Rabbit Fever in Organ Transplant Recipients

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hi, this is Sarah Gregory, and I'm talking to Dr. Matthew Kuehnert, who's calling in from New Jersey. He's the medical director for MTF Biologics, which is the nation's largest tissue bank, and an associate editor with *EID*. Dr. Kuehnert was previously with CDC and has done another podcast with me about infections in transplants. Today, we'll be discussing an article about tularemia infection being spread through organ transplants. Glad you could be with us again, Dr. Kuehnert.

[Matthew Kuehnert] Well, thank you, Sarah. Thanks for the invitation.

[Sarah Gregory] While you aren't an author on the article, you are clearly an expert in this field. The article is about the transmission of tularemia, or rabbit fever, by way of solid organ transplants. Would you start by telling us about the bacteria that causes rabbit fever?

[Matthew Kuehnert] Sure. Tularemia is caused by the bacterium *Francisella tularensis*, which is a gram-negative organism and most commonly infects rodents, rabbits, and other mammals. It can also infect ticks that feed on these animals. But humans can also be infected. The symptoms depend on the…how the person was exposed to the bacteria. For instance, a person being bit by a tick might give you ulcers or swollen lymph nodes at the site, or inhaling the bacteria might give you pneumonia. So, the classic story, Sarah, is—in fact, this is a typical question on the infectious disease physician boards, on an exam—is that you have a gentleman who's riding his seated 50-horsepower lawnmower in Martha's Vineyard, and he runs over a rabbit, which kills the creature, and then the patient develops a fever and cough. So, as soon as you see that on the exam, the answer is "tularemia," and that's from inhaled exposure. And there was a…there was an article many years ago in the *New England Journal* that looked at this and that rabbits live in shallow nests on lawns. They peek their heads out a little bit, you've got these big lawn mowers and they get run over and that's the way tularemia has been transmitted, and not only in Martha's Vineyard, but in other places in the United States.

[Sarah Gregory] Well, that's sad and disturbing!

[Matthew Kuehnert] Well, if you have a big lawnmower, you know, it happens, but yeah.

[Sarah Gregory] I understand that *Francisella tularensis* is classified as a bioterrorism threat. Tell us about that.

[Matthew Kuehnert] Sure. Well, first I just want to say that there's a fair amount of naturally acquired tularemia in the United States. Every year there are about a hundred cases reported to CDC, but the numbers are going up—in some years, two to three hundred—and it's not clear the reason for that. It's both a tickborne disease and a zoonotic disease, so that could be related to other, you know, changes occurring in climate or in animal vectors.

But concerning the bioterrorism threat, it's a Tier I bioterrorism agent, and that's a big deal. This is because of a number of factors. One, it has a very low infective dose, it has an ability to aerosolize—remember the example of the rabbit and the lawnmower—and also, there's a history of countries developing it as a BT agent. And it's even been acquired in the laboratory when it's been worked on. So, all these things make it a very concerning as a possible biological weapon.

Now, it's not spread person-to-person, but exposed people who do get sick, get sick at a high rate. So, that's really the concern.

[Sarah Gregory] Okay, so, how common are infections transmitted by transplants?

[Matthew Kuehnert] Well, in general, just looking in general for transplant-transmitted infections, unexpected events are very rare. And it's less than…far less than one percent of all organ transplants. The difference between unexpected and expected are important, because viruses are commonly transmitted through organ transplant, such as herpes viruses, like Epstein-Barr virus and CMV—EBV is the virus that causes mononucleosis—and most people are exposed and are infected by these viruses at a very early age. So, it's commonplace to test the donor and test the recipient and treat, as needed, with medications and by changing immunosuppression. Also, bacteria can be transmitted when the resistant antibiotics or, again, it's unexpected from the donor.

What we're talking about here and what was published in the article, is when the cause is an emerging pathogen and causes severe complications. And because of the rarity of those sorts of events, the benefits…it's important to understand that the benefits of an organ transplant far outweighs the risk of remaining on the transplant list. So, transmission of emerging pathogens are very unusual and should not deter an organ candidate from accepting an organ, in general. There's also transmission of malignancies or cancers, as well, but that's also unusual, and probably, you know, a topic for another day.

[Sarah Gregory] Okay, we'll leave it for another day. How are they detected? It seems it would be a pretty complicated process since you're dealing with the recipient and the organs of another person—so, where to begin?

[Matthew Kuehnert] Well, that's a good question. Organ donors are screened with an extremely complicated process. First of all, as you might imagine, you can't test for everything. And no one is proposing that all organ donors, for instance, be screened for tularemia with a laboratory test, because it's just too unusual. There's a limited number of laboratory tests that are done for organ donors. Some would include HIV, hepatitis B, hepatitis C, syphilis, the herpesviruses EBV and CMV that I mentioned just now.

But more aren't done because of a couple of different reasons. One is the timing. The offer of the organ to the recipient has to be done quickly, before the organ loses function from lack of blood flow. So, that decision has to be made very quickly, before extremely complicated tests can be done. And then, also, there's the risk of false positive tests. The more tests you do, the more chance that there's going to be a test where it's positive, but it doesn't really reflect the infection, and we don't want to waste organs.

So, because we can't test for everything, there's also an extensive donor history questionnaire to cover other risks. And that's similar to what's asked for blood donors, but instead, the next of kin of the deceased donor is asked these questions. Now, the issue with that is that it's not always so accurate, because you're asking, you know, someone who's close to the donor, not the donor themselves, but it's the best that you can do. I mean, who knows exactly what you were up to or how you were feeling in the last week. It's sometimes difficult to get that information, but we do the best we can.

[Sarah Gregory] What do we need to do to improve screening in the future?

[Matthew Kuehnert] Well, here's where we get to the fascinating future of what's called "next generation testing" or "next generation sequencing," which is using the sequences of all the DNA and RNA, all the genetic material in a sample from the donor. So, you have a blood sample from the donor, you subtract all the human DNA that's in the sample, and then you look at what remains. And what there are there are all the viruses and bacteria in the sample. We're not quite there yet with the technology, at least not for organ donor screening.

What's interesting is that you might think, "Well, how many viruses is there going to be in the average person's blood?" But, actually, there's a human virome in the patient's blood, and sometimes even a bacteriome, that can be analyzed. So, in the future, what you could have is an ability to analyze for all those viruses and all those bacteria in a person, and then look at the ones that are pathologic or have pathogens, and then screen those donors out *or* put the recipient on appropriate medication to be able to eliminate those pathogens.

For right now, all we can do is we can put groups of tests together on an assay; that's called multiplexing. But even that method is limited right now and, again, the limiting factors are the time needed to do the test and the transport to a lab that can do that test. Again, after a donor dies, most organs last only about six hours. And kidneys are the exception, but even those last less than 24 hours.

[Sarah Gregory] Back to my earlier comment that identifying the cause of infection must be difficult—so, what kind of communication exists between the various clinicians when these events occur?

[Matthew Kuehnert] Yes. So, this is so important. Of course, this isn't the first time that an emerging infection like tularemia has been transmitted through organ transplantation. There have been many high-profile events—HIV; hepatitis C; some might remember West Nile virus; rabies; parasites, including Balamuthia; there was a rodent virus called lymphocytic choriomeningitis virus, or LCMV, and that was transmitted by a hamster, so that's a whole different story—but very similar to the one that we're talking about today in terms of an animal vector.

The thing to remember is that public health investigations and public health, in general, would never know anything about any of these transmissions unless there was an astute clinician, either a transplant surgeon, an infectious disease transplant expert, a pathologist looking at an autopsy, maybe a laboratory tech. All these people might have looked at the patients for one of their tests and said, "Hey! You know, that looks unusual. You know, I wonder if this could have come from the donor?" There have even been investigations started because family members from different recipients were talking together in the ICU waiting room and said, "Wow! All our loved ones have a similar thing, I wonder if it all could be from the same thing."

Now, that ICU story, that happened a long time ago, and putting the pieces together has gotten a lot easier than it used to be. In the last 15 years, an organization that coordinates organ offers to transplant candidates—it's called UNOS—has a function called the Disease Transmission Advisory Committee, or DTAC. And it's made up of infectious disease experts and others to look at events and see if they could be disease transmissions. And if it looks like something of public health concern, then CDC is notified.

[Sarah Gregory] The particulars of this article are about transmission of this pathogen into three transplant recipients. Tell us what happened to them?

[Matthew Kuehnert] So, there were three transplant recipients. The first patient was a kidney recipient who developed septic shock and died. After death, blood cultures, which were taken while the patient was ill, grew an organism that looked a lot like *Francisella tularensis*. So, according to protocol as a possible bioterrorism agent, they sent it to a special public health lab to confirm it.

Now, at the same time that this was going on, the other kidney recipient developed similar symptoms. And they sort of scratched their heads and thought, "Well, you know, what could this be?" And a lot of things happened at the same time. They also took blood and other cultures from this patient. It started to grow something, they weren't sure what it was, and at the same time, they were told that the other patient had died of septic shock. So, they sort of put this all together and added an antibiotic that's used for unusual organisms, like for tularemia—it's called doxycycline. And they happened to guess right. The organism was *Francisella tularensis* and the patient ended up having positive blood cultures, as well, but survived.

There was also a third recipient, of a heart, who had some symptoms after transplant—it's not clear whether it was from tularemia or not, but that patient spontaneously recovered. And that possibly could be because their antibiotic regimen, that was given both before the transplant and after contained an antibiotic that can treat tularemia, fluoroquinolone, such as ciprofloxacin. So, that recipient also survived. So, two patients survived and one, unfortunately, died.

[Sarah Gregory] Okay, well, how was the rabbit fever infection finally diagnosed?

[Matthew Kuehnert] Well, to me, this is one of the most fascinating things in the article. What they did was is they went to the donor residence and looked around the property. They looked for, because they were looking for vectors for tularemia, they didn't find any ticks or deer flies or other vectors like that, but what they did find was two what they described as "animal lagomorphs." And that just means "something that looks like a rabbit." And they were carcasses—all that was left were some bones. So you'd think, "Well, what are they going to do with this?" What they did was is they tested the femur, or long bone, and found marrow in that bone and tested it. And guess what? They found tularemia! What they did is they used a test to look for the bacterial genetic material. And once they were able to sequence that out, they matched it and found it to be indistinguishable from the bacteria that infected the organ transplant recipients. So, that's what I call an elegant study. And they proved the transmission in that way.

[Sarah Gregory] That is some serious disease detection there. So, let me go back just for a second. Who went traipsing through the yard looking for…stuff?

[Matthew Kuehnert] These are investigators from a public health department. I don't think they name what state it was or what, you know, what the particulars were. We only know that is was from the Southwestern United States and it was from tribal lands. So, my guess is—I wasn't involved in the investigation—is that they had folks from the Indian Health Service who were involved, who were onsite and performed these sampling and further work.

[Sarah Gregory] That's quite impressive. Okay, so what's the most important aspect of this study and why is this study important to us?

[Matthew Kuehnert] Well, first of all, clinicians need to think about infections in transplant recipients that might have come from the donor. It's easy to forget sometimes that, after the organ is transplanted, that the person has tissue from another person. And it sounds kind of weird to say that but, you know, you're taking care of a patient, the patient is sick, and you sort of may lose that perspective. But it's important to always keep that in mind and a paper like this reminds clinicians of that issue. You know, it's also so important because, when a patient gets sick soon after a transplant, the first thing the team often thinks of is that the organ is being rejected, and that makes sense, because usually that's what it is. But by increasing the immunosuppression medication, what they're doing when someone is infected with something like this, is stepping on the gas instead of stepping on the brakes when they need to. So, this is not only an article about something interesting and unusual, but something for the transplant community to stop and think about.

[Sarah Gregory] What other kinds of studies on this topic…I don't know, tularemia itself or just organ transplant issues, infections, and then, should be done or would you like to see done?

[Matthew Kuehnert] Well, I think one of them is what I had mentioned before about next-generation sequencing and multiplexing. You know, studies on laboratory diagnostics and screening would be very useful so that a large array of pathogens can be tested for at the same time. The other aspect is trying to compare lab results and the transmissions that we see, with what the answers that come with the donor history questionnaire that I mentioned. It's a really long questionnaire that's given to next-of-kin, and we don't really know how effective it is for organ and tissue donors. So, being able to evaluate that critically with…compared with the transmissions that we see, would be really useful—to look at the questions that, you know, are highly complementary to the lab testing that we already do versus the ones that, you know, really don't matter and just prolong the process.

[Sarah Gregory] Are there questions patients or family members could or should ask or tests they should request before transplantation? I know there's the issue with the timeline, but still…

[Matthew Kuehnert] Sure. The testing and questionnaire are the same for every patient, so really patients and their families should focus on their own benefit of receiving a transplant and what the risk is of turning down an organ and staying on the transplant list. If there's an issue with an organ, either, whether it's risk of infection or organ quality, in most cases it's better to accept that organ. But each decision is different, and that's a decision a patient needs to make with their transplant team. The bottom line is they need to have consent for what they're being offered, and the best consent is the most informed one.

[Sarah Gregory] Alright, well, what is most challenging about all of this, with the transplants, and patients, and family, and what they need to know, and how to deal with it all?

[Matthew Kuehnert] One of the most challenging issues is informed consent by the recipient. Many organs get turned down because they're afraid of catching a disease. And there's an entire category of increased-risk donors for transmitting an infection, but it turns out it really was only generated for HIV risk and hepatitis risk. So, the risk of contracting any of these infections are really miniscule compared with the greater risk of staying on the transplant list. Some forward-

thinking surgeons are even transplanting known hepatitis C–infected organs because they know the recipient can be treated and the patient can get that sort of organ, you know, faster than a hepatitis C–negative organ.

So, transplant teams need to be educated also, as well as the patients, about the risks and benefits, so that they can communicate to the patient in the way that they understand. And this is a big problem in this area right now. There's efforts going on at CDC, Georgia Tech, Northwestern, Johns Hopkins, to name a few, in an effort to improve both the patient education and their informed consent, and also what transplant teams know about the risk of transmitted infection. But a national collaboration on this would be very, very helpful.

[Sarah Gregory] Are you optimistic about the future of organ transplants?

[Matthew Kuehnert] Absolutely! Innovation is always happening, whether you're looking at helping recipients survive longer, detecting new organisms, or making informed consent clearer—all these things are being improved constantly. There's great research going on. So, absolutely.

[Sarah Gregory] So, this is the "tell us about yourself" portion. Tell us about your job. You used to work at CDC, as I mentioned. Where do you work now and what do you do? And what interests you about organ transplants? And, finally, just sort of really personally, what do you do for fun?

[Matthew Kuehnert] Well, I worked at CDC for 20 years and it was great. I was the director of Blood, Organ, and Tissue Safety for much of that time. Now I'm the medical director of MTF Biologics, which is the largest tissue bank in the world. It's a nonprofit organization and a forward-thinking leader on providing all sorts of tissues—includes bone, tendons, cartilage, and skin—from donors to patients who need them. So, saving and healing lives is our mission. We actually also work with organ recovery groups, so there's a tie to organ donation, as well, because organ donors are also tissue donors. So, some of these issues are still things that I work on every day, and it's a very rewarding field. There's always something new in transplant infectious diseases, so it's always interesting.

As far as fun, I moved with my family from Atlanta to the New York City area, recently, in New Jersey, so finding the best pizza places with my wife and kids has been great. And, also, if you follow me on Twitter—@DrKuehnert—you'll know I'm from Western New York, so I'm a big Buffalo sports fan. So, go Bills, go Sabres—some year, they'll win one!

[Sarah Gregory] Okay, well, thank you so much for taking the time to talk with me today, Dr. Kuehnert.

[Matthew Kuehnert] My pleasure. Thank you very much, Sarah.

[Sarah Gregory] And thanks for joining me out there. You can read the April 2019 article, *Francisella tularensis* Transmission by Solid Organ Transplantation, 2017, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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