Crimean-Congo Hemorrhagic Fever Virus for Clinicians—An Overview

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

[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 Hoffman. In this episode of the EID podcast, we're focusing on Crimean-Congo hemorrhagic fever virus, or CCHF, a viral hemorrhagic fever that might not be a household name in the United States but is of significant concern in other parts of the world.

[Gaby Frank] Hi, I'm Gaby Frank. I'm a hospitalist at Denver Health Hospital Authority in Denver, Colorado. I am also the medical director for the Bio-Containment Unit, that is one of the 13 regional emerging special pathogens treatment centers in the US. And I am a professor of medicine for the University of Colorado School of Medicine.

[Candice Hoffmann] That was Dr. Gaby Frank. We spoke with Dr. Frank about a series of papers she and her colleagues published in the May 2024 issue of *Emerging Infectious Diseases* about CCHF.

These articles cover three topic areas: virology, pathogenesis, and pathology; epidemiology, clinical manifestations, and prevention; and diagnosis, clinical management, and therapeutics.

We asked Dr. Frank to set the stage by telling us what CCHF is and how big of a global threat it presents.

[Gaby Frank] So, Crimean-Congo hemorrhagic fever is the actually most widely distributed tickborne viral hemorrhagic fever and is present in over 30 countries. In most cases, actually, it can be sub-clinical or asymptomatic in over 88% of the cases. But in the other part, it can cause severe disease, with a fatality rate that is pretty high. So, it causes a viral hemorrhagic fever. The WHO reports 10,000 to 15,000 cases annually, globally, of CCHF.

[Candice Hoffmann] The virus that causes CCHF is carried by ticks and can be spread to humans through the bite of an infected tick. But it's not spread by just any tick.

[Gaby Frank] So, this type of ticks that actually spread Crimean Congo hemorrhagic fever, they are the rigid shield ticks that are part of the Ixodidae family and the genus *Hyalomma*. The genus *Hyalomma* is the most common. There's two more genus that actually can spread Crimean-Congo hemorrhagic fever, but the most common vector and reservoir for Crimean-Congo hemorrhagic fever are all species from the *Hyalomma* genus.

[Candice Hoffmann] The *Hyalomma* tick has a wide geographic distribution, that is, it is found in many parts of the world.

[Gaby Frank] It's present in Africa, Asia, and Southern Europe. So, all regions that are below the 50th parallel north.

[Candice Hoffmann] And these ticks have some unique behaviors that Dr. Frank finds fascinating.

[Gaby Frank] One thing that is very cool—this is like the little story—is the *Hyalomma marginatum*, that is the most common of all the species that actually transmits CCHF, is called "hunting tick". And that is that this *Hyalomma marginatum* ticks can actually quest up to 400 meters to actually find their host to be able to feed. So, it's known that they will ambush, which is some different types of ticks, but the *Hyalomma marginatum* will actually quest. And that's why they call them "hunting ticks".

[Candice Hoffmann] If, like most of our listeners, you're listening from the United States, you may find it reassuring that these "hunting ticks" don't live here.

[Gaby Frank] We don't have *Hyalomma* ticks in the US. However, they're not the only species that can transmit CCHF. So, at this point, there was a lot of research done with a lot of the ticks that we're used to in the US are the soft body ticks. And those actually are not competent vectors. Even though they can get infected with CCHF, they actually cannot reproduce it and sustain the infection.

[Candice Hoffmann] So, the ticks currently found in the United States aren't likely to spread CCHF.

[Gaby Frank] And this, as I said before, the *Hyalomma marginatum* is the most common of the vectors. It has what is called a two-host tick. So, they will usually when they're in larvae and nymph stages, they will feed from smaller animals such as hares or crawling vertebrates. But when they go into the adult stages, they actually like to feed from bigger animals. And that's when they go to either sheep or cattle. And those are the stages that will go into humans. And they can quest. If they don't find any large animal, they can actually find a human to actually feed. But it's usually not their preference, right? They're trying to stick within animals.

[Candice Hoffmann] This brings us to an interesting point. While the most common way people get infected with CCHF virus is through the bite of an infected tick, it is not the only way. Exposure to the body fluids of an infected animal is another way this virus spreads to humans.

[Gaby Frank] But going back to the modes of transmission. So, the most common one is actually from a tick bite. The second is usually the people who are at risk are people that will work with either animals or they will get exposed to bodily fluids of animals. So, we can think about people working in slaughterhouses, of course, farmers when we're talking about exposure to the ticks, as well as veterinarians.

But healthcare workers, because of nosocomial transmission, is actually considered the second largest risk group at this point. So, even though we say the most common form of transmission is from the tick bite and then the second one was to get exposed to infected bodily fluids, it also goes to if we have a sick person that has virus in the bodily fluids, exposure to bodily fluids of a sick person, and that's why nosocomial infection is a problem.

[Candice Hoffmann] Nosocomial infections, also known as healthcare-associated infections, are a concern for healthcare workers who may be treating patients with CCHF.

Another concern Dr. Frank raised is that travelers could spread CCHF from a region of the world where it is endemic, that is, where it is commonly found, to another region where it is not. In

these places, doctors and other healthcare workers may be less familiar with CCHF, or not familiar with it at all.

[Gaby Frank] So, usually patients will develop…like, let's talk about humans, right? A patient will develop symptoms within like three to seven days of exposure to the Crimean-Congo hemorrhagic fever virus.

So, the likelihood of maybe traveling is low, but you know, global travel actually can get a patient. As in 2023, they had a patient in the UK that actually had recently returned from Central Asia that actually was treated and managed in the UK for Crimean-Congo hemorrhagic fever. In 2009, there was a US soldier that acquired CCHF in Afghanistan and was transferred and treated in Germany.

[Candice Hoffmann] Two healthcare workers were infected after treating the patient Dr. Frank just mentioned. So, this is an example of how travelers can spread the virus to healthcare workers, which might be a way we could see more cases of CCHF in new places.

[Gaby Frank] So, we can see cases that are not necessarily in the endemic area, but because they're traveling. When we're thinking about can the tick be in different places, there's ticks in a lot of different countries that normally don't report disease. So, those are potential places where there could be disease that, so far, is not described. So, recently in the last 10 years, there have been two new countries that reported CCHF where there was no CCHF before—one is Spain, another one is Jordan. So, we know that the area is expanding because there is the presence of the vector.

There are two different ways in which—other than a human getting on a plane and flying after being exposed—there's two other different ways that the geographic area can expand. And one is…they're all a hypothesis and there are proposed ways in which the area can expand, and one is by birds. So, birds actually do not, other than ostriches, all other birds that have been tested don't develop viremia.

[Candice Hoffmann] Viremia, meaning, the viruses are in the animal’s bloodstream and bodily fluids.

[Gaby Frank] So it's not their bodily fluids that would expose people, but they will transfer in a way when they fly the ticks to a different area. So, if the area has the right climate, the tick could actually survive in the area, and if it's infected with CCHF, could be a new area that didn't previously have CCHF and now they do. And the other one is actually international transport of livestock that may…we're not thinking in this case about the viremia because the viremia is very short, but they could be actually infested with ticks that actually have the virus. So, those are two ways in which this geographic area could expand. But, because we said that nosocomial transmission is, and healthcare workers are the second most risk group at this point, it's important to actually think about it and recognize CCHF so we can isolate those patients and treat them appropriately while keeping our healthcare workers safe.

[Candice Hoffmann] You can learn more about how healthcare workers can protect themselves when treating patients who have CCHF in the second article in this series, which focuses on epidemiology, clinical manifestations, and prevention.

Patients who have CCHF won't necessarily know that the CCHF virus is causing their illness. If their symptoms are severe enough, they will seek healthcare. Dr. Frank described for us what some of these symptoms may look like.

[Gaby Frank] As I said before, the majority of the patients will have subclinical disease or like asymptomatic disease. And that's in some series report that is up to 88% of the infected people that will not develop any clinical signs. Those who actually do will usually develop the sudden onset of fever after an incubation of three to seven days. And that fever is associated with headache in the majority of the cases. So, up to 70% of the patients will have a headache. And some of those cases resembles a migraine headache. So, they will also have the photophobia and sonophobia and nausea and vomiting.

[Candice Hoffmann] Photophobia and sonophobia are sensitivity to light and sound, which are symptoms often associated with migraines. However, as Dr. Frank notes, these can also be symptoms of CCHF.

[Gaby Frank] And that's usually, as I said before, three to seven days after the exposure. Some patients will only have what is called the pre-hemorrhagic phase—that is when they have this kind of flu-like syndrome that is very, very uncharacteristic, right? They have fever, headache, maybe muscle aches everywhere. But the other thing that is characteristic that not all the patients develop is the upper body hyperemia. So, they get a redness of like from the upper chest up to the neck and head, as well as conjunctivitis. And that is something that is characteristic, but it's not necessarily unique to CCHF, but it maybe is different than the typical flu-like syndrome that we will see around.

And then usually after three to five days of the onset of symptoms, a lot of the patients will develop the hemorrhagic phase of the disease. That is when they develop…usually they start with some petechiae of the mucosa and the skin and then progress to more severe hemorrhagic disease of like a lot of different…like it's multisystem and multi-organ. And all the fatal cases actually die from multi-organ failure and shock.

[Candice Hoffmann] Dr. Frank described petechiae, one of the symptoms that affects the skin and mucosa, also known as mucous membrane, further.

[Gaby Frank] The petechiae are like small, dotted hemorrhages of the skin and the mucosa and you can see it as small dots that are purplish and if you push on them, they don't disappear, you can still see them. So, they're like small punctate hemorrhages of the skin and the mucosa. The more severe cases after 50% of the patients will have epistaxis or nose bleeds, 35% of those more severe cases will also have hematemesis, that is a gastrointestinal bleed that usually that is vomiting blood. And there have been described cases with gastrointestinal bleed, genitourinary bleed with blood in the urine, big ecchymosis, and that is up to 45% of the patients. Ecchymosis are big hemorrhages of the skin that look like big plaques that are violaceous, or purplish, on the skin. And that's also very characteristic of CCHF. There have been some cases where there are spontaneous hemorrhages on the brain, so there could be bleeding in a lot of different organs and systems.

[Candice Hoffmann] We asked Dr. Frank about CCHF's case fatality rate and what can be done in severe cases that are at risk of becoming fatal. A case fatality rate is a measure of how many cases of the disease result in death.

[Gaby Frank] So, the fatality rate or the case fatality rate for Crimean-Congo hemorrhagic fever varies depending on the series from 5% to 35%. And some series report up to a 60 to 65% mortality. So, when these patients get hospitalized, they're usually pretty severe, and the patients that develop hemorrhages, they're usually pretty severe. There are different scoring systems to have a prognosis of how likely it is that the patient will actually have a fatal course of the disease versus those who will survive. And again, we have all this in the article and different scoring systems that have been used that people can read in more detail, but there's different scoring systems to help us predict. The treatment at this point is supportive care. Even though endemic areas will use some off-label antivirals, the treatment is supportive care and do some organ replacement when necessary, such as hemodialysis when the patients develop renal failure or mechanical ventilation when they're developing ventilatory failure or acute respiratory syndrome.

[Candice Hoffmann] Supportive care is an important part of CCHF treatment, and the paper in the May 2024 issue of EID on diagnosis, clinical management, and therapeutics provides more details on what this entails.

[Gaby Frank] Supportive care will basically will treat the symptoms and the signs of the disease. So, for example, we will…if the patient is bleeding, we will actually give some blood products if necessary and do blood transfusions will actually support the kidney function until the body can actually recover. So, supportive care is IV fluids if the patient is dehydrated, we're going to treat the headaches and the muscle aches. We try to avoid some antiplatelet medications because again, these patients actually do have a bleeding disorder. So, we try to not use, for example, ibuprofen and go to Tylenol instead. We do some other medications to treat pain, but also to treat, if they're bleeding, we need to maybe replace some blood or give platelets or do a fresh frozen plasma if necessary.

[Candice Hoffmann] While there is no approved antiviral therapy specific for CCHF, some antivirals have been used off-label.

[Gaby Frank] So, there's no approved antiviral therapy for Crimean-Congo hemorrhagic fever. There are two antivirals that have been used off-label in endemic areas. One, the most commonly used is ribavirin. And that medication, as well as favipiravir (that is also experimental use), they have been used very commonly. So, there's a lot of case series that are showing better outcomes. The truth is there's no true data showing their effectiveness. So, there's no blind placebo control trials to say that those medications are better than not doing anything. However, those are being used off-label in endemic areas when they have cases.

[Candice Hoffmann] We asked Dr. Frank about what would tip off a first-line healthcare provider that their patient might have CCHF, given that this disease is not endemic in the US, and it may not be one they are necessarily thinking about.

[Gaby Frank] This is where it gets tricky, right? So, I think that everybody in med school or nurse practitioner school or PA school, they always teach you that a good history and physical, like a good history is 80% of the diagnosis. And then when you add the exam, you just get like 90% of your diagnosis is by doing a good history and physical. That's what they teach you in med school.

Reality, on the other hand, is harder because if you have 30 patients in the waiting room, maybe your history is a little shorter than what is recommended. So, I think that reading these articles

and putting information out there is for people to get the curiosity to go and read more about it. So, if they have a case and somebody reports that they just came from travel, they can go and read more and say, will this patient fit this or not? Because, I would say that probably if the ER has every room filled, or the urgent care and they have patients in the waiting room, they may not be asking every single question.

So, I think that when we discuss these diseases that are not necessarily on the news all the time…like if there's an Ebola outbreak, it's going to be on the news. But CCHF is endemic in a lot of different countries and there's always small outbreaks and case reports in different countries. So, it's not something that makes it to the news. So, it's harder to be aware of it and ask the right questions.

[Candice Hoffmann] Asking patients good questions about their medical and travel history may lead to a more accurate and faster diagnosis.

Another topic mentioned in the articles is vaccines. Vaccines are available for many infectious diseases, including CCHF. However, the existing vaccine is currently only available in Bulgaria. We asked Dr. Frank to tell us more about that vaccine and whether any new ones are in the works.

[Gaby Frank] The Bulgarian vaccine is an inactivated virus vaccine that is actually…they use suckling mice brain to actually recover the virus and then it's inactivated. It's been in use in Bulgaria since the mid-1970s. The thing about this vaccine and that the reason why it's not widely available, is because there's no actual efficacy data. So, there has been a decrease in report of cases in Bulgaria since the introduction of the vaccine, but there's no placebo control trials that actually say that the vaccine is the one that is actually preventing the CCHF cases.

At this point, there's a lot of different vaccine candidates to… middle of 2023, there was only one other vaccine that had been tested in humans that is advancing. But in August 2023, the University of Oxford reported that one of their vaccine candidates was starting human trials. And they're doing the clinical trial just to check for adverse reactions as well as immune response to the vaccine. So, it's in the first stages of human trials. But the development of vaccines for CCHF, considering it’s so widely spread and a lot of the countries that actually are endemic for CCHF maybe don't have the resources, have been considered a priority by the WHO. So, there's a lot of different candidates, two that are doing the test in humans now, so that is encouraging. But as of now, the only one that is in use is the Bulgarian one. But we don't know there's efficacy data on the vaccine, to be honest.

[Candice Hoffmann] While the candidate vaccines in the works are not ready for the world stage, there are still public health measures that can be taken.

[Gaby Frank] We’re in the warmer months. People are traveling, they like hiking. So, I think that the big public health…so, how do we prevent this, right? And how to be aware. So, for healthcare workers is we need to be aware that this is out there, so if we have a returning traveler that has a potential exposure so we can identify the disease. But also, for those people that do recreational activities, it's like how to stay safe. And that is like how to use preventive measures such as not expose skin if they are in a tick endemic area as well as using DEET insect repellent to actually prevent tick bites.

The other thing that is important is that in June, there's over 90 countries that are actually celebrating Eid al-Adha festivities. And usually there's an uptick of cases around this celebration and it's because there's a sacrificial animal involved and one, if the animal is very big, the people who are handling the animal could get exposed to the bodily fluids, but also because the animal could have ticks. So, there's…the celebrations will occur in all those 90-something countries between June 16th and 18th of this year. So, it is important there's many recommendations in endemic areas on how to protect themselves, like how to use appropriate gloves and PPE when they handle the animals, but also to do a 30-day quarantine of the animals and use acaricide just to make sure that there's no ticks on the animals. So, that is also something to keep in mind because if the patient actually was visiting in a country and participated in the festivities, and now they are back in the US and they're having symptoms, this is something that we need to think about.

[Candice Hoffmann] These three papers in the May 2024 issue of *Emerging Infectious Diseases* cover a lot of ground regarding CCHF. However, there is always more to learn. We asked Dr. Frank what advice she would have for researchers who want to build on the knowledge of CCHF that was presented in this series of papers.

[Gaby Frank] There's a lot of research opportunities on CCHF. And as I said before, the vaccine research for CCHF is one of WHO's priorities. So, there's a lot of, for management of CCHF, understanding which patients will develop symptoms versus which ones won't develop symptoms, is also a huge area of research. And again, because the US is not an endemic area, we don't have the patients available to say who's going to develop symptoms and who isn't.

So, I think that there's a lot of room for research and expanding the knowledge that we have about CCHF. And there's great researchers in the US that actually focus on CCHF, like Dr. Pente and Galveston. So, there's a lot of people in the US working at a basic lab level of research for CCHF. So, there's a lot of knowledge in the works. It's not out there. And I think there's a lot of room for CCHF. There's a lot of unanswered questions. And there's a lack of animal models because, as we said before, animals don't develop the disease. So, it's very hard to do research when we cannot reproduce the disease in an animal. For animal advocates, this is great. But when we're trying to advance the science, it's one of the challenges. There are two animal models right now that have been developed that people can do research on. But that is tricky.

But my big thing for anybody who's starting is, all this field is fascinating. So, just become passionate and study whatever you're passionate about because passion is what drives research. So, if you read about it, get curious, I mean, curiosity is key because you get curious, you read something like, oh my God, this is so awesome, this is fascinating. I want to know more. And then you know more. And it's like, but I want to know more and there's no more to know yet. So how can I build that knowledge? So then there's more to learn for who comes after me.

[Candice Hoffmann] We hope you'll want to learn more about CCHF and other infectious diseases highlighted in EID. And, if you aren't already, we hope that you, like Dr. Frank, will become an avid reader of the journal.

[Gaby Frank] Well, I have been reading EID since the mid-90s. I used to live in Argentina, and when I started my first residency in Argentina and did my ID rotation, it was introduced to us what EID was and I signed up for it. And I used to receive the paper version of EID at my house

in Buenos Aires. So, when I moved to the US in 2004, I brought my paper collection with me to here, and I continue to be 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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