Mpox Update: Clinical Presentation, Vaccination Guidance, and Management

Ahuva Cices, MD; Sonya Prasad, MSc; Melissa Akselrad, MD; Nicholas Sells, MD; Krystina Woods, MD; Nanette B. Silverberg, MD; Bernard Camins, MD

PRACTICE **POINTS**

- Mpox (monkeypox) lesions typically present as well-circumscribed, painful, umbilicated papules, vesicles, or pustules, with recent cases having a predilection for an anogenital distribution accompanied by systemic viral symptoms.
- Health care workers treating suspected or confirmed cases of mpox should be familiar with current guidelines for controlling the spread of mpox, including proper personal protective equipment (gloves, disposable gowns, N95 or equivalent respirators, and eye protection) and indications for vaccination.

Following the eradication of smallpox, intermittent small outbreaks of mpox (monkeypox) have occurred with increasing frequency, primarily in endemic regions of Africa. With the rapid spread of mpox around the globe in 2022, we are approaching a second zoonotic pandemic of the 21st century. Given the predominance of cutaneous involvement in mpox, dermatologists should be prepared to recognize the clinical features and manage this increasingly prevalent disease. This article reviews a brief history of the mpox virus, clinical presentation, complications, approach to diagnosis, methods of transmission, infection control recommendations, indications for vaccination, and therapeutic options to inform dermatologists on the frontline of the mpox epidemic.

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The mpox (monkeypox) virus is a zoonotic orthopox DNA virus that results in a smallpoxlike illness.[1] Vaccination against smallpox protects against other orthopox infections, including mpox; however, unlike smallpox, mpox is notable for a variety of not-yet-confirmed animal reservoirs.[2] Mpox was first identified in Denmark in 1959 among nonhuman primates imported from Singapore, and the first case of human infection was diagnosed in 1970 in a 9-month-old child in the Democratic Republic of Congo.[3] Endemic regions of Africa have had sporadic outbreaks with increasing frequency over time since the cessation of smallpox vaccination in 1980.[2,4] Infections in nonendemic countries have occurred intermittently, including in 2003 in the Midwest United States. This outbreak was traced back to prairie dogs infected by exotic animals imported from the Republic of Ghana.[5]

Two genetic clades of mpox that differ in mortality rates have been identified: clade II (formerly the West African clade) generally is self-limited with an estimated mortality of 1% to 6%, whereas clade I (formerly the Congo Basin clade) is more transmissible, with a mortality of approximately 10%.[2,6,7] Notably, as of May 2, 2022, all polymerase chain reaction–confirmed cases of mpox in nonendemic countries were identified as clade II.[7] Following the continued international spread of mpox, the Director-General of the World Health Organization (WHO) declared the global outbreak a public health

From Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Cices, Ms. Prasad, Ms. Akselrad, and Dr. Silverberg are from the Department of Dermatology; Drs. Sells, Woods, and Camins are from the Division of Infectious Diseases; and Dr. Silverberg also is from the Department of Pediatrics.

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Correspondence: Nanette B. Silverberg, MD, Icahn School of Medicine at Mount Sinai, 5 E 98th St, 5th Floor, New York, NY 10029 (Nanette.silverberg@mountsinai.org).

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emergency of international concern on July 23, 2022.[8] As of March 1, 2023, the Centers for Disease Control and Prevention (CDC) reports that there have been more than 86,000 cases of laboratory-confirmed mpox worldwide and 105 deaths, 89 of which occurred in nonendemic regions.[9]

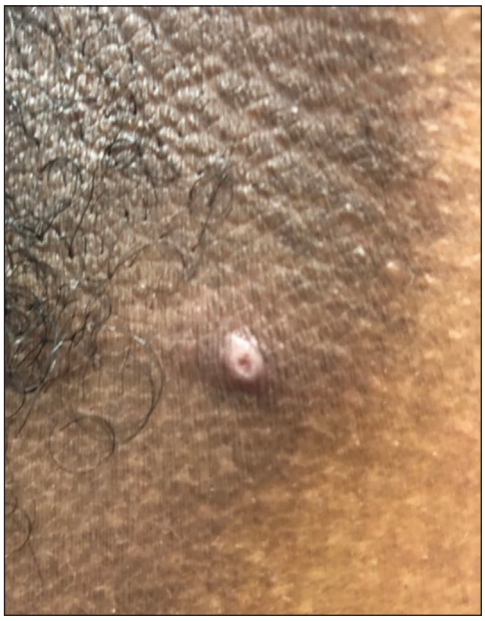
Transmission of Mpox

In endemic countries, cases have been largely reported secondary to zoonotic spillover from contact with an infected animal.[6] However, in nonendemic countries, mpox often results from human-to-human transmission, primarily via skin-to-skin contact with infected skin, but also may occur indirectly via contaminated fomites such as bedding or clothing, respiratory secretions, or vertical transmission.[6,10] The indirect transmission of mpox via contaminated fomites is controversial, though some studies have shown the virus can survive on surfaces for up to 15 days.[11] In the current outbreak, human-to-human transmission has been strongly associated with close contact during sexual activity, particularly among men who have sex with men (MSM), with notable physical concentration of initial lesions in the genital region.[12] Anyone can acquire mpox—infections are not exclusive to MSM populations, and cases have been reported in all demographic groups, including women and children. It is important to avoid stigmatization of MSM to prevent the propagation of homophobia as well as a false sense of complacency in non-MSM populations.[13]

Clinical Presentation of Mpox

The incubation period of mpox has been reported to last up to 21 days and is posited to depend on the mode of transmission, with complex invasive exposures having a shorter duration of approximately 9 days compared to noninvasive exposures, which have a duration of approximately 13 days.[14] In a recent report from the Netherlands, the average incubation time was 8.5 days in 18 men with exposure attributed to sexual encounters with men.[12] Following the incubation period, mpox infection typically presents with nonspecific systemic symptoms such as fever, malaise, sore throat, cough, and headache for approximately 2 days, followed by painful generalized or localized lymphadenopathy 1 to 2 days prior to the onset of skin lesions.[1,15] In a recent report from Portugal of more than 20 confirmed cases of mpox, approximately half of patients denied symptoms or had mild systemic symptoms, suggesting that many patients in the current outbreak do not endorse systemic symptoms.[16]

Classic cutaneous lesions are the hallmark feature of mpox.[17] Over a period of 1 to 2 weeks, each lesion progresses through morphologic stages of macule, papule (Figure), vesicle, and pustule, which then crusts over, forming a scab that falls off after another 1 to 2 weeks and can result in dyspigmented or pitted scars.[1,15] Lesions may be deep-seated or umbilicated; previously they were noted to typically start on the face and spread centrifugally, but recent cases have been notable for a predominance of anogenital lesions, often with the anogenital area as the sole or primary area of involvement.[18] Given the high proportion of anogenital lesions in 2022, symptoms such as anogenital pain, tenesmus, and diarrhea are not uncommon.[19] A recent study describing 528 international cases of mpox revealed that 95% of patients presented with a rash; nearly 75% had anogenital lesions; and 41%, 25%, and 10% had involvement of mucosae, the face, and palms/soles, respectively. More than half of patients had fewer than 10 lesions, and 10% presented with a single genital lesion.[19]



Mpox (monkeypox) papule.

Given the recent predilection of lesions for the anogenital area, the differential diagnosis of mpox should include other common infections localized to these areas. Unlike herpes simplex and varicella-zoster infections, mpox does not exhibit the classic herpetiform clustering of vesicles, and unlike the painless chancre of syphilis, the lesions of mpox are exquisitely painful. Similar to chancroid, mpox presents with painful genital lesions and lymphadenopathy, and the umbilicated papules of molluscum could easily be confused with mpox lesions. Proctitis caused by many sexually transmitted infections (STIs), including chlamydia and gonorrhea, may be difficult to differentiate from proctitis symptoms of mpox. Co-infection with HIV and other STIs is common among patients developing mpox in 2022, which is not surprising given that the primary mechanism of transmission of mpox at this time is through sexual contact, and cases are more common in patients with multiple recent sexual partners.[19] Considering these shared risk factors and similar presentation of multiple STIs, patients suspected of having an mpox infection should be tested for other STIs, including HIV.

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Complications of Mpox

Although mpox generally is characterized by a mild disease course, there is concern for adverse outcomes, particularly in more vulnerable populations, including immunocompromised, pregnant, and pediatric populations. Complications of infection can include sepsis, encephalitis, bronchopneumonia, and ophthalmic complications that can result in loss of vision.[6,17] The most common complications requiring hospitalization in a recent international report of 528 mpox cases were pain management, which was primarily due to severe anogenital pain, followed by soft-tissue superinfection, with other complications including severe pharyngitis limiting oral intake and infection control practices.[19] In addition to severe rectal pain, proctitis and even rectal perforation have been reported.[19,20]

Vertical transmission has been described with devastating outcomes in a case series from the Democratic Republic of Congo, where 4 cases of mpox were identified in pregnant women; 3 of these pregnancies resulted in fetal demise.[10] The only fetus to survive was born to a mother with mild infection. In comparison, 2 of 3 mothers with moderate to severe disease experienced spontaneous abortion in the first trimester, and 1 pregnancy ended due to intrauterine demise during the eighteenth week of gestation, likely a complication of mpox. These cases suggest that more severe disease may be linked to worse fetal outcomes.[10] Further epidemiologic studies will be crucial, given the potential implications.

Diagnosis

When considering a diagnosis of mpox, clinicians should inquire about recent travel, living arrangements, sexual history, and recent sick contacts.[6] A complete skin examination should include the oral and genital areas, given the high prevalence of lesions in these areas. A skin biopsy is not recommended for the diagnosis of mpox, as nonspecific viral changes cannot be differentiated from other viral exanthems, but it often is useful to rule out other differential diagnoses.[21] Additionally, immunohistochemistry and electron microscopy can be utilized to aid in a histologic diagnosis of mpox.

Polymerase chain reaction detection of orthopox or mpox DNA is the gold standard for diagnosis.[6] Two swabs should be collected from each lesion by swabbing vigorously using sterile swabs made of a synthetic material such as polyester, nylon, or Dacron and placed into a sterile container or viral transport medium.[22] Some laboratories may have different instructions for collection of samples, so clinicians are advised to check for instructions from their local laboratory. Deroofing lesions prior to swabbing is not necessary, and specimens can include lesional material or crust. Collection of specimens from 2 to 3 lesions is recommended, preferably from different body areas or lesions with varying morphologies. Anal or rectal swabs can be considered in patients presenting with anal pain or proctitis with clinical suspicion for mpox based on history.[19]

Infection Prevention

Interim guidance from the WHO on November 16, 2022, reiterated the goal of outbreak control primarily via public health measures, which includes targeted use of vaccines for at-risk populations or postexposure prophylactic vaccination within 4 days, but heavily relies on surveillance and containment techniques, such as contact tracing with monitoring of contacts for onset of symptoms and isolation of cases through the complete infectious period.[23] Patients are considered infectious from symptom onset until all cutaneous lesions are re-epithelized and should remain in isolation, including from household contacts and domestic and wildlife animals, for the duration of illness.[24,25] Individuals exposed to humans or animals with confirmed mpox should be monitored for the development of symptoms for 21 days following last known exposure, regardless of vaccination status, and should be instructed to measure their temperature twice daily.[26] Pets exposed to mpox should be isolated from other animals and humans for 21 days following last known contact.[24] Vaccination strategies for preexposure and postexposure prophylaxis (PEP) are discussed below in further detail. Postinfection, the WHO suggests use of condoms for all oral, vaginal, and anal sexual activity for 12 weeks after recovery.[7]

Patients with suspected or confirmed mpox in a hospital should be in a single private room on special droplet and contact precautions.[27] No special air handling or negative pressure isolation is needed unless the patient is undergoing an aerosol-generating procedure (eg, intubation, endoscopy, bronchoscopy). When hospitalized, patients should have a dedicated bathroom, if possible, and at-home patients should be isolated from household members until contagion risk resolves; this includes the use of a separate bathroom, when possible. Health care personnel entering the room of a patient should don appropriate personal protective equipment (PPE), including a disposable gown, gloves, eye protection, and N95 respirator or equivalent. Recommendations include standard practices for cleaning, with wet cleaning methods preferred over dry methods, using a disinfectant that covers emerging viral pathogens, and avoidance of shaking linens to prevent the spread of infectious particles.[27] A variety of Environmental Protection Agency–registered wipes with virucidal activity against emerging viruses, including those with active ingredients such as quaternary ammonium, hydrogen peroxide, and hypochlorous acid, should be used for disinfecting surfaces.[28]

Vaccination

ACAM2000 (Emergent Bio Solutions) and JYNNEOS (Bavarian Nordic)(also known as Imvamune or Imvanex) are available in the United States for the prevention of mpox infection.[29] ACAM2000, a second-generation, replication-competent, live smallpox vaccine administered as a single percutaneous injection, is contraindicated in immunocompromised populations, including patients

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with HIV or on immunosuppressive or biologic therapy, pregnant individuals, people with a history of atopic dermatitis or other exfoliative skin diseases with impaired barrier function, and patients with a history of cardiac disease due to the risk of myocarditis and pericarditis.[30]

JYNNEOS is a nonreplicating live vaccine approved by the US Food and Drug Administration (FDA) for the prevention of mpox in individuals older than 18 years administered as 2 subcutaneous doses 4 weeks apart. Patients are considered fully vaccinated 2 weeks after the second dose, and JYNNEOS is available to pediatric patients with a single patient expanded access use authorization from the FDA.[29,30] More recently, the FDA issued an emergency use authorization (EUA) for administration of the vaccine to patients younger than 18 years who are at high risk of infection after exposure.[31] More importantly, the FDA also issued an EUA for the intradermal administration of JYNNEOS at one-fifth of the subcutaneous dose to expand the current vaccine supply. This EUA is based on research by Frey et al,[32] which showed that intradermal administration, even at a lower dose, elicited similar immune responses among study participants as the higher dose administered subcutaneously.

JYNNEOS is the preferred vaccine for the prevention of mpox because of its poor ability to replicate in human cells and resultant safety for use in populations that are immunocompromised, pregnant, or have skin barrier defects such as atopic dermatitis, without the risk of myocarditis or pericarditis. However, current supplies are limited. JYNNEOS was specifically studied in patients with atopic dermatitis and has been shown to be safe and effective in patients with a history of atopic dermatitis and active disease with a SCORAD (SCORing Atopic Dermatitis) score of 30 or lower.[33] Of note, JYNNEOS is contraindicated in patients allergic to components of the vaccine, including egg, gentamicin, and ciprofloxacin. Although JYNNEOS is safe to administer to persons with immunocompromising conditions, the CDC reports that such persons might be at increased risk for severe disease if an occupational infection occurs, and in the setting of immunocompromise, such persons may be less likely to mount an effective response to vaccination. Therefore, the risk-benefit ratio should be considered to determine if an immunocompromised person should be vaccinated with JYNNEOS.[30]

The WHO and the CDC do not recommended mass vaccination of the general public for outbreaks of mpox in nonendemic countries, with immunization reserved for appropriate PEP and pre-exposure prophylaxis in intermediate- to high-risk individuals.[23,26] The CDC recommends PEP vaccination for individuals with a high degree of exposure that includes unprotected contact of the skin or mucous membranes of an individual to the skin, lesions, body fluids, or contaminated fomites from a patient with mpox, as well as being within 6 feet of a patient during an aerosolization procedure without proper PPE. Following an intermediate degree of exposure, which includes being within 6 feet for 3 or more hours wearing at minimum a surgical mask or contact with fomites while wearing incomplete PPE, the CDC recommends monitoring and shared decision-making regarding risks and benefits of PEP vaccination. Monitoring without PEP is indicated for low and uncertain degrees of exposure, including entering a room without full PPE such as eye protection, regardless of the duration of contact.[23,26]

Postexposure prophylaxis vaccination should be administered within 4 days of a known high-level exposure to mpox to prevent infection.[29] If administered within 4 to 14 days postexposure, vaccination may reduce disease severity but will not prevent infection.[34]

Pre-exposure prophylaxis is recommended for individuals at high risk for exposure to mpox, including health care workers such as laboratory personnel who handle mpox specimens and health care workers who administer ACAM2000 vaccinations or anticipate providing care for many patients with mpox.[34]

Management

Most cases of mpox are characterized by mild to moderate disease with a self-limited course. Most commonly, medical management of mpox involves supportive care such as fluid resuscitation, supplemental oxygen, and pain management.[6] Treatment of superinfected skin lesions may require antibiotics. In the event of ophthalmologic involvement, patients should be referred to an ophthalmologist for further management.

Currently, there are no FDA-approved therapies for mpox; however, tecovirimat, cidofovir, brincidofovir, and vaccinia immune globulin intravenous are available under expanded access Investigational New Drug protocols.[6,35] Human data for cidofovir, brincidofovir, and vaccinia immune globulin intravenous in the treatment of mpox are lacking, while cidofovir and brincidofovir have shown efficacy against orthopoxviruses in in vitro and animal studies, but are available therapeutic options.[35]

Tecovirimat is an antiviral that is FDA approved for smallpox with efficacy data against mpox in animal studies. It is the first-line treatment for patients with severe disease requiring hospitalization or 1 or more complications, including dehydration or secondary skin infections, as well as for populations at risk for severe disease, which includes immunocompromised patients, pediatric patients younger than 8 years, pregnant or breastfeeding individuals, or patients with a history of atopic dermatitis or active exfoliative skin conditions.[36] In this current outbreak, both intravenous and oral tecovirimat are weight based in adult and pediatric patients for 14 days, with the intravenous form dosed every 12 hours by infusion over 6 hours, and the oral doses administered every 8 to 12 hours based on patient weight.[37] Tecovirimat generally is well tolerated with mild side effects but is notably contraindicated in patients with severe renal impairment with a creatinine clearance less than 30 mL/min, and renal monitoring is

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indicated in pediatric patients younger than 2 years and in all patients receiving intravenous treatment.

Conclusion

Given that cutaneous lesions are the most specific presenting sign of mpox infection, dermatologists will play an integral role in identifying future cases and managing future outbreaks. Mpox should be considered in the differential diagnosis for all patients presenting with umbilicated or papulovesicular lesions, particularly in an anogenital distribution. The classic presentation of mpox may be more common among patients who are not considered high risk and have not been exposed via sexual activity. All patients with suspicious lesions should be managed following appropriate infection control precautions and should undergo molecular diagnostic assay of swabbed lesions to confirm the diagnosis. JYNNEOS is the only vaccine that is currently being distributed in the United States and is safe to administer to immunocompromised populations. The risks and benefits of vaccination should be considered on an individual basis between a patient and their provider. Taking into consideration that patients with atopic dermatitis are at risk for severe disease if infected with mpox, vaccination should be strongly encouraged if indicated based on patient risk factors. For atopic dermatitis patients treated with dupilumab, shared decision-making is essential given the FDA label, which recommends avoiding the use of live vaccines.[38]

The mpox epidemic occurring amidst the ongoing COVID-19 pandemic should serve as a wake-up call to the importance of pandemic preparedness and the global health response strategies in the modern era of globalization. Looking forward, widespread vaccination against mpox may be necessary to control the spread of the disease and to protect vulnerable populations, including pregnant individuals. In the current climate of hesitancy surrounding vaccines and the erosion of trust in public health agencies, it is incumbent upon health care providers to educate patients regarding the role of vaccines and public health measures to control this developing global health crisis.

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