test results that first pointed to Rocky Mountain spotted fever.

The first case-patient mentioned in the article presented to the emergency department here in the San Francisco Bay Area in July 2023 after experiencing three days of flu-like symptoms. He had no visible rash. He had no eschars. And he was given antimicrobials but not doxycycline.

After three additional days, his symptoms became more severe and included encephalopathy and seizures, and he was moved to the ICU. Rickettsial diseases were then suspected after an infectious disease consult, and he was given doxycycline on hospital day three.

Thankfully, he was able to be discharged, but not after having spent 22 days in the hospital with very severe symptoms that included septic shock, coma, and gangrene of fingers on both hands. His diagnostic testing five days post onset included serologic testing and blood cultures, and they were all negative for spotted fever group *Rickettsia*. But a plasma sample that was collected at day seven tested positive for rickettsial DNA by the Karius Test. This is a test that detects microbial cell-free DNA that's circulating in the bloodstream. Metagenomic sequencing by Karius found a close match with DNA fragments of both *Rickettsia rickettsii* and *Rickettsia slovaca*, which is *Rickettsia* that's found most in Europe.

This residual plasma sample was then sent to the California Department of Public Health's Viral and Rickettsial Disease Laboratory for confirmatory testing. The sample is tested here by an in-house RT-PCR assay and found it was positive for the genus *Rickettsia*, but to our surprise, it was not positive for *Rickettsia rickettsii*. Further comparative sequence analysis found the sequences from *Rickettsia* and the plasma matched, again, neither *Rickettsia rickettsii* nor *Rickettsia* 364D, which Dr. Kjemtrup mentioned is a *Rickettsia* that's more commonly found here in California (it's a spotted fever group *Rickettsia* that causes disease). But it instead matched a genetic sequence most closely to *Rickettsia* CA6269, which is a sequence in GenBank that was described from nymphal rabbit ticks—and these are called *Haemaphysalis leporispalustris*—that me and my colleagues collected in Sonoma County, California, back in 2009. So, this was a completely unexpected result.

[Candice Hoffmann] So, this was the first case of illness caused by *Rickettsia* CA6269 that the researchers reported in this article. They weren't expecting to find it, but the discovery of this case reminded them of something they had seen before, a long time ago.

[Kerry Padgett] We then recalled a similar severe case presentation of what was classified as Rocky Mountain spotted fever almost 20 years earlier in late June 2004, also in a resident of the San Francisco Bay Area. And because of the severe case presentation and the location of the residence of this patient, we wondered if this individual might have been infected with this novel *Rickettsia* instead of *Rickettsia rickettsii*.

Twenty years ago, this patient was diagnosed using serologic testing, so antibodies in a serum reacted to *Rickettsia rickettsii* antigen. And since it's well known that serologic testing is not specific—it can't distinguish among all the different spotted fever group *Rickettsia*—we wondered if this or other Rocky Mountain spotted fever cases in our archive, especially those that were tested by serology, might have also been due to this novel pathogen.

We are very fortunate that our state public health laboratory maintains excellent archives of clinical samples. So, lo and behold, PCR testing and comparative sequence analysis revealed that the 2004 Rocky Mountain spotted fever patient instead had been infected with *Rickettsia* CA6269. So, while this 2004 patient also presented with severe illness, which included encephalitis, sepsis, and coma, additional clinical manifestations in the second case—which actually in time is the first case—included a maculopapular rash on his arms and legs, which is a symptom more commonly observed in Rocky Mountain spotted fever as described by Dr. Kjemtrup.

[Candice Hoffmann] So, chronologically, the second reported case featured in this article was actually the first. However, Dr. Padgett wonders if it's possible more cases could be found by looking back at other samples taken from patients who experienced similar illnesses and might have been diagnosed with Rocky Mountain spotted fever.

[Kerry Padgett] I think this is a really interesting question and not only in our archive, but also perhaps in other archives (CDC, other states), it would be interesting to see if *Rickettsia* CA6269 is actually cryptically, actually been diagnosed as Rocky Mountain spotted fever, especially in those cases that were diagnosed by serology.

[Candice Hoffmann] Another important aspect of this article is the new test to distinguish what species of *Rickettsia* caused a patient's illness. Dr. Kjemtrup told us more about it.

[Anne Kjemtrup] So, this new test is important to differentiate or to really help identify infection with what species of *Rickettsia* people are being infected with. There are molecular tests out there today in some commercial laboratories that allow us to say, "oh, this is a *Rickettsia*, or this is something else." However, with this more specific test, that can really help us hone in on what *Rickettsia* is this, and how the person may be exposed. It can give us a lot more information about these different *Rickettsia*. And it will, of course, help us describe what the clinical array of diseases looks like in this *Rickettsia* group.

[Candice Hoffmann] The new test that was developed is a type of laboratory test known as a PCR assay. PCR stands for polymerase chain reaction. This is a laboratory procedure that is used to detect and identify genetic material, such as DNA or RNA, in a sample. PCR tests are often used to identify specific organisms, such as viruses or bacteria, that are causing a person's illness. Dr. Padgett described the new PCR assay and why it is a groundbreaking development.

[Kerry Padgett] This specific real-time PCR assay for *Rickettsia* CA6269, which was developed by Dr. Will Probert, who is the lead author of our EID paper, has the potential to assist in our clinical testing for *Rickettsia* suspect cases here in California, as well as in other states. Potentially, this new assay can be adopted and implemented by clinical and public health laboratories to provide a rapid and accurate laboratory test for differentiating *Rickettsia* CA6269 from *Rickettsia rickettsii* infections.

[Candice Hoffmann] This new test was developed specifically for *Rickettsia* CA6269 to improve diagnosis and better understand the range of symptoms and how the disease affects people, as well as how it spreads in the environment.

Tick collection was another important aspect of this work. Dr. Padgett told us about how the team of researchers looked at ticks to find out more about potential vectors for *Rickettsia* CA6269.

[Kerry Padgett] Back in 2009 while investigating another spotted fever group *Rickettsia* called *Rickettsia* 364D, which is the agent of Pacific Coast tick fever, we collaborated with colleagues from Georgia Southern University and the CDC to test rabbit ticks for spotted fever group *Rickettsia*. But instead of finding *Rickettsia* 364D, we found a novel *Rickettsia*, CA6269, in larval and nymphal rabbit ticks—again, these are *Haemaphysalis leporispalustris*—collected at a park in Northern California.

While rabbit ticks are common ticks throughout North and South America, they have a huge range. It extends from Alaska all the way down to Argentina. They very rarely bite humans, but they can be really important in transmitting and maintaining spotted fever group *Rickettsia* among rabbit hosts and potentially can contribute to transmission to people.

So, more recently as follow up to the two severe novel *Rickettsia* cases, field investigators were able to collect American dog ticks and Pacific coast ticks, which are two *Dermacentor* species of ticks, but weren't able to collect any rabbit ticks. None of these ticks tested positive. So, to date, the only tick species that has tested positive for *Rickettsia* CA6269 have been rabbit ticks.

So, while rabbit ticks may be the vector of this *Rickettsia* to humans and should certainly be the focus of investigation, it is wise to cast a very wide net to test other tick species that may more commonly bite people. The vertebrate reservoir hosts and the geographic distribution of this agent are currently unknown. But thankfully, the *Rickettsia* CA 6269 assays should facilitate environmental studies that will help us understand how this novel *Rickettsia* is maintained in nature by identifying potential vertebrate reservoir hosts, arthropod vectors, as well as defining its geographic distribution.

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[Candice Hoffmann] Future environmental studies might uncover more about how *Rickettsia* CA6269 spreads and answer some of the ongoing questions about what types of ticks may carry it and how it may spread to other animals and to people.

In the meantime, Dr. Kjemtrup has an important recommendation that healthcare providers can follow now.

[Anne Kjemtrup] If we haven't conveyed the message enough, I'm going to emphasize it again as our number one recommendation is if they suspect a rickettsial disease to commence treatment with doxycycline, regardless of the patient age, right away. It should not be delayed awaiting test results. And in assessing a febrile patient, really getting information about tick bite exposure and travel history can be really to help think about *Rickettsia*. So, the development of the CA6269 test emphasizes the importance of molecular testing for *Rickettsia* detection. So, serologic tests are widely available commercially, but since antibodies don't develop for seven days, it can actually take a little longer to think about this disease. So, the molecular testing is available in some commercial laboratories and though can't necessarily provide species-specific identification, it can prompt rapid treatment. And then we would recommend for those positive samples to be sent to reference laboratories such as the CDC or our viral and rickettsial disease laboratory. And public health surveillance recommendations then should focus on identification of these cases to better describe the clinical course and outcome. You know, we only have these two cases to date. So, identification by molecular testing of suspect fever cases, or as Dr. Padgett mentioned, other samples from previous studies, that really might help us understand and get a better understanding of the scope of disease and will ultimately be a benefit in case management. And then also with this diagnostic tool, it can really help us focus on the identification of the tick vector and the mammalian reservoirs. So, the rabbit tick, as Dr. Padgett mentioned, is our focus. And so, this test will really help us look at this tick and others.

[Candice Hoffmann] There's also something all of us can do to avoid *Rickettsia* CA 6269, and a host of other tickborne diseases.

[Anne Kjemtrup] Last, but definitely not least, we have to focus on what people can do to prevent getting the disease and that is to prevent getting bitten by a tick in the first place. So, the California Department of Public Health, the Centers for Disease Control, we both have very comprehensive websites on tick bite prevention. But I'd like to highlight a few aspects about tick bite prevention related to the *Rickettsia* California 6269. So, when in natural areas where these ticks can be found, it's really important to look for these ticks that may crawl on you. And since we really suspect that it's the earlier life stages—so like, the really tiny nymph and larvae that are transmitting it—you really have to look hard. And to say that you're looking for a poppy seed is not an exaggeration. These are tiny. And then you need to do a complete body check when you're at home. And one way we also try to encourage people to look for these tiny ticks is to say, look for a new freckle. Maybe there's something there you didn't see. So, it's really important to get these ticks off because *Rickettsia* can transmit pretty much soon after the tick attaches. And so, to take a tick off, it's taking tweezers or one of these tick removal tools and grabbing the tick as close to the mouth part as possible and pulling straight out. Really, the easiest and the most

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important thing people can do is to plan for prevention. And that means when you're going out into these areas, think about using a tick repellent that contains 20% DEET or picaridin, which you can use on your skin or clothing. Or you can use permethrin-treated clothing and hiking gear before going outdoors. So really, tick avoidance is the key.

[Candice Hoffmann] The authors of this article hope that their findings will lead to further research on *Rickettsia* CA6269.

We asked both Dr. Padgett and Dr. Kjemtrup what would their advice be for future researchers who want to know more about this disease.

Dr. Padgett sees the importance of a culture and of enhancing testing.

[Kerry Padgett] So, in discussing this question with my colleagues, the first thing that everybody said was, we need to obtain a culture. A culture would allow for research on reservoir and vector competence for this new pathogen, and a culture would allow for high-quality whole-genome sequencing, which opens up the doors for all sorts of additional studies. For example, comparative genomics of *Rickettsia* CA6269 with other spotted fever group *Rickettsia*, such as *Rickettsia* 364D and *Rickettsia rickettsii*. It can also inform the pathogenesis of these agents, some of which are highly pathogenic, such as *Rickettsia rickettsii* and others more mild like *Rickettsia* 364D. Furthermore, whole-genome sequence data that are publicly available will streamline development of assays to detect this and other rickettsioses.

Currently, specific testing for this *Rickettsia* is only available at our California State Reference Laboratory and the CDC. So clearly, development of additional tests, point-of-care clinical tests would be, you know, obviously ideal, and would assist in understanding this pathogen and support accurate and rapid diagnosis of patients, which is important for all rickettsioses.

In terms of our understanding of this disease, we are working with colleagues at local vector control agencies, state vector biologists, universities, and the CDC to identify those tick species that are infected with and those that could potentially transmit CA6269 to people. I'm happy to report that hundreds of ticks, including rabbit ticks, have been collected this summer in the San Francisco Bay Area and are awaiting testing. So, this is going to be key to making a culture isolate of *Rickettsia* CA6269.

And lastly, a culture isolate of this *Rickettsia* will help determine if this agent meets the current criteria to be given a new species designation. We've suggested the name *Rickettsia lanii* in 2009 after the entomologist Robert Lane, who spent a long career first at the California Department of Public Health and then at University of California at Berkeley working on tickborne diseases in California, including *Rickettsia* and rabbit ticks.

[Candice Hoffmann] Dr. Kjemtrup sees how vital collaboration will be.

[Anne Kjemtrup] What I have seen with *Rickettsia* research is collaboration is key. So, they really are the quintessential One Health organism because they do involve the health of people, the health of animals. They are emerging in areas where socioeconomic conditions promote that. And we have now a variety of different ticks involved. So, you know, as you heard from Dr.

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Padgett about some of our future research needs, we need molecular biologists and laboratorians to be able to get us those isolates. We need epidemiologists and vector professionals to be out and collecting these ticks. We're doing some of that work in collaboration with UC Davis (University of California at Davis), down at the border regions. And certainly, we try to involve as many people as possible. And we have been contacted by different research groups who focus on different aspects, and we welcome those collaborations and those contacts.

[Candice Hoffmann] After hearing this podcast, we hope that you will want to read more of *Emerging Infectious Diseases*, like Dr. Padgett has been doing for a long time.

[Kerry Padgett] I might even have in my office some of the paper copies. So, when I first started at the California Department of Public Health back in 2003, that was one of the first things I did. I thought it was very mature of me to have a collection of *Emerging Infectious Diseases* on my shelf, and I haven't thrown them away. So, I've been a long-time reader and I really still check in, even though it's not on paper anymore.

[Candice Hoffmann] Or, you can take Dr. Kjemtrup's word for it:

[Anne Kjemtrup] So, I don't think you can call yourself an epidemiologist and not be a reader of *Emerging Infectious Diseases*. It's not only a great way to get out the information and the research that you do to the people who know and will understand and will take action on what you say, but it's also a great way to get that information. So, yeah, definitely a regular reader.

[Candice Hoffmann] Thanks for listening to our podcast. You can read the *Emerging Infectious Diseases* journal at cdc.gov/eid. You can also follow EID on X and Instagram @eidjournal, and on LinkedIn @eid-journal.

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