OVERVIEW AND CURRENT PREVENTION STRATEGIES OF MONKEYPOX DISEASE

Aabir Pramanik[1], Abhishek Samanta[2], Bibek Mondal[3]

[1]Department of Pharmacognosy, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat-387481, India
[2,3]Eminent College of Pharmaceutical Technology, Moshpukur, Barbaria, West Bengal-700126, India

Abstract - The current 2022 monkeypox outbreak is the biggest ever recorded outside of Africa. Because of the rise in recent years in the frequency of human outbreaks, monkeypox is an emerging zoonotic disease that has long been considered an infectious disease with substantial pandemic potential. According to reports, the virus can also spread through close physical contacts, such as skin-to-skin contact or sexual contact, respiratory droplets, and household items like towels and blankets. There are several medicinal countermeasures on hand for orthopoxviruses like monkeypox. JYNNEOSTM (live, replication-incompetent vaccinia virus) and ACAM2000® are the two vaccines that are now available (live, replication-competent vaccinia virus). Although supportive care is usually sufficient for the majority of monkeypox patients, which have a moderate and self-limited illness, there are antivirals (such as tecovirimat, Brincidofovir, and cidofovir) and vaccinia immune globulin intravenous (VIGIV) that can be used as therapies. Antivirals should be considered in cases of severe illness, immunosuppressed individuals, children, pregnant and nursing women, complex lesions, and when lesions develop close to the mouth, eyes, or genitalia. Healthcare practitioners worldwide are attempting to get familiar with the varied clinical manifestations and therapy as public health organizations seek to limit the current outbreak. Considering the current outbreaks worldwide, we provide updated information on monkeypox for healthcare professionals in this review.

Key words - Monkeypox, smallpox, virus, outbreak, transmission, rash, vaccine, antiviral

I. INTRODUCTION

While the world is still dealing with the Coronavirus disease-19(COVID-19) pandemic, a new danger is approaching the world. The World Health Organization (WHO) declared monkeypox a Public Health Emergency of International Concern (PHEIC) on July 23rd,2022 (1). Research on vaccines and other preventative measures is being conducted worldwide in response to this new disease as a result of the emerging pandemic during this outbreak of monkeypox. According to WHO, 190 countries are affected by monkeypox. From 1st January 2022 to 26th October 2022, a total of 76768 confirmed cases and 3850 probable cases, including 36 deaths have been reported.In 1958, Monkeypox was first discovered in colonies of cynomolgus monkeys at Statens Serum Institutes in Copenhagen, hence the name Monkeypox (2–5). The first human case of a nine-month-old infant was infected in the Democratic Republic of Congo (DRC) in 1970 (4,6,7,8). Human monkeypox, a double standard deoxyribonucleic acid, comes under the Poxviridae family, and infects mammals, birds, reptiles, insects, and birds (9). The *Poxviridae* is further classified into 2 families 1) *Chordopoxvirinae* with 18 genera and 52 species and 2) *Entemopovirinae* with 4 genera and 30 species (6,9). Human monkeypox falls under the Orthopoxvirus, a genera of *Chordopoxvirinae* (Fig. 1**)** (6,8,10). The majority of the virus is zoonotic in the Chordopoxvirinae family (6).

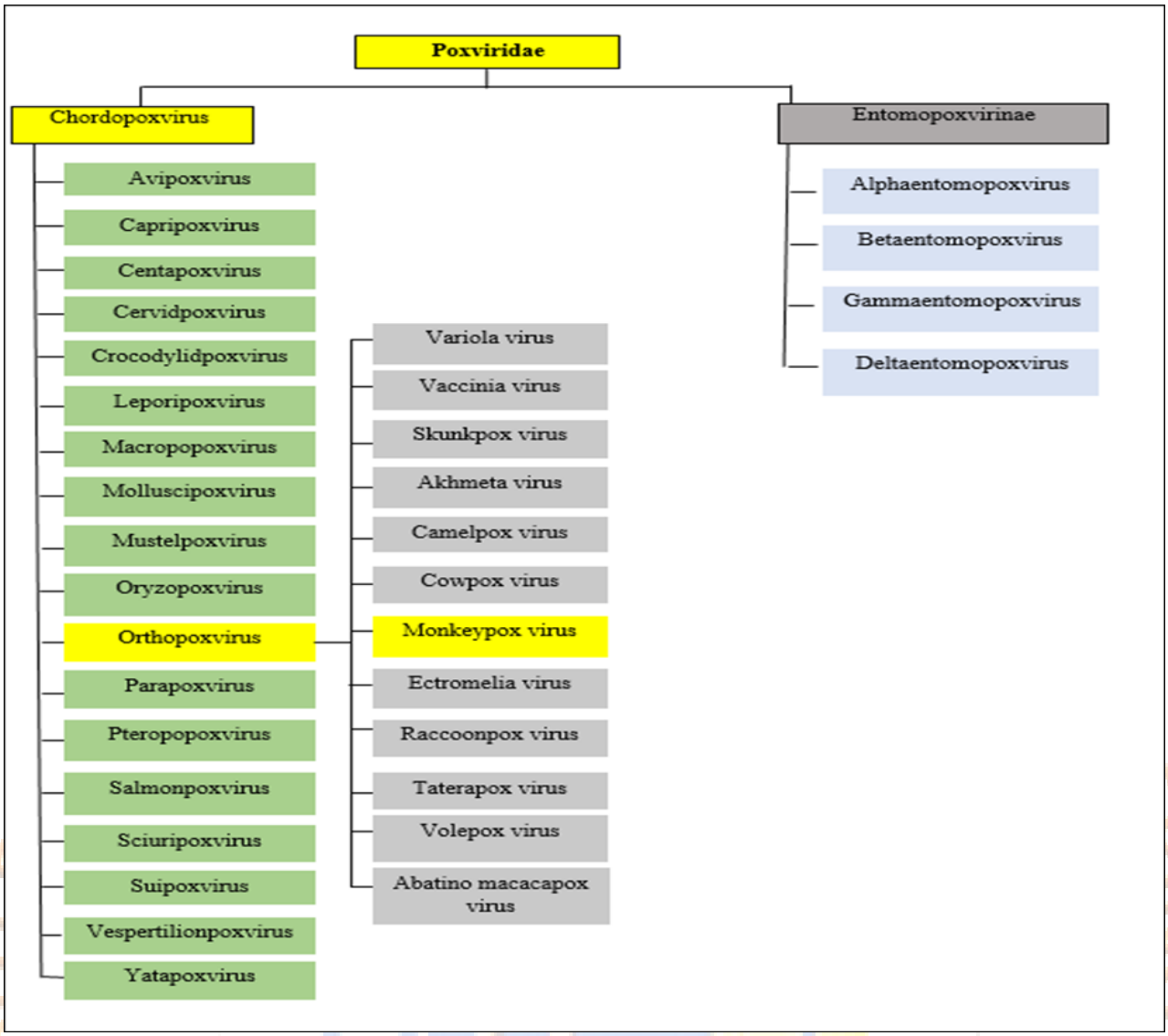

Fig. 1: Taxonomy and Classification of Monkeypox virus within the Poxviridae family

Human monkeypox virus is complex double-stranded DNA viruses that replicate in the cytoplasm of cells belonging to vertebrate or invertebrate species collectively referred to as Poxviridae (11,12). The closely related variola (VAR), vaccinia (VAC), and cowpox (CPV) viruses are examples of poxviruses that fall under the orthopoxviral genus (13). Human smallpox, an epidemic disease with mortality rates of 10–40%, was eradicated by a strategy of case identification and prophylactic vaccination of contacts with live VAC thanks to the concerted efforts of the international community under the direction of the World Health Organization (14,15). VAR is the etiologic agent of smallpox. Following the elimination of smallpox in 1977, vaccination stopped, which led to a loss in immunity to both VAR and other orthopoxviruses. As a result, zoonotic orthopoxviruses including MPV, CPV, and VAC strains are much more dangerous. These viruses might potentially become more harmful or transmissible as a result of increasing circulation among humans. The main reason MPV is a problem is because human monkeypox, a sporadic illness found in tropical rainforest areas of Central and Western Africa, resembles smallpox in terms of clinical symptoms and seems to be spreading more often (16,17).

The monkeypox virus is transmitted from human to human through large respiratory droplets, direct contact with a lesion on the skin, and indirect contact with contaminated bedding or clothing of an infected person (4,9,11). The virus can be spread by skin and mucosa during sex (18). Monkeypox can spread to a fetus through the placenta of a pregnant woman (Fig. 3) (19). Many cases of the United states monkeypox virus outbreak have been traced to sexual transmission, especially gay bisexual or men-to-men sexual contact (20),(21). Humans are infected by animals by bite or scratch, by eating poorly cooked meat of infected animals, and by close contact with an infected animal (Fig. 2) (4),(18). The natural reservoir of monkeypox includes monkeys, rope squirrels, tree squirrels, apes, Gambian pouched rats, dormice, and other species (21). Currently, there is no cure for the infection caused by the monkeypox virus. Antivirals created for patients with smallpox could be beneficial in treating monkeypox (22). Tecovirimat(known as TPOXX), Brincidofovir, and Cidofovir are the antiviral drugs approved by the USFDA (United States Food and Drug Administration) (23,24). But it is also hard to get (25). ACAM2000 and JYNNEOS are the two vaccines that may be useful for the prevention of the monkeypox virus (19,20,(28). Vaccinia immune globulin intravenous (VIGIV) is also available for treatment (21).

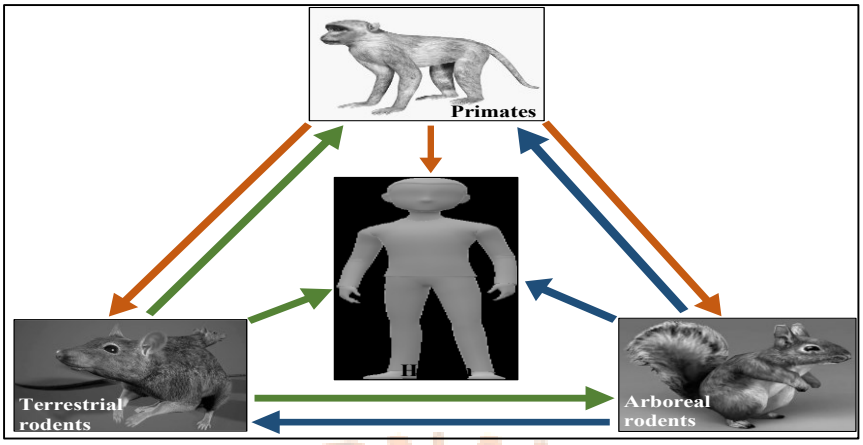

Fig. 2: Animals to Human Transmission (1° Transmission)

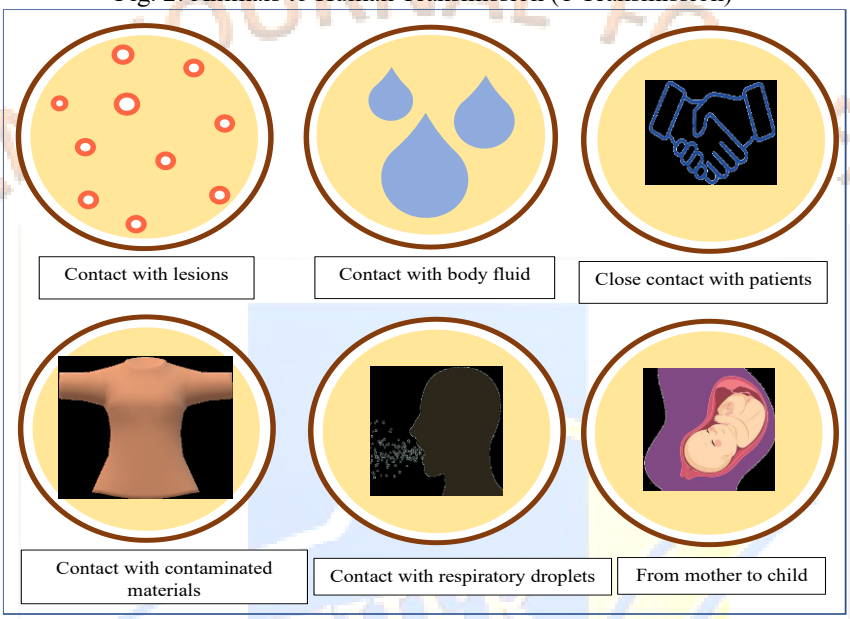

Fig. 3: Human to Human Transmission (2° Transmission)

Here in this review, we describe the clinical features, diagnosis, treatment, and management of monkeypox disease. We also report the viral kinetics and the use of Cidofovir, Brincidofovir, and tecovirimat to treat human monkeypox.

II. Historical Outbreaks

A nine-month-old infant was first infected by human monkeypox in the Democratic Republic of Congo in 1970 (8). After that many cases have been reported before 2022 mainly in Central and West African countries such as the Democratic Republic of Congo, Republic of Congo, Central African Republic, Cameroon, Cote d'Ivoire, Cameroon, Gabon, Liberia, Nigeria, Sierra Leone, Benin, South Sudan, Ghana (Identified in the animals only (9). Outside Africa, cases of monkeypox were also reported in the United States, United Kingdom, Israel, Netherlands, France, Germany, Italy, Sweden, Spain, Portugal, Austria, Canada, Australia, Canary Islands, Singapore, Switzerland, and India (29),(30),(6),(13),(4),(9),(18). The Central African and West African clade are two genetic clades of monkeypox (7),(10),(9). There is a difference in virulence between Central African and West African genetic clades. Comparing the two clades in the west African clade have less human-to-human transmission and a milder form of the disease with low fatality (10). Democratic Republic of Congo (DRC) is the most affected country where the number of cases increases rapidly (Fig. 4). 38 cases between 1970-1979, 511 cases between 1990-1999, and 18,788 cases have been reported between 2010-2019. Nigeria (181 cases) is the second most affected country. The Republic of Congo (97 cases) and the Central African Republic (67 cases) is the third and fourth most affected country (18). Outside Africa, the first case was reported in the United States (53 cases) in 2003, when the Centre for Disease Control and Prevention (CDC) received a report from the central US of patients with fever and rashes after close contact with prairie dogs (6),(31),(18). The first case of monkeypox was identified in India on 14 July 2022 after that 4 cases were identified on 24 July 2022 (18).

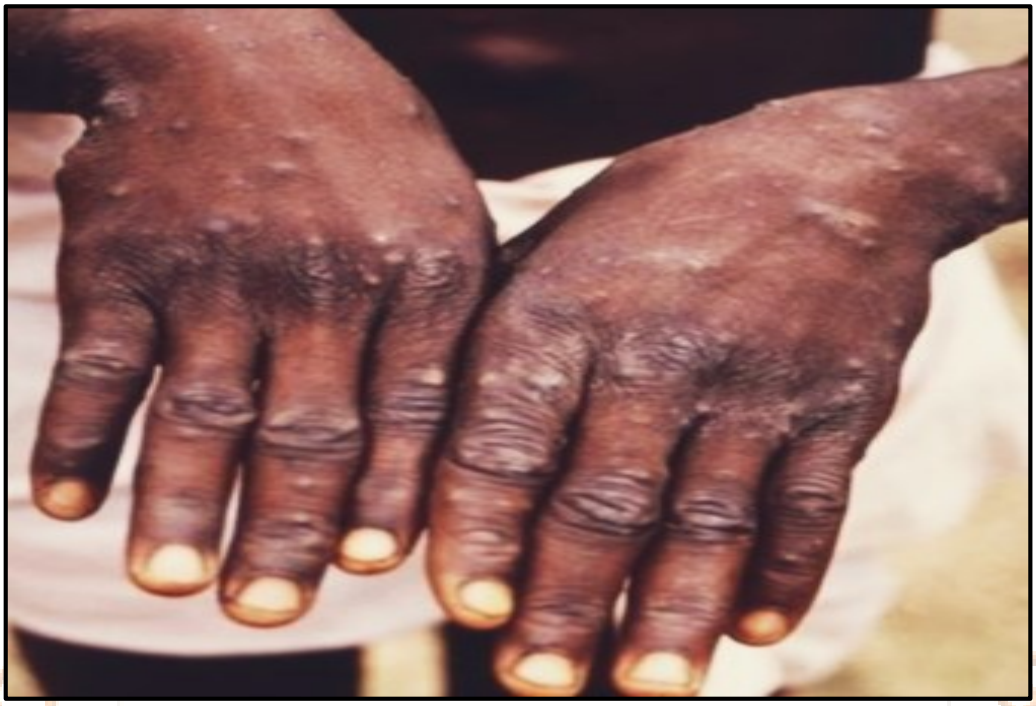

Fig. 4: This picture was taken during monkeypox outbreak in Democratic Republic of Congo (DRC), 1997. This is the dorsal surface of a patient's hand who was suffering from monkeypox

III. Clinical Features

Studies show that most males are more affected than females by this virus. Monkeypox is a self-limited disease and its symptoms last from two to four weeks (4),(32),(33). There are three periods in the clinical characteristic of monkeypox Incubation period (7-17 days), the Prodromal period (1-4 days), and the Rash period (14-28 days) (7),(4). The incubation period lasts for approximately 7-17 days. Patients are non-contagious in this period (6),(34). In this period the patients do not have any signs or symptoms and may feel fine (33). After that, the prodromal period last generally 1-4 days (7). During this phase, the patient faces fever (between 38.5˚C-40.5˚C), fatigue, headache, lethargy, myalgia, rash (35), lymphadenopathy (36) (Typically with the onset of fever), sweats, sore throat and cough (7),(4),(37),(32),(10),(18),(38) (Fig. 5). The last period is the Rash period which lasts generally 14- 28 days and is the most painful. This period is considered to be the most contagious phase. The rash begins as maculopapular lesions sizes that range from 0.2-1cm (10). Enanthem, Macules, Papules, Vesicles, Pustules, and crusting stages involve in rash in monkeypox patients (Table 1), (Fig. 6) (6),(39),(4),(31),(18),(40).

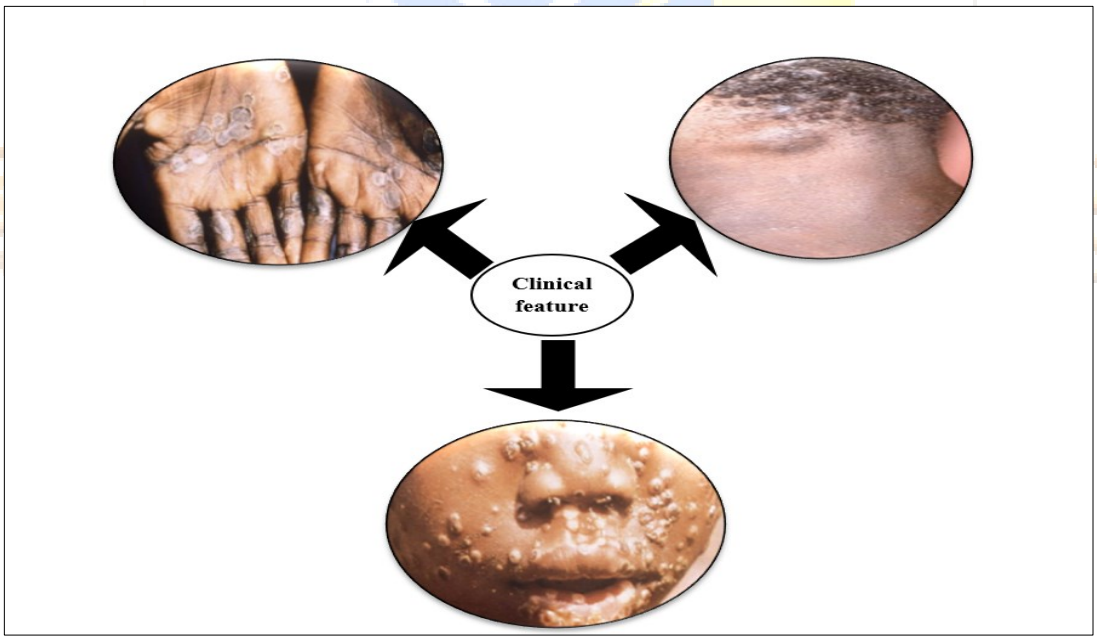

Fig. 5: Symptoms of rash period

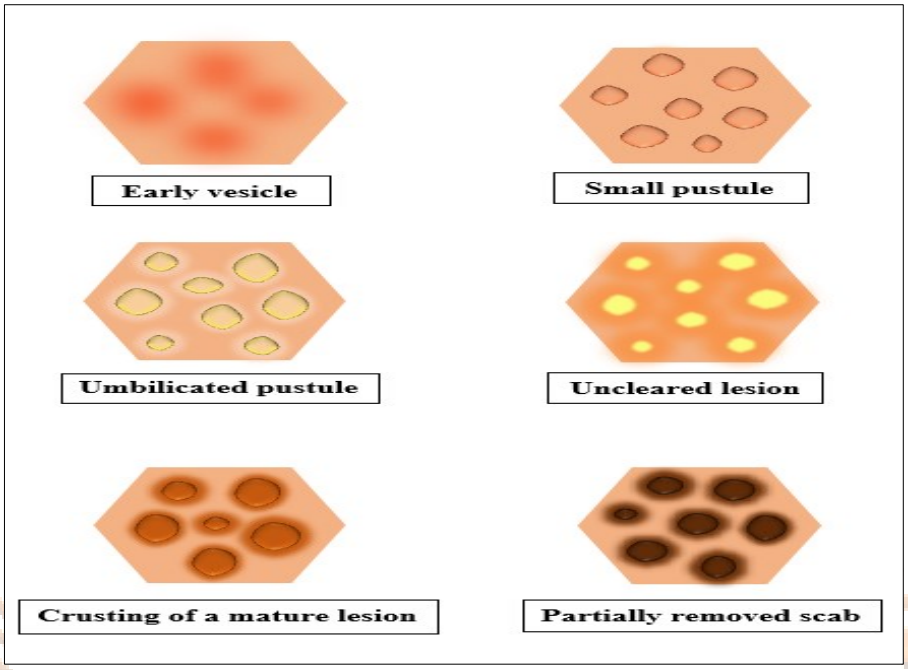

Fig. 6: Stages of monkeypox rash on the skin

Table 1: Stages of Lesions in skin, Duration, and symptoms

Stages	Duration	Symptoms
Enanthem		Lesions appear in the tongue and mouth first
Macules	1-2 days	Flat lesions that started on the face spread to arms, legs to hands, and feet.
Papules	1-2 days	Flat lesions progress to become raised
Vesicles	1-2 days	Lesions filled with clear fluid become vesicles
Pustules	5-7 days	Lesions filled with opaque fluid and sharply raised, round, firm, and deep-seated.
Crusting	7-14 days	At last, they dry up and crust over. The scabs stayed for a week and then fell off.

IV. DIAGNOSIS

Chickenpox is the most common differential diagnosis of monkeypox (4),(18),(41). Monkeypox has longer Incubation and Prodrome period (days) than chickenpox (18),(41). Clinical characteristics of monkeypox and chickenpox are shown in the (Table 2) (7),(41).

Table 2: Clinical characteristics of Monkeypox and Chickenpox (Varicella)

Clinical characteristics	Monkeypox	Chickenpox (Varicella)
Time(days)		
➢ Incubation period	7-17	12-14
➢ Prodrome period	1-4	0-2
➢ Rash period	14-28	10-21
Symptoms		
➢ Fever(temp)	Yes,38.5˚C-40.5˚C	Yes, not more than 38.8˚C
➢ Malaise	Yes	Yes
➢ Lymphadenopathy	Yes	No
➢ Headache	Yes	Yes
➢ Frequency of lesions of palm or soles	Yes	Rare

Lesions ➢ Distribution ➢ Evaluation(rash) ➢ Depth(mm)	Centrifugal Homogenous Superficial-Deep (4-6)	Centripetal Heterogeneous Superficial (2-4)

Disseminated herpes simplex, Disseminated herpes zoster, Secondary syphilis, Measles, Hand foot mouth disease, Chancroid, Molluscum contagiosum, and Infectious mononucleosis are the other differentials of monkeypox disease (39),(4),(18).

In laboratory testing, the sample has been taken from the patients. The sample should be collected from multiple sites of the body (4),(9),(31). Fluid from vesicles and pustules (collected with an intradermal syringe), and dried scabs (collected in a plain tube) consider the best diagnostic sample for monkeypox (8). The other samples include lesion roof (collected in a plain tube), lesion base scrapings (collected in a plain tube), blood collected in EDTA, Blood collected in SSGT, serum urine (sterile urine container), nasopharyngeal/oropharyngeal swab, semen and feces (4),(8),(18). The viral DNA is present in the sample, so it is stored in a sterile tube, cool environment, and dry and dark place (7),(8).

The RT-PCR (Real-time polymerase chain reaction) is the most effective method for the identification of monkeypox viral DNA present in the sample (4),(8),(31). Viral culture/isolation (lesion fluid is used), Electron microscopy (Vascular fluid, biopsy specimen, scab material is used), Immunohistochemistry (biopsy specimen is used), Anti-Orthopoxvirus IgG (biopsy specimen is used), Anti-Orthopoxvirus IgM (biopsy specimen is used), Tetracore Orthopox BioThreat Alert tests are also can be used to diagnosis of monkeypox (39),(7),(38).

V. PREVENTION AND MANAGEMENT

A. IMMUNIZATION

i. Pre-Exposure vaccine

It was found that immunization by smallpox vaccine, before exposure to monkeypox virus can prevent the disease. The two licensed smallpox vaccines are ACAM2000 and JYNNEOSTM (brand names- IMVAMUNE, MVA-BN, IMVANEX), approved by the US FDA. These are the most popular vaccines for smallpox. APSV can be used but as per IND protocol or exclusively for emergency purposes when other mentioned vaccines are not available. LC16m8 is another vaccine licensed in Japan (18),(38). The differences between ACAM-2000 and JYNNEOS are shown in the below (Table 3) (21).

Table 3: Main differences between ACAM-2000 and JYNNEOS

	ACAM-2000	**JYNNEOS**
US-FDA approval	August 2007	September 2019
Generation	Second generation vaccine	Third generation vaccine
Type	Replication-competent vaccinia virus	Nonreplicating modified Vaccinia Ankara virus vaccine
Dose	Single dose administration by multiple pricking the skin surface using a special needle.	Given 2 weeks subcutaneous 4 weeks apart.
Age restrictions	Infants under 12 months cannot get the vaccine.	Infants under 12 months can get the vaccine.
Reaction on site of inoculation	It produces a visible cutaneous reaction.	It does not show any reaction sign.
Limitation	It cannot be used people are suffering from immunosuppressive disorders like HIV, Cancer because it responsible for progressive vaccinia and eczema vaccinatum.	There is no such limitation.

ACAM-2000 has more side effects than the JYNNEOS vaccine. People who have a weak immune system, pregnant, breastfeeding women, have heart disease, have skin conditions (like eczema, psoriasis, or dermatitis), and history of a severe allergic reaction should not get ACAM-2000 (28). The most common side effects of ACAM-2000 vaccine are redness and itching at the vaccination site, headache, fever, tiredness, muscle ache, and swollen glands (28),(26). People who are already exposed (direct contact with a monkeypox patient, one of the sex partners has been diagnosed with monkeypox in the past 2 weeks, a man who has had sex with men) need to be vaccinated (27).

ii. Post-Exposure vaccine

Monkeypox requires long exposure and direct utterance for transmission from affected individuals to healthy people. Health Workers with PPE kits and maintaining standard protocol have less chance to catch monkeypox, thus reducing high risk for the same (42). However, CDC frames guidelines to arrest the risk of exposure. According to the CDC, the 1st dose of vaccine should be taken within 4 days of utterance to arrest disease. The vaccine can only reduce the symptoms if the affected person takes the vaccine after 4-14 days of utterance (43).

B. CLINICAL MANAGEMENT

Currently, there is no proven treatment found but three drugs Cidofovir, Brincidofovir, and Tecovirimat may be useful for the treatment of monkeypox (Table 4) (39). All the treatments are happening based on the *In-vitro* data, animal studies, case reports, case series, human pharmacokinetics, and human pharmacodynamic data (9).

i. Cidofovir

Cidofovir[1-(S)-[3-hydroxy-2-(phosphonomethoxy) propyl]cytosine] also known as HPMPC is a potent anti-DNA viral drug useful for cytomegalovirus retinitis approved with Acquired Immune Deficiency Syndrome(AIDS) without renal dysfunction approved by US-FDA in 1996 (44),(45). It is a nucleotide analogue (46). There is currently a lack of information on cidofovir's effectiveness in treating monkeypox in persons (47). However, this drug has a lot of side effects. Cidofovir is not recommended for pregnant women, breast-feeding women, patients under 18 years of age, and geriatrics (48),(44).

ii. Brincidofovir

Brincidofovir[(2S)-1-(4-amino-2-oxopyrimidin-1-yl)-3-hydroxypropan-2-yl]oxymethyl-(3-hexadecoxypropoxy)phosphinic acid] is a lipid conjugated analog of cidofovir useful for smallpox in adult and pediatrics, including neonates approved by US-FDA in 2021 (9),(6),(44). There is currently a lack of information on brincidofovir's effectiveness in treating monkeypox in person. However, this drug has a lot of side effects but fewer than cidofovir.

iii. Tecovirimat

Tecovirimat[N-{3,5-Dioxo-4-azatetracyclo[5.3.2.0{2,6}.0{8,10}]dodec-11-en-4-yl}-4 (trifluoromethyl)benzamide] also known as TPOXX is useful for treatment in the smallpox of adults and pediatric approved by US-FDA in 2018 (47),(44). There are no data on tecovirimat's effectiveness in treating monkeypox infections in humans, however research on a range of animal species has demonstrated that tecovirimat is useful in treating diseases brought on by orthopoxviruses (49),(6),(22).

iv. VIG-IV

The FDA authorized the use of Vaccinia immune globulin intravenous in 2005 for the treatment of problems resulting after immunization with the Vaccinia virus (Table 4) (50). Before this, intramuscular (IM) injections of vaccine immune globulin were used for administration (51). It has been thoroughly examined and summarized how IM Vaccinia immune globulin has been used historically. In some published studies for human OPXV infections, the FDA-approved intravenous version of vaccinia immunoglobulin (VIGIV) has been employed (52),(53),(54),53,54). A patient with inflammatory bowel illness who contracted an infection after being exposed to a vaccinia-rabies glycoprotein recombinant virus used in animal bait to help prevent the spread of rabies in the animal population also received vaccination immune globulin intravenously. Additionally, it was used to treat two patients who had contracted Vaccinia through secondary and tertiary transmission following the original sexual encounter between one of the case patients and a smallpox vaccine recipient (57).

Overall, mild to moderate illness with a self-limited course is the natural history of MPXV infection in humans (56,57). The following conditions should be evaluated with antiviral therapy: hospital-acquired severe illness; ocular, oral, and/or perineal involvement; and in patients thought to be at higher risk for developing the severe disease (immunocompromised, children under the age of 8, pregnant women, or people who are nursing), as well as when atopic dermatitis or other active exfoliative skin conditions are present. The chosen antiviral medication, tecovirimat, has the most real-world clinical experience (60). Wherever possible, treatment for MPXV infection should preferably be administered as part of a clinical study to produce long-term data that may help determine how patients should be treated in the future. Clinicians are urged to coordinate treatment plans and strategies with public health officials and infectious disease specialists (58,59).

Table 4: Drugs and vaccine use for the treatment of Monkeypox

Treatment	MOA	Dose	Adverse effects
Cidofovir	Prevents the production of viral DNA by competitively inhibiting DNA polymerase	5mg/kg once a week for about two doses (with concomitant probenecid).	Nausea, vomiting, reduced intraocular pressure, neutropenia, and nephrotoxicity
Brincidofovir	Lipid conjugate cidofovir prodrug.	4 mg/kg twice a week for a total of 200 mg per dosage	Increase liver transaminases, bilirubin, nausea, vomiting, and abdominal discomfort.
Tecovirimat	Blocks the production of virions that can be discharged from an infected host cell, restricting replication and spread inside the host, by inhibiting the function of the protein VP37.	IV: From 35 to 120 kg, 200 mg every 12 hours; from 120 kg, 300 mg every 12 hours Oral: 40–120 kg: 600 mg every 12 hours; 120 kg: 600 mg every 8 hours. Everything is for 14 days.	IV: Extravasation at the infusion site, discomfort and edema, and a headache Oral: nausea, vomiting, headaches, and stomach discomfort.

VIG-IV	Passive protection using OPXV-specific antibodies collected from pooled human plasma of smallpox vaccination recipients	A single dosage of 6000 units/kg (up to 9000 units/kg) If necessary, repeat the dose based on your symptoms.	Local injection-site response during infusion (contraindicated in persons with IgA deficiency and possible IgA hypersensitivity).

VI. CURRENT TRENDS

A familial cluster of two instances of monkeypox were recorded in the United Kingdom (UK) on May 14, 2022, as reported by the UK Health Security Agency (UKHSA). There was no previous travel history of the case patients to an endemic country (62). Since then, numerous nations in Europe, South America, the Middle East, Canada, and the United States have received thousands of cases (9). Since May 14, there have been 37 confirmed cases of monkeypox worldwide, 26 of which have occurred in EU/EEA nations. Most of the incidents are found in young males who identify as men who have sex with men (MSM). No fatalities have been reported, although two hospitalizations for conditions other than isolation have been noted globally. Lesions on the genitalia or peri-genital region were found in the majority of patients, indicating that close physical contact during sexual activities is where transmission most frequently happens (63). It is now under investigation whether or not monkeypox can be sexually transmitted in the conventional sense. For instance, in Italy and Germany, minor quantities of the virus have been identified in patient semen (9). Despite the lack of evidence at this time, those who have been diagnosed with monkeypox are encouraged to wear condoms for eight weeks after their diagnosis as a precaution (64).

VII. CONCLUSION

As case detection accelerates in the following months, we will become more certain of the extent of the present outbreak. For it to be contained, immediate and proactive action will be essential. The secret to success will be making sure that we take lessons from prior epidemics and soon and early disseminate the available tools. There have been indicators of monkeypox being a global public health issue for many years. Now is the time to adopt a truly global approach that addresses this problem definitively not only in wealthy countries but also, critically, in the endemic countries that have been responding to monkeypox for decades.

VIII. REFERENCES

1. Wilck MB, Seaman MS, Baden LR, Walsh SR, Grandpre LE, Devoy C, et al. Safely and immunogenicity of modified vaccinia ankara (ACAM3000): Effect of dose and route of administration. J Infect Dis. 2010;201(9):1361–70.
2. Africa I. Monkeypox Virus Common Human Exposure Routes : Disease Agent Characteristics : Disease Name : Priority Level : Background : 2003;130–2.
3. VII. Ecology of Monkeypox Virus. 2015;111–24.
4. GUIDELINES FOR MANAGEMENT Ministry of Health and Family Welfare. :1–23.
5. Knud Birkum Petersen B, Preben Von Magnus B, Krag Andersen E. a Pox-Like Disease in Cynomolgus Monkeys. 1958;
6. Kaler J, Hussain A, Flores G, Kheiri S, Desrosiers D. Monkeypox: A Comprehensive Review of Transmission, Pathogenesis, and Manifestation. Cureus. 2022;14(7):1–11.
7. Wilson ME, Hughes JM, McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis. 2014;58(2):260–7.
8. Di Gennaro F, Veronese N, Marotta C, Shin J Il, Koyanagi A, Silenzi A, et al. Human Monkeypox: A Comprehensive Narrative Review and Analysis of the Public Health Implications. Microorganisms. 2022;10(8):1–10.
9. Titanji BK, Tegomoh B, Nematollahi S, Konomos M, Kulkarni PA. Monkeypox: A Contemporary Review for Healthcare Professionals. Open Forum Infect Dis [Internet]. 2022;9(7):1–13. Available from: https://doi.org/10.1093/ofid/ofac310
10. Weaver JR, Isaacs SN. proteins. 2009;(2):96–113.
11. Moss B. Poxvirus DNA replication. Cold Spring Harb Perspect Biol. 2013;5(9):1–12.
12. Shchelkunov SN, Totmenin A V., Safronov PF, Mikheev M V., Gutorov V V., Ryazankina OI, et al. Analysis of the monkeypox virus genome. Virology. 2002;297(2):172–94.
13. Cho CT, Wenner HA. Monkeypox virus. Bacteriol Rev. 1973;37(1):1–18.
14. Damaso CRA, Esposito JJ, Condit RC, Moussatché N. An emergent poxvirus from humans and cattle in Rio de Janeiro state: Cantagalo virus may derive from brazilian smallpox vaccine. Virology. 2000;277(2):439–49.
15. Darling RG, Burgess TH, Lawler J V., Endy TP. Virologic and Pathogenic Aspects of the Variola Virus (Smallpox) as a Bioweapon. Biol Weapons Def. 2005;99–120.
16. Press B, Wm S. Re-emergence of human monkeypox in Zaire in 1996 Glutathione S-transferase theta 1 (GSTT1) gene defect in myelodysplasia and acute myeloid leukaemia Glutathione S-transferase gene deletions in myelodysplasia. 1997;349:1449–50.
17. Arita I, Gispen R, Kalter SS, Wah LT, Marennikova SS, Netter R, et al. Outbreaks of monkeypox and serological surveys in nonhuman primates. Bull World Health Organ. 1972;46(5):625–31.
18. Singhal T, Rakesh SKK. Monkeypox : A Review. 2022;
19. Animals I. Monkeypox How It Spreads Close or Intimate Contact Scientists are Still Researching. 2022;22–3.
20. Kozlov M. How does monkeypox spread? What scientists know. Nature. 2022;608(7924):655–6.
21. Rizk JG, Lippi G, Henry BM, Forthal DN, Rizk Y. Prevention and Treatment of Monkeypox. Drugs [Internet]. 2022;82(9):957–63. Available from: https://doi.org/10.1007/s40265-022-01742-y
22. Guidance IC, Available MC. Monkeypox Treatment Information for Healthcare Professionals Interim Clinical Guidance for the Treatment of Monkeypox Medical Countermeasures Available for the Treatment of Monkeypox. 2022;3–5.

23. Agency EM. List of critical medicines for COVID-19 public health emergency (PHE) under Regulation (EU) 2022/123. 2022;2(August):2–4. Available from: List of critical medicines for COVID-19 public health emergency (PHE) under Regulation (EU) 2022/123
24. Edition E. Monkeypox : we have vaccines and drugs to treat it. 2022;9–11.
25. Africa W. There Is an Effective Treatment for Monkeypox, but It's Hard to Get. Sci Am [Internet]. 2022; Available from: https://www.scientificamerican.com/article/there-is-an-effective-treatment-for-monkeypox-but-it-rsquo-s-hard-to-get/?utm_source=researcher_app&utm_medium=referral&utm_campaign=RESR_MRKT_Researcher_inbound
26. Information G, Effectiveness V, Protection L. Monkeypox Long-Term Protection What to Expect When You Get the Vaccine. 2022;1–2.
27. Should W, Vaccinated G. Monkeypox Monkeypox Vaccination Basics. 2022;3–5.
28. Information G, Effectiveness V, Protection L, Who P, Not S, Vaccinated G. Monkeypox ACAM2000 Vaccine Long-Term Protection. 2022;1–2.
29. 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(4):1027–43.
30. 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(4):782–5.
31. Giulio DB Di, Eckburg PB. Reviews Human monkeypox : an emerging zoonosis. 2004;4(January):15–25.
32. Javier F, Sánchez M, Martínez-sellés M, Ruiz-galiana J, Ramos PDL. Monkeypox in humans : a new outbreak. 2022;
33. Monkeypox M, Photos R. Monkeypox Key Characteristics for Identifying Monkeypox. 2022;10–2.
34. Protocol I. Monkeypox Monkeypox Surveillance and Investigation Protocol. 2022;(July):1–13.
35. Details - Public Health Image Library(PHIL) [Internet]. [cited 2023 Jan 11]. Available from: https://phil.cdc.gov/Details.aspx?pid=12761
36. Details - Public Health Image Library(PHIL) [Internet]. [cited 2023 Jan 11]. Available from: https://phil.cdc.gov/Details.aspx?pid=12778
37. What Is Monkeypox ? 2022;328(2):2022.
38. Cheema AY, Ogedegbe OJ, Munir M, Alugba G, Ojo TK. Monkeypox : A Review of Clinical Features , Diagnosis , and Treatment. 2022;14(7):14–7.
39. Editor D, Africa W, Kim DH, Cho SI. Monkeypox virus infection : what dermatologist needs to know ? 2022;656–8.
40. Eid R El, Allaw F, Haddad SF, Id SSK. Human monkeypox : A review of the literature. 2022;1–11.
41. Nalca A, Rimoin AW, Bavari S, Whitehouse CA. Reemergence of Monkeypox : Prevalence , Diagnostics , and Countermeasures. 2005;21702:1765–71.
42. Home M. Monkeypox Monitoring and Risk Assessment for Persons Exposed in the Community How to monitor. 2022;1–4.
43. Effectiveness V. Monkeypox Monkeypox and Smallpox Vaccine Guidance Receiving Vaccine After Exposure to Monkeypox Virus Vaccine Risks vs . Monkeypox Disease. 2022;2021–2.
44. Agency EM. Evidence summary Antiviral treatment options for human monkeypox infection Tecovirimat Brincidofovir Cidofovir Tecovirimat Brincidofovir Cidofovir. 2022;(June):1–6.
45. Krec M. Antiviral Activity of Triazine Analogues of 1- (S) - [3-Hydroxy-2- (phosphonomethoxy) propyl] cytosine (Cidofovir) and Related Compounds. 2007;1069–77.
46. Information G, Studies D. Observational studies. (Cmv):3–7.
47. Soheili M, Nasseri S, Afraie M, Khateri S, Moradi Y, Maryam S, et al. Monkeypox : Virology , Pathophysiology , Clinical Epidemiology , Vaccines , Diagnosis , and Treatments Characteristics ,. 2022;297–322.
48. Injection C. CIDOFOVIR INJECTION Marcan Pharmaceuticals Inc. Page 1 of 28. 2018;(200865):1–28.
49. Monkeypox : a visual guide. 2022;1–8.
50. Vaccinia Immune Globulin Intravenous (Human) | FDA [Internet]. [cited 2023 Jan 11]. Available from: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/vaccinia-immune-globulin-intravenous-human
51. Hopkins RJ, Lane JM. Clinical efficacy of intramuscular vaccinia immune globulin: a literature review. Clin Infect Dis [Internet]. 2004 Sep 15 [cited 2023 Jan 11];39(6):819–26. Available from: https://pubmed.ncbi.nlm.nih.gov/15472814/
52. Lederman ER, Davidson W, Groff HL, Smith SK, Warkentien T, Li Y, et al. Progressive vaccinia: Case description and laboratory-guided therapy with vaccinia immune globulin, ST-246, and CMX001. J Infect Dis. 2012;206(9):1372–85.
53. Vora S, Damon I, Fulginiti V, Weber SG, Kahana M, Stein SL, et al. Severe eczema vaccinatum in a household contact of a smallpox vaccinee. Clin Infect Dis. 2008;46(10):1555–61.
54. Society ID. Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2014. This work is written by (a) US Government employee(s) and is in the public domain in the US. 2014;1–4.
55. Evaluation D. Clinical review(s).
56. Whitehouse ER, Rao AK, Yu YC, Yu PA, Griffin M, Gorman S, et al. Novel Treatment of a Vaccinia Virus Infection from an Occupational. 2019;68(42):943–6. Available from: https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6842a2-H.pdf
57. Tack DM, Karem KL, Montgomery JR, Collins L, Bryant-Genevier MG, Tiernan R, et al. Unintentional transfer of vaccinia virus associated with smallpox vaccines. https://doi.org/104161/hv24319. 2013 Jul;9(7):1489–96.
58. Monkeypox: Montreal public health to expand vaccination as Quebec cases grow to 132 | CTV News [Internet]. [cited 2023 Jan 11]. Available from: https://montreal.ctvnews.ca/montreal-public-health-shifting-vaccination-plan-as-monkeypox-cases-grow-to-126-1.5946380
59. Titanji BK, Tegomoh B, Nematollahi S, Konomos M, Kulkarni PA. Monkeypox: A Contemporary Review for Healthcare Professionals. Open Forum Infect Dis [Internet]. 2022 Jul 4 [cited 2023 Jan 11];9(7). Available from: https://academic.oup.com/ofid/article/9/7/ofac310/6615388
60. Ogoina D, Iroezindu M, James HI, Oladokun R, Yinka-Ogunleye A, Wakama P, et al. Clinical Course and Outcome of Human Monkeypox in Nigeria. Clin Infect Dis. 2020 Oct 15;71(8):E210–4.
61. UK Health Security Agency. Recommendations for the use of pre-and post-exposure vaccination during a monkeypox incident. 2022;(August). Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1100600/recommendations-for-pre-and-post-exposure-vaccination-during-a-monkeypox-incident-26-august-2022.pdf

62. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, et al. The changing epidemiology of human monkeypox—A potential threat? A systematic review. PLoS Negl Trop Dis [Internet]. 2022 Feb 1 [cited 2023 Jan 10];16(2). Available from: https://www.ecdc.europa.eu/en/news-events/epidemiological-update-monkeypox-outbreak

63. Epidemiological update: Monkeypox outbreak [Internet]. [cited 2023 Jan 10]. Available from: https://www.ecdc.europa.eu/en/news-events/epidemiological-update-monkeypox-outbreak

64. Monkeypox infections rise as guidance advises cases to abstain from sex - BBC News [Internet]. [cited 2022 Nov 13]. Available from: https://www.bbc.com/news/health-61640196