Nota de Medicina

PROVISIONAL MONKEYPOX (MPX) RAPID REVIEW

REVISIÓN RÁPIDA PROVISIONAL DE LA VIRUELA SÍMICA

Pablo Madrigal MD[1], Daniel Castrillón MD CRC[1], Sara Arbeláez Mejía[1], Raúl Daza MD[2], Adriana Higuera MD[3]

1 Healthcare analysis and optimization unit. Keralty SAS
2 Sanitas Medical Centers. USA

DEFINITION

Monkeypox (MPX) is a viral zoonotic disease caused by a virus with the same name that belongs to the Orthopoxvirus (OPX) genus of the Poxviridae family (1-3). Two distinct strains of monkeypox exist in different geographic regions of Africa: The strain isolated from Central Africa, and the strain from West Africa, which is less virulent (1). As of 07/07/2022 there have been 7594 confirmed monkeypox cases worldwide, (4) of which 700 belong to 36 states in the US (5).

DIAGNOSTIC APPROACH (2)

Key points to evaluate in medical history: (1-3,6-8)

- Incubation period usually goes from 5 to 15 days (range 4-21 days).
- Prodromal symptoms (1 to 5 days): Fever, intense headache, lymphadenopathy, back pain, myalgia, severe fatigue.
- Appearance of rash (Appears after 1 to 4 days of fever): Starts as an enanthem in mouth and rapidly progresses through several stages: macules (1-2 days), papules (1-2 days), vesicles (1-2 days), pustules (5-7 days) and crusts (7-14 days).

Patients become infectious from the beginning of the skin rash until the healing process (with viable virus present in the scabs), however, there is a risk of transmission from the prodromal phase of the disease.

Transmission: (1-3,6-8)

- Can occur when a person comes into close contact with an infected animal (i.e. Rodents are believed to be the main animal reservoir for transmission to humans).

Person-to-person transmission occurs through close contact with:

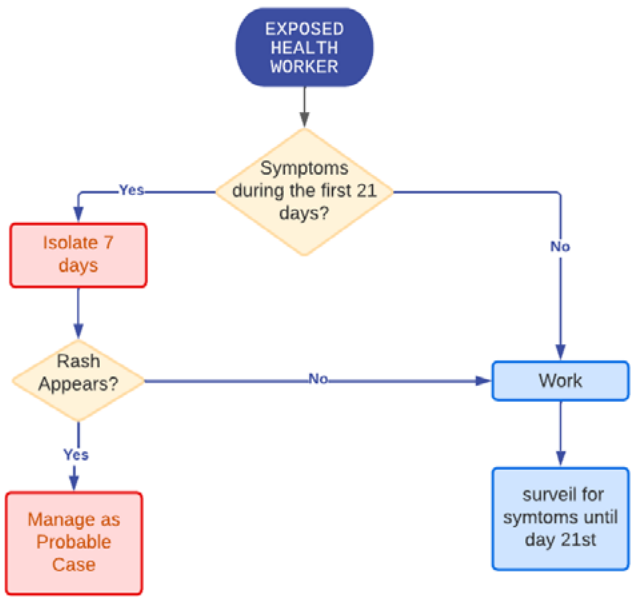
- Infected secretions or mucous membranes from the respiratory tract (droplets) in people who cough or sneeze.

Recibido: 09/09/2022
Aceptado: 13/09/2022
Correspondencia: nyomayusa@colsanitas.com

- Skin lesions or crusts, even if not visible (Direct contact with infectious skin or muco-cutaneous lesions, includes face-to-face, skin-to-skin, mouth-to-mouth, mouth-to-skin contact, or genital contact (There is still no evidence that the virus is transmitted sexually, however, the close contact that intercourse represents poses a high risk of contagion (WHO)).
- Objects recently contaminated with the patient's fluids or materials from the lesion.
- Through the placenta (congenital monkeypox).

Healthcare workers who have unprotected exposures (i.e., without appropriate personal protection equipment (PPE)) to monkeypox patients or possibly contaminated materials are not required to stop working if they are asymptomatic (Figure 1). However, should be actively monitored for symptoms, follow-up should be performed daily for the appearance of specific signs or symptoms such as headache, fever, chills, sore throat, malaise, fatigue, rash, and lymphadenopathy for 21 days from last contact with a probable or confirmed case/patient, or contaminated materials.

FIGURE 1. Exposed health worker (2,3)



Any contact who develops initial signs or symptoms other than rash should be isolated and closely monitored for signs of rash/exanthema for the next 7 days. If no rash develops, the contact will be advised to re-monitor temperature for the remaining 21 days. If the contact develops the rash, it should be isolated and evaluated as a probable case, and tested for monkeypox.

"More information is needed to better understand other possible modes of transmission and persistence through contact with other body fluids (such as breast milk, semen, vaginal fluid, amniotic fluid, or blood) and to better understand respiratory droplet and aerosol transmission.

Keypoint to prevent transmission (1-3,6-8)

Before a face-to-face evaluation, healthcare staff should use adequate PPE, follow general recommendations and dispose used and contaminated materials accordingly to avoid contagion and transmission.

a. Isolate each patient alone in a single-person room with a private bathroom, maintaining the door closed if possible.
b. Allow patient transport only for essential needs (e.g., lab works). When transportation is required, provide the patient with a disposable surgical face mask, and cover skin lesions with a robe.
c. Providers should use PPE all the time when interacting with patients. This includes appropriate and disposable clothing (i.e., gowns and aprons), an N-95 or equivalent respirator and gloves, and protective goggles or a face shield. Special air handling is not required if the other measures are warranted.
d. Avoid to overturn dry material from lesions (i.e. The use of portable fans, dry dusting, sweeping, or vacuuming).
e. Airborne precautions should be implemented if procedures that generate aerosols are performed. (i.e. Intubation and extubation, and

any procedures that may spread oral secretions, should be performed in an airborne infection isolation room).

f. Standard cleaning and disinfection procedures must be performed with an EPA-registered hospital-grade disinfectant with an emerging viral pathogen claim. (Clean and disinfect medical devices and supplies used such as thermometer, stethoscope, blood pressure monitor, pulse oximeter, pens, charts).
g. Food service items should also be isolated until all lesions have crusted over.
h. Isolated patients with monkeypox should have strategies to ensure interaction with family members to promote well-being.

Key points in physical examination (1-3,6-7)

- Lymphadenopathies may be or localized to several areas.
- Initial enanthema may develop in oral mucosa and conjunctive, and can present with proctitis or genital and perianal lesions.
- Rash: Similar to smallpox; begins as 2 to 5 mm diameter macules, evolving to several stages of often painful lesions (macules start to appear in face and spread in centrifugal distribution, followed by papules which turn to umbilicated pustules, ending with itchy crusts).
- Lesion features: Well-circumscribed, deep-seated, often with central umbilication and progression through specific sequential same-sized lesions at the same stage of development on a single site of body (e.g., pustules on face, vesicles on body, papules on legs).

Key point on severity and disease prognosis (1-3,6-7)

- Previous vaccination status (serious complications and sequelae have been reported more frequently among those not vaccinated against smallpox (74%) compared to those vaccinated (39.5%).
- General health condition, comorbidities.
- Route of exposure.
- Strain of the infecting virus. (West African monkeypox is generally associated with milder disease, fewer deaths, and limited person-to-person transmission).

Serious complications are rare. The most notorious being superinfections of skin lesions, generating cellulitis, abscesses, necrotizing infections of soft tissues, subcutaneous accumulation of fluid in the scab formation phase that in severe cases leads to states of intravascular depletion and shock, and finally extensive areas of exfoliation and inflammation that usually require surgical debridement and grafting.

Less frequently reported: Severe pneumonia, respiratory distress, corneal infection, loss of appetite, vomiting, diarrhea, electrolyte abnormalities, cervical lymphadenopathy, laboratory abnormalities (leukocytosis, elevated transaminases, low blood urea nitrogen, and hypoalbuminemia) and shock.

More information is needed on the clinical characterization of medium- and long-term effects.

Epidemiologic criteria

- Recent travel (within 21 days) to areas with confirmed cases/outbreaks of monkeypox, in or outside the US.
- Close or intimate in-person contact with confirmed patients: Direct skin contact, or through large respiratory droplets after prolonged exposure (e.g., within a 6-foot radius for ≥3 hours in the absence of personal protection equipment [PPE]).
- Contact with exotic dead or live wild African endemic animal species.
- Contact with contaminated fomites from confirmed patients (e.g., bedding, personal clothes, towels).

CASE DEFINITION (7)

- Suspected: New characteristic rash, or meets one of the epidemiologic criteria.
- Probable: No suspicion of recent (21 days) OPX exposure, and demonstration of either OPX presence (i.e., by DNA, immunohistochemical or electron microscopy testing) or detectable levels of anti-OPX IgM antibodies within 4-56 days after rash onset.
- Confirmed: Demonstration of the presence of Monkeypox virus DNA by PCR or isolation of the virus in culture from clinical specimen.
- Excluded: If an alternative diagnosis that explains the illness is confirmed, or if the symptomatic patient does not develop a rash within 5 days, or when high-quality specimens do not demonstrate the presence of OPX, Monkeypox virus, or antibodies to OPX.

PATIENT APPROACH AND MANAGEMENT (1-3,8-16)

Apply Keypoint to prevent transmission (See above)

1. Comprehensive medical history: Consider the typical sequence of clinical manifestations, social history and epidemiologic criteria.
2. Consider differential diagnosis in all cases (Table 1).
3. Physical examination: Consider probable complications in high-risk persons (Table 2). If present, refer to ER.
4. OPX specific testing: If the case remains suspected/probable, a polymerase chain reaction (PCR) testing for OPX should be performed on samples of the lesions. At least two specimens should be collected per patient and sent to the CDC. Other option is to send them to the Laboratory Response Network (LRN) which performs generic OPX tests. Throat swabs are not recommended to confirm diagnosis, and decision to perform a serologic testing should be made in conjunction with public health officials.
5. Additional lab works: Testing to evaluate differential diagnoses and complications should continue while awaiting OPX test results.
6. Until obtaining test results and when confirmed, patients should be isolated until all lesions have resolved, the scabs have fallen off, and a fresh layer of intact skin has formed.
7. If there are any risk conditions or complications (Table 2), refer to ER. Otherwise, patients can be safely managed at home.
8. Confirmed cases should be reported to local public health authorities. (Table 3 for each state's health department website).
9. Medical management: All patients should receive symptomatic treatment (e.g., pain and fever management) (Table 4):

    a. Ensure proper nutrition and hydration in all patients
    b. Instruct patients with mild disease about probable signs and symptoms of complications, and when to go to ER (Table 2).
    c. Use conservative measures for the management of skin lesions (i.e., continuous self-monitoring, gently cleansing with sterile water or antiseptic solutions) unless there are skin complications (e.g., pyomyositis, abscess).
    d. Avoid prophylactic antibiotic therapy in mild uncomplicated MPX.
    e. Assess for anxiety and depressive symptoms all patients with MPX.

TABLE 1. DIFFERENTIAL DIAGNOSIS TO CONSIDER IN MONKEYPOX INFECTION	
Infection	Clinical consideration in comparison to monkeypox
Varicella	Usually presents without lymphadenopathy Vesicular lesions are usually in different stages of development in the same body region compared
Herpes simplex virus	Systemic symptoms are usually milder, if they are present, especially in persons with recurrent infection
Sexually transmitted infections	Consider sexually transmitted infections that present with genital ulcers or a macular rash on the palms and soles, based on a comprehensive medical history: secondary syphilis, lymphogranuloma venereum, chancroid
Smallpox	Lymphadenopathy is absent
Other poxviruses and parapoxviruses	**Tanapox infection**: Another African poxvirus that causes a very similar presentation a febrile prodrome and skin lesions that resolve over several weeks without sequelae. Currently not in outbreak. Differential diagnosis is made by electron microscopy and DNA analysis
	Orf and bovine stomatitis: Produces localized skin lesions similar to monkeypox. Can be differentiated on electron microscopy

TABLE 2. RISK FACTORS AND CLINICAL FINDINGS DESCRIBED AS BEING ASSOCIATED WITH SEVERE AND POOR OUTCOMES IN MONKEYPOX INFECTION*		
Patient groups at higher risk for severe disease or complications	Children < 8 years of age	
	Pregnant and breastfeeding women	
	Persons who are immunosuppressed (e.g., persons living with HIV, cancer (i.e., leukemia, lymphoma, generalized malignancy), solid organ transplantation, being a recipient with hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, therapy with alkylating agents, pharmacological immunosuppression (e.g., antimetabolites, radiation, tumor necrosis factor inhibitors, high-dose corticosteroids), autoimmune disease with immunodeficiency as clinical component	
	Patients with chronic skin conditions (i.e., atopic dermatitis or other exfoliative skin conditions, severe acne, psoriasis)	
	Acute skin conditions (i.e., burns, overlapped infection with herpes simplex or varicella zoster virus, impetigo)	
Clinical signs and symptoms of complications	Severe nausea/vomiting or diarrhea	Hepatomegaly
	Poor oral intake	Sepsis
	Eye pain or vision abnormalities	Dehydration
	Confluent lesions	Respiratory distress
	Secondary bacterial skin infection	Bronchopneumonia
	Altered mental status (signs of encephalopathy)	Painful cervical lymphadenopathy causing dysphagia
	Hemorrhagic disease	
	Aberrant infections involving accidental implantation in eyes, mouth, or other anatomic areas where Monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus)	
Laboratory abnormalities	Elevated hepatic transaminases (AST and/or ALT)	
	Low blood urea nitrogen (BUN)	
	Low albumin	
	Elevated white blood count (WBC)	
	Low platelet count	
Skin lesion severity score (derived from smallpox experience)	Mild (< 25 skin lesions)	
	Moderate (25–99 skin lesions)	
	Severe (100–250 skin lesions)	
	Very severe (> 250 skin lesions)	

**Based on small, uncontrolled, observational studies*

Pharmacological management: Currently, there is no specific treatment approved for the management of MPX. Some antivirals may prove beneficial for persons at high-risk for severe disease (Table 2), but since most people have a mild, self-limiting disease course in the absence of specific therapy, its prescription is limited and regulated by the CDC in the US (Table 4).

TABLE 3. STATE-SPECIFIC DEPARTMENT OF HEALTH SERVICES WHERE CASES SHOULD BE REPORTED

Florida HEALTH	https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/
TN Department of Health	https://www.tn.gov/content/tn/health/cedep/reportable-diseases/monkeypox.html
TEXAS Health and Human Services — Texas Department of State Health Services	https://www.dshs.state.tx.us/IDCU/disease/monkeypox/Monkeypox-Reporting/
NJ Health — Improving Health Through Leadership and Innovation	https://www.nj.gov/health/cd/topics/monkeypox.shtml

**(Report persons under investigation [suspected and probable], confirmed cases of monkeypox, and laboratory tests)*

TABLE 4. GENERAL AND SPECIFIC PHARMACOLOGICAL MANAGEMENT AND INDICATIONS (INCLUDING VACCINATIONS) FOR ADULTS

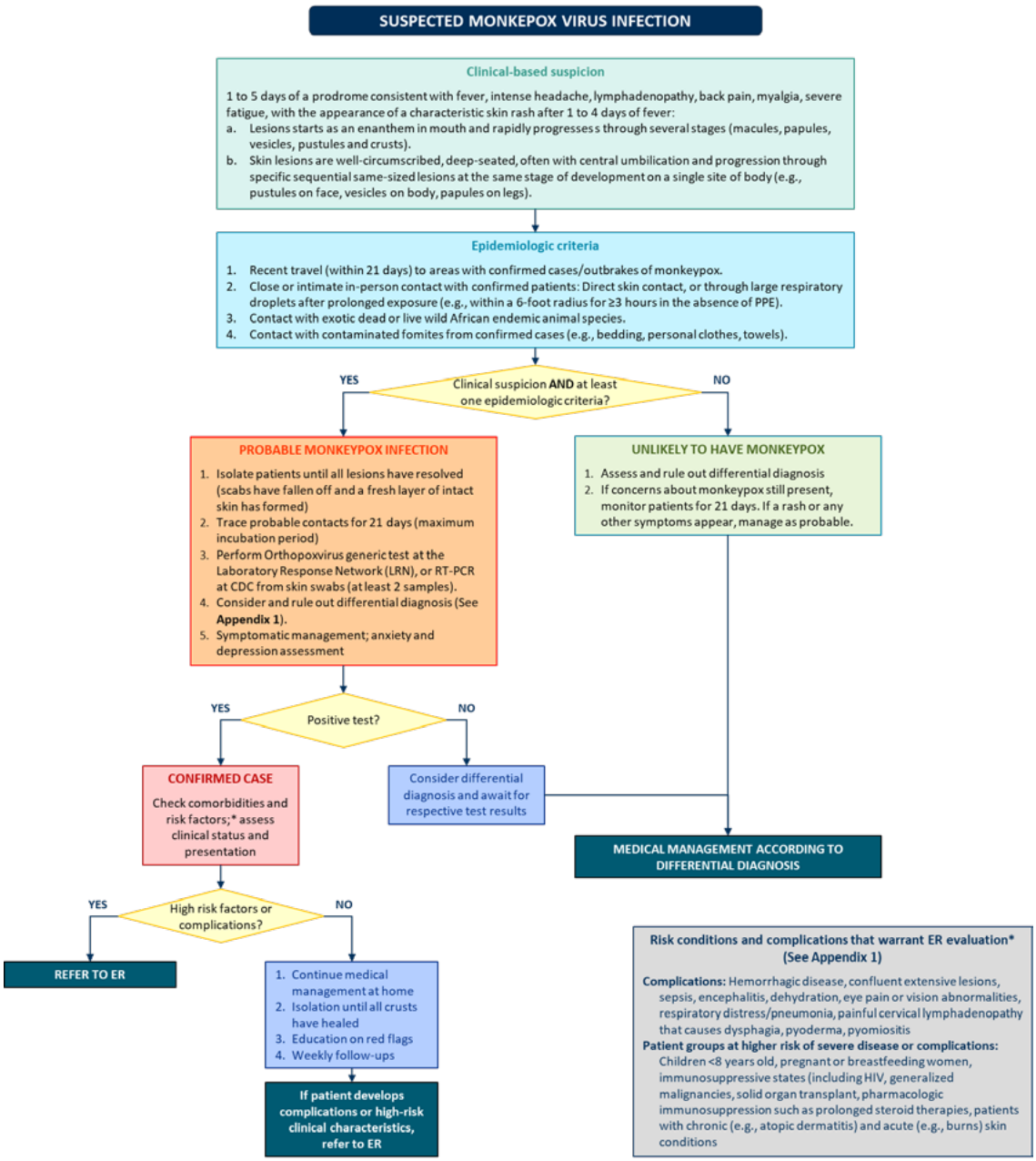
Agent	Indication, dosage, and recommendations		
Medications			
Paracetamol (Acetaminophen)	Dosage: 1 g PO q6h (maximum dose 4 g every 24h, 2 g if history of chronic liver disease) Indication: Fever and mild pain control		
Loratadine	Dosage: 10 mg PO QD Indication: For pruritus and itching	**Omeprazole**	Dosage: 40mg PO QD Indication: Dyspepsia
Ondansetron	Dosage: 8 mg PO q12h PRN Indication: Nausea and vomiting *(can prolong QT interval)*		
Countermeasures available from the Strategic National Stockpile (SNS) as options for the treatment of monkeypox*			
Tecovirimat (TPOXX, ST-246)	Approved by the FDA only for smallpox caused by Varicela virus infection. Requires informed consent, FDA form 1571, photos of lesions, a patient intake form, adverse event form, and a clinical outcomes form.		
Brincidofovir (CMX001 or Tembexa)	Approved by the FDA for the treatment of human smallpox disease. Currently, an Expanded Access – Investigational New Drug (EA-IND) protocol is being developed by the CDC.		
Cidofovir (Vistide)	Approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). An EA-IND protocol allows its prescription for Monkeypox virus infection.		
Vaccinia Immune Globulin Intravenous (VIGIV)	Licensed by FDA for the treatment of complications due to vaccinia vaccination (a "pox"-type virus related to smallpox) against Varicela virus infection. Can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox vaccination is contraindicated.		
Vaccinations			
ACAM2000	Currently recommended only for laboratorians working with Orthopoxviruses (PCR, cultures, or other testing and research settings), military personnel, and certain healthcare and public health response team members designated by public health authorities		
JYNNEOS™ (Imvamune or Imvanex)			

*****Only available through a request to the CDC Emergency Operations Center made by state and territorial health authorities.* **IV: intravenous PO:** *per os (orally)* **PRN:** *pro re nata (as needed)* **QD:** *quaque die (every day)*

Vaccination is recommended as preexposure prophylaxis in selected cases approved by the CDC (Table 4)

Follow-up: Patients should be advised to consult their doctors via telemedicine unless there are any complications that require a face-to-face evaluation (Figure 2). Follow-up should be performed on a weekly basis to evaluate progression and reassure patients.

FIGURE 2. Diagnosis and management of monkeypox infection (2,3)



REFERENCES

1. Isaacs SN, Shenoy ES. Monkeypox. UpToDate. Accessed July 2022. Updated July 01, 2022. https://www.uptodate.com/contents/monkeypox
2. Instituto Global de Excelencia Clínica. Presidencia de Salud e Innovación. Alerta epidemiológica Viruela símica (viruela del mono o Monkeypox) 2022. Orientación provisional para el abordaje de personas con sospecha de viruela símica. Keralty. Version 1. Julio 2022.
3. World Health Organization. Clinical Management and Infection Prevention and Control for Monkeypox. Interim rapid response guidance. Published June 10, 2022. Accessed July 2022. https://www.who.int/publications/i/item/WHO-MPX-Clinical-and-IPC-2022.1
4. Centers for Disease Control and Prevention. Monkeypox. 2022 Global Map & Case Count. U.S. Department of Health & Human Services. Updated July 7, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html
5. Centers for Disease Control and Prevention. Monkeypox. 2022 U.S Map & Case Count. U.S. Department of Health & Human Services. Updated July 7, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/response/2022/us-map.html
6. Centers for Disease Control and Prevention. Monkeypox. Clinical Recognition. U.S. Department of Health & Human Services. Updated June 24, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html
7. Centers for Disease Control and Prevention. Monkeypox. Case Definitions for Use in the 2022 Monkeypox Response. U.S. Department of Health & Human Services. Updated June 8, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html
8. Centers for Disease Control and Prevention. Monkeypox in the United States: What Clinicians Need to Know. U.S. Department of Health & Human Services. Published June 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/pdf/What-Clinicians-Need-to-Know-about-Monkeypox-6-21-2022.pdf
9. World Health Organization. Laboratory testing for the monkeypox virus. Interim guidance. Published May 23, 2022. https://apps.who.int/iris/bitstream/handle/10665/354488/WHO-MPX-Laboratory-2022.1-eng.pdf
10. Centers for Disease Control and Prevention. Monkeypox. Laboratory testing for the monkeypox virus. Interim guidance. Department of Health & Human Services. Updated June 29, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/prep-collection-specimens.html
11. The Florida Department of Health. Monkeypox. Accessed July 2022. https://www.floridahealth.gov/diseases-and-conditions/monkeypox/index.html
12. Centers for Disease Control and Prevention. Monkeypox. Laboratory Procedures and Biosafety Guidelines. Department of Health & Human Services. Updated June 29, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/lab-personnel/lab-procedures.html
13. Centers for Disease Control and Prevention. Diagnostic Process for Monkeypox Virus Testing. U.S. Department of Health & Human Services. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/pdf/Monkeypox-lab-process.pdf
14. Centers for Disease Control and Prevention. Monkeypox. Diagnostic Process for Monkeypox Virus Testing. U.S. Department of Health & Human Services. Updated May 31, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/isolation-procedures.html
15. Centers for Disease Control and Prevention. Monkeypox. Diagnostic Process for Monkeypox Virus Testing. U.S. Department of Health & Human Services. Updated June 17, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html
16. Centers for Disease Control and Prevention. Monkeypox. Monkeypox and Smallpox Vaccine Guidance. U.S. Department of Health & Human Services. Updated June 2, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html
17. Centers for Disease Control and Prevention. Monkeypox. Guidance for Tecovirimat Use Under Expanded Access Investigational New Drug Protocol during 2022 U.S. Monkeypox Cases. U.S. Department of Health & Human Services. Updated June 10, 2022. Accessed July 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html