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Diagnosis and Management of Monkeypox: A Review for the Emergency Clinician

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The outbreak of monkeypox in May and June 2022 is the largest outside of central and western Africa since the 2003 outbreak in the United States. Monkeypox, like smallpox, is caused by an orthopoxvirus, though its clinical manifestations tend to be less severe. It is characterized by a prodromal flu-like illness with lymphadenopathy followed by a centrifugally spreading rash, sometimes involving the face, palms, soles, and oral mucosa. Although the vast majority of cases resolve with symptomatic management, a small number of patients can suffer severe outcomes including, but not limited to, secondary bacterial skin infections, pneumonitis, ocular sequelae, encephalitis, hypovolemia, and death. Local, state, and federal health authorities should be involved in the care of people under investigation for this illness. With confirmed cases worldwide and the possibility of community spread, emergency clinicians need to be aware of the manifestations and management of this disease, both to treat those with the disease as well as to provide education to those exposed and at risk of infection. [Ann Emerg Med. 2022;■:1-11.]

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INTRODUCTION

Monkeypox is a viral disease that has been endemic to Central and Western Africa for over 50 years and has drawn international attention beginning in May 2022 owing to the appearance of cases outside of Africa, most notably in Europe and North America.[1] However, most recent cases have no history of recent travel to endemic areas or exposure to sick contacts.[2] The classic stigmata of the disease is a progressive rash that develops on the face and/or oral mucosa and spreads centrifugally, sometimes including the palms and soles. Although most cases resolve with supportive or expectant management, many patients will likely seek evaluation in emergency departments for evaluation of acute symptoms.[3] As of July 8, 2022, over 8,200 cases have been identified worldwide.[4] Therefore, emergency clinicians must understand the current evidence regarding this disease. This review seeks to provide emergency clinicians with the most up-to-date information necessary to diagnose, manage, and provide guidance regarding quarantine to patients and close contacts.

EPIDEMIOLOGY

Though it was initially discovered in 1958 in laboratory monkeys, the first case in humans was not detected until 1970, when a child in the Democratic Republic of the Congo contracted the disease 9 months after smallpox eradication in the country.[5] Monkeypox is endemic to a number of central and western African countries, including but not limited to the Democratic Republic of the Congo, the Central African Republic, Nigeria, and Liberia.[6] A number of mammalian species are susceptible to the virus, including humans and other primates, rope squirrels, tree squirrels, Gambian pouched rats, and dormice.[6] However, despite the name, the primary reservoir is likely a rodent species.[7]

Monkeypox is rarely seen outside endemic countries in central and western Africa. The first outbreak outside these regions occurred in 2003 in the midwestern United States. This was attributed to rodents imported from Ghana, which infected prairie dogs, which subsequently infected humans handling or buying them as pets. Of 79 total cases, 2 were described as severe: one with encephalitis and the other with airway compromise because of lymphadenopathy and a large retropharyngeal abscess. However, there were no deaths.[3,8,9] The 2003 outbreak was ultimately contained through contact tracing, administration of the smallpox vaccine to close contacts, and an embargo on the importation of African rodents.[10] Subsequent cases in nonendemic regions have been isolated and sporadic, occurring in patients with direct links to western Africa (in particular Nigeria) or their direct contacts, including health care workers.[11-13] This changed in the current outbreak. Of the individuals who have been infected during the outbreak in May and June 2022, a disproportionate number have had no recent travel to endemic regions. The Centers for Disease Control and Prevention (CDC) reports that most cases have occurred in

individuals self-identifying as gay, bisexual, or men who have sex with men. At present, it remains unclear why the virus is spreading at this rate.[2]

There are 2 clades of monkeypox virus: the Central African "Congo Basin" clade, noted for higher virulence and infectivity, and the West African clade, which tends to be less severe with lower mortality. The West African clade is suspected to be primarily responsible for the current outbreak as well as the outbreak in 2003.[14,15]

Smallpox vaccination has an estimated 85% efficacy in protecting against monkeypox.[6] However, as widespread smallpox vaccination programs were discontinued amidst smallpox eradication, some experts have theorized that declining worldwide immunity has opened a niche for monkeypox to take root.[6,16] The date that routine smallpox vaccination was discontinued varies by nation, ending in the United States in 1972. The disease was declared globally eradicated in 1980.[17] The number of annual monkeypox cases in humans has increased since its discovery, such as in the Democratic Republic of the Congo, where the incidence has increased from 0.64 cases per 100,000 in 2001 to 2.82 cases per 100,000 in 2013.[18]

PATHOPHYSIOLOGY

Monkeypox is a double-stranded DNA virus of the *Orthopoxvirus* genus, similar to smallpox and cowpox, and is the most important active virus remaining in the genus in the postsmallpox eradication era.

Transmission of monkeypox occurs through contact with an infected animal or human or through contact with material contaminated by the virus.[19,20] Viral transmission can occur through direct and indirect contact with live or dead animals, including handling wild game, a bite or scratch, or contact with fluids or lesions from an infected animal.[19,20] Human-to-human transmission likely occurs through contact with lesions, body fluids, contaminated bedding or clothing, and exposure to respiratory droplets from infected persons. In addition, emerging evidence suggests aerosolized transmission may be possible.[6,19,20] Localized genital lesions have occurred in many patients during the current outbreak, disproportionately among young adult males who reported having sex with males; this suggests that sexual transmission plays a role in the current outbreak.[14,19,20] A systematic review estimated the secondary attack rate to be between 0.3% to 10.2%, though data suggest it could be as high as 50% among household contacts.[18] However, it can be as low as 0% with appropriate personal protective equipment.[13] The time from exposure to onset of symptoms is approximately 12 days.[19-21] During this incubation period, the virus replicates at the inoculation site and then spreads to the lymphatic system. A viremia develops, allowing the virus to spread to other organs and ultimately resulting in the onset of symptoms.[19,20,22]

CLINICAL PRESENTATION

In most patients, symptoms begin with a viral prodrome lasting 1 to 5 days. In the 2003 United States outbreak, prodromal symptoms included fever (85%), lymphadenopathy (71%), chills (71%), and headache (65%). Sore throat, myalgias, cough, congestion, nausea and/or vomiting, back pain, mouth sores, and shortness of breath were individually reported in 20% to 60% of cases.[3] Patients develop the characteristic pruritic or painful indurated and umbilicated rash on days 1 to 3, affecting the face (up to 95%), upper extremities (81.3%), lower extremities (65.6%), oral mucosa (70%), genitalia (30%), and conjunctivae (20%) (Figure). The rash spreads centrifugally and can involve the palms and soles (up to 75%).[3,20,23,24] These lesions progress in 1-to-2-day increments from maculopapular to vesicular to pustular in nature, remaining in the pustule stage for 5 to 7 days. Subsequently, they crust over before falling off in 1 to 2

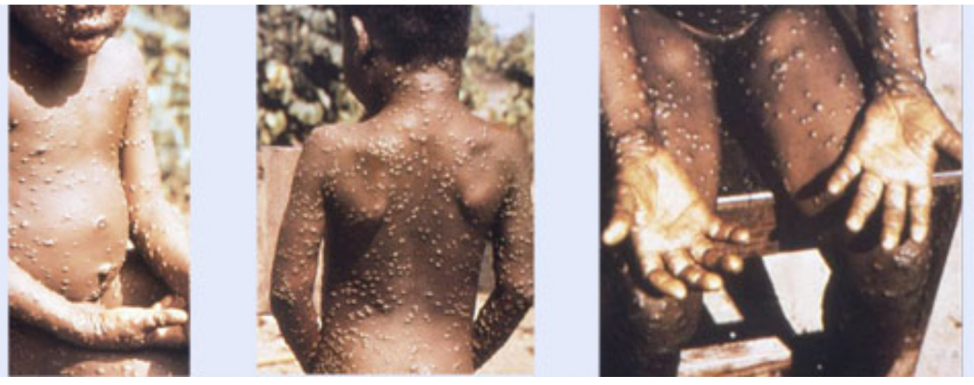

Figure. Characteristic Monkey Pox Lesions. (Obtained from https://www.cdc.gov/poxvirus/monkeypox/index.html.[26])

Table 1. Defining clinical characteristics of monkeypox, chickenpox, and smallpox.

Characteristic	Monkeypox	Chickenpox	Smallpox
Incubation period, days	7 to 17	12 to 14	7 to 17
Length of prodromal phase, days	1 to 4	0 to 2	2 to 4
Stages of development of lesions	Usually at the same stage of development but can also be at different stages	Lesions at different stages of development	Lesions at the same stage of development
Rash distribution	Centrifugal	Centripetal	Centrifugal
Frequency of lesions on palms or soles	Common	Rare	Common
Lesion depth, mm	Superficial to deep, up to 6	Superficial, 2 to 3	Deep, 4 to 6
Length of time until crusting of pustules, days	5 to 7	Within 24 hours	5 to 8
Length of time from rash onset to desquamation, days	14 to 21	6 to 14	14 to 21
Lymphadenopathy	Moderate to severe	Absent	Absent

weeks. The rash typically lasts approximately 2 to 3 weeks from onset to desquamation.[20,24] Lesions might all be in the same development phase, akin to smallpox, or they might appear in crops at various phases of development, akin to chickenpox.[25,26]

In most cases, symptoms resolve over a two-to-four-week course. However, severe illness or death can occur. Manifestations of severe disease include secondary bacterial skin infections (19%), pneumonitis (12%), ocular complications (4%-5%), and encephalitis (<1%).[20,27] Although data are limited, findings suggest that patients at higher risk for complicated clinical courses include those with rashes involving more than 100 lesions and mucosal lesions causing dysphagia or oral intolerance.[27] These patients are at greater risk for volume depletion through decreased oral intake and insensible losses by the lesions.[28,29] Conversely, the presence of less than 25 lesions portends a benign course.[3] Severe outcomes are more common in the Central African clade than in the West African clade, possibly accounting for the difference in mortality rates as discussed above.[15] However, these mortality estimates are primarily based on patients in Africa. Notably, during the 2003 outbreak in the United States, there were 0 deaths among 79 patients.[9,18]

Several patient populations appear to be at higher risk for severe outcomes. Children, young adults, and individuals not immunized against smallpox are likely at higher risk for severe illness.[7,14] Patients with HIV are more likely to have skin rashes ≥2 cm, genital ulcers, secondary bacterial skin infections, and a longer duration of illness.[28,30] Finally, patients with malignancy, diabetes mellitus, emphysema, heart failure, and other immunodeficiencies, including those undergoing treatment with radiation, cytotoxic chemotherapy, antirejection medications, or chronic steroids, could be at risk for severe outcomes.[20,31]

EMERGENCY DEPARTMENT EVALUATION AND DIAGNOSIS

Personal protective equipment using standard contact and droplet precautions is recommended for all health care workers caring for a patient with suspected monkeypox. Because of the theoretical risk of aerosolized transmission and the potential for the patient to have chickenpox, the CDC recommends airborne precautions. This includes using a disposable gown and gloves, an N95 respirator, eye protection, and isolating the patient to a single-person room with the door closed, if feasible.[32] These precautions were followed when a patient in Singapore presented with monkeypox, and none of the health care workers involved in the patient's care developed symptoms.[13]

Diagnostic evaluation of monkeypox should be initiated based on clinical suspicion. History should include recent travel to endemic areas, exposure to infected individuals, the date of onset of symptoms, sexual history, and history of smallpox vaccination.[6] In addition, a full skin examination should be performed, and the stage of rashes noted. This includes inspection of the oral mucosa, as mucosal lesions can lead to intolerance to oral intake and dehydration. Thorough ocular, pulmonary, and neurological examinations are particularly useful in assessing for severe disease manifestations.

The primary alternative diagnoses include chickenpox (*Varicella zoster* virus) and smallpox (*Variola major* or *minor* virus). The most distinguishing characteristic of monkeypox is its likelihood to produce moderate to severe lymphadenopathy. Chickenpox lesions are also more superficial and progress more rapidly, often progressing from the pustule stage to crusting within 24 hours (Table 1).[24,25,32,33] Though lesions are usually all at the same stage of development, similar to smallpox,

Table 2. CDC case definition.[42]

Suspect Case:
- New characteristic rash* or
- Meets one of the epidemiologic criteria and has a high clinical suspicion† for monkeypox

Probable Case:
- No suspicion of other recent *Orthopoxvirus* exposure (eg, *Vaccinia virus* in ACAM2000 vaccination) and demonstration of the presence of
  - *Orthopoxvirus* DNA by a polymerase chain reaction of a clinical specimen or
  - *Orthopoxvirus* using immunohistochemical or electron microscopy testing methods or
  - Demonstration of detectable levels of antiorthopoxvirus IgM antibody during the period of 4 to 56 days after rash onset

Confirmed Case:
- Demonstration of the presence of *Monkeypox virus* DNA by polymerase chain reaction testing or Next-Generation sequencing of a clinical specimen or isolation of *Monkeypox virus* in culture from a clinical specimen

Epidemiologic Criteria:
Within 21 days of illness onset:
- Reports having contact with a person or people with a similar appearing rash or who received a diagnosis of confirmed or probable monkeypox or
- Had close or intimate in-person contact with individuals in a social network experiencing monkeypox activity; this includes men who have sex with men who meet partners through an online website, digital application ("app"), or social event (eg, a bar or party) or
- Traveled outside the United States to a country with confirmed cases of monkeypox or where the *Monkeypox virus* is endemic or
- Had contact with a dead or alive wild animal or exotic pet that is an African endemic species or used a product derived from such animals (eg, game meat, creams, lotions, powders, etc)

Exclusion Criteria:
A case may be excluded as a suspect, probable, or confirmed case if:
- An alternative diagnosis* can fully explain the illness or
- An individual with symptoms consistent with monkeypox does not develop a rash within 5 days of illness onset or
- A case where high-quality specimens do not demonstrate the presence of *Orthopoxvirus* or *Monkeypox virus* or antibodies to orthopoxvirus

*Deep-seated and well-circumscribed lesions, often with central umbilication, and lesion progression through specific sequential stages—macules, papules, vesicles, pustules, and scabs; this can sometimes be confused with other diseases that are more commonly encountered in clinical practice (eg, secondary syphilis, herpes, and varicella zoster). Historically, sporadic accounts of patients coinfected with *Monkeypox virus* and other infectious agents (eg, varicella zoster, syphilis) have been reported, so patients with a characteristic rash should be considered for testing even if other tests are positive.
†Clinical suspicion may exist if the presentation is consistent with illnesses confused with monkeypox (eg, secondary syphilis, herpes, and varicella zoster).

this is not a reliable defining characteristic of monkeypox. One study found lesions occurring in crops similar to chickenpox; this occurred in 18% of patients not previously vaccinated for smallpox and 31% of patients who had been vaccinated.[25] Although no cases of smallpox have been documented since 1977, there remain concerns about bioterrorism.[34] Smallpox will present with lesions at the same development stage, but lymphadenopathy is uncommon.[35] Other differential diagnoses include molluscum contagiosum (poxvirus), hand-foot-mouth disease (Coxsackie virus), Rocky Mountain Spotted Fever or other Rickettsial infection, Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, measles (rubeola), Tinea species, syphilis, erythema multiforme, and scabies. Cowpox is possible, though exceedingly rare. Particularly in the current outbreak,

Table 3. CDC recommended populations for treatment.[43]

- Patients with severe disease (eg, sepsis, encephalitis, hemorrhagic disease, confluent lesions, or other conditions requiring hospitalization)
- Patients at high risk of severe disease:
  - Immunocompromised state (eg, HIV/AIDS, leukemia, lymphoma, generalized malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, TNF inhibitors, high-dose steroids, being a recipient with hematopoietic stem cell transplant <24 months posttransplant or ≥24 months but with GVHD or disease relapse, or autoimmune disease with immunodeficiency)
  - Pediatric patients (particularly patients <8 y)
  - Patients with a history or presence of atopic dermatitis or other active exfoliative skin conditions (eg, eczema, burns, impetigo, VZV infection, HSV infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or keratosis follicularis)
  - Pregnant or breastfeeding women
  - Patients with complications (eg, secondary bacterial skin infection; gastroenteritis with severe nausea/vomiting, diarrhea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities)
- Patients with infections in aberrant locations (eg, eyes, mouth, genitals, and anus)

GVHD, Graft-versus-host disease; *HSV,* herpes simplex virus; *TNF,* tumor necrosis factor; *VZV,* varicella zoster virus.

Table 4. Possible treatments for monkeypox.

Name	Dose	Approval Status	Contraindications	Side Effects
Brincidofovir[43,45,51,52]	• <10 kg: 6 mg/kg oral suspension once weekly for 2 doses • 10 to <48 kg: 4 mg/kg oral suspension once weekly for 2 doses • ≥48 kg: 200 mg tablets once weekly for 2 doses	FDA-approved smallpox treatment for all ages. Not available commercially.	None	Common: • Nausea and vomiting • Diarrhea • Abdominal pain Serious: • Transaminitis • Male fertility impairment • Fetal toxicity
Cidofovir[43,46,53]	• 3 to 5 mg/kg IV once (extrapolated from CMV retinitis dosing) • Administer 1 L of normal saline before and after Cidofovir infusion • Administer probenecid 2 g PO 3 hours prior to infusion, then 1 g each at 2 hours and 8 hours after	FDA approved for AIDS-related CMV retinitis in adults. Not FDA approved for smallpox treatment. CDC will consider under the investigational new drug or Emergency Use Authorization Protocols in the event of a smallpox outbreak.	Absolute: • Serum creatinine >1.5 mg/dL • ≥2+ proteinuria Relative: • Renal impairment (which can be mitigated with the administration of normal saline and probenecid as noted)	Common: • Fever • Nausea and vomiting • Proteinuria Serious: • Nephrotoxicity • Neutropenia • Decreased intraocular pressure • Anterior uveitis or iritis • Fanconi syndrome
Tecovirimat[44,50,54,55]	Capsule: • 13 to <25 kg: 200 mg BID • 25 to <40 kg: 400 mg BID • 40 to <120 kg: 600 mg BID • ≥120 kg: 600 mg TID • Must be taken with a full, fatty meal Injection: • 3 to <35 kg: 6 mg/kg BID • 35 to <120 kg: 200 mg BID • ≥120 kg: 300 mg BID • Injections are administered over 6 hours • Duration of treatment for both formulations is 14 days • Injection indication limited to oral intolerance • Once oral tolerance is achieved, the patient can begin capsules at the next timed dose	FDA approved for smallpox treatment in all ages (≥3 kg). CDC holds expanded access investigational new drug to allow use in the primary or early empiric treatment of monkeypox in all ages.	Capsule: • None Injection: • Creatinine clearance <30 mL per minute	Common: • Headache • Nausea and vomiting • Abdominal pain Serious: • Decreased hemoglobin and/or hematocrit • Electrocardiogram changes

Table 4. Continued.

Name	Dose	Approval Status	Contraindications	Side Effects
Vaccinia Immunoglobulin[50,56,57]	• 6,000 units/kg IV as soon as symptoms appear • May repeat dose based on the severity of symptoms and response to treatment (specific data are lacking) • 9,000 to 24,000 units/kg IV may be considered if the patient does not respond to the initial dose	FDA approved smallpox treatment in individuals aged ≥16 y. CDC holds expanded access investigational new drug for severe cases or in individuals in whom smallpox vaccination is contraindicated.	Absolute: • Isolated vaccinia keratitis • History of anaphylaxis or prior severe systemic reaction associated with the parenteral administration of VIGIV or other human immune globulin preparations • IgA-deficient patients with antibodies against IgA and a history of IgA hypersensitivity	Common: • Headache • Nausea • Rigors • Dizziness Serious: • Anaphylaxis • Renal dysfunction • Artificially high glucose readings that mask hypoglycemia • Thrombotic events • Aseptic meningitis • Hemolysis • Noncardiogenic pulmonary edema

BID, twice a day; *CDC*, Centers for Disease Control and Prevention; *CMV*, cytomegalovirus; *FDA*, Food and Drug Administration; *IV*, intravenous; *PO*, per os; *TID*, three times a day; *VIGIV*, vaccinia immune globulin intravenous.

lack of known contact with a monkeypox patient or travel to endemic areas is not necessarily reassuring against monkeypox.[24]

Laboratory findings observed in monkeypox can include low blood urea nitrogen (BUN) (61%), elevated transaminase levels (50%), hypoalbuminemia (50%), leukocytosis (45%), and thrombocytopenia (35%). Hypoalbuminemia and/or low BUN could indicate poor nutritional state or large gastrointestinal losses, including from mucosal involvement of lesions. It is unclear whether these correlate with disease severity.[3]

The preferred testing modality is nucleic acid amplification testing using real-time polymerase chain reaction, with sensitivities and specificities approaching 100%.[23,36-41] Samples should be obtained from lesions and/or exudates.[23,36,40] Two swab specimens from a minimum of 3 lesions should be obtained using sterile dry polyester, nylon, or Dacron swabs.[40] Dry lesion swabs in viral transport media and samples of lesion crusts are also acceptable.[40] Serologic antigen or antibody testing is also available, but because of cross-reactivity between orthopoxviruses, it is insufficiently specific.[37,38] Consultation with the state health department and the CDC is necessary prior to testing, as there are no commercial assays available as of June 2022.[39] The CDC case definition is depicted in Table 2.[42]

MANAGEMENT

Management of patients with monkeypox is largely supportive, focusing on hydration, pain control, and treating complications. This may include but is not limited to fluid resuscitation, empiric antibiotic treatment of secondary skin infections or conjunctivitis, and respiratory support for pneumonitis.

No medications have been specifically approved for the treatment of monkeypox.[20,43] However, several medications have been approved by the United States Food and Drug Administration to treat smallpox. Given that monkeypox is a fellow orthopoxvirus, it is possible that these medications could have efficacy against monkeypox. These medications include brincidofovir, cidofovir, and tecovirimat.[43-46] Though no clinical trials in humans have been performed, in vitro and in vivo studies in animals demonstrate the efficacy of all these medications against monkeypox.[47-50] In addition, although vaccinia immunoglobulin has been postulated as a treatment, no studies have established effectiveness against monkeypox.[20,43] Therefore, the CDC recommends that treatment should be considered in several populations, as shown in Table 3.[43] Table 4 demonstrates the treatment possibilities.[43-46,50-57]

Table 5. Postexposure prophylaxis considerations.[59]

Exposure Category	Characteristics	Recommendation
High	Unprotected contact with a person's skin or mucous membranes and the skin, lesions, or bodily fluids from a patient (eg, sexual contact, inadvertent splashes of patient saliva to the eyes or oral cavity of a person, ungloved contact with the patient), or contaminated materials (eg, linens and clothing) OR Being inside the patient's room or within 6 feet of a patient during any aerosolizing procedures involving oral secretions, skin lesions, or resuspension of dried exudates (eg, shaking soiled linens), without wearing an N95 or equivalent respirator (or higher) and eye protection OR Exposure that, at the discretion of public health authorities, was recategorized to this risk level (ie, exposure that ordinarily would be considered a lower risk exposure, raised to this risk level because of unique circumstances)	PEP – Recommended
Intermediate	Being within 6 feet for $\geq$3 hours of an unmasked patient without wearing a surgical mask at a minimum OR Activities resulting in contact between sleeves and other parts of an individual's clothing and the patient's skin lesions or bodily fluids or their soiled linens or dressings (eg, turning, bathing, or assisting with transfer) while wearing gloves but not wearing a gown OR Exposure that, at the discretion of public health authorities, was recategorized to this risk level because of unique circumstances (eg, if the potential for aerosol exposure is uncertain, public health authorities may choose to decrease the risk level from high to intermediate)	PEP – Informed clinical decisionmaking recommended on an individual basis to determine whether the benefits of PEP outweigh the risks
Low	Entered the patient room without wearing eye protection on one or more occasions, regardless of the duration of exposure OR During all entries in the patient care area or room (except for during any procedures listed above in the high-risk category), wear a gown, gloves, eye protection, and at minimum, a surgical mask OR Being within 6 feet of an unmasked patient for <3 hours without wearing, at minimum, a surgical mask OR Exposure that, at the discretion of public health authorities, was recategorized to this risk level based on unique circumstances (eg, uncertainty about whether monkeypox virus was present on a surface and/or whether a person touched that surface)	No PEP

PEP, Postexposure prophylaxis.

There are no specific criteria established for admission versus discharge. However, as in any illness, the inability to tolerate oral intake and uncontrolled pain point to a need for admission, as would the need for intravenous medication administration directed at the virus or its complications. Emergency clinicians are urged to combine their clinical judgment with consultations from infectious disease specialists and local, state, and federal health authorities in determining an appropriate disposition.

Patients not requiring admission should be advised to strictly quarantine from others, including mammalian animals. Isolation should be discontinued only in consultation with local or state health authorities; the patient should be cautioned that they will, at a minimum, need to be isolated until all lesions have resolved, including scabs falling off and a new layer of skin formed, or longer if required by public health authorities.[20,31,58] If a patient has no choice but to break isolation, such as to pursue medical treatment, the patient should be advised to wear a surgical-grade mask. They should wear long sleeves and pants to protect others from accidental contact with lesions.[20,58]

If patients live with others, the CDC advises isolation in a separate room.[20,58] If there is no choice but to share a common space, patients should do their best to cover their lesions and keep as much distance from others as practical. In this scenario, patients and cohabitants alike should wear at least surgical masks and consider N95 respirator masks if available. The CDC currently reports that dirty laundry from infected patients can be washed on warm settings in a standard laundry machine; bleach is optional.[20,58] Similarly, the CDC reports that soiled dishes and utensils from infected patients can be washed in a shared dishwasher or by hand with warm water and soap. However, contaminated surfaces should be thoroughly disinfected with household cleaning products after use.[20,58]

POSTEXPOSURE PROPHYLAXIS

Postexposure treatment may be considered in certain patient populations. Postexposure vaccination should be

Table 6. Products available for postexposure prophylaxis.

Product	Administration	Contraindications	Adverse Reactions
JYNNEOS[61]	Subcutaneous injection of 2 doses (0.5 mL each) 4 weeks apart.	**Absolute**: • None **Relative**: • Immunocompromised persons could have diminished immune response	**Common**: • Injection site reactions • Constitutional symptoms **Serious**: • Crohn's disease • Sarcoidosis • Extraocular muscle paresis • Throat tightness
ACAM2000[63]	Percutaneous administration with a single drop of vaccine suspension then 15 needle punctures (using the same bifurcated needle) into the superficial skin.	**Absolute**: • None **Relative**: Not advised in nonemergency settings if any of the following are present: • Immunodeficiency or close contact with immunodeficient persons • Coronary artery disease • Cardiomyopathy • ≥3 major atherosclerotic risk factors • Eczema • Pregnancy • Pediatric patients • History of anaphylaxis to polymyxin B sulfate or neomycin	**Common**: • Injection site reactions • Constitutional symptoms **Serious**: • Myocarditis • Pericarditis • Encephalitis, encephalomyelitis, and/or encephalopathy • Erythema multiforme major • Progressive or generalized vaccinia • Eczema vaccinatum

considered based on the degree of exposure (Table 5).[58,59] The optimal time for postexposure vaccination is within 4 days, though it can be considered up to 14 days after exposure.[58]

JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating, by Bavarian Nordic) and ACAM2000 (Smallpox Vaccinia Vaccine, Live, by Sanofi Pasteur Biologics Co) are 2 vaccines approved in the United States and stored in the Strategic National Stockpile for the prevention of smallpox; the former is also licensed to prevent monkeypox, while the latter can be considered for monkeypox exposure under an expanded access Investigational New Drug.[20,60]

JYNNEOS contains live but nonreplicating Modified *Vaccinia* Ankara. There is no risk of contracting smallpox, monkeypox, or *Vaccinia* from the JYNNEOS. JYNNEOS is administered in 2 doses, 4 weeks apart.[60,61] Common reactions include localized pain, swelling, erythema of the injection site, as well as headache, myalgias, fatigue, nausea, fever, and chills.[60] It does not carry as many risks as ACAM2000, making it a preferred choice. In the current outbreak, the CDC has released doses of JYNNEOS for postexposure prophylaxis, including close contact with patients and health care workers involved in monkeypox patient care. However, in May 2022, there were only approximately 1000 doses available in the Strategic National Stockpile. Therefore, production would need to increase to preclude the need for ACAM2000 use in monkeypox postexposure prophylaxis.[62]

ACAM2000 is a live attenuated vaccine containing the *Vaccinia* virus.[60,63] It is administered as a single dose. Although it also carries the common risks of localized pain, swelling, and erythema, ACAM2000 carries a US Food and Drug Administration Black Box warning of myocarditis and/or pericarditis, occurring in 5.7 per 1,000 primary vaccines. Other rare but severe complications include encephalitis, encephalomyelitis, encephalopathy, and erythema multiforme major, including Stevens-Johnson syndrome, progressive vaccinia, generalized vaccinia, and eczema vaccinatum.[60,63] These risks may be higher in patients with comorbidities such as cardiac disease (including those with ≥3 atherosclerotic risk factors), immunodeficiency (including HIV), and skin conditions such as eczema and psoriasis, which are all relative contraindications to the ACAM2000 vaccination.[60,63,64] The CDC advises disregarding these contraindications in smallpox exposure, but clear guidelines are unavailable for monkeypox.[60,65] It is not possible to contract smallpox from the vaccination. However, patients should be advised to wash their hands thoroughly after changing bandages overlying the vaccination site owing to the risk of autoinoculation of the eyes or inoculation of others with *Vaccinia*.[65] There are approximately 100 million doses of ACAM2000 available

in the Strategic National Stockpile.[63] Table 6 depicts postexposure prophylaxis for monkeypox.[61,63]

Requests for monkeypox therapeutics as well as postexposure monkeypox vaccination should be directed to the CDC Emergency Operations Center by calling (770) 388-7100.

In conclusion, the monkeypox outbreak in May and June 2022 occurred outside the typical endemic regions of central and western Africa and has spread largely in the absence of travel or exposure to known sick contacts. This provides the impetus for emergency clinicians to gather expertise in diagnosing and managing monkeypox. Additionally, they must educate monkeypox patients and the worried well about the disease, given their role as frontline and safety net providers. Finally, although this review summarizes current knowledge about the diagnosis and management of the virus, clinicians must continue to stay apprised of updates to recommendations from local, state, and federal health authorities as more is learned about this outbreak.

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