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A Comprehensive Review: Epidemiology, Prevention, and Treatment of Monkeypox

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HUMAN

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ABSTRACT

As per World Health Organization (WHO), in the current series of episodes being announced, this is the initial occasion when chains of transmission are accounted for in Europe without known epidemiological connections to West or Central Africa. Human monkeypox is a zoonotic orthopoxvirus with a show like smallpox. Monkeypox is sent unexpectedly to people when they experience tainted creatures. Reports have demonstrated the way that the infection can likewise be sent through direct contact (sexual or skin-to-skin), respiratory beads, and using fomites like towels and bedding. Numerous clinical countermeasures are stored for orthopoxviruses, for example, monkeypox. Two immunizations are right now accessible, JYNNEOSTM (live, replication awkward vaccinia infection) and ACAM2000® (live, replication equipped vaccinia infection). While most instances ofmonkeypox will have gentle and self-restricted infection, with steady consideration being regularly sufficient, antivirals (for example tecovirimat, brincidofovir, cidofovir) and vaccinia insusceptible globulin intravenous (VIGIV) are accessible as medicines. Antivirals can be thought about in extreme illness, immunocompromised patients, pediatrics, pregnant and breastfeeding ladies, muddled injuries, and when sores show up close to the mouth, eyes, and private parts. The motivation behind this short survey is to depict each of these countermeasures.

INTRODUCTION

As per World Health Organization (WHO), in the current series of episodes being announced, this is the initial occasion when chains of transmission are accounted for in Europe without known epidemiological connections to West or Central Africa. Monkeypox has been accounted for as endemic in a few other focal and western African nations, for example, Cameroon, Central African Republic, Cote d'Ivoire, the Democratic Republic of the Congo, Gabon, Liberia, Nigeria, Republic of the Congo, and Sierra Leone(1). This has been likewise detailed in specific non-endemic nations for example USA, UK Belgium, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Australia, Canada, Austria, Canary Islands, Israel, and Switzerland.

The 2022 flare-up of monkeypox in numerous nations in both endemic and nonendemic areas has created significant worldwide interest(2). A once-ignored zoonotic virus endemic to West and Central Africa, monkeypox infection was first distinguished in 1958 in nonhuman primates saved for research in Denmark. The first case in quite a while was accounted for in 1970 in the Democratic Republic of Congo. Over the past 50 years, irregular flare-ups have been accounted for fundamentally in African nations, with a few thousand human cases recorded until this point. Incidental cases and restricted flare-ups connected to travel or on the other hand importation of VE(3).

has for quite some time been a theoretical worry that monkeypox infection and other zoonotic poxviruses could over the long haul extend to fill the natural specialty once involved by the firmly related variola infection(4). The combined impacts of deforestation, populace development, encroachment on creature repository living spaces, expanding human development, and upgraded worldwide interconnectedness have made this chance all the more genuine over the most recent 20 years(5).

With expanding case numbers being accounted for in the current episode, it is significant for clinicians wherever to refresh their information on this zoonotic contamination, including its anticipation, clinical administration, prophylaxis, and fundamentals of disease control, to figure out the more extensive ramifications of the ongoing episode(6). In this audit, we give an outline of monkeypox infection contamination to act as an introduction for medical services experts who may encounter this condition in their training(7).

Monkeypox infection is a double-stranded DNA infection of the variety of orthopoxviruses, which additionally incorporates variola, cowpox (CPX), and vaccinia infections. Monkeypox infection was first confined to monkeys; however, the regular host of monkeypox infection additionally incorporates rope squirrels, tree squirrels, Gambian pouched rodents, and dormice. Two primary clades of monkeypox infection have been identified such long ways in Central and West Africa, the previous related to more extreme sickness (8). Many cases in the ongoing flare-up have been followed to sexual transmission, particularly among men who recognize as gay, sexually open, or men who have inter course with men(9).

The infection can likewise be sent through direct contact with irresistible injuries, scabs, or body fluids, furthermore, as shared sheet material/clothing. The signs and side effects are however less extreme than smallpox, and include a trademark rash gone before by gentle prodromal side effects (e.g., fever, lymphadenopathy, and fu-like side effects)(10).In the ongoing episode, cases have been abnormal, with the trademark rash beginning in the genital and perianal regions regardless of scattering to different pieces of the body(11).

Patients are viewed as irresistible once the prodrome or rash starts, until sores scab and the scabs fall off. Identification of viral DNA in swabs taken from hulls of vesicles orulcers address the favored technique for diagnosing dynamic monkeypox cases(12).At the hour of composing, there are no specific medicines for patients with monkeypox infection disease for each the Center for infectious prevention and Prevention (CDC), and steady consideration is commonly sufficient. In any case, minor flare-ups have been controlled utilizing smallpox antibodies, antivirals, also, vaccinia invulnerable globulin (VIG), with these treatments being accessible through interviews with the CDC(13). Prevention and the board of monkeypox are like that of other orthopoxvirus contaminations, and all confirmed orthodox virus cases ought to be treated as though they are monkeypox until demonstrated in any case.

PATHOLOGY

The Poxviridae family are twofold abandoned deoxyribonucleic corrosive infections which contaminate a scope of creatures including birds, reptiles, bugs, and vertebrates. The family comprises 2 subfamilies: Chordopoxvirinae (with 18 genera and 52 species) and Entomopoxvarinae (with 4 genera and 30 species)(14). Monkeypox has a place within the Poxviridae family, the Chordopoxvirinae subfamily, and the class Orthopoxvirus. A few poxvirus animal varieties have been displayed to cause human contaminations including Variola (smallpox), Cowpox, Monkeypox, Vaccinia, Camelpox, Alaskapox, Yaba monkey

tumor virus Tanapox infection, Orf infection, Pseudocowpox infection, Bovine papular stomatitis infection, Buffalopox, and Molluscum contagiosum. People are the repository host of Variola and Molluscum contagiosum infections (15). Monkeypox infection(MPXV) has an extensive variety of potential host life forms, which has permitted it to the course in wild creatures for a drawn-out period while irregularly causing human sickness through overflow occasions. More critically, Orthopoxviruses(OPXV) show immunological cross-reactivity and cross-protection, and contamination with any individual from the sort presents some assurance from disease with some other individuals from the same class(16).

Orthopoxviruses are enormous (size range: 140-450 nm) infections with a block-like construction and a genome comprising around 200-500kbp kb that codes for more than 200qualities. A significant number of the qualities encoded by the OPXV genome are not fundamental for infection replication in cell culture however could play important jobs in the host antiviral reaction(17). All poxviruses complete their replication cycle in the cytoplasm of tainted cells utilizing complicated atomic pathways. This intracellular replication cycle has been very much portrayed for Vaccinia infection, which was utilized to foster the immunization that assisted with destroying smallpox around the world; key highlights of this replication cycle are comparative for all poxviruses (18). The contamination cycle can be started by two particular types of infection the intracellular mature virion and the extracellular wrapped virion, which varyin their appearance of surface glycoproteins. Glycosaminoglycans, which are pervasively communicated on the outer layer of mammalian cells, are believed to be significant for restricting the virion to the cell layer, albeit all cell receptors have not been completely portrayed. A nitty gritty portrayal of the replication cycle is past the extent of this survey however has been portrayed previously (19).

Smallpox is assessed to have caused a huge number of fatalities overall and was one of the absolute most feared irresistible diseases in mankind's set of experiences. The effect of smallpox fills in as a reminder that OPXV can be impressive microorganisms (20). Albeit the starting points of smallpox are not known, there is some proof that recommends that Variola infection might have developed from an ancient rat poxvirus millennia prior. The increasing risk of zoonotic OPXV diseases, for example, MPXV has been perceived for quite a while. As a result of inoculation programs against smallpox finishing more than 40 years back, a critical extent of the worldwide populace doesn't have resistance against smallpox and zoonotic OPXV (21). All of this raises the likelihood that given the right circumstances, such as expanding occurrence of human diseases and long haul absence of immunization

insusceptibility, a zoonotic orthopoxvirus like MPXV could secure the capacity to all the more productively communicate between people and cause bigger episodes(22).

EPIDEMIOLOGY

Specialist

Monkeypox infection (MPXV) is a wrapped twofold abandoned DNA infection that has a place with the Orthopoxvirus variety of the Poxviridae family. There are two particular hereditary clades of the monkeypox infection - the Central African (Congo Basin) clade and the West African clade (23). The Congo Basin clade has generally caused more extreme illness and was believed to be more contagious. The geological division between the two clades has so far been in Cameroon - the main nation where both infection clades have been found (24).

Host

Regular supply is yet obscure. Nonetheless, certain rodents (counting rope squirrels, tree squirrels, Gambian pouched rodents, and dormice) and non-human primates are known to normally be defenseless to monkeypox infection (25).

Incubation period

The hatching time frame (stretch from contamination to beginning of side effects) of monkeypox is ordinarily from 6 to 13 days yet can go from 5 to 21 days (26).

Period of coherence

1-2 days before the rash until every one of the scabs tumbles off/gets died down (27).

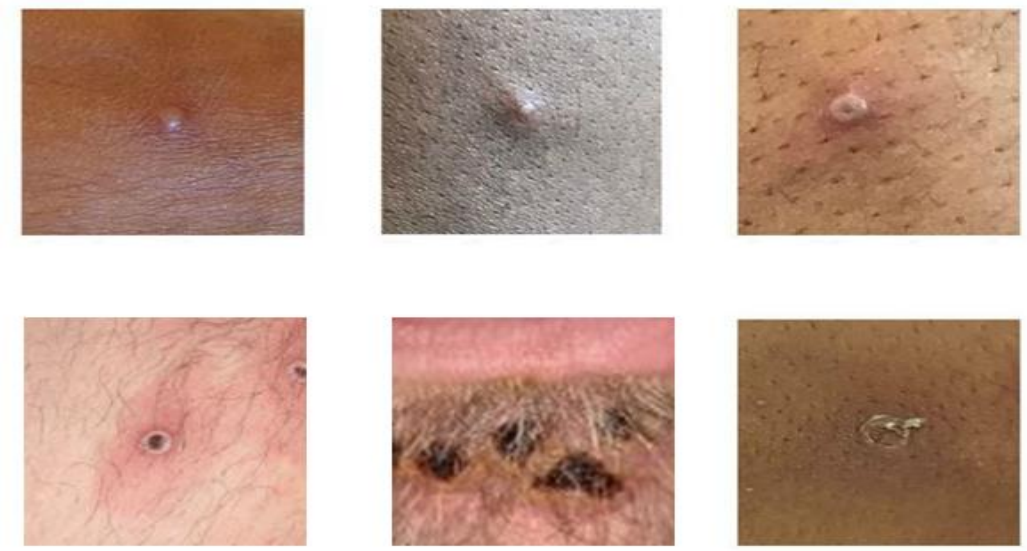
Mode of transmission

Human-to-human transmission is known to happen fundamentally through enormous respiratory beads for the most part requiring a drawn-out close contact. It can likewise be sent through direct contact with body liquids or injury material, and circuitous contact with sore material, like through debased apparel or cloths of a contaminated individual(28).

Creature to-human transmission

May happen by chomping or scratch of tainted creatures like little warm-blooded creatures including rodents (rodents, squirrels) and non-human primates (monkeys, chimps), or through shrub meal planning(29).

VARIOUS STAGES OF MONKEYPOX



PREVENTION

Information recommends that earlier inoculation with smallpox immunization may have a defensive effect against monkeypox infection and may work on clinical appearances of contamination (30). At present, there are three smallpox immunizations in the US Strategic National Stockpile (SNS): JYNNEOSTM (likewise known as IMVAMUNE, IMVANEX, MVA-BN) and ACAM2000® are authorized for smallpox; the Aventis Pasteur Smallpox Vaccine (APSV) could be utilized for smallpox under an investigational new medication (IND) convention (31).

JYNNEOSTM is a live popular immunization created from the adjusted vaccinia Ankara-Bavarian Nordic (MVA-BN strain) and is a weakened, non-recreating orthopoxvirus. It was authorized by the US Food and Drug Administration (FDA) in September 2019 and is presently demonstrated for counteraction of smallpox and monkeypox illness in grown-ups 18 years old or not entirely settled to be at high gamble for smallpox or monkeypox disease (32). Verifiable information has shown that smallpox immunization with vaccinia infection was around 85% effective against monkeypox. The antibody is supported in Europe for

smallpox as IMVANEX®, albeit the UK has been involving it of name in reaction to monkeypox cases(33).

ACAM2000® likewise comprises live vaccinia infection. It was authorized by the FDA in August 2007, supplanting the past orthopoxvirus immunization Dryvax®, which was removed by the maker. ACAM2000® is shown for dynamic vaccination against smallpox illness for people determined to be at high gamble for smallpox disease(34). The CDC holds a crisis access IND convention, which permits the utilization of ACAM2000® for non-variola orthopoxvirus contamination (e.g., monkeypox) during an episode.

There are a few differences between JYNNEOSTM and ACAM2000®. ACAM2000® is a replication-competent vaccinia infection, while JYNNEOSTM is a replication-deficient modified vaccinia Ankara infection. All things considered, ACAM2000® produces a significant cutaneous response at the site of vaccination, while JYNNEOSTM doesn't. Consequently, there is a gamble of unintentional immunization and autoinoculation with ACAM2000®, however, no such gamble happens with JYNNEOSTM(35). With replication-skillful vaccinia antibodies, for example, ACAM2000®, skin inflammation vaccinatum and moderate vaccinia can happen due to uncontrolled viral replication in specific people. Moderate vaccinia is by and large seen in immunocompromised people, while dermatitis vaccinatum can happen in people with atopic dermatitis or skin inflammation. Rules suggest avoiding ACAM2000® among immunosuppressed people (e.g., HIV-contaminated people), making it a sensible practice to keep away from ACAM2000® in populaces that are at expanded risk of unnoticed HIV, at present the populace with which latest non-African cases are being identified, and a populace from which monkeypox may very much spread more broadly (e.g., sex laborers)(36).

What's more, accidental transmission can happen with replication-skillful antibodies, including vertical transmission bringing about fetal vaccinia, which can be deadly to the hatchling or on the other hand infant. Other serious unfriendly occasions seen more frequently with ACAM2000® than with JYNNEOSTM incorporate myopericarditis (expected to happen in 5.7 per 1,000 essential ACAM2000® vaccinees and post-antibody encephalitis (37).

The FDA surveyed the effectiveness of ACAM2000® by contrasting immunologic reactions and "take" rates of ACAM2000® to Dryvax[16, 19]. Also, the FDA evaluated the effectiveness of JYNNEOSTM by contrasting the immunologic reaction of JYNNEOSTM to

ACAM2000® and likewise consolidated steady creature studies. ACAM2000® is given percutaneously by the different cut strategy in a solitary portion utilizing a bifurcated needle, while JYNNEOSTM is regulated subcutaneously in two portions, 28 days separated(38). Aventis Pasteur Smallpox Vaccine (APSV) is a replication-equipped vaccinia immunization that might be utilized under an IND or Emergency Use Authorization (EUA) to forestall smallpox assuming the authorized immunizations are inaccessible or contraindicated. It isn't known, in any case, if this immunization could be utilized for monkeypox(39).

Pre-exposure Prophylaxis and Post-exposure Prophylaxis

The Advisory Committee and Immunization Practices (ACIP) suggests inoculation for select people at risk for word-related openness to orthopoxviruses. Research lab staff, clinical lab personnel performing demonstrative testing for orthopoxviruses, and assigned reaction colleagues in danger for word-related openness to orthopoxviruses are prescribed to be vaccinated. Also, medical care staff who direct. ACAM2000® or care for patients contaminated with replication-capable orthopoxviruses can be offered inoculation based on shared clinical independent direction (40).

In the ongoing episode occurring in nonendemic nations, immunization is managed as post-openness prophylaxis. (PEP) for close contacts with high-risk openings and uncovered medical services laborers is in progress in a few European Union nations the UK, the United States, and Canada, and being considered in others(41). Openness hazards can be classified into three classifications: high, middle, and low/uncertain. High-risk openings incorporate direct contact between the uncovered individual's messed-up skin or mucous layers and the "materials, skin, injuries, or body liquids" of a patient. Being in close contact with a patient during a spray-producing methodology while not wearing respiratory security is likewise considered a high-risk openness. Transitional gamble openings incorporate direct contact between the uncovered individual's unblemished skin whats more "materials, skin, sores, or body liquids" of the record patient. Middle-of-the-road risk openings additionally incorporate being within six feet of a case patient for over three hours or conveying clinical consideration to patients with the disease without proper individual defensive gear (PPE). An okay openness includes giving clinical consideration to patients while wearing appropriate PPE (42). All the more critically, numerous novel openness circumstances don't squeeze into one of these categories. In these cases, individual gamble appraisal ought to be not set in stone in a joint effort with general wellbeing specialists (43).

CLINICAL FEATURES

Monkeypox is typically a self-restricted infection with side effects enduring from 2 to about a month. Extreme cases happen all the more normally among youngsters and are connected with the degree of infection openness, patient wellbeing status, and nature of inconveniences. The degree to which asymptomatic contamination happens is obscure. The case casualty proportion of monkeypox has generally gone from 0 to 11% in everyone and has been higher among small kids. As of late, the case casualty proportion has been around 3-6 %(44).

Common symptoms and signs

Prodrome (0-5 days)

- Fever
- Lymphadenopathy
- Typically occurs with fever onset
- Periauricular, axillary, cervical or inguinal
- Unilateral or bilateral
- Headache, muscle aches, exhaustion
- Chills and/or sweats
- Sore throat and cough(45)

Skin involvement (rash)

- Usually begins within 1-3 days of fever onset, lasting for around 2-4 weeks
- Deep-seated, well-circumscribed, and often develop umbilication
- Lesions are often described as painful until the healing phase when they become

Itchy (in the crust stage)(46)

Stages of rash (slow evolution)

- Enanthem- first lesions on tongue and mouth

➢ Macules start from the face spreading to arms, legs, palms, and soles (centrifugal distribution), within 24 hours.

➢ The rash goes through the macular, papular, vesicular, and pustular phases. Classic lesion is vesicopustular.

➢ Involvement by area: face (98%), palms and soles (95%), oral mucous membranes (70%), genitalia (28%), conjunctiva (20%). Generally skin rashes are more apparent on the limbs and face than on the trunk. Notably the genitalia can be involved and can be a diagnostic dilemma in the STD population.

➢ By 3rd-day lesions progress to papules.

➢ By the 4th to 5thday, lesions become vesicles (raised and fluid-filled).

➢ By the 6th to 7thday lesions become pustular, sharply raised, filled with opaque fluid, firm and deep-seated.

➢ May umbilicate or become confluent

➢ By the end of 2nd week, they dry up and crust

➢ Scabs remain for a week before falling off

➢ The lesion heals with hyperpigmented atrophic scars, hypopigmented atrophic scars, patchy alopecia, hypertrophic skin scarring, and contracture/deformity of facial muscles following healing of ulcerated facial lesions.

➢ A notable predilection for palm and soles is characteristic of monkeypox.

➢ The skin manifestation depends on vaccination status, age, nutritional status, associated HIV status. Monkeypox chiefly occurs in communities where there is often a high background prevalence of malnutrition, parasitic infections, and other significant heath-compromising conditions, any of which could impact the prognosis of a patient with MPX.

➢ The total lesion burden at the apex of rash can be quite high (>500 lesions) or relatively slight (<25).(47).

MANAGEMENT OF MONKEYPOX

Component ofmanagement	Symptoms/Signs	Management
Protection of compromised skin and mucous membranes	Skin rash	• Clean with simple antiseptic • Mupironic Acid/Fucidin • Cover with light dressing if extensive lesion present • Do not touch/ scratch the lesions • In case of secondary infection, relevant systematic antibiotics may be considered
	Genital ulcers	• Sitz bath
	Oral ulcers	• Warm saline gargles/ oral topical anti-inflammatory gel
	Conjunctivitis	• Usually, self-limiting • Consult Ophthalmologist if symptoms persist or if there are pain/ visual disturbances
Rehydration therapyand nutritional support	Dehydration can occur in association with poor appetite,nausea, vomiting, and diarrhea	• Encourage ORS or oral fluids • Intravenous fluids if indicated • Encourage a nutritious and adequate diet
Symptom alleviation	Fever	• Tepid sponging • Paracetamol as required
	Itching/Pruritus	• Topical Calamine lotion • Antihistaminics
	Headache	• Paracetamol and adequate hydration
	Nausea and vomiting	• Consider anti-emetics(48)

TREATMENTS

Strong Care

Most patients with monkeypox contamination recuperate without clinical treatment. Those with gastrointestinal side effects (e.g., regurgitating, the runs) will require oral/intravenous rehydration to limit gastrointestinal fluid misfortunes (49).

Antivirals

A few antivirals might be effective in treating monkeypox disease, albeit these medications were supported for the management of smallpox in light of creature models. Portion studies for these medications have been directed at people, however, the efficacy of these specialists has not been completely defined (50).

Tecovirimat

Tecovirimat (otherwise called TPOXX or ST-246) is the first antiviral shown for the treatment of smallpox in grown-ups Furthermore, pediatric patients gauging something like 3 kg and are considered the treatment of decision. In patients with serious illness, double treatment with tecovirimat and brincidofovir maybe utilized(51). Tecovirimat works by repressing the viral envelope protein VP37, which hinders the final steps in viral maturation and delivery from the contaminated cell, consequently restraining the spread of the infection inside a contaminated host. While the efficacy of this specialist in people against monkeypox has not been tried, studies have revealed superior endurance from deadly monkeypox infection diseases in tecovirimat-treated creatures contrasted with fake treatment treated creatures at different phases of sickness. In an extended security investigation of359 human workers put on tecovirimat, the fake treatment side-effect profile was generally like that of tecovirimat(52). In little examinations, tecovirimat was utilized in combination with vaccinia safe globulin (VIG) in patients with difficulties from smallpox immunization, for example, skin inflammation vaccinatum and moderate vaccininia. The CDC held Emergency Access Investigational New Protocol permits the utilization of tecovirimat for non-variola orthopoxvirus contamination, for example, monkeypox. The convention likewise incorporates remittance for opening an oral container and blending its substance in with liquid or delicate nourishment for pediatric patients weighing under 13kg. Tecovirimat is accessible through the Strategic National Store as an oral case plan or an intravenous vial(53).

Brincidofovir and Cidofovir

Brincidofovir has been endorsed for the treatment of smallpox in the US since June 2021 Brincidofovir (oral) is simple of the intravenous medication cidofovir, and may have a further developed wellbeing profile, in particular less renal poisonousness, analyzed to cidofovir(54). These medications work by hindering the viral *DNA polymerase*. While studies assessing the utilization of brincidofovir for treating monkeypox contaminations in creature models are scant, brincidofovir has been demonstrated to be effective against orthopoxvirus contaminations(55). Clinical information to efficacy of cidofovir against monkeypox in people is missing, yet *in vitro* action and efficacy against deadly monkeypox infection diseases in creatures has been detailed. Intravenous typical saline and probenicid treatment should be given simultaneously with cidofovir. Forbrincidofovir, liver capability tests previously and during treatment should be finished, as brincidofovir may cause expansions in serum transaminases and serum bilirubin. These treatments are accessible under a EUA or IND(56).

Vaccinia Immune Globulin (VIG)

VIG is a hyperimmune globulin authorized by the FDA for treatment of specific confusions of vaccinia immunization. These incorporate dermatitis vaccinatum, moderate vaccinia, extreme summed up vaccinia, vaccinia diseases in people who have skin conditions, and deviant infections prompted by vaccinia infection (besides in instances of detached keratitis, e.g., visual contaminations(57). While a likely treatment, information on the effectiveness of VIG against monkeypox what's more, smallpox is to a great extent lacking, and utilization of VIG for monkeypox or smallpox has not been tried in people. Since immunization with vaccinia infection antibody is contraindicated in patients with serious immunodeficiency in T-cell function, such patients with openness history may on the other hand be given VIG. Treatment with VIG ought to be led under an IND application(58,59).

TREATMENT OPTIONS FOR MONKEYPOX INFECTION

Drug	Mechanism of Action	Dosing	Formulation	Adverse Events
Cidofovir	Blocks viral DNA synthesis through competitive inhibition of DNA polymerase	5 mg/kg per dose once weekly for ≥2 doses (with concomitant probenecid)	IV; off-label: topical, intravesicular	IV; off-label: topical, intravesicular.
Tecovirimat	Inhibits the activity of the protein VP37, which prevents the creation of virions that can be released from an infected host cell, thereby preventing replication and dissemination within the host.	200 mg q12 hours, 300 mg q12 hours Oral: 600 mg q12 hours. All regimens for 14 days	IV and oral (off-label topical)	pain and swelling at the infusion site; extravasation at the infusion site; headache (60) Oral: headache, abdominal pain, nausea, vomiting.
Brincidofovir	Lipid conjugate prodrug of cidofovir	4 mg/kg once weekly for 2 doses (max 200 mg/ dose)	Oral	Abdominal pain, nausea, vomiting, diarrhea, elevated liver transaminases, and bilirubin(61).
VIGIV	Passive immunity through OPXV-specific antibodies collected from pooled human plasma of persons immunized with the smallpox vaccine	6000 units/kg as a single dose (up to 9000 units/ kg) Dose can be repeated depending upon symptoms.	IV	Infusion reaction; local injection-site reaction (contraindicated in persons with IgA deficiency and possible IgA hypersensitivity)(62,63).

CONCLUSION

Before long, we will acquire clearness on the magnitude of the ongoing episode as case tracking down escalates. Numerous people tainted with monkeypox infection have a gentle, self-restricting sickness course even in then on appearance of specific treatment, however, the anticipation for monkeypox may rely upon different factors, for example, past inoculation status, introductory wellbeing status, and simultaneous ailments or comorbidities. Subsequently, creating individualized medicines because of the singular gamble of treating serious diseases gives off an impression of being the most sensible procedure. Acting rapidly and proactively will be significant for containing it. Guaranteeing that we gain from ongoing pestilences and offer available assets early and immediately will be the way to progress. The cautioning signals on monkeypox turning into a worldwide general well-being concern have been available for a long time. Right now is an ideal opportunity to take on a genuinely worldwide methodology that resolves this issue definitively in rich nations as well as, fundamentally, in the endemic nations that have been answering monkeypox for a long time.

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