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MINIREVIEWS

Monkeypox in humans: Transmission, pathophysiology, diagnosis, treatment, prevention, and all recent updates

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Abstract

The Centers for Disease Control and Prevention (CDC) is monitoring an epidemic of monkeypox infection in the United States. The outbreak is now global and more than 6900 cases have already been reported. There are 83 confirmed cases among children and adolescents, as shown in the report published on November 3, 2022, in the USA. However, monkeypox in pediatric patients is still infrequent (< 0.3% of total cases). Among cases in the United States, 16 cases were in children < 5 years, 12 in the age group 5-12 years, and 55 cases in adolescents 13-17 years old. In the adolescent age group, 89% were male. For children < 12 years of age, close physical contact with an adult household with monkeypox was the primary exposure, but for adolescents, male-to-male sexual contact was found more frequently. The CDC advised United States healthcare providers to remain vigilant for patients with a rash resembling monkeypox, even if there is no history

of travel to a country with high risk. This article summarizes the history and epidemiology of monkeypox with a specific emphasis on clinical features and management in pediatric patients.

Key Words: Pediatric monkeypox; Smallpox; Monkeypox case definition; JYNNEOS vaccine; ACAM2000

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Core Tip: This article describes current updates on the clinical features and management of pediatric monkeypox infection.

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INTRODUCTION

The monkeypox virus is an orthopoxvirus that causes monkeypox. Orthpoxviruses that infect humans range from lethal small poxviruses to highly contagious but benign molluscum contagiosum viruses[1]. Monkeypox has always been found in West and Central Africa. However, in May 2022, the United States and other countries reported cases of monkeypox, even though there was not previously documented monkeypox transmission[2]. There are two distinct monkeypox virus classes: The Congo basin clade, mainly in central Africa, and the West Africa clade[3]. The Congo basin clade is known to cause disease with a severe impact and causes more morbidity and mortality. Human-to-human transmission has also been reported more frequently with the Congo basin clade.

Monkeypox in non-human primates

The monkeypox virus was first discovered in 1958 from a monkey in Copenhagen, Denmark, at the Staten's Serum Institute - and that is how it got its name[4]; monkeypox virus-hosts also include dormice, pouched rats, rope squirrels, and tree squirrels. Like many other zoonoses, Pox virus is known to be transmitted accidentally to a human when dealing with infected animals.

Monkeypox in humans

The Dominican Republic (DR) of the Congo noted the first known human case of monkeypox in 1970. Six unvaccinated people from the DR of Congo, Liberia, and Sierra Leone presented with an illness similar to smallpox on clinical presentation[5]. The DR Congo reported the first pediatric case in a 9-month-old infant. Four other children from Bouduo and Liberia aged 4 to 9 years were also affected. Three children close to these cases also developed a rash in the following days, indicating possible exposure. There was also the case of the 24-year-old male reported in Sierra Leone who was reported to have removed the stomach and intestine from a red monkey, and after 3-4 wk, he felt ill. No one died of monkeypox.

In the United States, monkeypox cases were first reported in 2003[6]. Seventy-one people were infected by Gambian pouched rats and prairie dogs, when they received a shipment of these infected animals as pets. The Centers for Disease Control and Prevention (CDC) and Wisconsin Research Department mentioned this outbreak in which patients presented with febrile illness with vesiculopustular eruption between May and June 2003. The five male and six female patients were aged between 3 and 43 years. The possible epidemiology, clinical, and laboratory investigations in this outbreak were also summarized. Contact with ill pet prairie dogs exposed to sick rodents from West Africa and Ghana was identified in all these patients. The illness started with a fever with or without chills, skin rash, and excessive sweating. All patients reported papular skin rash and headache; many reported fevers, chills, sweating, or persistent cough, and approximately half of the patients had lymphadenopathy. The characteristic rash started as a papule followed by a vesiculopustular lesion surrounded by erythema. Lesions finally resolved with serous fluid and a hemorrhagic crust with a mean duration of 12 d (3-25 d). All cases had a mild disease course, and only four were hospitalized, but recovered quickly. This was the first time monkeypox was identified among humans in the Western world. Only five adults were vaccinated against smallpox, while others were too young to receive the vaccine.

An outbreak of human monkeypox occurred in Nigeria in 2017[7]. There were 38 suspected cases, of which 18 received laboratory confirmation, three cases were probable, and 17 did not meet the case definition. Most of the confirmed cases were male adults. There was an association with varicella, syphilis, and human immunodeficiency virus (HIV) in two confirmed cases, and one healthcare worker had a nosocomial infection.

In September 2018, the United Kingdom reported monkeypox transmission from a patient to a healthcare worker[8]. The possible source of infection was contaminated bedding. The hospital undertook all possible infection control measures to control the outbreak. Four of the 134 possible cases exposed became ill, but the clinical course was mild.

Transmission

Monkeypox infection resembles smallpox, and the illness may be initially diagnosed as smallpox as both illnesses share similar clinical features[9]. Monkeypox was identified after the eradication of smallpox. Monkeypox is a zoonosis, although human-to-human transmission can occur. Monkeypox can spread due to close or skin-to-skin contact. Direct contact with monkeypox rash and contact with the patient's saliva, upper respiratory secretions, and areas around the anus, rectum, or vagina can lead to infection. It is not as contagious as smallpox among humans. Although monkeys and other primates are the primary reservoirs, other animals, such as squirrels and other rodents, can also be reservoir hosts for this virus. Pox virus deoxyribonucleic acid (DNA) has been identified in anal and urethral swabs from persons who neither demonstrated clinical signs nor reported symptoms of illness at the time of specimen collection. Few cases remained asymptomatic despite having known or possible sexual exposure to infected personnel[10].

How monkeypox relates to smallpox

In 1980 smallpox was declared eradicated worldwide, and the last reported case was in 1977. However, Huang *et al*[11] reported that it had been over 40 years since all countries stopped administering the smallpox vaccine. Previous history of vaccination against smallpox can provide some protection against monkeypox, but it is uncertain how long this protection lasts. In the 2003 monkeypox outbreak and 2022 outbreak, multiple infected patients with monkeypox had a history of smallpox vaccination in past decades[12].

Pathophysiology

The monkeypox virus enters the body *via* routes such as the oropharynx, nasopharynx, or intradermal and replicates at the inoculation site, then spreads to local lymph nodes[13], followed by viremia and infection of organs. The incubation period typically ranges from 7 to 14 d, with a maximum of 21 d. Symptoms start with fever and lymphadenopathy 1-2 d before developing skin lesions. In the 2022 outbreak, it was noted that monkeypox spread from when symptoms appeared to the phase where the rash had healed completely, and a new layer of skin had formed[14].

Case definition and clinical features

Below is the Case definition by the CDC and European Centre for Disease Prevention and Control guidance[14,15] (Table 1).

Exclusion criteria

Another diagnosis is made or an individual with suspected monkeypox does not develop clinical symptoms or a rash within five days or suspicious clinical specimens fail to demonstrate orthopoxvirus infection or antibodies against the infection.

Clinical features

Monkeypox rash begins with macules followed by papules, vesicles, and pustules. Pustules are characteristically deep-seated, firm, and well-circumscribed. These lesions can progress to become umbilicated or confluent but ultimately progress to scabs[16]. The rash can also spread to other parts of the body. Lesions on a distinct body part are at the same stage in classic monkeypox.

Classic symptomatology during monkeypox infection includes fever with chills, malaise, sore throat, and lymphadenopathy, followed by a characteristic rash. However, in the 2022 outbreak, some patients developed perianal and genital lesions but no fever or other systemic symptoms.

Monkeypox rash can mimic other common illnesses in clinical practice such as syphilis, herpes simplex virus and varicella zoster infection, chancroid, and molluscum contagiosum, and these illnesses can frequently be associated with monkeypox. Therefore, it is necessary that the clinician remains vigilant, especially with patients who present with the characteristic rash and men who practice sex with men (Table 2).

How long is monkeypox contagious?

As shown by Guarner *et al*[1], the infected person is not contagious during the incubation period. However, humans can be infectious as soon as symptoms begin until all scabs on the pox lesions fall off.

Diagnosis

When monkeypox is suspected in the United States; the clinician should contact the health department to determine the availability of testing, and lesions should be thoroughly swabbed and sent to testing laboratories. The monkeypox virus can be detected by an orthopoxviral polymerase chain reaction (PCR) test at a designated laboratory, and a positive PCR is enough for the diagnosis of monkeypox. When complex cases or positive laboratory results do not meet epidemiological criteria, the CDC should be consulted so that additional tests such as viral-specific or clade-specific PCR and blood testing can be conducted.

Complications

Reported complications are encephalitis, secondary skin infections, conjunctivitis, keratitis, and secondary pneumonia. During outbreaks in epidemic areas, mortality can be between 0% and 11%, affecting significantly young children[17]. Severe monkeypox infection is common in immunocompromised patients. Patients with HIV infection suffered more during the 2017 Nigeria outbreak than HIV-negative patients, with severe skin lesions and genital ulcers. However, no

Table 1 Case definition and clinical features

Suspect case	New-onset typical rash
	Fulfill one of the epidemiologic criteria and have a solid clinical possibility of monkeypox
Probable case	No other possible orthopoxviral exposure (*e.g.*, vaccination), and evidence of the presence of
	orthopoxviral DNA by PCR in the patient's sample
	Presence of orthopoxvirus using immunohistochemical or electron microscopy testing methods
	Positive anti-orthopoxviral IgM antibody after onset of rash for a duration of 4 to 56 d. Men who practice sex with men
Confirmed case	Evidence of monkeypox virus DNA detected by PCR in a patient specimen or detection of virus in clinical specimen culture
	Epidemiological criteria: Within three weeks of beginning the illness: Possible exposure to a person with a characteristic rash or who was diagnosed with monkeypox or a probable case, or following intimate exposure to individuals with monkeypox-like symptoms. Travel to a monkeypox endemic country outside the United States or a country with a monkeypox outbreak, or contact with a dead or live wild animal or pet from an endemic African region or a product obtained from such animals

DNA: Deoxyribonucleic acid; PCR: Polymerase chain reaction; IgM: Immunoglobulin M.

Table 2 Monkeypox symptoms and treatment options

Monkeypox symptoms	Treatment options
Monkeypox symptoms: Itchy, painful pimple/blister-like rash with several stages	Oral antihistamines, creams, and lotions such as calamine lotion. Keep the rash covered, do not scratch, soak in a warm bath, use oatmeal
Fever, chills, lymph node swelling, body ache, URI symptoms	Symptomatic pain medications
Severe disease involving eyes, mouth, throat, genitals and anus	Antiviral tecovirimat

URI: Upper respiratory infection.

deaths were reported. Between September 2017 and June 2022, Nigeria reported 257 confirmed cases, with nine deaths; of the nine patients who died, five were immunocompromised[18]. Disfiguring scars and corneal damage can be frequent significant sequelae. It was noted that vaccinated patients experienced fewer complications, and the secondary case rate in such households was lower[19]. As shown by Mbala *et al*[20], pregnant patients had more complications, including preterm delivery, fetal death, or congenital diseases. An observational study was performed at the Hospital in Kole between 2007 and 2011, which showed that of four pregnant women with monkeypox, who were included in the study, one had a full-term, healthy baby, two experienced a stillbirth in the first trimester, and the remaining patient experienced fetal death.

Precautions

Monkeypox spreads from human to human *via* exposure to the rash, close contact, or articles contaminated with contagious inflammation or body secretions[21]. Standard care is required for all suspected monkeypox patients. People with monkeypox who are not hospitalized require isolation at home. For confirmed monkeypox, isolation must continue until the rash has healed, the scabs have fallen off, and skin is intact.

Treatment

As shown by Rizk *et al*[22], monkeypox does not require treatment in all patients. Immunocompromised patients, children under eight years of age, pregnant or breastfeeding women, and those with eczema or exfoliative skin lesions are considered high risk. Also, patients with severe complications or rashes involving the eyes, mouth, and private areas may qualify for treatment.

Unfortunately, there are no treatment protocols for pediatric patients with monkeypox; however, local public health officials can help with CDC consultation to initiate antiviral therapy.

Tecovirimat was developed to treat smallpox, which can be used for monkeypox and is currently the first-line treatment for children. An oral dose in children of more than 13 kg is possible, which can be taken as a capsule, or the capsule's content can be mixed with food. In children less than 13 kg, the intravenous formulation can be considered depending on clinical status. Monitoring renal function is recommended, especially in children under two years of age.

The CDC is also developing a protocol for intravenous immunoglobulin in patients with monkeypox, but its effectiveness has not been established.

Brincidofovir was Food and Drug Administration (FDA) approved for smallpox treatment, and cidofovir was FDA-approved for cytomegalovirus retinitis in acquired immunodeficiency syndrome in the pediatric population. However,

there is still a lack of data on the effectiveness of brincidofoir and cidofovir in treating pediatric monkeypox.

Post-exposure prophylaxis

The CDC is conducting studies to determine how long immunity lasts after vaccination. They are looking at specimen samples from infected patients to determine whether the virus has changed. The CDC works closely with local and state partners to determine how the virus spreads among monkeypox patients. Studies have been carried out to assess how many patients were vaccinated, if they were fully vaccinated, and when they were vaccinated. Close monitoring of those newly diagnosed with monkeypox after vaccination is ongoing.

Two vaccines can be given to people who have been in contact with a monkeypox patient[23]. Data on post-exposure prophylaxis (PEP) in children are limited. JYNNEOS is the only vaccine that can be used in pediatrics. The decision to vaccinate must be made according to the level of risk in terms of the patient's exposure and health conditions. While vaccination is preferred in most cases, immunoglobulin may be considered in an infant less than six months of age. There is the possibility of using anti-viral medication after consultation with the appropriate CDC facility for PEP.

JYNNEOS

This vaccine has not been extensively studied in pediatrics for monkeypox; it contains non-replicating vaccine virus. This vaccine has been used in pediatrics for illnesses such as tuberculosis, Ebola, and measles without major side effects. In 2018-2019, this vaccine was used in the United Kingdom in pediatrics following monkeypox exposure without any major side effects. In the current outbreak, JYNNOS is available for children and adolescents under 18 years of age, who are classified as having high-risk exposure according to the CDC[24]. The dose is 0.5 mL for each subcutaneous injection with a two-dose series, and ideally, the first dose should be given within 96 h post-exposure[24].

ACAM2000

As shown by Singhal *et al*[25], this vaccine contains replicating viruses associated with side effects such as uncontrolled viral replication and eczema vaccinatum. It is not a preferred vaccine for pediatrics and should only be considered if JYNNEOS is unavailable or contraindicated.

Immunoglobulin: Immunoglobulin is approved under the emergency authorization for the prevention of monkeypox and is preferred for infants less than six months old with high-risk exposure[26].

CONCLUSION

Monkeypox virus is a very contagious orthopoxvirus currently causing a global outbreak, and primarily affecting men who have sex with men. After discontinuing the smallpox vaccine, population immunity decreased and led to an increase in monkeypox cases. Furthermore, the increased number of cases outside Africa demonstrates the global spread of the disease. Obtaining control over this infection requires doctors, hospitals, and health care officials to work together and define appropriate diagnostic testing, contact tracing, and availability of medical care to the affected patient. It is very important that pediatric physicians should be aware of the clinical course and possible outcomes in pediatric patients. Monkeypox seems scary, but it is still a sporadic disease, especially in pediatrics. However, it is always good to be aware of health risks.

FOOTNOTES

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