



INFORMATION GUIDE

Mpox Clinical Guide

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ABOUT THIS INFORMATION GUIDE

This guide was developed for health care professionals involved in the care of persons with mpox (formerly monkeypox).This guide is produced by the University of Washington Infectious Diseases Education and Assessment Program (IDEA).

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LAST UPDATED

This educational guide was last updated *February 7, 2023*.

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MONKEYPOX VIRUS STRUCTURE

Virus structure description

Mpox is a disease caused by the monkeypox virus, a member of the orthopoxvirus family. Orthopoxviruses are characterized by an ovoid brick-shaped morphology as seen on cryoelectron tomography. Monkeypox virus is 360 nm x 270 nm x 250 nm in size and contains linear double stranded DNA of approximately 197 kilobases (kb). This genome encodes for more than 200 proteins that are essential for the virus life cycle, virus assembly, and evasion of host immune defenses. Monkeypox infectious virus can exist as two distinct forms: extracellular enveloped virus (EEV, also abbreviated as EV), and intracellular mature virus (IMV, also abbreviated as MV).



MONKEYPOX VIRUS LIFE CYCLE DESCRIPTION



- 1. **Virion Entry:** Monkeypox virus can attach to and enter a host cell in the form of an extracellular enveloped virus (EEV) or a mature virus (MV). The entry and fusion of the MV envelope with the plasma or endocytic membrane involves multiple viral proteins.
- 2. Early Transcription and Translation: Some monkeypox DNA is immediately transcribed and translated to produce early proteins, including growth factors, immune response modulators, and factors needed for DNA replication. This early step occurs in the host cell cytoplasm.
- 3. **Uncoating:** After cell entry, the uncoating of the viral core occurs, with shedding of the outer membranes and release of the core into the cytoplasm. The uncoating of the core facilitates DNA replication.
- 4. **DNA Replication:** Most of the monkeypox DNA replicates to form concatemeric DNA (long continuous DNA molecules that contain the same DNA sequence linked in series). This process occurs in a localized cytoplasmic region denoted as the viral factory.
- 5. Intermediate Gene Transcription and Translation: Within the viral factory region, the newly replicated (progeny) monkeypox viral DNA can undergo intermediate transcription and translation, generating intermediate proteins that include transcription factors required for late transcription. In addition, late proteins are generated, with some contributing to the viral structure and others playing a role in early transcription and translation.
- 6. Late Gene Transcription and Translation: Also, within the viral factory region, the progeny monkeypox viral DNA can undergo late transcription and translation, which produces late proteins, including some that contribute to the viral assembly process.
- 7. **Assembly:** The monkeypox DNA is resolved into single genomes and packaged into the core along with proteins necessary for early transcription.
- 8. **Morphogenesis:** The assembled core is moved out of the viral factory region where it obtains an outer membrane and becomes a mature virus (MV). The MV generally remains trapped within the cell, except in the rare event of cell lysis.
- 9. Wrapping: Some portion of the total virus particles produced are further wrapped by trans-Golgi/late endosomal double membranes to form the intracellular enveloped virus (IEV).
- 10. **Exocytosis:** The IEV migrate to the cell periphery on microtubules and are released by exocytosis to become cell-associated enveloped virus (CEV). The CEV can infect neighboring cells. Approximately 1% of CEV are released into the extracellular space via motile actin tail formation to become extracellular enveloped virus (EEV). EEV are responsible for long-range dissemination of the virus.

CLINICAL PRESENTATION

Mpox presentation
and symptomsPeople with mpox may present with a combination of signs and symptoms that may
include rash, fever, malaise, chills, headache, and lymphadenopathy. Rash is the most
common manifestation and it typically evolves from initial macular lesions to form
papules, vesicles, and pustules. Over time, some of the pustular lesions ulcerate, but
nearly all lesions eventually become crusted and then scabbed.For persons who have potential recent exposure to mpox, clinicians should maintain
suspicion for mpox even when only some of the less common symptoms and
manifestations are present, including rectal (pain, tenesmus, and/or bleeding),
genitourinary (dysuria and/or urethritis), and oropharyngeal (pain and/or
adenopathy). Recent data show that some people can spread monkeypox virus to
others from 1-4 days before symptoms of mpox appear.

MPOX CASES REPORTED TO CDC: SIGNS AND SYMPTOMS



Source: Centers for Disease Control and Prevention. Mpox cases reported to CDC: Signs and Symptoms, 2022 Outbreak Cases and Data. December 21, 2022.

EDITOR'S NOTES

Oropharyngeal symptoms are not one of the symptoms included in the CDC mpox case reporting. Based on case series, oropharyngeal symptoms, including pharyngitis, are common in persons diagnosed with mpox, manifesting in 2-29% of mpox cases.

CLINICAL PRESENTATION

Mpox lesion progression	Lesions can appear anywhere on the body. Among cases reported in the 2022 mpox outbreak, lesions most frequently involved the anogenital region, but were also commonly found on the mouth, hands, face, feet, or chest.
	Sometimes, lesions first form on the tongue and in the mouth. This is called enanthem.
	Lesions typically progress through the six stages shown below.

MPOX LESION PROGRESSION DESCRIPTION AND TIMELINE



ORAL AND CUTANEOUS MPOX LESIONS



Ulcerated lesion on upper palate



Tonsillar exudate in mpox pharyngitis



Ulcerated lesion below lower lip with secondary infection



Macules on hand and finger



Multiple stages of evolutions of macules on palm



Crusted lesion on face



Erythematous pustular lesion in inguinal crease



Vesicular lesion on forearm



Pustular lesion in genital region

INFECTION PREVENTION/CONTROL IN CLINICAL SETTINGS



EDITOR'S NOTES

Health care personnel with exposures to mpox without wearing full PPE, and who are asymptomatic, should self-monitor symptoms for 21 days but can continue to work if they remain asymptomatic. Depending on the exposure, health care workers may be recommended to receive postexposure prophylaxis JYNNEOS vaccination.

After cleaning the room, new patients may be roomed without issue.

DIAGNOSIS & TESTING

Diagnosis of mpox

A definitive diagnosis of mpox is made by detection of the monkeypox virus from a specimen obtained from a cutaneous or mucocutaneous site. The following shows the proper technique for collecting a clinical specimen for the molecular detection of monkeypox virus.

OVERVIEW

2

Collect 2 specimens from at least 2 lesions



SUPPLY LIST

- At least 4 synthetic swabs
- Container for each swab*
- Specimen bags
- Patient labels
- Sterile gauze
- EPA-registered disinfectant wipes
- Any supplies needed for basic patient care

*The type of container, swab, and transport medium may differ per local laboratory guidelines; please ask your local testing site for preference.

1) Before swabbing: Perform hand hygiene and don PPE prior to entering patient room.

At first lesion site: Do NOT clean the lesion area with ethanol or other disinfectant prior to swabbing.



B

C 180°

D

Grasp swab firmly. Avoid touching shaft at least an inch before the tip.

Ε

Vigorously rub the swab back and forth on lesion surface 3x. If lesion ruptures, ensure swab collects lesion fluid. Unroofing the lesion is not recommended and is unnecessary

Rotate the swab 180 degrees. Vigorously swab the lesion 3x again.



REPEAT Step 2, A through D on the same lesion with a second swab.

3) At second lesion site: At second lesion site, repeat step 2, A through E.

The second lesion is ideally on a different part of the body and/or has a different appearance.



Label and package specimens:

Label, package, store, and ship specimens following specifications put forth by testing laboratory.

EDITOR'S NOTES

With antecedent sexual exposure, maintain a high degree of suspicion for mpox (even in the absence of skin lesions) in clinical syndromes such as dysuria, pharyngitis, and proctitis. Test for typical pathogens implicated in these syndromes, including gonorrhea, chlamydia, syphilis, and herpes simplex virus (HSV). If there is high clinical suspicion for HSV and/or varicella zoster virus, and testing is also being performed for these viruses, the clinician should very carefully unroof the lesion. There are reports of needlestick injury leading to transmission of monkeypox virus in health care workers.

MANAGEMENT OF PATIENTS WITH MPOX

What supportive care should be offered to patients?	 Pain is a common symptom in people with mpox. This includes topical pain (from rash) as well as pain at the site of mucous membrane lesions (rectal, urethral, oropharyngeal). Pain control is a cornerstone of treatment. Strategies for pain control include over the counter pain relievers, such as nonsteroidal anti-inflammatory drugs and acetaminophen, and, if needed, prescription opioids. For cases of proctitis and severe rectal pain, topical lidocaine, stool softeners, and sitz baths can be utilized. Gabapentin has also been empirically tried with some reporting positive results. Topical steroids can be considered, though should be used with caution given risk of thinning the rectal mucosa and worsening extent of disease or injury. For cases of oropharyngeal pain, viscous lidocaine and salt-water gargle can be utilized. Intractable pain or oropharyngeal pain that limits oral intake may be an indication for hospitalization.
Who should be considered for medication treatment?	Certain individuals may be candidates for pharmacologic treatment. These include those with severe disease (e.g., hemorrhagic disease, large confluent lesions or those with severe secondary infection, sepsis, ocular infections, or with pain requiring hospitalization). Treatment should also be considered in those at high risk for developing severe disease, including those who are severely immunocompromised, pediatric populations, people who are pregnant or breastfeeding, or those with skin conditions compromising skin integrity.
How should a patient awaiting test results be counseled?	Patients with possible mpox should stay isolated if possible. This means staying at home and separated from others, without attending work, school, or other public settings. They should avoid public or other group transportation, if possible. If use of public transportation is unavoidable, they should wear a mask, ensure all lesions are covered, and avoid any physical contact with others. Persons awaiting test results who need further medical care should inform their medical provider that they have been tested for monkeypox. If there is an unavoidable need to seek medical care (for example for further medical testing or treatment), the patient should ensure the rash is fully covered and wear a mask during the entire medical visit. If possible, consider isolation from pets such as dogs, as human-to-dog transmission has been documented.
How should a patient with a positive test result be counseled?	Persons with mpox should follow isolation instructions as described above for patients waiting test results. If someone with mpox cannot fully separate from others in the household, they should wear a face mask, avoid physical contact, and cover any lesions when in shared spaces. They should try and use a separate bathroom if available. Patients should wash their hands often with soap and water, or use an alcohol-based hand sanitizer. Any item that has been touched should be cleaned; clothing items should ideally be machine washed. Patients should stay isolated until any rash is fully resolved, all scabs have fallen off, and new skin is forming underneath. This usually takes 2-4 weeks. If they did not have a rash, they should be counseled to stay isolated until all symptoms (e.g., rectal pain, urethral pain) have fully resolved.

TECOVIRIMAT

Background

Tecovirimat (*Tpoxx*, ST-246) is an antiviral medication that inhibits an orthopoxvirus specific envelope wrapping protein (p37). Tecovirimat is FDA-approved for the treatment of smallpox. Animal studies have shown that it is effective in treating disease caused by orthopoxviruses, including mpox virus. It has been demonstrated to be safe in healthy adults, and is the focus of multiple ongoing human efficacy trials.



Indications

Tecovirimat should be considered for use in the following situations:

- Patients with severe mpox disease, including hemorrhagic disease, large number of lesions, ocular or periorbital infection, sepsis, encephalitis, or other manifestation that requires hospital admission.
- Patients with mpox involvement of anatomic areas that may result in serious adverse sequelae, including scarring or strictures.
- People who are at high risk of developing severe mpox-related disease, including immunocompromised individuals, children (especially those younger than 8 years of age), pregnant or breastfeeding people, and people who have a medical condition that affects skin integrity.

TECOVIRIMAT CONT.

Dosing	Tecovirimat is available in both PO (200 mg capsules) and IV formulations. Dosing is weight based; for most adults (weight 40 kg-120 kg) dosing is 600 mg PO every 12 hours, or 200 mg every 12 hours by IV infusion, with each infusion administered
	slowly over 6 hours. Duration of therapy in most cases is 14 days. For complete
	dosing recommendations, please refer to CDC IND.

Weight (kg)*	Recommended Dose (mg)	Recommended Dose (capsules)
25 kg to <40 kg	400 mg q12h	2 capsules q12h
40 kg to <120 kg	600 mg q12h	3 capsules q12h
120 kg and above	600 mg q8h	3 capsules q8h

*Specific pediatric dosing recommendations are available in the IND and may require pediatric consultation.

Access	Currently, tecovirimat can only be accessed through (1) the STOMP Clinical Study (stomptpoxx.org) or (2) from the Strategic National Stockpile through the <u>CDC</u> <u>Investigational New Drug (IND) protocol</u> .
Clinical considerations	No clinical studies have been performed with children or with people who are pregnant or breastfeeding. Nevertheless, children, pregnant people, and breastfeeding people should not be excluded from treatment if treatment with tecovirimat for mpox infection is considered appropriate. The use of tecovirimat in these situations should involve a close clinical assessment and a thorough discussion with the patient (or parents) regarding the risks and benefits of tecovirimat therapy. Children younger than 2 years of age should have renal monitoring during treatment, due to the risk from high exposure to hydroxypropyl-β-cyclodextrin, which is an ingredient in IV tecovirimat.
Adverse reactions	The most common adverse effects with oral tecovirimat are headache, nausea, abdominal pain, and vomiting; with parenteral tecovirimat, the most common adverse effects are infusion site reactions (pain, swelling, erythema, and extravasation) and headache.



Oral tecovirimat must be taken with a high fat, high calorie meal with each dose.



Consider food insecurity when providing oral tecovirimat.



Consider supplying patients with high fat foods such as nut butters if access to food is limited.

BRINCIDOFOVIR

Background

Brincidofovir (*Tembexa*), a prodrug of cidofovir, is a nucleotide analog DNA polymerase inhibitor. Brincidofovir has activity against orthopoxviruses and it is FDA-approved for the treatment of smallpox in adults and pediatric patients. Animal and in vitro studies have shown it is effective in treating disease caused by orthopoxviruses, including monkeypox virus. Brincidofovir contains a large lipophilic side chain that facilitates penetration across the host lipid membrane. Inside the cell, brincidofovir is converted to cidofovir, with the cleavage of the lipid ester linkage of the lipophilic side chain. Cidofovir is then phosphorylated to cidofovir diphosphate, which is the active antiviral moiety that inhibits DNA polymerase when cidofovir is incorporated into the growing viral DNA chain and subsequently slows further viral DNA chain extension.



BRINCIDOFOVIR CONT.

Indications	 Brincidofovir can be considered for use in the following situations: Patients with severe mpox disease OR are at high risk for progression to severe mpox disease AND meet either of the following: Experience clinically significant mpox disease progression while receiving tecovirimat or who develop recrudescence (initial improvement followed by worsening) of mpox disease after an initial period of improvement on tecovirimat, <i>OR</i> Are otherwise ineligible or have a contraindication for oral or intravenous tecovirimat
Dosing	Brincidofovir is available as a tablet (100 mg) or as an oral suspension (10 mg/mL).

Both preparations are given once weekly for a total of 2 doses (given on days 1 and 8). Dosing for both preparations is weight based:

Age Group	Weight (kg)	Tablet (mg)	Oral Suspension (mg)
Adult and Pediatric	≥48 kg	200 mg once weekly x 2 doses	20 mL (200 mg) once weekly x 2 doses
Adult and Pediatric	≥10 kg and <48 kg	NA	200 mg once weekly x 2 doses
Pediatric	<10 kg	NA	6 mg/kg once weekly x 2 doses

Access	Brincidofovir is available for the treatment of mpox infection as an FDA-authorized single-patient emergency use IND (e-IND). Clinicians with mpox patients who require brincidofovir treatment need to submit an e-IND request to FDA by email (DDI.EIND@fda.hhs.gov) or phone 301-796-3400 or 1-855-543-3784.
Clinical considerations	Brincidofovir is not recommended for use during pregnancy or when breastfeeding. For persons with childbearing potential, pregnancy testing is recommended prior to administering brincidofovir.
Adverse reactions	Adverse reactions related to brincidofovir include nausea, vomiting, diarrhea, hepatitis, and abdominal pain. Brincidofovir may also cause asymptomatic increases in serum transaminase (ALT or AST) and bilirubin levels. Serum transaminase levels should be obtained prior to treatment initiation. Brincidofovir does not cause nephrotoxicity and does not require dosage adjustment with mild, moderate, or severe renal impairment.
Drug Interactions	Brincidofovir should never be coadministered with cidofovir. Concomitant use of brincidofovir with OATP1B1 and 1B3 inhibitors (e.g., clarithromycin, cyclosporine, erythromycin, gemfibrozil, rifampin, HIV protease inhibitors, and hepatitis C virus protease inhibitors) may increase brincidofovir levels and increase brincidofovir- related toxicity.

CIDOFOVIR

Background

Cidofovir (*Vistide*) is a DNA polymerase inhibitor with activity against orthopoxviruses, as described in the previous brincidofovir section. Cidofovir is FDA-approved for treatment of CMV retinitis.



CIDOFOVIR CONT.

Indications	Use of cidofovir may be considered in instances of severe mpox infection refractory to tecovirimat treatment or in persons who cannot tolerate tecovirimat and brincidofovir may not be readily available. Cidofovir is contraindicated in those with history of clinically severe hypersensitivity to probenecid or other sulfa drugs, those with serum creatinine >1.5 mg/dL, or CrCl ≤55 mL/minute. It should not be used with other nephrotoxic agents.
Dosing	As extrapolated from the approved dosing for CMV, cidofovir should be dosed 5 mg/ kg once weekly for 2 weeks. Maintenance dosing thereafter is 5 mg/kg every 2 weeks. Adult patients should be premedicated with probenecid 2 grams 3 hours prior to cidofovir, then 1 gram 2 hours and 8 hours after infusion. In addition, patients should receive at least 1 L of normal saline in the 1-2 hours prior to infusion. If they can tolerate the fluid load, they should also receive a second liter of normal saline either during or immediately after the drug infusion. For children, the premedication and intravenous fluid instructions are different and should be determined in consultation with a pediatrician.
Access	Cidofovir is commercially available.
Clinical considerations	Use is not recommended in the first trimester of pregnancy.
Adverse reactions	Cidofovir is associated with significant risk of renal impairment and acute renal failure; to minimize this risk, it should be coadministered with prehydration and probenecid. It is contraindicated in those with renal dysfunction (CrCl ≤55 mL/min) and renal function should be monitored during therapy. Cidofovir has also been associated with neutropenia. Adverse clinical reactions include metabolic derangement, fever, nausea, vomiting, iritis, and uveitis.
Drug interactions	Cidofovir should never be coadministered with brincidofovir. Cidofovir may increase levels of tenofovir, and vice versa; cidofovir may impact effect of cladribine and increase levels of cabozantinib.

VACCINIA IMMUNE GLOBULIN (VIGIV)

Background	Vaccinia immune globulin intravenous (VIGIV) is a product derived from purified human plasma. It has been FDA approved for the treatment of complications from vaccinia vaccination, including eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in those with underlying skin conditions, and other infections induced by replication competent vaccinia virus. There are no data regarding efficacy of VIGIV in mpox.
Indications	Use of VIGIV can be considered in patients with severe mpox infection, especially in those with immunocompromising conditions that may preclude robust antibody responses. It can also be considered for prophylactic use for those exposed to mpox in whom vaccination is contraindicated and who may have severe immune impairment (most specifically in T-cell function).
Dosing	VIGIV is given IV only and is dosed generally at 6,000 U/kg to 9,000 U/Kg. It should be given through a dedicated line.
	Repeat dosing can be considered depending on the severity of the symptoms and response to treatment, but repeat dosing should be based on clinical judgment and administered after obtaining expert consultation.
Access	VIGIV can only be obtained with clinical consultation with the CDC through an expanded access investigational new drug program (e-IND). Clinicians who have a patient with mpox that may benefit from VIGIV should contact the CDC via email (<u>eocevent482@cdc.gov</u>) or phone (CDC Emergency Operations Center, 770-488-7100). Prior to administration, an informed consent must be obtained (<u>https://www.cdc.gov/poxvirus/monkeypox/pdf/Attachment-2_VIGIV-Informed-Consent-Form.pdf</u>)
Clinical considerations	Administration of VIGIV should be avoided in those with a diagnosis of IgA deficiency.
Adverse reactions	Adverse events associated with VIGIV include headache, nausea, rigors, and dizziness; other immunoglobulin infusions have been associated with hypotension, drowsiness, rash, and other effects. Patients should be monitored for the rare effect of anaphylactic reactions due to immune globulin.
Drug interactions	Live attenuated virus vaccines (including measles, mumps, rubella, varicella, and JYNNEOS/ACAM2000) should be deferred until about 3 months post VIGIV administration due to impaired vaccine responses caused by immune globulin administration.
	Because VIGIV contains maltose, it can interfere with the accuracy of some blood glucose monitoring systems and cause falsely elevated glucose readings. Therefore, for persons receiving VIGIV, only glucose-specific testing systems should be used for blood glucose monitoring.

VACCINATION

What vaccine is used?	At this time, the preferred vaccine for mpox protection is JYNNEOS. The vaccine requires 2 doses spaced 4 weeks apart. The vaccine recommendations on this page are for the context of the 2022 mpox outbreak.
Who should be vaccinated?	 Groups recommended for vaccination fall under two indications: (1) postexposure prophylaxis (PEP) for persons who have already been exposed to a person with mpox and (2) as prevention for persons who might be exposed in the future. The vaccine dosing and dosing schedule are the same regardless of the indication. Postexposure prophylaxis (PEP): JYNNEOS vaccine is indicated for persons who have recently had close contact with someone with mpox. Those receiving mpox PEP should ideally receive vaccination within 4 days of a known exposure to mpox. If more than 4 days have elapsed since the exposure, postexposure prophylaxis vaccination can be considered—if the exposure was within 14 days, but note that vaccination after day 4 is less likely to be effective than if given within 4 days of the exposure. Prevention: JYNNEOS vaccine is indicated as prevention for persons considered at risk for acquiring mpox. Persons considered at higher risk include gay, bisexual, or other men or transgender people who have sex with men and have multiple partners, have had recent prior sexually transmitted infections, and/ or have recent attendance at or participation in group sex settings. People who should be considered for mpox prevention vaccination include those with the mpox exposure risks described above within the past 6 months or who anticipate experiencing those risks in the future.



EDITOR'S NOTES

In general, intradermal vaccination is preferred over subcutaneous vaccination when vaccine demand is greater than supply, since only one-fifth the amount of vaccine is required to achieve an equivalent immune response.

If a patient has received subcutaneous vaccination, the second dose can be either subcutaneous or intradermal, and vice versa.

Patients with a history of developing keloid scars should be offered subcutaneous over intradermal administration to minimize the risk of scarring.

VACCINATION CONTINUED

Recommended Vaccination Timeline



The recommended time between vaccine doses is 28 days; the second dose may be given up to 4 days early and up to 7 days late. However, there is no recommendation to restart the vaccine series if the second dose is given earlier than day 24 or later than day 35.

What are vaccine coadministration considerations?	Vaccine may be administered at the same time as any other vaccines, though ideally in different limbs. Providers and patients may consider waiting 4 weeks after vaccination against COVID-19 (with Moderna, Pfizer, or Novavax vaccines) because of the rare side effects of myocarditis or pericarditis associated with both those vaccines and ACAM2000, a live smallpox vaccine. Recent data suggests the risk of myocarditis associated with JYNNEOS is extremely low. We recommend vaccination against mpox in eligible groups regardless of prior smallpox vaccination status given the possibility of waning immunity.
What is the duration of protection?	Peak immunity is expected around two weeks after the second dose of the vaccine. The expected duration of immunity is unknown.

EDITOR'S NOTES

For those who develop mpox disease, there is no current recommendation to subsequently receive mpox vaccination, including receipt of second dose if infection occurs between vaccine doses 1 and 2.

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DISCLOSURES

The authors for this guide do not have any disclosures or conflicts of interest.

ACKNOWLEDGEMENT

The authors would like to thank Inger K. Damon, MD, PhD, FIDSA for careful review and input on the content in sections on monkeypox structure, life cycle, and drug mechanisms of action. Thanks to Negusse Ocbamichael, PA-C for all of the clinical pictures presented in the guide. The authors would also like to thank Peter Harrison, MPH for his design and production work and Cognition Studio, Inc. for all of the illustrations in this guide.



