Hot Topic

National STD Curriculum Podcast

Monkeypox: What Do We Know?

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Season 2, Episode 9

While human monkeypox is not typically considered an STI, reported cases of this current outbreak in 2022 have been identified at sexual health clinics in different countries and there are features to suggest close human-to-human transmission of this virus is playing a major role. This episode reviews three articles on monkeypox. An article on the effectiveness of oral tecovirimat for treatment is also discussed. For additional information and helpful pictures of lesions, two other 2022 articles are recommended. Clinicians are encouraged to visit the Centers for Disease Control and Prevention to keep updated on the evolving situation.

Topics:

- STI
- monkeypox
- smallpox
- outbreak
- tecovirmat
- monkeypox lesions

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Disclosures

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Transcript

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In this episode:

[00.00] Introduction

Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

[00.21] Background
We've been hearing a lot about monkeypox recently, and I thought this would be a good episode to review this disease as well as some recent published literature. While monkeypox is not typically considered an STI [sexually transmitted infection], there are features of the current outbreak in Europe as well as the United States that suggest it is predominantly being driven by human-to-human transmission. Now monkeypox virus was first discovered in 1958 as the cause of a pox-like illness among monkeys at a research facility in Copenhagen, Denmark. But the first human case of monkeypox was reported in the Democratic Republic of Congo in 1970. Human monkeypox is endemic in several African countries, and until recently, most cases have involved animal-to-human transmission and have been rare outside the African continent.

But how quickly can things change? In 2022 we are in the midst of a global monkeypox outbreak, and there have been more than 2,000 confirmed cases of monkeypox in a total of 37 countries, with nearly all involving countries that are not endemic for monkeypox virus. Now, the bulk of those cases have been reported in Europe, and many of the cases have been identified at sexual health clinics in the United Kingdom, Spain, Italy, and Portugal. In the current outbreak in Europe, monkeypox virus is thought to be spread predominantly from close human-to-human contact involving exchange of bodily fluids. In the U.S., as of June 17, 2022, there have been 100 confirmed monkeypox cases, including clusters of cases among men who have sex with men—we'll likely hear more details about these cases in the U.S. in the weeks and months to come. If you're interested in learning more about monkeypox, I suggest visiting the CDC website on the 2022 U.S. monkeypox investigation. Since few clinicians practicing in the U.S. have ever seen a case of monkeypox infection, I was interested in learning more about what has been recently published on this topic for this episode, so let's dive in.

[02.23] Paper #1

Perez Duque M, Ribeiro S, Martins JV, et al. Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022. Euro Surveill. 2022 Jun;27(22):2200424. **[PubMed Abstract]**

Other articles:

Heskin J, Belfield A, Milne C, et al. Transmission of monkeypox virus through sexual contact - A novel route of infection. J Infect. 2022 Jun 1:S0163-4453(22)00335-8. Epub ahead of print. **[PubMed Abstract]**

Bížová B, Veselý D, Trojánek M, Rob F. Coinfection of syphilis and monkeypox in HIV positive man in Prague, Czech Republic. Travel Med Infect Dis. 2022 Jun 2;49:102368. Epub ahead of print. **[PubMed Abstract]**

This first article to review was published in *Eurosurveillance* in June 2022 by Dr. Perez Duque and colleagues. It is titled "Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022." So, interesting features of this article:

1. Portugal has detected 96 confirmed cases of monkeypox in the current outbreak as of May 27th of 2022. This article describes the detailed clinical information of 27 individuals with confirmed monkeypox.
2. The median age of the cases was 33 years, and the range was 22-51 years old. All cases were male, and 14 cases were persons with HIV. They had data on sexual history of 19 cases, and they found 18 cases reported sex with men and one case who reported sex with women only. Fourteen out of 16

cases with available data reported having sex with multiple partners.
3. Now, many cases did not have a known exposure history during the 21 days prior to the onset of symptoms. Only one case had contact with a person with similar symptoms, four cases had travel abroad, and three cases had contact with animals.
4. The authors found that the most common symptoms were a rash, inguinal lymphadenopathy, and fever. The lesions appeared predominantly in the genital or anal area, manifesting as ulcers or vesicles. Three cases required hospitalization, and thankfully there were no deaths. Providers recommended home isolation for patients until all the lesions resolved.
5. But the authors did find that contact tracing was difficult as a large proportion of cases engaged in sex with multiple and/or anonymous partners.

So this was a nice summary of some detailed information of 27 confirmed monkeypox cases in Portugal. It's reassuring overall that the clinical manifestations were mild, and there were no deaths from this infection. What's interesting is that the lesions were reported to start in the genital area instead of the face, which is a usual feature with monkeypox infection in the historical past. Most cases were not part of the usual identified chains of transmission for monkeypox, but cases did have multiple and/or anonymous sexual partners, and so they actually might not be aware of all their potential contacts. I think it's important to raise awareness of this outbreak so we can increase a timely diagnosis for individuals, and I anticipate we'll have more information published soon.

If you're interested in learning more, I suggest reading an article that was published by Dr. Heskin and colleagues, and it was titled "Transmission of monkeypox virus through sexual contact - A novel route of infection," and this was published in *The Journal of Infection.* There was also a case report presented in *Travel Medicine and Infectious Disease* by Dr. Bizova and colleagues, and it was titled "Coinfection of syphilis and monkeypox in HIV positive man in Prague, Czech Republic." Both of these articles have helpful pictures of monkeypox lesions in different areas of the body, and both were published in May or June of 2022, so I encourage you to read them.

[05.24] Paper #2

Whitehouse ER, Bonwitt J, Hughes CM, et al. Clinical and epidemiological findings from enhanced monkeypox surveillance in Tshuapa Province, Democratic Republic of the Congo during 2011-2015. J Infect Dis. 2021 Jun 4;223(11):1870-1878. **[PubMed Abstract]**

I wanted to see what has been published in the literature on features of human monkeypox disease prior to the current outbreak. So this led me to an article that we're going to discuss, which was published by Dr. Whitehouse and colleagues, and this was published in *The Journal of Infectious Diseases* in June of 2021. It is titled "Clinical and epidemiological findings from enhanced monkeypox surveillance in Tshuapa Province, Democratic Republic of the Congo during 2011-2015."

1. So in this study, the authors evaluated the incidence, exposures, and clinical presentation of PCR [polymerase chain reaction]-confirmed cases of monkeypox during this time period in this region in the Democratic Republic of the Congo.
2. A suspected case was defined as an individual with a vesicular or pustular rash and at least one or more of the following symptoms: Individuals needed to have a fever preceding the rash, or lymphadenopathy, or pustules or crusts on the palms or soles. They confirmed a suspected monkeypox case with PCR or isolation of monkeypox virus in culture.
3. From 2011-2015, there were more than 3,600 suspected monkeypox case notifications, and 47% of these were investigated. A total of 1,057 cases were confirmed as monkeypox, with an annual incidence of 14.1 per 100,000 persons. So, this is more than *twice* that reported in a past period of active surveillance during 1980-1985 in an area just north of this province, suggesting either an increase in cases, or an increase in recognition and surveillance, or possibly both. Fifty-four percent of the cases were male.

4. The authors had complete exposure history on 837 confirmed cases and found 37% (or 309 cases) reported contact with at least one domestic or wild animal in the three weeks prior to symptom onset. The majority of individuals (or 198 individuals) had exposure to nonhuman primates: 51 individuals were exposed to rats, 30 individuals were exposed to squirrels, and the rest of the individuals were exposed to other animals not detailed. Now, some individuals reported contact with a person with monkeypox-like symptoms as their only exposure prior to symptom onset, and this was 279 individuals (or 33%) of the cases they investigated. An additional 109 confirmed cases reported contact with both animals and symptomatic humans. One-hundred-forty cases reported no known exposures, and males were more likely than females to report animal exposures.
5. Among 264 individuals with information on contact with symptomatic humans, family members were the most frequently reported contact suggesting secondary exposures among household members are relatively common.
6. All 1,057 confirmed cases reported a cutaneous rash, and 99% of those cases reported a fever just before the rash onset. Of the 1,025 confirmed cases involving individuals with a known lesion distribution, 97% of these presented with a centrifugal distribution, and that's with lesions on the face and distal extremities. The median lesion count was 102. Patients also reported other systemic symptoms such as a cough, lymphadenopathy, dysphagia, headache, and conjunctivitis. Of note, this is a bit different than what is reported in the current 2022 outbreak. In the 2022 outbreak, many patients are presenting with genital lesions and lymphadenopathy; and some individuals present with or without fever.
7. Now going back to the study, the authors found that the incidence differed based on smallpox vaccination status: the rate of monkeypox confirmed cases was almost three times higher among those presumed unvaccinated than among those who were presumed vaccinated for smallpox. This suggests that there might be an increase in cases in recent years linked to declining immunity provided by smallpox vaccination.

Based on five years of enhanced monkeypox surveillance in this region, this article provides some insight into the clinical and epidemiological features of monkeypox in an endemic setting. In these areas, monkeypox virus is often introduced into communities by zoonotic transmission rather than sustained human-to-human transmission, but there has been increasing number of cases in more recent years. So this might be due to several reasons, including waning of immunity since the eradication of smallpox as well as the cessation of routine smallpox vaccination, population growth, increased human interaction with monkeypox virus reservoirs in animals, let's say due to deforestation and climate change. But there might be other reasons as well.

[10.12] Paper #3

Grosenbach DW, Honeychurch K, Rose EA, et al. Oral tecovirimat for the treatment of smallpox. N Engl J Med. 2018 Jul 5;379(1):44-53. **[PubMed Abstract]**

Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: A retrospective observational study in the UK. Lancet Infect Dis. 2022 May 24:S1473-3099(22)00228-6. Epub ahead of print. Erratum in: Lancet Infect Dis. 2022 May 26; Erratum in: Lancet Infect Dis. 2022 Jun 2. **[PubMed Abstract]**

So how do we treat monkeypox? Let's say the patient requires treatment. Most of the cases seem to be mild and resolve without treatment, but medications, which have activity against monkeypox and other orthopoxvirus infections include cidofovir, brincidofovir, and tecovirimat. Now, I've never used the antiviral medication tecovirimat, which is FDA-approved for the treatment of smallpox, and I wanted to delve into any published articles on this medication further. So the third article to discuss was published in July of 2018 in the *New England Journal of Medicine* by Dr. Grosenbach and colleagues. It is titled "Oral tecovirimat for the treatment of smallpox."

1. Now, tecovirimat inhibits all orthopoxviruses in vitro, and it prevents the formation and egress of

enveloped virions from infected cells. This study evaluated the efficacy of tecovirimat in the nonhuman primate model using monkeypox.
2. Macaques were infected with a lethal dose of monkeypox virus on day 0, and tecovirimat treatment at doses of 0 mg/kg, which is also considered placebo, 0.3, 1, 3, and 10 mg/kg of body weight were evaluated for efficacy. Tecovirimat treatment was initiated on or after day four of exposure and after the onset of clinical signs, which were pock lesions in nonhuman primates.
3. The minimum effective dose was determined to be 3 to 10 mg/kg. And this provided nearly full protection from death, and reduced viral reservoirs and lesion counts. The dose of 10 mg/kg reduced viral load and lesion counts to a greater extent than the dose of 3 mg/kg. Now, the minimum dose of tecovirimat required to achieve more than 90% survival in the monkeypox model was found to be 10 mg/kg of body weight for 14 days.
4. The authors also performed a multicenter, randomized, double-blind expanded safety trial involving healthy human volunteers from ages 18-79 years old. They chose a dose that provided maximal efficacy in nonhuman primates but below the highest level that was associated with no adverse effects in toxicologic studies in animals.
5. They enrolled 452 participants who underwent randomization and were assigned to receive tecovirimat at 600 mg orally twice daily (and this included 361 participants) or a matching placebo (and this was a group of 91 participants) for 14 consecutive days. A total of 431 participants completed the trial. The overall rate of adherence was 94% in the placebo group and 94% in the tecovirimat group.
6. There were 386 nonserious adverse effects reported by 164 participants: 208 of these were thought to be related to tecovirimat or placebo, and the adverse events related to the trial regimen were similar in the two groups. Adverse events of grade 3 or higher occurred at a frequency of 1.1% in both the tecovirimat as well as the placebo group, and it included headache, osteoarthritis, and hidradenitis. There was one fatal adverse event that was found to be unrelated to tecovirimat. Now, eight participants (two in the placebo group and six in the tecovirimat group) discontinued the trial regimen because of an adverse event.

So, this report presented the safety, pharmacokinetics, and efficacy data from animal models and noninfected human volunteers. A dose of tecovirimat at 600 mg orally twice daily for 14 days was used, and no safety concerns were identified. Most reported adverse events were mild, and discontinuation of the trial was rare among participants. There's also an article that was published by Dr. Adler and colleagues in *The Lancet Infectious Diseases* in May of 2022, and it was titled "Clinical features and management of human monkeypox: A retrospective observational study in the UK." In this article, the authors reported the features as well as response to antivirals in seven patients with monkeypox diagnosed in the UK from 2018-2021. Three patients were treated with brincidofovir at 200 mg orally once a week for three weeks, but all of them developed elevated liver enzymes resulting in cessation of therapy. One patient received tecovirimat at 600 mg orally twice daily for two weeks and experienced *no* adverse effects. This patient was found to have a shorter duration of viral shedding, as well as illness, compared to the other patients. Tecovirimat is not FDA-approved for monkeypox, but it is currently available in the United States under an expanded access Investigational New Drug status, and it can be considered among people with severe monkeypox or those who are at high risk of severe disease. If you're interested in learning more, more information can be found on the CDC's website.

[15.15] Summary

To conclude, I'd like to summarize some key points from this session:

1. While human monkeypox is not typically considered an STI, reported cases of this current outbreak in 2022 have been identified at sexual health clinics in different countries, and there are features to suggest close human-to-human transmission of this virus is playing a major role in the current 2022 outbreak.
2. Persons in the 2022 outbreak are typically presenting with a rash, with findings that may include papules, vesicles, pustules, umbilicated pustules, ulcerating lesions, and scabs. Some, but not all, patients have developed fever and lymphadenopathy.

3. While cases of monkeypox are endemic in some African countries, the clinical manifestations and routes of transmission with this current outbreak are a bit different than what has historically been reported.
4. In the current monkeypox outbreak, most cases have been mild without the need for treatment.
5. Tecovirimat is FDA-approved as a treatment for smallpox, and it is a potential treatment for those with severe monkeypox disease. Available data suggest that tecovirimat is safe as well as well tolerated at a dose of 600 mg orally twice daily for 14 days.
6. Clinicians who suspect cases of monkeypox should immediately contact local health departments. In the current ongoing monkeypox outbreak, health professionals working in STI clinics may be the most likely to identify new patients with monkeypox, and increased awareness and prompt recognition will be helpful for patient care.

[16.45] Credits

This podcast is brought to you by the National STD Curriculum, the University of Washington STD Prevention Training Center, and is funded by the Centers for Disease Control and Prevention.

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