

# Three Cases of *Bordetella hinzii*, United States

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

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. James Fleckenstein, a professor of medicine and molecular microbiology at Washington University School of Medicine in St. Louis. We'll be discussing three cases of *Bordetella hinzii* syndromes.

Welcome, Dr. Fleckenstein.

[James Fleckenstein] Good morning.

[Sarah Gregory] Let's get started with what is *Bordetella hinzii*?

[James Fleckenstein] So *Bordetella hinzii* belongs to a family of gram-negative bacteria and previously they've really been found mostly in animals, particularly in birds, and only infrequently associated with human infections. And the organism itself is named after a German microbiologist K. H. Hinz, who characterized many of those *Bordetella* infections in birds, particularly poultry.

[Sarah Gregory] Is this the same *Bordetella* as *Bordetella pertussis* (whooping cough) or the *Bordetella* that pet dogs are vaccinated against?

[James Fleckenstein] While it's kin to those bacteria, it's a distinct species. So it shares the genus name *Bordetella*—the organism *Bordetella pertussis* that causes pertussis or whooping cough in humans, and *Bordetella bronchiseptica* that will be familiar to dog owners as the cause of kennel cough.

[Sarah Gregory] When and how was it first identified (*Bordetella hinzii*)?

[James Fleckenstein] The first case that I was able to find actually dates way back to 1995 in humans. And about that time, investigators at the University of Ghent in Belgium actually described an organism that was closely related to another *Bordetella* species known as *Bordetella avium*, which was a known bird pathogen. And the same investigators were the ones who identified that organism now known as *Bordetella hinzii* in the blood of a patient with advanced HIV or AIDS. And this was prior to the ready availability of DNA sequencing technologies that we have today, so the investigators had to go through a series of complicated steps including DNA hybridization studies and fatty acid analysis and analysis of the proteins to actually define it as a new species. And that early paper actually describes another sputum isolate that was possibly *B. hinzii* dating way back to 1957. So it's possible that this organism has actually been with us for a while.

[Sarah Gregory] Okay. So on that note, it has a fascinating history, first not thought to be pathogenic in birds and then either it was misunderstood (sort of what you were saying) or it changed and is now accepted as causing animal disease. But there are very few human infections documented, and even fewer manifestations such as pneumonia and secondary bacteremia. EID published in September, 3 articles documenting it with meningitis, peritonitis, and co-infection with COVID, respectively. Why these 3 cases now?

[James Fleckenstein] The cases seem to have some common features that may provide some clues. Each case relied on a technique known as mass spectrometry to identify the organisms. And that's basically where parts of the bacteria are actually separated based on their mass and charge, and that provides a unique signature for each pathogen. And that wasn't something that

was available in clinical microbiology labs until recently, and the typical biochemical techniques that we've relied on for many years wouldn't have pulled this out as a distinct pathogen. It may have identified it as *Bordetella* as in our case, but really we relied on mass spectrometry to actually identify the organism.

The other thing that seems to be in common in all of the cases that I was able to find in humans is that they have some element of immunosuppression or serious underlying illness. And that might make sense because the organisms seem to lack a lot of the virulence factors that we associate with *Bordetella pertussis* that causes infection in humans.

[Sarah Gregory] And is there something different happening now along those same lines that this organism is manifested in these different human syndromes? I mean, I understand identifying it now because we have better technology, but these different kinds of cases....

[James Fleckenstein] I think it mostly relates to the fact that these techniques (like mass spectrometry) have come online and are being increasingly used in the laboratory. I don't get the sense that the organism is really new and that maybe it has been there for a while, we just haven't been able to identify it routinely.

[Sarah Gregory] And there are no confirmed exposures from animals in these cases that EID published (although some guesses are mentioned). Is this unusual?

[James Fleckenstein] I think in our case, we suggested that maybe the patient had been exposed to birds or animals with an ongoing infection. But we don't really have any clear evidence to date that these are being transmitted from some kind of animal reservoir. And I think it's too early to tell really whether or not there's animal to human transmission.

[Sarah Gregory] And are *Bordetella hinzii* isolates similar to each other in human infections?

[James Fleckenstein] Based on the limited data we have to date, the organisms don't really appear to be all that dissimilar although not all of the isolates have really undergone DNA sequencing, which should really be the best way to tell.

[Sarah Gregory] It seems that the literature is limited to single case reports—certainly these three articles we published are. Is there a similarity to those cultures from animals?

[James Fleckenstein] They don't appear to be all that different from the isolates that have been reported in animals to date. I think what we can say from the data that we have so far is it doesn't appear as if the organisms have required some new virulence factors that are allowing them to gain a foothold in humans.

[Sarah Gregory] For these three cases, maybe I'm being redundant here, but would there be a way to compare the isolates and see if they do have a common source?

[James Fleckenstein] Yeah, and I think, again, the best way to compare them would be whole genome sequencing as was done in our paper and then we could compare those multiple isolates across the board to see whether or not there's a common thread.

[Sarah Gregory] But this has not been done previously?

[James Fleckenstein] Not that I'm aware of. Although, I have come across some pending publications where investigators actually examined cases in their own area (and these were cases of bacteremia), and their own sequencing, although it has not been published yet, suggested that they did not come from a single point source.

[Sarah Gregory] What about the antimicrobial susceptibility profiles? Are they similar, possibly giving us a clue to relatedness?

[James Fleckenstein] One of the problems that we encountered in our case is that there aren't really good, well-defined cut offs for antibiotic sensitivities that we have for most common pathogens. And that's because most microbiology labs haven't really had to deal with these organisms. We did find in our sequencing that there was a novel beta-lactamase gene, and so those are genes that encode enzymes that actually degrade antibiotics like penicillins and cephalosporins. So that is one thing that seems to be in common with all of the genomes that have been sequenced to date. And in that way, they are related.

[Sarah Gregory] Okay. So we've discussed antimicrobial resistance many times on this podcast. So you're saying that there are some antimicrobial drugs that it's resistant to?

[James Fleckenstein] Again, we don't have really good standards for sensitivity and resistance like we have for most other pathogens. So typically we know what concentrations of antibiotics are clinically useful for most pathogens, and that's something we don't yet have for this particular organism. But we could anticipate because of that novel beta-lactamase gene that the cephalosporins and penicillins may not be the best first choice for these pathogens.

[Sarah Gregory] And I think you mentioned immunocompromised. Are those the people who are most likely to get it?

[James Fleckenstein] I think that's the case. Almost all of the cases that I've seen to date have had either some very serious underlying illness. As in our case, patients had had advanced liver disease or overt immunosuppression, similar to the index patient back in 1995 that had advanced HIV infection.

[Sarah Gregory] Okay. So this is a rare disease, or we think it's rare or we're not quite sure it's rare, but how are people getting it? Where are they...I mean, you have to contract it from something.

[James Fleckenstein] I think that the best guess at this point is that these are really opportunists, and they can maybe colonize patients that are already compromised in some way or they find portals of entry through intravenous lines to establish bloodstream infections, or something of that nature. So because they lack, kind of many of the traditional virulence factors, they're probably relying on immunosuppression to gain an entry and gain a foothold.

[Sarah Gregory] So they're just kind of lying around, already there somewhere? That's the part I'm not getting, I guess.

[James Fleckenstein] I think we don't really know at this point. It may be that they're relatively common in our environment and we just really haven't sampled enough to know.

[Sarah Gregory] So... but you don't think it can spread from person to person?

[James Fleckenstein] I don't think we have any evidence for that. You know, the fact that they lack many of the traditional virulence factors that we associate with pertussis, which certainly is highly contagious, and it makes me think that would be not likely.

[Sarah Gregory] So what were the symptoms of these three infections in these three cases? Were they similar?

[James Fleckenstein] Well, they varied depending on the case description. So there was a case of sepsis and a case of meningitis presented with headache and fever, and then certainly shortness of breath and chest pain and fever in the patients that initially presented with COVID-19 infection.

[Sarah Gregory] Apparently we don't really know this because we know very little about it, but can it be like COVID and remain asymptomatic, do you think? If people catch it?

[James Fleckenstein] It's a really interesting question, but we really don't have an answer to that at present. It's not something we've really tried to screen for in asymptomatic patients, or asymptomatic individuals, rather. It wouldn't come as a great surprise since there's not many virulence factors that we associate with the other *Bordetella* that, you know, patients or people could eventually become colonized with these bacteria and not really present with any symptoms.

[Sarah Gregory] Are there specific tests used to detect it now since it's so rare or unidentified?

[James Fleckenstein] Well, certainly there are no rapid tests, and I noted that mass spectrometry can definitively identify these bugs. So if that's not available in your local microbiology lab, the organisms can be shipped off to a reference laboratory, as was done in our case, and mass spectrometry can then be used to identify the organism.

[Sarah Gregory] And you mentioned that you didn't think that penicillin and cephalosporins were best first-line treatment. How is it treated then and if it's difficult? It must be difficult if people don't know how to treat it.

[James Fleckenstein] There are some tests that we can use for organisms for which we don't have standards, and those are antibiotic-impregnated drips that we can see whether the organism grows up to the strip or not, and that can give us some clues. In our case, the organism seems to be very sensitive to a class of antibiotics known as carbapenems. That would include drugs like meropenem or ertapenem that were used in treating our patients.

[Sarah Gregory] And what can happen if someone goes untreated?

[James Fleckenstein] I think, just as we've seen in our case, potentially fatal outcomes if the organism is not treated, particularly in an immunodeficient host. I think our patient presented with very serious infection and was septic at the time of admission and was initially admitted to the intensive care unit. So although it's an opportunist, it's one we don't really want to leave unchecked.

[Sarah Gregory] And as we all know by now, COVID-19 has a significant impact on people's respiratory systems, and one of these cases was in a COVID patient. Does having COVID make you more susceptible to it, do you think?

[James Fleckenstein] We've seen a lot of COVID-19 at this point with nearly 45 million cases and nearly three quarters of a million deaths. And as far as I know, this is the only reported case of coinfection.

[Sarah Gregory] Do you think we'll start seeing more cases of this in the future?

[James Fleckenstein] I suspect that we will see more cases overall, largely because it's in the literature now and I think other clinicians will begin to look for it and may go the next step of actually sending their organisms off for mass spectrometry, which will identify the organism.

[Sarah Gregory] Okay. So you wrote the article (one of the three) about the case of *Bordetella hinzii* in Missouri. Tell us a little bit about that case.

[James Fleckenstein] So this case occurred in a gentleman that had really significant underlying illness, notable decompensated cirrhosis or end-stage liver disease. And he had recently been hospitalized with bacteremia and what's known as spontaneous bacterial peritonitis, which is an infection in the abdominal cavity that occurs in patients with end-stage liver failure. And that was due to another organism (*Streptococcal* species) for which it completed a four-week course of antibiotics. He recovered from that infection and then presented with the recurrence of his spontaneous bacterial peritonitis, this time accompanied by low blood pressure and basically sepsis, that landed him in the intensive care unit.

[Sarah Gregory] And how was it determined that he had *Bordetella hinzii*?

[James Fleckenstein] So our microbiology lab at the VA initially identified small, gram-negative bacteria in his blood and also in his peritoneal fluid. And those organisms were ultimately shipped off to the microbiology lab at the Missouri State Public Health Laboratory where they perform mass spectrometry and identified the organism as *B. hinzii*. Because this was an unusual case, Grace Wang, the resident who was on the service at that time, actually managed to retrieve the organisms and archive them, and then we contacted our friend and colleague Dr. Gautam Dantas here at Wash. U., and he was kind enough with Miranda Wallace and his lab to perform the whole genome sequencing that really nailed down the identification of the organism and allowed us to compare it to what has been previously been published.

[Sarah Gregory] And I know you said it's really hard to identify where people might get it from, but I know in your article there was some speculation. There was a wife that fed wild birds, there was a dog that had a cough, there was a cat with stomach issues. Do you think it's traceable to any of those?

[James Fleckenstein] We can only speculate at this point because we didn't really have access to the animals at the home. It's kind of intriguing but I think it's premature to say that they're definitely related.

[Sarah Gregory] So this patient underwent an astounding number of treatments over a period of time. Did he survive?

[James Fleckenstein] He did survive his *B. hinzii* infection and seemed to respond well to the carbapenems, initially meropenem and then ertapenem. And unfortunately, he ultimately succumbed to his underlying liver disease.

[Sarah Gregory] Since there already exists a vaccine for pertussis and one for *Bordetella* in dogs, can't they be adapted for *hinzii*?

[James Fleckenstein] That's a really interesting question, Sarah. Basically the pertussis vaccine that we use in humans today varies from one manufacturer to the next, but they all contain pertussis toxoid or inactivated version of pertussis toxin. And several molecules that typically allow the organism to stick to the lung or respiratory epithelia. As far as we can tell, *B. hinzii* lacks all of those and so we could anticipate that the pertussis vaccine—at least the one that's used for humans, I don't know about the one that's used for kennel cough—wouldn't actually protect humans against these infections.

[Sarah Gregory] That's a pity. What do you think are the most significant points of these articles?

[James Fleckenstein] I think they point to kind of a constellation of serious infections, including pneumonia, blood stream infection, and as in our case, spontaneous bacterial meningitis and then in the other case, meningitis, that are caused by an organism that won't be familiar to most clinicians, including most infectious disease consultants. And so it's an organism that really hasn't been on our radar screen, and so I think these will serve kind of as an alert to, certainly, clinicians that this is something that we need to look out for.

[Sarah Gregory] Okay. So along the same lines, how do you hope these articles contribute to public health?

[James Fleckenstein] I think they really point to an organism that we need to take seriously. Whether they're very prevalent at this point remains to be seen, but I anticipate that we'll see more over time because of the advent of technologies like mass spectrometry.

[Sarah Gregory] Dr. Fleckenstein, tell us about your job and how you became interested in infectious diseases and *Bordetella hinzii*, in particular.

[James Fleckenstein] I was attracted to infectious diseases very early in my career from the time I was in medical school, and certainly that was amplified during my residency in internal medicine. And it was really a time when a lot of pathogens, including HIV and hepatitis C virus and *Helicobacter pylori* as a cause of stomach ulcers, were all being identified. I think one of the attractive things for many people that enter infectious diseases as a specialty is that it's one where you can be guaranteed that there's always something new on the horizon. And certainly COVID-19, and maybe to a certain extent *B. hinzii*, are examples of the kind of dynamic nature of the pathogens that find their way into humans.

[Sarah Gregory] Yes. Well, it's certainly what keeps the *EID* journal going and these podcasts. I've got something new and horrifying every week to talk about.

In what ways has the COVID pandemic affected your work as a physician and a researcher?

[James Fleckenstein] Certainly from the clinical perspective I think the pandemic has presented some pretty considerable challenges across medicine, not just for infectious diseases. My infectious disease training occurred very early in the HIV epidemic before we really had an effective antiretroviral therapy and we watched many of our patients succumb to their infections. And I think from that perspective I can really appreciate the tremendously accelerated development of COVID vaccines and therapeutics, including monoclonal antibodies that we have at our disposal, that we can use to both prevent infection and treat patients. From a research perspective, the biggest disruption has been to our collaborative efforts, both domestically and abroad. You know, science is increasingly a team effort that requires close interactions between multiple groups. And certainly, there's some of those that just can't be faithfully recapitulated on zoom, and you miss that close interaction with your colleagues and sort of the serendipity of discussions that happen when you're together in person.

[Sarah Gregory] Well thank you so much for taking the time to talk with me today, Dr. Fleckenstein. And also, thank you so much for taking on all three of these articles to help us understand them.

[James Fleckenstein] It's really been my pleasure. Thank you very much, Sarah.

[Sarah Gregory] And thanks for joining me out there. You can read the November 2021 articles, *Bordetella hinzii* Meningitis in Patient with History of Kidney Transplant, Virginia,

USA; *Bordetella hinzii* Pneumonia and Bacteremia in a Patient with SARS-CoV-2 Infection; and Dr. Fleckenstein's article, Spontaneous Bacterial Peritonitis Caused by *Bordetella hinzii*, online at [cdc.gov/eid](https://cdc.gov/eid).

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

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