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Prevention and Treatment of Monkeypox

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Abstract

Human monkeypox is a zoonotic orthopoxvirus with presentation similar to smallpox. Monkeypox is transmitted incidentally to humans when they encounter infected animals. Reports have shown that the virus can also be transmitted through direct contact (sexual or skin-to-skin), respiratory droplets, and via fomites such as towels and bedding. Multiple medical countermeasures are stockpiled for orthopoxviruses such as monkeypox. Two vaccines are currently available, JYNNEOSTM (live, replication incompetent vaccinia virus) and ACAM2000[®] (live, replication competent vaccinia virus). While most cases of monkeypox will have mild and self-limited disease, with supportive care being typically sufficient, antivirals (e.g. tecovirimat, brincidofovir, cidofovir) and vaccinia immune globulin intravenous (VIGIV) are available as treatments. Antivirals can be considered in severe disease, immunocompromised patients, pediatrics, pregnant and breastfeeding women, complicated lesions, and when lesions appear near the mouth, eyes, and genitals. The purpose of this short review is to describe each of these countermeasures.

Key Points

Prevention and management of monkeypox is similar to that of other orthopoxvirus infections.

Immunization with smallpox vaccines (JYNNEOSTM and ACAM2000[®]) may have a protective effect against monkeypox virus and improve clinical manifestations.

Most patients have mild disease and recover without medical intervention, but treatment with antivirals or vaccinia immune globulin may be used in seriously ill or immunocompromised individuals.

1 Introduction

While the world is still challenged by the coronavirus disease 2019 (COVID-19) pandemic, the emergence of a new outbreak caused by monkeypox virus has raised concern among public health authorities as to whether it would constitute a new threat [1, 2]. Monkeypox virus is a double-stranded DNA virus of the genus orthopoxviruses, which also includes variola, cowpox (CPX), and vaccinia viruses [3]. Monkeypox virus was first isolated from monkeys; however, the natural host of monkeypox virus also includes rope squirrels, tree squirrels, Gambian pouched rats, and dormice [4].

Two main clades of monkeypox virus have been identified so far in Central and West Africa, the former associated with more severe illness [5]. Many cases in the current outbreak have been traced to sexual transmission, especially among men who identify as gay, bisexual, or men who have sex

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with men [6]. The virus can also be transmitted through direct contact with infectious sores, scabs, or body fluids, and shared bedding/clothing [7]. The signs and symptoms are similar to but less severe than smallpox, and involve a characteristic rash preceded by mild prodromal symptoms (e.g., fever, lymphadenopathy, and flu-like symptoms) [8]. In the current outbreak, cases have been atypical, with the characteristic rash starting in the genital and perianal areas with or without dissemination to other parts of the body [9]. Patients are considered infectious once the prodrome or rash begins, until lesions scab and the scabs fall off. Identification of viral DNA in swabs taken from crusts of vesicles or ulcers represent the preferred strategy for diagnosing active monkeypox cases [5].

At the time of writing, there are no specific treatments for patients with a monkeypox virus infection per the Center for Disease Control and Prevention (CDC), and supportive care is typically sufficient [10, 11]. However, minor outbreaks have been controlled using smallpox vaccines, antivirals, and vaccinia immune globulin (VIG), with these therapies being available through consultation with the CDC. Prevention and management of monkeypox is similar to that of other orthopoxvirus infections, and all confirmed orthopoxvirus cases should be treated as if they are monkeypox until proven otherwise.

2 Prevention

Data suggest that prior immunization with smallpox vaccine may have a protective effect against monkeypox virus and may improve clinical manifestations of infection [12, 13]. Currently, there are three smallpox vaccines in the US Strategic National Stockpile (SNS): JYNNEOS™ (also known as IMVAMUNE, IMVANEX, MVA-BN) and ACAM2000® are licensed for smallpox; the Aventis Pasteur Smallpox Vaccine (APSV) could be used for smallpox under an investigational new drug (IND) protocol.

JYNNEOS™ is a live viral vaccine produced from the modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain) and is an attenuated, non-replicating orthopoxvirus [14]. It was licensed by the US Food and Drug Administration (FDA) in September 2019 and is now indicated for prevention of smallpox and monkeypox disease in adults 18 years of age or older determined to be at high risk for smallpox or monkeypox infection [15, 16]. Historical data have shown that smallpox vaccination with vaccinia virus was approximately 85% effective against monkeypox [17]. The vaccine is approved in Europe for smallpox as IMVANEX®, although the UK has been using it off-label in response to monkeypox cases [18].

ACAM2000® also consists of live vaccinia virus. It was licensed by the FDA in August 2007, replacing the previous orthopoxvirus vaccine Dryvax®, which was withdrawn by the manufacturer [19]. ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection. The CDC holds an emergency access IND protocol, which allows the use of ACAM2000® for non-variola orthopoxvirus infection (e.g., monkeypox) during an outbreak [20].

There are several differences between JYNNEOS™ and ACAM2000® [20]. ACAM2000® is a replication-competent vaccinia virus, whereas JYNNEOS™ is a replication-deficient modified vaccinia Ankara virus [16]. As such, ACAM2000® produces a major cutaneous reaction at the site of inoculation, while JYNNEOS™ does not. Consequently, there is a risk of inadvertent inoculation and auto-inoculation with ACAM2000®, but no such risk occurs with JYNNEOS™. With replication-competent vaccinia vaccines, such as ACAM2000®, eczema vaccinatum and progressive vaccinia can occur due to uncontrolled viral replication in certain individuals [19]. Progressive vaccinia is generally seen in immunocompromised individuals, whereas eczema vaccinatum can occur in individuals with atopic dermatitis or eczema. Guidelines recommend avoiding ACAM2000® among immunosuppressed persons (e.g., HIV-infected persons), making it a reasonable practice to avoid ACAM2000® in populations that are at increased risk of unrecognized HIV, currently the population with which most current non-African cases are being identified, and a population from which monkeypox may well spread more widely (e.g., sex workers) [21].

In addition, inadvertent transmission can occur with replication-competent vaccines, including vertical transmission resulting in fetal vaccinia, which can be fatal to the fetus or newborn. Other serious adverse events seen more frequently with ACAM2000® than with JYNNEOSTM include myopericarditis (expected to occur in 5.7 per 1,000 primary ACAM2000® vaccinees [19]) and post-vaccine encephalitis.

The FDA assessed the effectiveness of ACAM2000® by comparing immunologic responses and “take” rates of ACAM2000® to Dryvax [16, 19]. Similarly, the FDA assessed the effectiveness of JYNNEOS™ by comparing the immunologic response of JYNNEOS™ to ACAM2000® and also incorporated supportive animal studies. ACAM2000® is given percutaneously by the multiple puncture technique in a single dose using a bifurcated needle, while JYNNEOS™ is administered subcutaneously in two doses, 28 days apart.

Aventis Pasteur Smallpox Vaccine (APSV) is a replication-competent vaccinia vaccine that may be used under an IND or Emergency Use Authorization (EUA) to prevent smallpox if the licensed vaccines are unavailable or contraindicated [14]. It is not known, however, if this vaccine could be used for monkeypox.

2.1 Pre-exposure Prophylaxis

The Advisory Committee and Immunization Practices (ACIP) recommends vaccination for select persons at risk for occupational exposure to orthopoxviruses [22]. Research laboratory personnel, clinical laboratory personnel performing diagnostic testing for orthopoxviruses, and designated response team members at risk for occupational exposure to orthopoxviruses are recommended to be vaccinated. In addition, healthcare personnel who administer ACAM2000[®] or care for patients infected with replication competent orthopoxviruses can be offered vaccination based on shared clinical decision-making. ACIP contraindications for ACAM2000[®] and JYNNEOS[™] for PrEP are summarized in Table 1 [23].

2.2 Post-exposure Prophylaxis

Transmission of monkeypox requires prolonged close interaction with a symptomatic individual. Brief interactions and those conducted using appropriate protective personal equipment (PPE) in accordance with standard precautions are not high risk and generally do not warrant post-exposure prophylaxis (PEP) [24]. The CDC has created informed guidance to assess the risk of exposures and make informed decisions with regards to PEP. The CDC recommends that the first dose of vaccine be given within 4 days of exposure to prevent disease. If given 4–14 days after the exposure date, vaccination may reduce the symptoms of disease but may not prevent disease onset [25].

High-degree exposures are recommended to be monitored as well as receive PEP vaccination. High degree exposure includes: [24]

- Unprotected contact between a person's skin and the mucous membranes, skin, lesions, bodily fluids (e.g., any sexual contact, inadvertent splashes of patient saliva to the eyes or oral cavity of a person, ungloved contacts with patient), or contaminated materials (e.g., linen, clothing).
- Being inside a patient's room or within 6 ft of a patient during any procedures that may create aerosols from oral secretions, skin lesions, or resuspension of dried exudates (e.g., shaking of soiled linen) without wearing an N95 or equivalent respirator (or higher) and eye protection.
- Exposure that, at the discretion of public health authorities, is recategorized to this risk level (i.e., exposure that ordinarily would be considered a lower-risk exposure, raised to this risk level because of unique circumstances).

An intermediate degree of exposure would carry a recommendation for monitoring as well as informed clinical decision making recommended on an individual basis to determine whether benefits of PEP outweigh the risks [24]. Exposure characteristics for intermediate degree of exposure include:

- Being within 6 ft for 3 h or more of an unmasked patient without wearing, at a minimum, a surgical mask.
- 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 (e.g., turning, bathing, or assisting with transfer) while wearing gloves but not wearing a gown.
- Exposure that, at the discretion of public health authorities, is recategorized to this risk level because of unique circumstances (e.g., if the potential for an aerosol expo-

Table 1 Advisory Committee on Immunization Practices contraindications to using ACAM2000[®] and JYNNEOS[™] smallpox vaccines in laboratory and healthcare personnel at risk for occupational exposures to orthopoxviruses

Contraindication	Primary vaccinees (ACAM2000 [®])	Revaccinees (ACAM2000 [®])	Household contacts ^a (ACAM2000 [®])	JYNNEOS [™]
History or presence of atopic dermatitis	X	X	X	
Other active exfoliative skin conditions	X	X	X	
Conditions associated with immunosuppression	X	X	X	
Pregnancy	X	X	X	
Aged < 1 year	X	X	X	
Breastfeeding	X	X		
Serious vaccine component allergy	X	X		X
Known underlying heart disease (e.g., coronary artery disease or cardiomyopathy)	X	X		
Three or more known major cardiac risk factors	X			

^aHousehold contacts include persons with prolonged intimate contact with the potential vaccinee (e.g., sexual contacts) and others who might have direct contact with the vaccination site or with potentially contaminated materials (e.g., dressings or clothing)

sure is uncertain, public health authorities may choose to decrease risk level from high to intermediate).

Low or uncertain exposures have a recommendation for monitoring but no recommendation for PEP [24].

3 Treatments

3.1 Supportive Care

Most patients with monkeypox infection recover without medical treatment. Those with gastrointestinal symptoms (e.g., vomiting, diarrhea) will require oral/intravenous rehydration to minimize gastrointestinal fluid losses [26].

3.2 Antivirals

Several antivirals may be effective in treating monkeypox infections, although these drugs were approved for the management of smallpox based on animal models. Dose studies for these drugs have been conducted in humans, but the efficacy of these agents has not been thoroughly defined [27].

3.2.1 Tecovirimat

Tecovirimat (also known as TPOXX or ST-246) is the first antiviral indicated for the treatment of smallpox in adults and pediatric patients weighing at least 3 kg and is considered the treatment of choice [28]. In patients with severe disease, dual therapy with tecovirimat and brincidofovir may be used. Tecovirimat works by inhibiting the viral envelope protein VP37, which blocks the final steps in viral maturation and release from the infected cell, thus inhibiting the spread of the virus within an infected host [29]. While the efficacy of this agent in humans against monkeypox has not been tested, studies have reported improved survival from lethal monkeypox virus infections in tecovirimat-treated animals compared to placebo-treated animals at different stages of disease [30, 31]. In an expanded safety study of 359 human volunteers placed on tecovirimat, the placebo side-effect profile was largely similar to that of tecovirimat [30]. In small studies, tecovirimat was used in combination with vaccinia immune globulin (VIG) in patients with complications from smallpox vaccine, such as eczema vaccinatum [32, 33] and progressive vaccinia [34]. The CDC-held Emergency Access Investigational New Protocol allows use of tecovirimat for non-variola orthopoxvirus infection such as monkeypox. The protocol also includes allowance for opening an oral capsule and mixing its content with liquid or soft food for pediatric patients weighing less than 13 kg. Tecovirimat is available through the Strategic National

Stockpile as an oral capsule formulation or an intravenous vial [28].

3.2.2 Brincidofovir and Cidofovir

Brincidofovir has been approved for treatment of smallpox in the US since June 2021 [35]. Brincidofovir (oral) is an analogue of the intravenous drug cidofovir, and may have an improved safety profile, namely less renal toxicity, compared to cidofovir [36]. These drugs work by inhibiting the viral DNA polymerase [37]. While studies evaluating the use of brincidofovir for treating monkeypox infections in animal models are scarce, brincidofovir has been shown to be effective against orthopoxvirus infections [38, 39]. Clinical data regarding the efficacy of cidofovir against monkeypox in humans is lacking, yet in vitro activity and efficacy against lethal monkeypox virus infections in animals has been reported [40, 41]. Intravenous normal saline and probenecid therapy must be given concurrently with cidofovir. For brincidofovir, liver function tests before and during treatment must be done, as brincidofovir may cause increases in serum transaminases and serum bilirubin. These therapies are available under an EUA or IND.

3.3 Vaccinia Immune Globulin (VIG)

VIG is a hyperimmune globulin licensed by the FDA for treatment of certain complications of vaccinia vaccination [42]. These include eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in individuals who have skin conditions, and aberrant infections induced by vaccinia virus (except in cases of isolated keratitis, e.g., ocular infections) [42]. While a potential treatment, data on the effectiveness of VIG against monkeypox and smallpox is largely lacking, and use of VIG for monkeypox or smallpox has not been tested in humans. Since vaccination with vaccinia virus vaccine is contraindicated in patients with severe immunodeficiency in T-cell function, such patients with exposure history may alternatively be given VIG [43]. Treatment with VIG should be conducted under an IND application.

See Table 2 for a summary of these therapeutic agents.

4 Conclusion

CDC is developing interim guidance for treatment of monkeypox. Many individuals infected with monkeypox virus have a mild, self-limiting disease course even in the absence of specific therapy, but the prognosis for monkeypox may depend on multiple factors such as previous vaccination status, initial health status, and concurrent

Table 2 Summary of therapies for the management of monkeypox

Treatments	Route	Dosing	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Tecovirimat	PO, IV (approved in May 2022)	Adults: 600 mg twice daily for 14 days; pediatric (13 kg or more), if 13 kg to less than 25 kg: 200 mg BID for 14 days, if 25 kg to less than 40 kg: 400 mg twice daily for 14 days, if 40 kg or more: 600 mg twice daily for 14 days	Orthopoxvirus VP37 envelope wrapping protein inhibitor	Headache, nausea, abdominal pain, vomiting. Infusion-site reactions may occur with IV form	None	Repaglinide (hypoglycemia), Midazolam (decreased effectiveness of midazolam) Note: Co-administration with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co-administration	PO: Hepatic/renal adjustment not required. IV: should not be administered to patients with severe renal impairment
Brincidofovir	PO (tablets, oral suspension)	Adults weighing ≥ 48 kg: 200 mg once weekly for two doses; adults and pediatric patients weighing ≥ 10 kg to less than 48 kg: 4 mg/kg of the oral suspension once weekly for two doses; pediatric patients weighing less than 10 kg, the dose is 6 mg/kg of the oral suspension once weekly for 2 doses	Phosphorylated to active metabolite, cidofovir diphosphate, which selectively inhibits orthopoxvirus DNA polymerase-mediated viral DNA synthesis	Diarrhea, nausea, vomiting, and abdominal pain	None	OATP1B1 and 1B3 inhibitors increase Brincidofovir exposure which may increase Brincidofovir-associated adverse reactions. Consider alternative medication that are not OATP1B1 or 1B3 inhibitors	Not recommended in pregnant and breastfeeding women (perform pregnancy test in women of childbearing potential before treatment). Perform liver function tests before and during treatment as brincidofovir may cause increases in serum transaminases and serum bilirubin
Cidofovir	IV	5 mg/kg once weekly for 2 weeks, followed by 5 mg/kg IV once every other week	Undergoes cellular phosphorylation, then selectively inhibits orthopoxvirus DNA polymerase-mediated viral DNA synthesis	Decreased serum bicarbonate, proteinuria, neutropenia, infection, hypotony of eye, iritis, uveitis, nephrotoxicity, fever	Hypersensitivity to cidofovir or any component of the formulation; history of clinically-severe hypersensitivity to probenecid or other sulfa-containing medications; serum creatinine > 1.5 mg/dL; CrCl ≤ 55 mL/minute; urine protein ≥ 100 mg/dL ($\geq 2+$ proteinuria); use with or within 7 days of nephrotoxic agents; direct intraocular injection	Probenecid, agents of nephrotoxic potential	Dose adjustment based on renal function is necessary: Serum creatinine > 1.5 mg/dL, CrCl ≤ 55 mL/minute, or urine protein ≥ 100 mg/dL ($\geq 2+$ proteinuria)

Table 2 (continued)

Treatments	Route	Dosing	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Vaccinia immune globulin	IV	6000 U/kg as soon as symptoms appear; may be repeated based on severity of symptoms and response to treatment; 9000 U/kg may be considered if patient does not respond to initial dose	Antibodies obtained from pooled human plasma of individuals immunized with the smallpox vaccine provide passive immunity	Headache, nausea, rigors, dizziness	Isolated vaccinia keratitis, history of anaphylactic or severe systemic reaction to human globulins, IgA deficiency with antibodies against IgA and a history of IgA hypersensitivity	Contains maltose: may result in elevated glucose readings that can lead to untreated hypoglycemia or inappropriate insulin administration; may impair efficacy of live attenuated virus vaccines; revaccination may be necessary; may interfere with some serological tests	No human or animal data in pregnant women; use only if clearly needed. Use caution in patients with renal insufficiency (minimum infusion rate)

BiD twice daily, *CrCl* creatinine clearance, *DNA* deoxyribonucleic acid, *IV* intravenous, *PO* per os (orally)

illnesses or comorbidities. Thus, developing personalized treatments based on the individual risk of developing severe illness appears to be the most reasonable strategy.

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Declarations

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