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A brief review on Pathogenesis, Transmission and Management of Monkeypox virus outbreaks

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ABSTRACT

As the threat of the coronavirus disease 2019 (COVID-19) pandemic recedes, nations throughout the globe are presently dealing with an epidemic centered on the prevalence of instances of monkeypox in various locations. Monkeypox was traditionally endemic to regions of Africa, but the bulk of cases associated with the 2022 epidemic are recorded in countries around Europe and the western hemisphere. Although several organizations are engaged in contact-tracing operations, it is still unknown what caused this epidemic. Monkeypox virus is one of the several zoonotic viruses of the Orthopoxvirus genus of the Poxviridae family. The recurrence of monkeypox drew attention on a global scale after smallpox was eradicated in the 1970s. The smallpox vaccination may provide a defense against the monkeypox virus. As soon as the smallpox vaccination was discontinued, monkeypox cases rose. Not until the US epidemic in 2003 did monkeypox finally come to the public's attention. The virus did not develop in monkeys, despite the name "monkeypox." Although various rodents and small animals have been connected to the virus, the precise origin of monkeypox is still a mystery. The term "monkeypox" originated when the viral illness was first discovered in macaque monkeys. Even though it is exceedingly rare, the spread of monkeypox from one person to another is typically related to respiratory droplets or close contact with mucocutaneous lesions of an infected individual. Although supportive therapies may be used to manage symptoms, there isn't yet a specific therapy for infected people; in the most serious circumstances, drugs such as tecovirimat may be utilized. Many treatments are arbitrary since there are no specific suggestions for symptom relief.

Keywords: *Monkeypox, poxviridae, chordopoxvirinae, poxvirus, orthopoxvirus*

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INTRODUCTION

There is a reason for concern since monkeypox outbreaks are happening all across the western hemisphere. The first human case was discovered in 1970 in a nine-month-old child from the Democratic Republic of the Congo. In 2003-2004, an epidemic of human monkeypox, a rare viral zoonosis that is endemic to central and western Africa, was reported in the United States (US)[1].Monkeypox is one of several zoonotic viruses that belong to the Orthopoxvirus genus of the Poxviridae family, as shown in Figure 1.[2]. The giant, containing Poxviridae viruses, which have been isolated from various animals, are double-stranded DNA viruses[3].The primary reservoirs of poxviruses, which may spread to people and result in human-to-human transmission, include rodents, rabbits, and non-human primates[4].Taxonomically, the Poxviridae family is further separated into two families:
Entopoxvirinae and Chorodopoxvirinae are related. Whether a virus will infect insects, as with Entemopovirinae, or vertebrates, like with Chorodopoxvirinae, determines its subfamily categorization[5].The Chorodopoxvirinae family is further split into 18 genera, as seen in Figure 1. Each of the 18 genera of the Chorodopoxvirinae subfamily has many viruses mentioned, most of which are zoonotic [6].

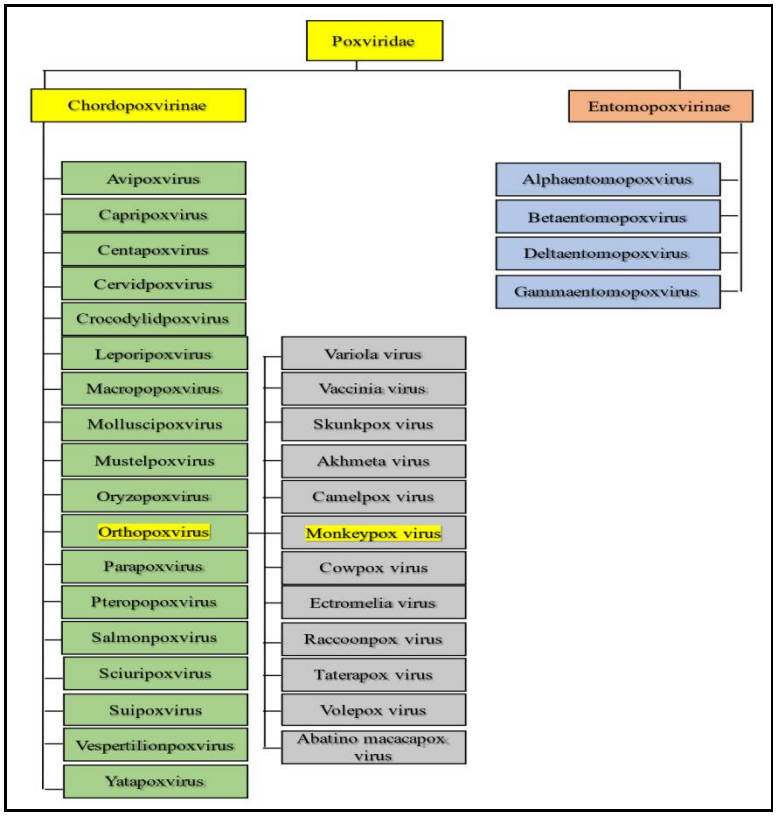

Figure 1The taxonomy and classification of monkeypox within the Poxviridae lineage.

Clinical signs of the monkeypox virus are similar to those of smallpox[7].Monkeypox cases are deadly in around 10% of instances compared to smallpox[8].Before 1970, monkeypox was exclusively recognized as affecting non-human hosts[8].According to reports, the lateral bodies of the monkeypox surround an enclosed, somewhat pleomorphic center[9].The monkeypox virus has two distinct genetic clades: the central African (Congo Basin) clade and the West African clade[10].The Congo Basin clade is thought to be the more virulent of the two genetic clades since it has historically been linked to more severe illness[11]. The 2003 US epidemic of human monkeypox was caused by the Congo Basin clade, which was associated with more excellentmorbidity rates, mortality, transmission from person to person, and viremia[12].Genome analyses of the west and central African strains revealed many candidate genes that may be related to the varied clade pathogenicity[13]. The open reading frames of the west African clade had deletions and fragments that reduced its pathogenicity[14].Because central African monkeypox prevents T-cell receptor-mediated T-cell activation, human cells derived from prior monkeypox patients cannot create inflammatory cytokines[15]. Hammarlund et al. discovered that T-cell-mediated cytokine responses were lowered by 80% in a low monkeypox virus load, suggesting that monkeypox may produce a modulator that reduces host T-cell responses[16].The monkeypox virus inhibitor of complement enzymes (a gene that suppresses complement enzymes), which is absent in west African strains, has been proposed to be a substantial immune-modulating factor explaining the increased virulence of central African strains. Apoptosis is preferentially suppressed by the central African strain, which also affects other host defense processes. According to studies on gene transcription, central African monkeypox seems to block the transcription of host immunity-related genes during infection preferentially[17].Large, linear, double-stranded DNA viruses called polioviruses may replicate in the cytoplasm of either vertebrate or invertebrate cells. Their genomes are between 130 and 360 kbp in size[18].Cellular proteins are often substantially used with DNA viral replication and expression in the nucleus; however, this is not the case for poxviruses. Poxviruses differ from other viruses because their capacity for cytoplasmic reproduction depends on proteins that the virus encodes[19].The genome's core region contains key genes involved in transcription and viral assembly processes, whereas those close to the termini are in charge of interactions between viruses and their hosts[20].All sequenced members of this family share 49 genes and 90 genes are shared by the chordopoxvirus subfamily out of the more than 150 genes that poxviruses encode[21]. Most of these genes, which comprise the bulk of a virus' core genome, are involved in viral function[22].

Poxviruses are more significant than other viruses, making it more challenging for viruses like monkeypox to traverse gap junctions and overcome host defenses[23]. Since the virus is more extensive, it is more difficult to reproduce effectively, and orthopoxviruses need a more comprehensive strategy to live within the host. The orthopoxviruses' greater size causes the body's immune system to become highly aware very quickly and makes it easier to produce an immune response[24].To escape the host immune system, orthopoxviruses are equipped with various compounds released by virulence genes that will act as modulators by being targeted against the host's immune system's components. These proteins that regulate the host's immune response may be split into two categories depending on whether they function intracellularly or extracellularly[25].

As seen in Figure 2, two kinds of proteins are in charge of modulating impacts on the host's immune response. Examples of intracellular proteins include virotransducer and virostealth proteins. The virotransducer proteins influence the cell's capacity to resist infection, including the oxidative burst and apoptotic pathways[26].The virostealth proteins, which also work intracellularly, downregulate the immune recognition molecules CD^{+4} and the major histocompatibility complex class 1 (MHC 1) to reduce the probability that the host's immune system will be able to recognize the virus[27].Viromimic proteins are the only kind of surface protein seen in monkeypox, although there are two separate subtypes of internal modulatory proteins that aid in thwarting the host's immune response. Viromimic proteins may be divided into two groups, as shown in Figure 2, and both of these groups can influence how the immune system responds. The viroreceptors, made or exist as cell surface glycoproteins, competitively bind the host cytokines and chemokines. Their functions are thus hindered as a consequence[28].Consequently, virokines produce viral mimics of host cytokines, chemokines, and growth factors that effectively prevent host responses detrimental to viral survival and promote responses favorable to viral replication and spread. These modulatory proteins concurrently work to undermine the host's immune response while facilitating viral multiplication. If these proteins were absent, orthopoxviruses like monkeypox and others could not evade the immune system[29].

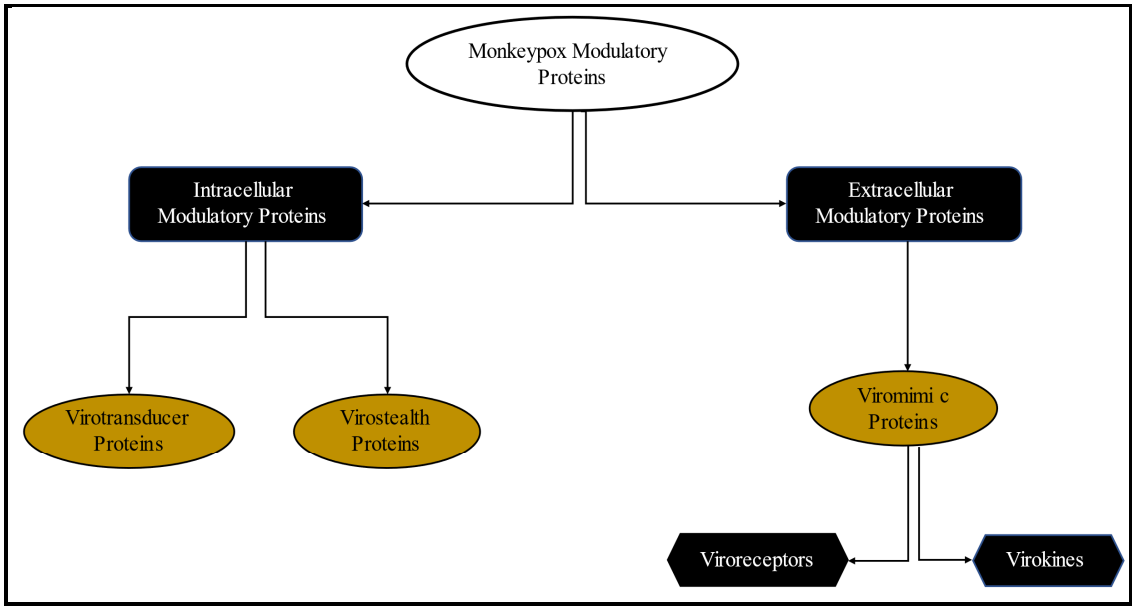

Figure 2Modulatory Proteins of Extracellular and Intracellular Origin Monkeypox

The replication cycle of poxyviruses offers information on how the monkeypox virus replicates[30].Like other viruses, poxviruses feature proteins that enable and ease the virus's fusion with a cell's membrane, attachment to a cell, and entrance into the host cell. In the case of the poxvirus, the mature virion (MV), which has a single membrane, and the extracellular enveloped virion (EV), which has a second outer membrane, are split apart beforethe union. The MV is connected to four viral proteins. And by binding to laminin or glycosaminoglycans in the host cell, all of these things working together will make it simpler for MV to adhere to that cell. The fusing of the virus to the host cell requires 11 to 12 non-glycosylated, transmembrane proteins that vary in size, regardless of whether the MV or EV mediate infection. Ranging from 4 to 43 kDa[31]. While MVs have a relatively solid outer membrane and are thought to facilitate transmission among host animals, EVs have a fragile outer membrane and are mainly specialized for exiting the intact cell and spreading inside the host[32].Poxvirus DNA replication occurs in cytoplasmic

structures formerly known as Guarnieri bodies and now more often known as factories[33].Each factory, which forms from a single infecting particle in the early stages of infection, is made up of compact DNA-containing structures that are surrounded by membranes that resemble the rough endoplasmic reticulum of the cell (RER)[34]. As DNA synthesis proceeds, these factories will expand, and as cavities containing viral mRNA and host translation factors appear, they will gradually seem uneven[35]. The endoplasmic reticulum membranes in the region are disrupted, and crescent-shaped substrates are produced as the replication cycle moves forward due to the combined action of a complex of late gene products and a set of viral membrane construction proteins. for putting together, the young virions (IV). The IV gives rise to the MV, the most common infectious species. These MV will depart the cell by fusing with the cytoplasmic membrane[36].

EPIDEMIOLOGY

Since humans were the first to get infected by the virus via intimate contact with infected animals, monkeypox has most likely been present in Sub-Saharan Africa for thousands of years. Smallpox was declared extinct in 1970, but it soon became apparent that rural regions still saw outbreaks of diseases comparable to smallpox. As a result, monkeypox was recognized as a distinct illness. In 1958, while studying at State Serum Institutes in Africa and Copenhagen, Denmark, the monkeypox virus was first found in lab monkeys. Monkeypox became a significant public health problem for the whole globe in 2003, after the first outbreak in the USA that was linked to infected pet prairie dogs. It was thought that local prairie dogs maintained with rats imported from Ghana in Western Africa were the primary source of the epidemic since most affected individuals became sick after interacting with pet prairie dogs[37].A cluster of cases in the US Midwest in the summer of 2003 had been linked to monkeypox. Since 2003, several cases of monkeypox have been documented in various countries, with Nigeria seeing the largest epidemic in 2017[38].In countries with little exposure to Orthopoxvirus species, the monkeypox R0 value varies from 1.10 to 2.40, according to epidemiological modeling research. Reproduction ratio, commonly referred to as R0, is another term for the illness's degree of transmissibility[39].This score suggests that a monkeypox pandemic will soon start in situations of imported human or animal infections. As was already indicated, the given R0 means that each infected person has the potential to infect one to two more people. The illness is infectious, a patient who is ill must go over and above to withdraw and remove himself from others[40].As of July 1, 2022, the Centers for Disease Control and Prevention (CDC) has documented 5783 confirmed cases of monkeypox scattered over 52 different countries[41].Figure 3 presents a visual representation of the geographical distribution of the cases globally. Most monkeypox cases now occur in the western hemisphere and in portions of Europe. Recent statistics indicate that the UK has the highest instances in all of Europe[42]. With a median age of 31 years, the majority of confirmed cases of monkeypox nowadays are identified in adults under the age of 40. Further evidence of the lack of cross-protective immunity comes from the fact that this population was only produced after the smallpox vaccination campaign was discontinued. Additionally, men are more likely to get monkeypox, however it is unclear what causes this [43].

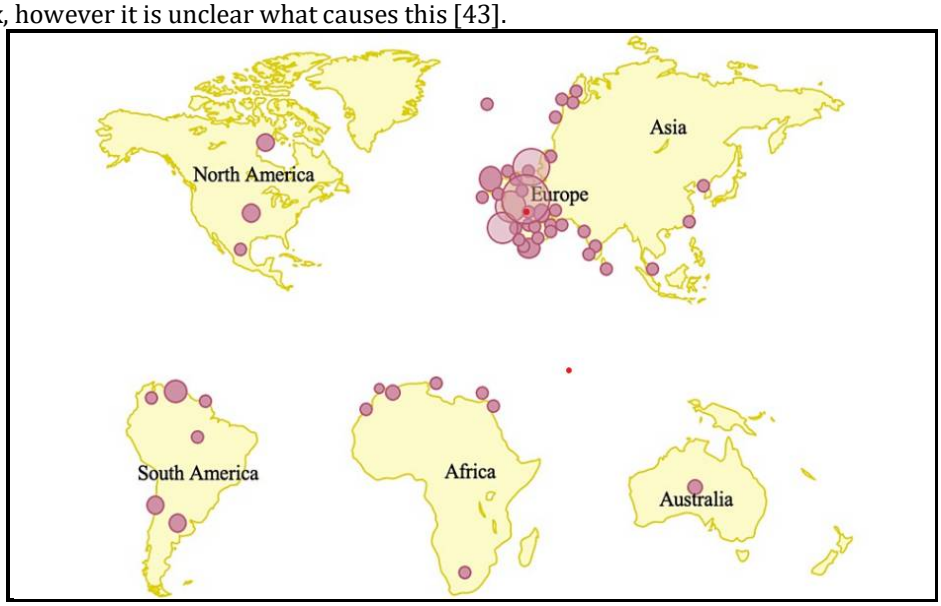

Figure 3Regional Distribution of Confirmed Cases of Monkeypox at present

Pathogenesis and Mode of transmission

Since several orthopoxviruses have similar genetic and antigenic properties, getting one may provide considerable protection against getting the other orthopoxvirus genus members[44]. Cross-immunity will result in an immune response to any illness by orthopoxvirus. Decrease the risk of acquiring another Orthopoxvirus [45]. It was shown in the past that smallpox immunization wasa defense against monkeypox. Since smallpox was eliminated in the 1970s, the vaccination has also been discontinued[46]. The efficacy of the smallpox vaccination to provide cross-immunity against other orthopoxviruses has started to wane. People under 50 are more likely and susceptible to getting other orthopoxviruses like monkeypox since they are less likely to have diabetes and have gotten a smallpox vaccine. During the worldwide smallpox eradication effort, it's possible that extensive smallpox immunisation in central Africa briefly reduced the frequency of human monkeypox[47]. Due to a lack of immunity in the generation born beginning the next year and forward and an increase in the dependency on hunting for food in places devasted by the civil war, the illness has resurfaced[15].

Although monkeypox was first found in a colony of Danish macaques, the specific animal reservoirs and the virus's initial animal-to-human transmission are still unclear[48].Before infecting humans, it has been shown that the virus may transmit from one animal to another in intermediate hosts[49]. The transmission of monkeypox from intermediate hosts to humans came before the 2003 US Midwest episode, in which it was thought that pet prairie dogs caught the virus from ill rodents brought to the US from Ghana[50].Studies show that monkeys are accidental hosts like humans and that the reservoir is likely to be one or more species of rodents or squirrels in the secondary forest of central Africa, even if the same reservoir for the monkeypox host is yet unclear[51].

The monkeypox virus is expected to spread in several ways, as indicated in Figure 4, many of which are connected to intimate contact with ill people or animals. Although interaction with animals has been related to human diseases, it may not be easy to pinpoint the precise exposure in a human case. Locations where a variety of kinds of bushmeat are often hunted or prepared, as well as places where mouse infestations in houses lead to human-animal interactions[52].

It is still unclear exactly how monkeypox spreads. The probable transmission methods shown in Figure 4 are includes risk factors for monkeypox infection, albeit they are currently under research. Animal-to-human transmission may occur via direct touch or exposure to infected animals and is often triggered by body fluids like saliva-excretions from the respiratory system or exudate from cutaneous or mucosal sores. Viral shedding from faeces may also expose people[53].Exposure to infectious animal faeces is a significant problem. Add to this the fact that because of inadequate resources and infrastructure in endemic areas of Africa, people often sleep outdoors, on the ground, or near woods where ill animals are more prevalent. In areas with low resources, households have no choice except to hunt and prepare a small quantity of food. They are increasing the risk of mammals coming into touch with monkeypox. Even while human-to-human transmission seldom occurs compared to animal-to-human transmission, it often involves prolonged face-to-face contact, breathing droplets, or touching an infected person's lesions. Living together, sharing a bed, or using the same dishes as an infected individual are all regarded as risk factors for viral transmission among family members. Other risk factors include using contaminated objects or surfaces. It has also been shown that men who have intercourse with other men are more likely to develop the sickness in the middle of the ongoing monkeypox epidemic. Although the World Health Organization (WHO) is unsure whether monkeypox is sexually transmitted, it may be spread via close contact. The etiology and pathophysiology of monkeypox begin with this transmission, whether the virus is transferred from human to human or from animal to human[45].

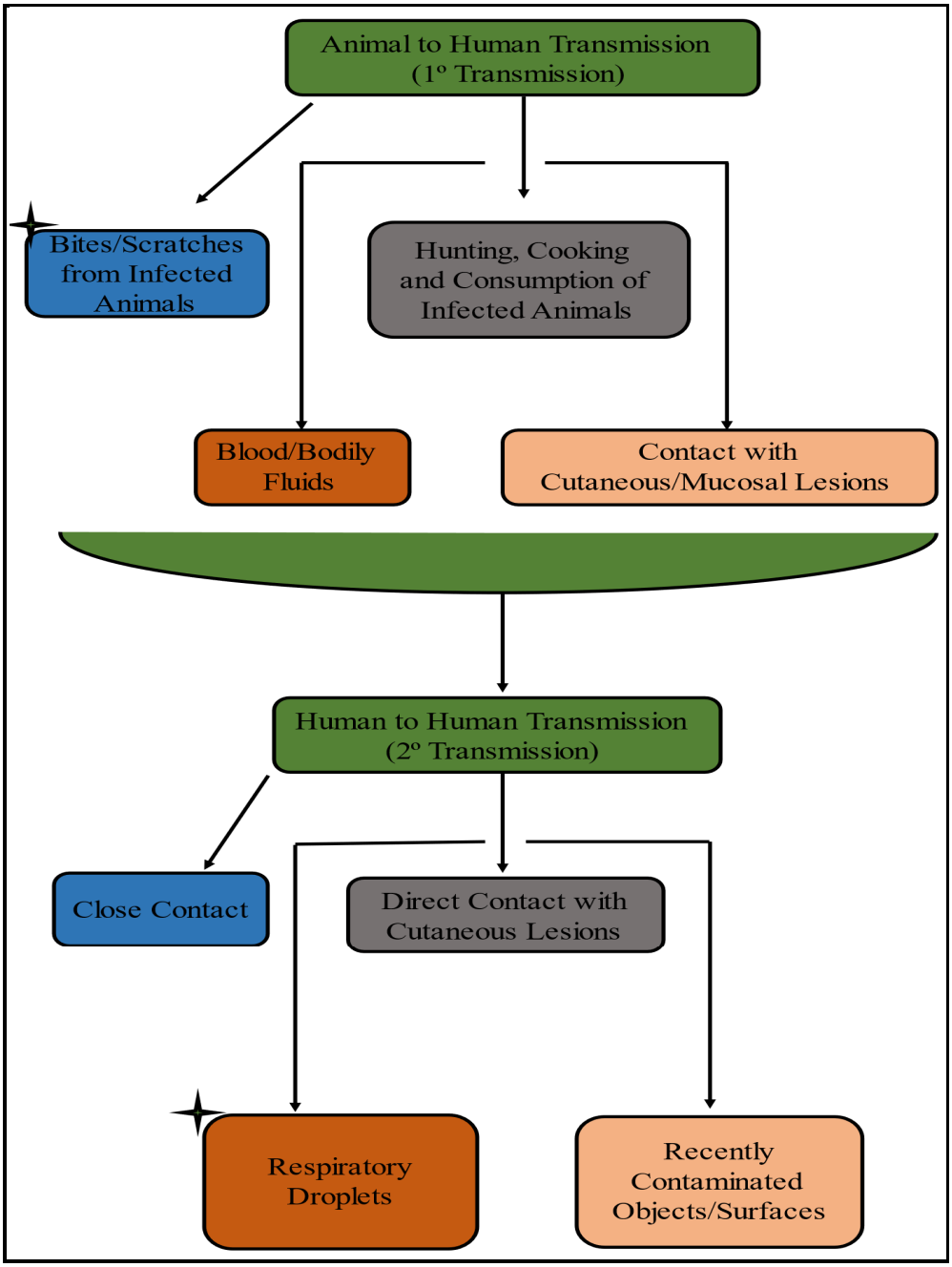

Figure 4Suspected Methods of Monkeypox Transmission to Humans

Despite the stigma they carry, respiratory droplets are the most common means of human-to-human transmission[54]. The list in Figure 5 includes direct contact with contaminated objects or surfaces and contact with mucocutaneous lesions on an infected individual. Similar to smallpox, the infectious cycle of the monkeypox virus begins with exposure of the host's oropharyngeal or respiratory mucosa. The monkeypox virus replicates at the site of injection, which in the case of human-to-human transmission, is the respiratory and oropharyngeal mucosa. In viremia, the neighborhood lymph nodes are affected by the viral load in primary, which occurs after viral replication[55]. In secondary viremia, the viral load spreads to distant lymph nodes and organs via the circulatory system. The process replicates the incubation period, which typically lasts seven to fourteen days but may last up to 21 days[56].The incubation stage is not contagious since the clinical symptoms of monkeypox are not evident during it. The prodromal phase is related to the clinical presentation and symptoms of monkeypox[57]. Before the prodromal stage, when secondary viremia first emerges and spreads from the lymphoid organs to the skin and tertiary organs, including the lungs, eyes, gastrointestinal system, etc[58]. When prodromal, a person is thought to be the

most contagious[59]. This is primarily due to mucocutaneous lesions and other symptoms, such as their appearance. Lymphadenopathy is one of many ambiguous symptoms[60].

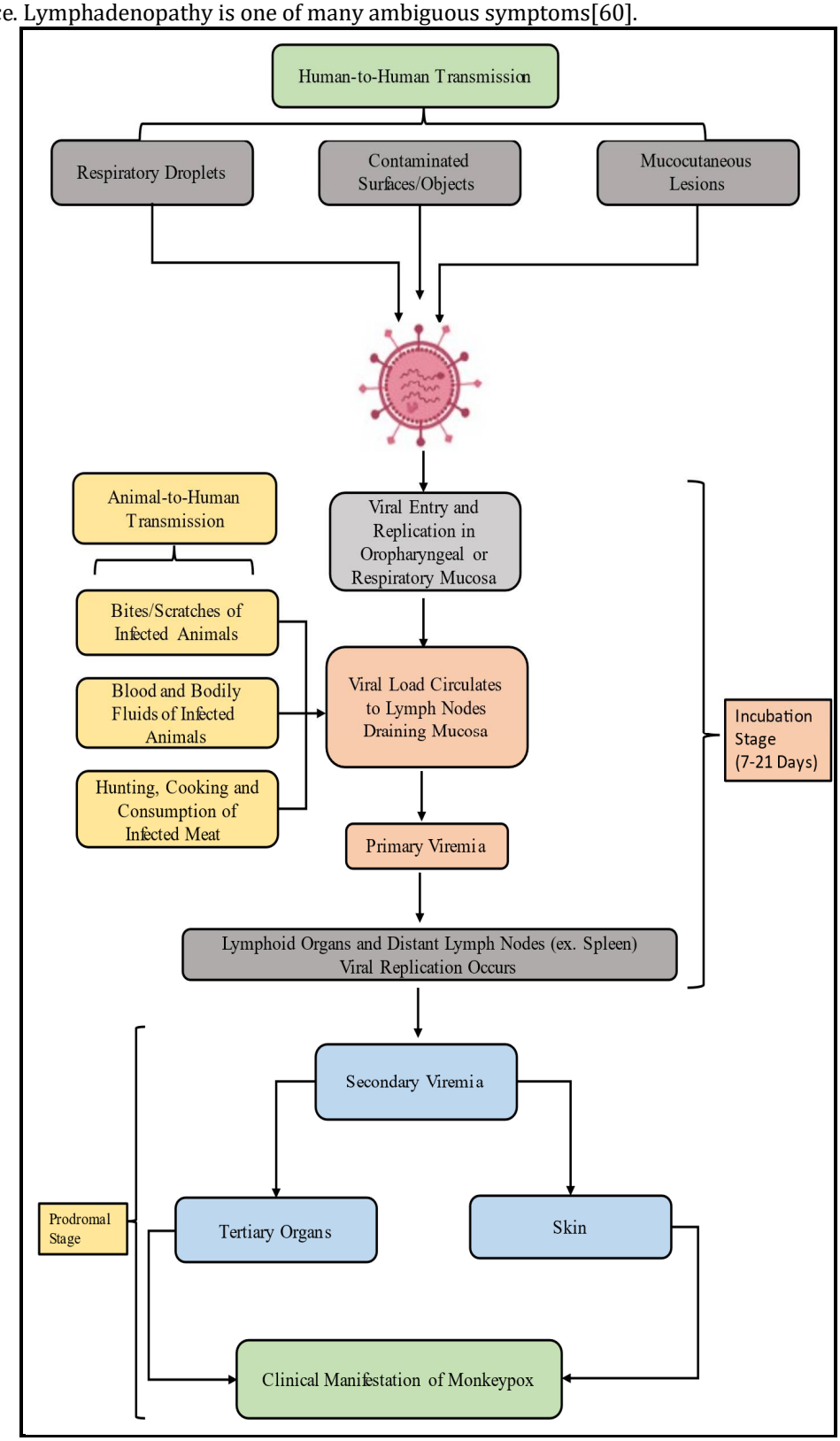

Figure 5Hypothesized Monkeypox Pathogenesis

Figure 6 depicts the generalized symptoms of monkeypox that occur one to two weeks following exposure to the monkeypox virus[61].The prodromal stage is characterized by the onset of fever, lymphadenopathy, myalgias, and other immune system-stimulating symptoms. Due to the lack of specificity, an infected individual may incorrectly think that these first symptoms are those of the common cold or seasonal flu. When the immune system is initially aroused, the maxillary, cervical, and

inguinal lymph nodes will invariably enlarge along with the onset of a fever. Before the 2022 pandemic, rashes would often begin to appear one to three days after the beginning of fever and lymphadenopathy[62]. Prodromal symptoms for certain patients at the beginning of these unusual instances may be limited or not even noticed, according to Harris, suggesting that some individuals may not be aware of any symptoms at all until the rash occurs. The day after the rash emerges or even up to three days later, the fever usually starts to subside[63]. The rash will first appear on the face and then quickly spread over the body in a centrifugal pattern. In a centrifugal distribution, there will be more lesions on the front and extremities than on the belly and trunk. Figure 6 depicts lesions that are often seen in the oral cavity. Cause eating and drinking issues, making it more difficult for an infected individual to get the nourishment they need. Significant skin disruption caused by the skin lesions raises concerns regarding bacterial skin infection, which has been linked to the condition in 19% of patients who are not immunized[64].The rash that is visible in infected individuals has a very distinct appearance.

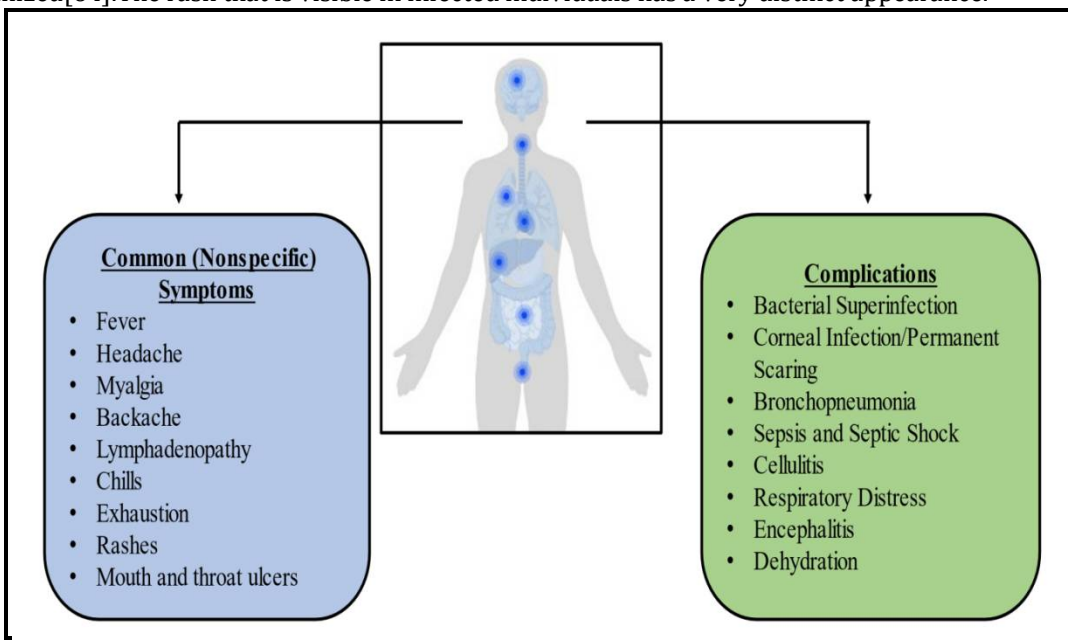

Figure 6 Classification of Nonspecific Symptoms and Monkeypox Complications

A widespread vesiculopustular rash is what distinguishes monkeypox from other skin conditions[65].The rash has been reported to progress through various phases before the desquamation phase, when the scabs start peeling off[27]. Enanthem, macular, papular, then vesicular and pustular lesions are typical manifestations of these diseases. These lesions will eventually form a crust in two to three weeks[66].Before the rash appears on the skin, a person will notice enanthem sores growing on their tongue and mouth. Once the crusted lesions peel off to show fresh skin below, the person is no longer considered contagious. This is referred to as the desquamation phase. People may leave behind scars as scabs break off. Some persons may even have hyper- and hypopigmented areas where the rash is more severe. Except for the desquamation stage, when the crusting is exceedingly irritating, all phases of the lesions are unpleasant. During the histopathologic evaluation of the early stage of lesion formation in humans, epidermal necrosis is found in the center of individual lesions and is linked to nascent expansion into the superficial layers of the dermis[67].When pustules swell, non-human primates with monkeypox infection also exhibit enhanced lesion pathology, such as interstitial hyperplasia, necrosis, and progressive ulceration. Additionally, edema is visible at the borders of necrotic regions, and clefts develop in the intercellular spaces where fluid and cellular debris accumulate. Eventually, the loss of sebaceous glands and follicles is apparent, and the superficial dermis mostly becomes irritated and necrotic. When these traits are combined, the injured regions are referred to as "partial-thickness wounds," and an injury of this size necessitates proactive avoidance of the adverse effects, such as subsequent bacterial infections and possible cellulitis. Interventional studies revealed that moist occlusive treatments significantly promoted re-epithelialization and healing at herpes lesions sites, therefore patients with rash lesions that cover a significant area of their faces may want to consider using moist occlusive dressings[68].

Clinical management and treatment

The vaccinia vaccine, cidofovir, tecovirimat, and vaccinia immune globulin (IVG) may help treat monkeypox, even though there are no proven cures for monkeypox[54].According to the World Health

Organization, the European Medicines Agency (EMA) approved tecovirimat for treatment against monkeypox in 2022. It was first developed to treat smallpox[69].The use of tecovirimat must be monitored appropriately since it is not yet widely available[70]. Cidofovir provides antiviral activity against various viruses by inhibiting viral DNA polymerase[71]. Numerous orthopoxviruses have been particularly vulnerable to tecovirimat, such as variola, vaccinia, cowpox, ectromelia, rabbitpox, and monkeypox[72]. Monkeypox treatment may benefit from using Tecovirimat, an oral inhibitor of intracellular viral release[73].Despite the recommended treatment options, supportive and symptomatic therapy is the cornerstone of managing a monkeypox virus infection[74]. Information on potential supportive treatment approaches is included in
Table 1 to assist those experiencing symptoms. Realize that there is no known treatment for monkeypox other than to manage symptoms and prevent complications[6].Given the 2003 US monkeypox epidemic and the current global case presentation, more research is needed before any therapeutic or vaccine can be created[75].

Table 1Symptoms, complications, and possible complementary therapies[59]

Symptom/Complication	Supportive Treatment
Respiratory distress/Bronchopneumonia	Oral/intravenous antibiotics for prophylaxis, nebulizer treatments, non-invasive ventilation (ex. CPAP)
Sepsis	Oral/intravenous antibiotics, supplemental oxygen, corticosteroids, insulin
Gastrointestinal/mouth and throat ulcers	Oral/intravenous antiemetic and antidiarrheal medications, oral/intravenous rehydration
Fever	Antipyretic medications, external cooling
Superinfection skin	Oral/intravenous antibiotics, incision, and drainage, advanced wound management (ex. negative pressure wound therapy
Inflammation/Lymphadenopathy	Oral/intravenous anti-inflammatory/analgesic medications
Corneal infection	Ophthalmic antibiotics/antivirals and corticosteroids
Skin scarring/Cellulitis/Skin lesions	Application of moist occlusive dressings to promote re-epithelization

CONCLUSION

Previously exclusive to some areas of Africa, the monkeypox virus is now a hazard to humans everywhere after isolated cases in the western hemisphere were discovered. The most frequent means of human-to-human transmission are respiratory droplets or direct contact with the mucocutaneous lesions of an infected individual. For the sick individual, social separation and contact tracking are crucial. Monkeypox cases have been verified in adults in their mid-twenties. The loss in cross-immunity from the smallpox vaccination reported in older individuals explains this. This virus multiplies in the cytoplasm before transforming into a primary viremia and infecting adjacent lymph nodes.
Additionally connected to the side effects of monkeypox infection include encephalitis, bronchopneumonia, dehydration, respiratory distress, etc. The danger that causes corneal scarring and might lead to vision loss is the one that people are most concerned. It is important. To lower the threat of these problems as much as possible, they need to be able to provide the appropriate supportive care. Supportive care, such as moist occlusive bandages, may be employed in areas where the rash is severely concentrated. As monkeypox cases are still being confirmed internationally, organizations focus on understanding how these cases are sporadically emerging throughout Europe and the western hemisphere. It's essential to investigate potential treatments and appreciate the extent of each monkeypox symptom and the virus's and symptoms' long-term effects.

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CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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