IJMS
Vol 49, No 1, January 2024

Review Article

Managing Monkeypox Virus Infections: A Contemporary Review

Fariba Asadi Noghabi[1], PhD; John G. Rizk[2], MD; Dheeraj Makkar[3], MD; Nasibeh Roozbeh[4], PhD; Soleyman Ghelichpour[5], BSN; Aref Zarei[1], MSc

[1]Department of Nursing, School of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran;
[2]Department of Pharmaceutical Health Services Research Center, School of Pharmacy, University of Maryland, Baltimore, MD, USA;
[3]NC Medical College, Panipat, Haryana, India;
[4]Mother and Child Welfare Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran;
[5]Student Research Committee, School of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Correspondence:
Aref Zarei MSc;
School of Nursing and Midwifery, University of Medical Sciences, Imam Hossein Blvd., Postal code: 79166-13885, Bandar Abbas, Iran
Tel: +98 76 33317723
Fax: +98 76 33370724
Email: Aref.zarei96@gmail.com
Received: 19 September 2022
Revised: 30 October 2022
Accepted: 22 November 2022

Abstract

Monkeypox is an infectious and contagious zoonotic disease caused by the Orthopoxvirus species and was first identified in Africa. Recently, this infectious disease has spread widely in many parts of the world. Fever, fatigue, headache, and rash are common symptoms of monkeypox. The presence of lymphadenopathy is another prominent and key symptom of monkeypox, which distinguishes this disease from other diseases and is useful for diagnosing the disease. This disease is transmitted to humans through contact with or eating infected animals as well as objects infected with the virus. One of the ways to diagnose this disease is through PCR testing of lesions and secretions. To prevent the disease, vaccines such as JYNNEOS and ACAM2000 are available, but they are not accessible to all people in the world, and their effectiveness and safety need further investigation. However, preventive measures such as avoiding contact with people infected with the virus and using appropriate personal protective equipment are mandatory. The disease therapy is based on medicines such as brincidofovir, cidofovir, and Vaccinia Immune Globulin Intravenous. The injectable format of tecovirimat was approved recently, in May 2022. Considering the importance of clinical care in this disease, awareness about the side effects of medicines, nutrition, care for conjunctivitis, skin rash, washing and bathing at home, and so on can be useful in controlling and managing the disease.

Please cite this article as: Asadi Noghabi F, Rizk JG, Makkar D, Roozbeh N, Ghelichpour S, Zarei A. Managing Monkeypox Virus Infections: A Contemporary Review. Iran J Med Sci. 2024;49(1):1-9. doi: 10.30476/IJMS.2022.96738.2837.

Keywords • Disease management • Monkeypox • Communicable diseases, Therapeutics

What's Known

- The quality of life of monkeypox patients is at a low level due to various reasons such as the lack of hygiene and specific treatment, insufficient information about the disease, as well as severe complications of the disease.

What's New

- Appropriate symptomatic treatments such as using plenty of fluids due to severe dehydration, surgery to maintain fitness due to body deformities, care for conjunctivitis, skin rashes, washing and bathing at home, and so on can be useful in preventing severe complications and better management of monkeypox disease.

Introduction

Etiology

Monkeypox is caused by the Monkeypox virus (MPXV), which is an Orthopoxvirus with similar manifestations to the smallpox virus in humans.[1] Orthopoxviruses are giant and double-stranded DNA viruses, which include species such as Variola virus, Vaccinia virus, Cowpox virus, MPXV, and newly discovered species such as Akhmeta virus and Alaskapox virus.[2]

Epidemiology

The first human case of monkeypox was found in the Democratic Republic of Congo in 1970.[3] MPXV was not detected outside of Africa before 2003. The most notable outbreak in the United States occurred in 2003, associated with the importation of African mice. In this outbreak, imported animals were kept

together with other animals such as dogs. 42 cases were reported in the United States, three people were seriously ill, and no deaths were recorded.[4] In recent years, the virus has spread to other African countries as well as outside of Africa. Sporadic cases of monkeypox have been reported in Nigeria in the years 2018 through 2022 with 49, 47, 8, 34, and 21 cases during that time period.[5] The mortality rate varies from 1 to 10% based on the type of MPXV strain and the availability of modern health care.[6]

There are two types of MPXV: Congo basin Clade (Central Africa) and West African Clade, with the former being more fatal. It is estimated that the death rate in the Congo region is 10.6% and in West Africa is 3.6%. Genetic data show that the 2022 MPXV belongs to the West African Clade and is most closely related to the MPXV that spread from Nigeria to the United Kingdom, Israel, and Singapore in 2018 and 2019.[7]

Clinical Presentation

The incubation period of monkeypox varies from 5 to 21 days, and it is not contagious until the symptoms begin.[4] The process of MPXV infection is mainly divided into two stages (1) the prodromal stage (fever, fatigue, severe headache, lymphadenopathy, and muscle pains), which lasts about 0-2 days, (2) the rash stage, which lasts 7 to 21 days. The rash usually appears within one to five days after the fever, and the patient is contagious when the rash appears. The rash is concentrated on the face and limbs and involves the face (95%), palms and soles (75%), oral mucosa (70%), genital tract (30%), and conjunctiva (20%). The rash lasts about two to four weeks and evolves from being a plaque to papules, blisters, pustules, scabs, and finally to shedding.[8] A prominent feature of monkeypox is lymphadenopathy, which occurs in 84% of unvaccinated patients and 54% of vaccinated patients.[9, 10] Lymphadenopathy can be unilateral or bilateral and occurs in submandibular, cervical, postauricular, axillary, or inguinal lymph nodes.[11] The severe complications of the disease are central nervous system involvement and airway compromise due to lymphadenopathy.[4] Other complications include hyperpigmentation, scarring, dehydration, and secondary bacterial infection that leads to septicemia.[12]

Transmission

Animal-to-human transmission (zoonosis) and human-to-human transmission of MPXV are possible. Animal-to-human transmission occurs through direct contact, bite, or scratch of an infected animal, or consumption of an animal host, such as rodents or mammals.[13] The virus can also be spread through respiratory droplets, body fluids, and wound secretions,[14] bedding, clothing, or contaminated surfaces,[15] and also through the placenta (congenital monkeypox).[16] Risk factors for zoonotic transmission of MPXV include living in forested or deforested areas, lack of smallpox vaccination, handling or eating dead bushmeat or monkeys, and sleeping on the ground (in endemic areas).[13]

Diagnosis

The diagnostic evaluation of monkeypox should include taking a specific medical history and evaluating the clinical appearance. A history of travel to an endemic area, interaction with a wild animal from an infected area, or care of an infected patient should always be considered to aid in the diagnosis. However, the final diagnosis should be justified by laboratory findings. One feature that can help to distinguish monkeypox from varicella and variola virus is lymphadenopathy in the prodromal phase.[17] Definitive diagnosis of the disease is done through the polymerase chain reaction (PCR) test of skin lesions or secretions.[4] Other methods such as virus isolation, immunohistochemistry, IgG and IgM enzyme-linked immunosorbent assay (ELISA), and electron microscopy can also be performed. Although, they certainly require more sophisticated tools and specialized facilities, such as a proper biosafety level for virus handling.[18]

Prevention

Until 1971, children in the United States got the Orthopox vaccine as part of standard childhood vaccines to prevent smallpox. However, with the World Health Organization's (WHO) proclamation of smallpox eradication in 1980, recommendations for routine immunization were discontinued worldwide. A few individuals in the United States continued to receive the Orthopox vaccine.[2]

In September 2019, Food and Drug Administration (FDA) approved the use of the replication-incompetent vaccine, JYNNEOS (Proper Name: Smallpox and Monkeypox Vaccine, Live, Non-Replicating/Manufacturer: Bavarian Nordic),[19] which is now being used to prevent monkeypox in people over the age of 18 years.[20] The Center for Disease Control and Prevention (CDC) is developing a new investigational drug protocol on a large scale to allow the use of the JYNNEOS vaccine for monkeypox in the pediatric population.[19] It is also safe to use this vaccine in high-risk groups such as people with HIV.[21] The vaccine is injected subcutaneously and preferably in the arm in two

doses (0.5 mL each time), with an interval of 28 days.[2, 22]

The safety of JYNNEOS was evaluated in a randomized, double-blind, placebo-controlled study conducted in the United States, in which vaccine-naïve subjects aged 18 to 40 years received both doses of the JYNNEOS vaccine. Reactions at the injection site and adverse systemic reactions (e.g., pain, redness, swelling, and itching) within eight days after administration of each dose of vaccine were 84.9%, 60.8%, 51.6%, and 43.1%, respectively. Other systemic reactions included muscle pain, headache, fatigue, nausea, chills, and fever.[23]

ACAM2000 (Proper Name: Smallpox Vaccine, Live/Manufacturer: Emergent Product Development Gaithersburg, Inc.) is another vaccine approved by the FDA in 2007 for the treatment of monkeypox.[24] Since ACAM2000 is a replication-competent vaccine, the risk of side effects such as progressive vaccinia and eczema vaccinatum is a concern. Other side effects include myopericarditis[2, 25] and post-vaccine encephalitis.[26] The risk of side effects is higher in infants less than 12 months old, people who use topical steroids to treat eye diseases and infections, and those who have a history of cardiovascular disease or the presence of eczema or other skin diseases.[27] The use of this vaccine is prohibited in pregnancy, HIV patients, and other immunocompromised people.[28] On November 3, 2021, Advisory Committee on Immunization Practices (ACIP) suggested that the JYNNEOS vaccine be used as prophylaxis before exposure to monkeypox, instead of the ACAM2000 vaccine for certain people who are at occupational risk of orthopoxviruses.[29]

Pre-exposure Prophylaxis

ACIP recommends vaccination for selected individuals at occupational risk of orthopoxvirus.[25] These include laboratory personnel who perform tests to detect orthopoxviruses, and workers of research laboratories who are in direct contact with cultures, infected animals, and equipment infected with orthopoxviruses.[29] Studies of monkeypox in Central Africa, where vaccines are not readily available, reported a mortality rate of ~11%.[29, 30] In contrast, most people who receive the smallpox or monkeypox vaccine have only minor reactions.[29]

Since transmission is possible through close contact, the use of Personal Protective Equipment (PPE) is crucial and includes an apron, a surgical-resistant mask, and gloves. In the case of unwell patients and patients with respiratory symptoms, the use of PPE should include a long-sleeved gown, filtering facepiece 3 (FFP3) mask, and eye protection.[31] People should avoid close and skin-to-skin contact with people who have a rash similar to monkeypox.[32]

Preventing the spread of MPXV in endemic areas is very challenging. This includes avoiding any contact with rodents and mammals, as well as limiting direct contact with blood and undercooked meat. Avoiding cooking meat and the consumption of wild animals is culturally and economically difficult, as this meat may be the only source of protein available to the poorest people in the region.[18] In the case of people who are in contact with animals, sick animals should be separated from the rest of the herd and quarantined at once. Any animal that may have come in contact with infected animals should be isolated for 30 days and monitored for signs of monkeypox. Finally, in the absence of a specific treatment or vaccine, the only approach to prevent infection is to increase public knowledge about risk factors and educate people about actions they may take to limit exposure to the virus.[16]

Post-exposure Prophylaxis

Transmission of monkeypox requires prolonged interaction with a symptomatic person. Short-term communications and those conducted using PPE and following standard precautions are not considered as high risks.[25] In general, the risk of exposure to the disease can be divided into three categories: high, medium, and low. High-risk exposure includes direct contact with the damaged skin or mucous membranes of the exposed person, very close contact with the patient, and contact with the patient's respiratory droplets while not using respiratory protection.[33] Moderate-risk exposure also includes direct skin contact with a patient, being within two meters of a patient for more than three hours, or providing medical care to patients with an infection without proper PPE. Moreover, supplying medical care to patients while wearing proper PPE is also a low exposure. Vaccination is recommended as post-exposure prophylaxis for individuals at a high risk of disease. In addition, the vaccine is recommended on a case-by-case basis for people who are exposed to moderate risk.[34] To this end, the CDC recommends that the first dose of the vaccine be administered as soon as possible and within four days of exposure to prevent the disease. If the vaccination is injected 4 to 14 days after the contact date, it may reduce the disease symptoms, but it may not prevent the onset of the disease.[29]

Treatment

Several antiviral drugs may be effective in treating monkeypox infections, although these

drugs have been approved for the management of smallpox based on animal models. Studies have been conducted on these drugs in humans, but their effectiveness has not been fully confirmed.[35]

Tecovirimat

Tecovirimat, also known as TPOXX or ST-246,[36, 37] was approved by the FDA in May 2018 based on animal and human studies, but it is not yet widely available to the public.[38] The intravenous form of the TPOXX was approved in May 2022 by the European Medicines Agency (EMA).[39]

The dosage for intravenous use in patients is as follows: for patients 3 to 35 Kg, the dose is 6 mg/Kg, which is prescribed over six hours every 12 hours for 14 days. For patients with a weight of 35 Kg to less than 120 Kg, the dose is 200 mg, and for patients with a weight of more than 120 Kg, it is 300 mg.[40]

TPOXX is recommended as a first-line therapy for the treatment of smallpox in adults and children weighing at least 13 Kg.[25]

The most common reported side effects of IV tecovirimat are injection site reactions and headache, whereas the oral form is associated with headaches, nausea, abdominal pain, and vomiting.[40] Besides, in diabetic patients treated with repaglinide, tecovirimat may increase the level of repaglinide, which can lead to hypoglycemia in the patient.[41] The effectiveness of this drug was evaluated in studies conducted on animals infected with Orthopoxvirus, as well as the effects of the drug on the human body and the way the drug is absorbed and excreted.[37, 42] According to the CDC, a human clinical trial with tecovirimat found the drug to be safe, but there is insufficient data on its effectiveness in treating human cases of MPXV. However, animal and laboratory studies using cidofovir and brincidofovir confirmed the effectiveness of these drugs.[10, 13, 43-45]

Brincidofovir

Brincidofovir inhibits the replication of the MPXV by blocking DNA synthesis by polymerases. It is available as a tablet (100 mg) or oral suspension (10 mg/mL), used in two doses with an interval of one week.[46] The recommended dose for children and adults is provided in table 1.[47] A recent study by Adler and colleagues on three patients that were treated with brincidofovir (200 mg once weekly orally) reported all patients developed elevated liver enzymes, and none completed the course of treatment.[35] Other side effects associated with brincidofovir include digestive symptoms of diarrhea, vomiting, and abdominal pain.[46] Brincidofovir has shown promising results in various Orthopoxvirus animal models.[48-50] However, in June 2021, brincidofovir was approved by the FDA as a drug for the treatment of smallpox and was marketed under the brand name Tembexa®.[51]

Cidofovir

Cidofovir (VISTIDE) is an antiviral drug approved by the FDA for the treatment of Cytomegalovirus (CMV) in patients with Acquired Immunodeficiency Syndrome (AIDS).[19, 52] The recommended dose of the drug is 5 mg/Kg intravenously, with an interval of one week.[46] Side effects include birth defects,[53] nephrotoxicity, electrolyte disorders, neutropenia, nausea, and muscle pain.[46] As of June 6, 2022, cidofovir is not approved by the US FDA for the treatment of monkeypox.[54]

Vaccinia Immune Globulin Intravenous

Vaccinia Immune Globulin Intravenous (VIGIV) is an immunoglobulin used to treat complications caused by vaccinia vaccination.[12] VIGIV can be considered for prophylactic use in an exposed person with a severe immunodeficiency in T-cell function.[55]

Symptomatic Treatments

Most patients with monkeypox infection recover without medical treatment. The clinical course of this infection is usually mild and self-limiting. Therefore, affected people rarely need special treatment. However, if people have certain symptoms of the disease, supportive measures are taken according to that problem.[12, 56]

Patients presenting with secondary bacterial infections should be treated with proper antibiotics. These infections can include pneumonia, sepsis, and infection of skin lesions.[57]

Table 1: Recommended Dosing of brincidofovir (TEMBEXA) in Pediatric and Adult Patients

Patient's Weight (Kg)	Brincidofovir Oral Suspension (10 mg/mL)	Brincidofovir Tablet (100 mg)
Less than 10 Kg	6 mg/Kg once weekly for 2 doses (on Days 1 and 8)	N/A
10 kg to less than 48 Kg	4 mg/Kg once weekly for 2 doses (on Days 1 and 8)	N/A
48 Kg and above	200 mg (20mL) once a week for 2 doses (on Days 1 and 8)	200 mg (two 100 mg tablets) once a week for 2 doses (on Days 1 and 8)

Severe dehydration and the possibility of hypovolemic shock are seen in patients with monkeypox due to the decrease in intravascular volume caused by severe rashes, fever, and digestive problems, such as diarrhea and vomiting, along with insufficient consumption of food and water. Severe dehydration should be treated at once with intravenous or intraosseous fluid therapy.[56, 58]

Patients may present with non-specific symptoms such as conjunctivitis. Treatment with vitamin A supplements can be helpful, especially in malnourished children. Besides, trifluridine 1% eye drops, which are sometimes used for herpes eye infections, may be used to accelerate the resolution of symptoms and prevent long-term damage caused by scarring, if any.[56, 59-61] For this purpose, trifluridine 1% eye drops are used every two hours or eight to nine times a day for 10 to 14 days.[62]

Limb deformity due to joint or skin lesions occurs in 2% of cases.[63] Therefore, it is necessary to take special fitness measures for these people. Based on previous information about chickenpox, elective surgery should be postponed until all crusts of the skin lesion are removed. It usually takes about three weeks from the start. After recovery from the disease, fitness for surgery should be evaluated on a case-by-case basis, considering possible systemic complications.[64]

Antipyretic drugs such as acetaminophen can be used to reduce fever in these patients.[65, 66] However, it is reasonable to limit Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) due to concerns about the development of hemorrhagic lesions. Additionally, in case of myalgias and painful mucosal lesions, especially in the mouth, eyes, and rectal area, it is necessary to use appropriate analgesics.[57]

Furthermore, Patients should avoid shaving the rash-covered areas of the body, because it can lead to the spread of the virus. For bathing, a separate bathroom should be used by the patient. If there is no separate bathroom at home, the patient should clean surfaces such as counters, toilet seats, and faucets using a suitable disinfectant after using the facilities in a common bathroom. Besides, if there is a rash on the hands, disposable gloves should be used while cleaning.[67]

Conclusion

Considering the wide spread of the disease and the global public concern about it, it is important to investigate different aspects of the virus such as clinical manifestations and ways of transmission. Moreover, using appropriate personal protective equipment and timely use of vaccines and medicines, if available, are needed to control and manage the disease. Although the existing drugs and vaccines have some complications, the evidence shows that their use has been effective in reducing mortality and increasing the quality of life of affected people. Obviously, symptomatic treatment should also be done if needed.

Authors' Contribution

J.R and A.R: design of the study and revising its criticality for important intellectual content. F.AN: design of the study and drafting of the work. N.R., D.M., and S.GH: contributed substantially to the conception and drafting of the work. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Conflict of Interest: None declared.

References

1 Joob B, Wiwanitkit V. Monkeypox: revisit of the old threat and emerging imported cases. Medical Journal of Dr DY Patil University. 2022;15:457-9. doi: 10.4103/mjdrdypu.mjdrdypu_440_22.

2 Rao AK, Petersen BW, Whitehill F, Razeq JH, Isaacs SN, Merchlinsky MJ, et al. Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71:734-42. doi: 10.15585/mmwr.mm7122e1. PubMed PMID: 35653347; PubMed Central PMCID: PMCPMC9169520

3 Shanmugaraj B, Khorattanakulchai N, Phoolcharoen W. Emergence of monkeypox: Another concern amidst COVID-19 crisis. Asian Pacific Journal of Tropical Medicine. 2022;15:193-5. doi: 10.4103/1995-7645.346081.

4 Adalja A, Inglesby T. A Novel International Monkeypox Outbreak. Ann Intern Med. 2022;175:1175-6. doi: 10.7326/M22-1581. PubMed PMID: 35605243.

5 Adegboye OA, Eugenia Castellanos M, Alele FO, Pak A, Ezechukwu HC, Hou K, et al. Travel-Related Monkeypox Outbreaks in the Era of COVID-19 Pandemic: Are We Prepared? Viruses. 2022;14. doi: 10.3390/

v14061283. PubMed PMID: 35746754; PubMed Central PMCID: PMCPMC9228578.
6 Kumar N, Acharya A, Gendelman HE, Byrareddy SN. The 2022 outbreak and the pathobiology of the monkeypox virus. J Autoimmun. 2022;131:102855. doi: 10.1016/j.jaut.2022.102855. PubMed PMID: 35760647; PubMed Central PMCID: PMCPMC9534147.
7 Otu A, Ebenso B, Walley J, Barcelo JM, Ochu CL. Global human monkeypox outbreak: atypical presentation demanding urgent public health action. Lancet Microbe. 2022;3:e554-e5. doi: 10.1016/S2666-5247(22)00153-7. PubMed PMID: 35688169; PubMed Central PMCID: PMCPMC9550615.
8 Gong Q, Wang C, Chuai X, Chiu S. Monkeypox virus: a re-emergent threat to humans. Virol Sin. 2022;37:477-82. doi: 10.1016/j.virs.2022.07.006. PubMed PMID: 35820590; PubMed Central PMCID: PMCPMC9437600.
9 Heymann DL, Simpson K. The Evolving Epidemiology of Human Monkeypox: Questions Still to Be Answered. J Infect Dis. 2021;223:1839-41. doi: 10.1093/infdis/jiab135. PubMed PMID: 33871010.
10 McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis. 2014;58:260-7. doi: 10.1093/cid/cit703. PubMed PMID: 24158414.
11 Quarleri J, Delpino MV, Galvan V. Monkeypox: considerations for the understanding and containment of the current outbreak in non-endemic countries. Geroscience. 2022;44:2095-103. doi: 10.1007/s11357-022-00611-6. PubMed PMID: 35726117; PubMed Central PMCID: PMCPMC9208705.
12 Cheema AY, Ogedegbe OJ, Munir M, Alugba G, Ojo TK. Monkeypox: a review of clinical features, diagnosis, and treatment. Cureus. 2022;14. doi: 10.7759/cureus.26756.
13 Brown K, Leggat PA. Human Monkeypox: Current State of Knowledge and Implications for the Future. Trop Med Infect Dis. 2016;1. doi: 10.3390/tropicalmed1010008. PubMed PMID: 30270859; PubMed Central PMCID: PMCPMC6082047.
14 Fatima N, Mandava K. Monkeypox-a menacing challenge or an endemic? Annals of Medicine and Surgery. 2022;79:103979. doi: 10.1016/j.amsu.2022.103979.
15 Parvin R, Ali A, Nagy A, Zhu Z, Zhao S, Paul A, et al. Monkeypox virus: A comprehensive review of taxonomy, evolution, epidemiology, diagnosis, prevention, and control regiments so far. Ger. J Microbiol. 2022;2:1-15. doi: 10.51585/gjm.2022.2.0014.
16 Pal M, Singh R, Gutama KP, Savalia C, Thakur R. Human monkeypox: an emerging and re-emerging infectious viral disease. Acta Scientific Microbiology (ISSN: 2581-3226). 2022;5:146-50. doi: 10.31080/ASMI.2022.05.1045.
17 Harapan H, Ophinni Y, Megawati D, Frediansyah A, Mamada SS, Salampe M, et al. Monkeypox: A Comprehensive Review. Viruses. 2022;14. doi: 10.3390/v14102155. PubMed PMID: 36298710; PubMed Central PMCID: PMCPMC9612348.
18 Petersen E, Kantele A, Koopmans M, Asogun D, Yinka-Ogunleye A, Ihekweazu C, et al. Human Monkeypox: Epidemiologic and Clinical Characteristics, Diagnosis, and Prevention. Infect Dis Clin North Am. 2019;33:1027-43. doi: 10.1016/j.idc.2019.03.001. PubMed PMID: 30981594; PubMed Central PMCID: PMCPMC9533922.
19 Rao A, Mena LA, Petersen B. Monkeypox: updates about clinical diagnosis and treatment. Clinician Outreach and Communication Activity. 2022.
20 Petersen E, Zumla A, Hui DS, Blumberg L, Valdoleiros SR, Amao L, et al. Vaccination for monkeypox prevention in persons with high-risk sexual behaviours to control on-going outbreak of monkeypox virus clade 3. Int J Infect Dis. 2022;122:569-71. doi: 10.1016/j.ijid.2022.06.047. PubMed PMID: 35788415; PubMed Central PMCID: PMCPMC9534076.
21 Radix M, Hoffmann CJ, Gonzalez CJ. Monkeypox Vaccination in Adults With HIV. 2022.
22 Administration [Internet]. Package Insert - JYNNEOS. c2021. Avialable from: https://www.fda.gov/media/131078/download
23 Overton ET, Lawrence SJ, Wagner E, Nopora K, Rosch S, Young P, et al. Immunogenicity and safety of three consecutive production lots of the non replicating smallpox vaccine MVA: A randomised, double blind, placebo controlled phase III trial. PLoS One. 2018;13:e0195897. doi: 10.1371/journal.pone.0195897. PubMed PMID: 29652929; PubMed Central PMCID: PMCPMC5898760.
24 Greenberg RN, Kennedy JS. ACAM2000: a newly licensed cell culture-based live vaccinia smallpox vaccine. Expert Opin Investig Drugs. 2008;17:555-64. doi: 10.1517/13543784.17.4.555. PubMed PMID: 18363519; PubMed Central PMCID: PMCPMC9491136.
25 Rizk JG, Lippi G, Henry BM, Forthal DN, Rizk Y. Prevention and Treatment of Monkeypox. Drugs. 2022;82:957-63. doi: 10.1007/s40265-022-01742-y. PubMed PMID: 35763248; PubMed Central PMCID: PMCPMC9244487.
26 Petersen BW, Harms TJ, Reynolds MG,

Harrison LH. Use of Vaccinia Virus Smallpox Vaccine in Laboratory and Health Care Personnel at Risk for Occupational Exposure to Orthopoxviruses - Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2015. MMWR Morb Mortal Wkly Rep. 2016;65:257-62. doi: 10.15585/mmwr.mm6510a2. PubMed PMID: 26985679.

27 Administration [Internet]. ACAM2000 Product Insert. c2018. Avialable from: https://www.fda.gov/media/75792/download

28 Farahat RA, Rackimuthu S, Umar TP, Siddiqui JA, Shrestha AB, Essar MY. Preparedness of South East Asia countries in view of monkeypox emergence: A call for action. Lancet Reg Health Southeast Asia. 2022;6:100074. doi: 10.1016/j.lansea.2022.100074. PubMed PMID: 36249534; PubMed Central PMCID: PMCPMC9534127.

29 Clinician Outreach and Communication [Internet]. Vaccine Considerations. c2022. Avialable from: https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html

30 Durski KN, McCollum AM, Nakazawa Y, Petersen BW, Reynolds MG, Briand S, et al. Emergence of Monkeypox - West and Central Africa, 1970-2017. MMWR Morb Mortal Wkly Rep. 2018;67:306-10. doi: 10.15585/mmwr.mm6710a5. PubMed PMID: 29543790; PubMed Central PMCID: PMCPMC5857192.

31 Vaughan A, Aarons E, Astbury J, Brooks T, Chand M, Flegg P, et al. Human-to-Human Transmission of Monkeypox Virus, United Kingdom, October 2018. Emerg Infect Dis. 2020;26:782-5. doi: 10.3201/eid2604.191164. PubMed PMID: 32023204; PubMed Central PMCID: PMCPMC7101111.

32 Clinician Outreach and Communication [Internet]. Prevention. [Updated July 11, 2022]. Available from: https://www.cdc.gov/poxvirus/monkeypox/prevention.html

33 Rao AK, Schulte J, Chen TH, Hughes CM, Davidson W, Neff JM, et al. Monkeypox in a Traveler Returning from Nigeria - Dallas, Texas, July 2021. MMWR Morb Mortal Wkly Rep. 2022;71:509-16. doi: 10.15585/mmwr.mm7114a1. PubMed PMID: 35389974; PubMed Central PMCID: PMCPMC8989376.

34 Titanji BK, Tegomoh B, Nematollahi S, Konomos M, Kulkarni PA. Monkeypox: A Contemporary Review for Healthcare Professionals. Open Forum Infect Dis. 2022;9:310. doi: 10.1093/ofid/ofac310. PubMed PMID: 35891689; PubMed Central PMCID: PMCPMC9307103.

35 Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022;22:1153-62. doi: 10.1016/S1473-3099(22)00228-6. PubMed PMID: 35623380; PubMed Central PMCID: PMCPMC9300470

36 Russo AT, Berhanu A, Bigger CB, Prigge J, Silvera PM, Grosenbach DW, et al. Co-administration of tecovirimat and ACAM2000 in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge. Vaccine. 2020;38:644-54. doi: 10.1016/j.vaccine.2019.10.049. PubMed PMID: 31677948; PubMed Central PMCID: PMCPMC6954297.

37 Mucker EM, Goff AJ, Shamblin JD, Grosenbach DW, Damon IK, Mehal JM, et al. Efficacy of tecovirimat (ST-246) in nonhuman primates infected with variola virus (Smallpox). Antimicrob Agents Chemother. 2013;57:6246-53. doi: 10.1128/AAC.00977-13. PubMed PMID: 24100494; PubMed Central PMCID: PMCPMC3837858.

38 Organization WH. WHO advisory committee on variola virus research: report of the twenty-second meeting. Geneva 4-5 November 2020. 2021.

39 Organization WH [Internet]. Mpox (monkeypox). c2022. Available from: https://www.who.int/news-room/fact-sheets/detail/monkeypox

40 FDA Uf. Amoxicillin; Clarithromy-Cin; Vonoprazan Fumarate. Pharmacy Today. 2022;28:12-4. doi: 10.1016/j.ptdy.2022.11.028.

41 Russo AT, Grosenbach DW, Chinsangaram J, Honeychurch KM, Long PG, Lovejoy C, et al. An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications. Expert Rev Anti Infect Ther. 2021;19:331-44. doi: 10.1080/14787210.2020.1819791. PubMed PMID: 32882158; PubMed Central PMCID: PMCPMC9491074.

42 Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, et al. Oral Tecovirimat for the Treatment of Smallpox. N Engl J Med. 2018;379:44-53. doi: 10.1056/NEJMoa1705688. PubMed PMID: 29972742; PubMed Central PMCID: PMCPMC6086581.

43 Kabuga AI, El Zowalaty ME. A review of the monkeypox virus and a recent outbreak of skin rash disease in Nigeria. J Med Virol. 2019;91:533-40. doi: 10.1002/jmv.25348. PubMed PMID: 30357851.

44 Fowotade A, Fasuyi T, Bakare R.

Re-emergence of monkeypox in Nigeria: A cause for concern and public enlightenment. African Journal of Clinical and Experimental Microbiology. 2018;19:307-13. doi: 10.4314/ajcem.v19i4.9.
45 Alakunle E, Moens U, Nchinda G, Okeke MI. Monkeypox Virus in Nigeria: Infection Biology, Epidemiology, and Evolution. Viruses. 2020;12. doi: 10.3390/v12111257. PubMed PMID: 33167496; PubMed Central PMCID: PMCPMC7694534.
46 Organization WH [Internet]. Clinical Management and Infection Prevention and Control for Monkeypox. c2022. Available from: https://apps.who.int/iris/bitstream/handle/10665/355798/WHO-MPXV-Clinical_and_IPC-2022.1-eng.pdf?sequence=1
47 Label [Internet]. US: FDA. [Cite 2021 12, June]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000
48 Hostetler KY, Beadle JR, Trahan J, Aldern KA, Owens G, Schriewer J, et al. Oral 1-O-octadecyl-2-O-benzyl-sn-glycero-3-cidofovir targets the lung and is effective against a lethal respiratory challenge with ectromelia virus in mice. Antiviral Res. 2007;73:212-8. doi: 10.1016/j.antiviral.2006.10.009. PubMed PMID: 17123638; PubMed Central PMCID: PMCPMC1859865.
49 Israely T, Paran N, Lustig S, Erez N, Politi B, Shafferman A, et al. A single cidofovir treatment rescues animals at progressive stages of lethal orthopoxvirus disease. Virol J. 2012;9:119. doi: 10.1186/1743-422X-9-119. PubMed PMID: 22709563; PubMed Central PMCID: PMCPMC3409050.
50 Rice AD, Adams MM, Lampert B, Foster S, Robertson A, Painter G, et al. Efficacy of CMX001 as a prophylactic and presymptomatic antiviral agent in New Zealand white rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans. Viruses. 2011;3:63-82. doi: 10.3390/v3020063. PubMed PMID: 21369346; PubMed Central PMCID: PMCPMC3045966.
51 Krecmerova M, Majer P, Rais R, Slusher BS. Phosphonates and Phosphonate Prodrugs in Medicinal Chemistry: Past Successes and Future Prospects. Front Chem. 2022;10:889737. doi: 10.3389/fchem.2022.889737. PubMed PMID: 35668826; PubMed Central PMCID: PMCPMC9163707.
52 Li G, De Clercq E. A medicinal chemist who reshaped the antiviral drug industry: John Charles Martin (1951-2021). Med Res Rev. 2022;42:647-53. doi: 10.1002/med.21858. PubMed PMID: 34636044.
53 Meaney-Delman DM, Galang RR, Petersen BW, Jamieson DJ. A Primer on Monkeypox Virus for Obstetrician-Gynecologists: Diagnosis, Prevention, and Treatment. Obstet Gynecol. 2022;140:391-7. doi: 10.1097/AOG.0000000000004909. PubMed PMID: 36356237; PubMed Central PMCID: PMCPMC9377490.
54 Koenig KL, Bey CK, Marty AM. Monkeypox 2022 Identify-Isolate-Inform: A 3I Tool for frontline clinicians for a zoonosis with escalating human community transmission. One Health. 2022;15:100410. doi: 10.1016/j.onehlt.2022.100410. PubMed PMID: 36249992; PubMed Central PMCID: PMCPMC9534172.
55 Tiecco G, Degli Antoni M, Storti S, Tomasoni LR, Castelli F, Quiros-Roldan E. Monkeypox, a Literature Review: What Is New and Where Does This concerning Virus Come From? Viruses. 2022;14. doi: 10.3390/v14091894. PubMed PMID: 36146705; PubMed Central PMCID: PMCPMC9501516.
56 Reynolds MG, McCollum AM, Nguete B, Shongo Lushima R, Petersen BW. Improving the Care and Treatment of Monkeypox Patients in Low-Resource Settings: Applying Evidence from Contemporary Biomedical and Smallpox Biodefense Research. Viruses. 2017;9. doi: 10.3390/v9120380. PubMed PMID: 29231870; PubMed Central PMCID: PMCPMC5744154.
57 Daskalakis D, McClung RP, Mena L, Mermin J, Centers for Disease C, Prevention's Monkeypox Response T. Monkeypox: Avoiding the Mistakes of Past Infectious Disease Epidemics. Ann Intern Med. 2022;175:1177-8. doi: 10.7326/M22-1748. PubMed PMID: 35709341.
58 Organization WH. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Geneva: World Health Organization; 2013.
59 Hughes C, McCollum A, Pukuta E, Karhemere S, Nguete B, Lushima RS, et al. Ocular complications associated with acute monkeypox virus infection, DRC. International Journal of Infectious Diseases. 2014;21:276-7. doi: 10.1016/j.ijid.2014.03.994.
60 Semba RD. The ocular complications of smallpox and smallpox immunization. Arch Ophthalmol. 2003;121:715-9. doi: 10.1001/archopht.121.5.715. PubMed PMID: 12742852.
61 Altmann S, Brandt CR, Murphy CJ, Patnaikuni R, Takla T, Toomey M, et al. Evaluation of therapeutic interventions for vaccinia

virus keratitis. J Infect Dis. 2011;203:683-90. doi: 10.1093/infdis/jiq103. PubMed PMID: 21278209; PubMed Central PMCID: PMCPMC3072718.
62 Hashmi MF, Gurnani B, Benson S, Price KL. Conjunctivitis (Nursing). Florida: StatPearls; 2021.
63 Berche P. Life and death of smallpox. Presse Med. 2022;51:104117. doi: 10.1016/j.lpm.2022.104117. PubMed PMID: 35143880.
64 Chowdhury SR, Datta PK, Maitra S. Monkeypox and its pandemic potential: what the anaesthetist should know. Br J Anaesth. 2022;129:e49-e52. doi: 10.1016/j.bja.2022.06.007. PubMed PMID: 35803753; PubMed Central PMCID: PMCPMC9628951.
65 Tan E, Braithwaite I, McKinlay CJD, Dalziel SR. Comparison of Acetaminophen (Paracetamol) With Ibuprofen for Treatment of Fever or Pain in Children Younger Than 2 Years: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3:e2022398. doi: 10.1001/jamanetworkopen.2020.22398. PubMed PMID: 33125495; PubMed Central PMCID: PMCPMC7599455
66 Hammond NE, Boyle M. Pharmacological versus non-pharmacological antipyretic treatments in febrile critically ill adult patients: a systematic review and meta-analysis. Aust Crit Care. 2011;24:4-17. doi: 10.1016/j.aucc.2010.11.002. PubMed PMID: 21168342.
67 Clinician Outreach and Communication [Internet]. Isolation & Infection Control at Home. [Update August 11, 2022]. Available from: www.cdc.gov/poxvirus/monkeypox/clinicians/infection-control-home.html