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Research on Pathogenesis, Diagnosis and Control Strategies Against Monkeypox Amidst the Global Resurgence

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Abstract. The resurgence of monkeypox, instigated by the monkeypox virus (MPXV), has escalated its status to a zoonotic disorder of pervasive global significance. The virus belongs to the Orthopoxvirus genus and is characterized by double-stranded DNA; in clinical manifestation, it bears resemblance to smallpox albeit with discernibly unique epidemiological and immunogenic characteristics. Utilization by MPXV of myriad immune escape methodologies—encompassing suppression of innate immune recognition, regulation of apoptotic processes, and disruption within interferon pathways—is observed to facilitate replication, persistency, alongside systemic dissemination, notably within immunocompromised hosts. Diagnosis determination hinges predominantly on polymerase chain reaction (PCR) assays, an approach augmented by serological analysis and histopathological evaluation. Universally sanctioned antiviral therapy remains unspecified despite tecovirimat and brincidofovir displaying remedial promise; underlying therapeutic management centralizes upon supportive care. Vaccine-based interventions employing JYNNEOS and ACAM2000 perpetuate as fundamental pillars of prophylaxis conjointly with rigorous hygienic protocols, prompt case detection, and vigilant surveillance activities. From such instances, advancing inquiry into viral pathogenic mechanisms, molecular evolutionary trends, and host-pathogen immune interactions emerges paramount to informing development of specialized antivirals and innovative vaccines, thereby enriching global readiness for foreseeable Orthopoxvirus eventualities.

Keywords: Monkeypox, Orthopoxvirus, diagnosis, immune evasion, vaccination, antiviral therapy

1. Introduction

Amidst the resurgence witnessed, post-global epidemics of recent occurrence, monkeypox assumes prominence anew within the infectious diseases research ambit. Distinct attention converges upon its morphing epidemiological landscape, variegated clinical presentations, diagnostic complexities emergent thereof, and therapeutic modalities managing said condition [1,2]. The clinical

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symptomatology it exhibits starkly paralleled with smallpox—a defunct Orthopoxvirus exemplar—is discerned to possess exclusive transmissions patterns alongside disparate risk demographics manifest therein [3,4]. Diseased entities frequently display disparate illness trajectories, fluctuating between confined dermal manifestations and systemic perturbations; imperative thus becomes expedient diagnosis in determining caregiving guidance coupled with contagion suppression measures [5,6]. Though Orthopoxvirus biological comprehension advanced appreciably, quintessential inquiries concerning monkeypox pathogenicity—specifically immune circumvention vis-à-vis disease severity modulation—remain inadequately elucidated, accentuating the necessity for exhaustive mechanistic explorations [7,8]. Integrating nascent treatments into conventional practice emerges as pivotal to ameliorate patient prognoses whilst impeding pathogen proliferation. Extrapolated study conclusions fortify public health safeguarding vis-à-vis ensuing prospective epidemics [9,10].

2. Epidemiology

Monkeypox is a highly infectious viral disease that was first identified in 1958 in Central and West Africa during an investigation involving monkeys [11]. Human transmission was initially linked to contact with infected rodents such as squirrels and rats but has increased over time due to the hunting and consumption of rodents and primates [3,12]. The first human case of monkeypox was identified in the Democratic Republic of the Congo in 1970 [13]. Since then, the number of human infections has gradually increased. Over the following two decades, more than 400 human cases of monkeypox were reported across Africa [1,14]. Initially, monkeypox was confined to Africa; the first documented case outside the continent occurred in the United States in 2003 [15]. The global outbreak in 2022 was preceded by several years of sporadic cases reported in regions outside Africa [16,17]. By 2022, a substantial number of monkeypox cases had been reported globally; for example, 21,984 in the United States, 6,749 in Spain, 6,033 in Brazil, 3,789 in France, 3,533 in Germany, and 3,491 in the United Kingdom [5]. Human-to-human transmission occurs primarily through direct contact with the bodily fluids of infected individuals or through broken skin [5,6,10].

3. Pathogenesis

Monkeypox is a viral infection caused by the monkeypox virus, a double-stranded DNA virus belonging to the Poxviridae family that infects both humans and animals [7,11,18]. Two genetic clades of the monkeypox virus have been identified: the West African clade and the Central African (Congo Basin) clade [18,19]. Poxviruses typically exhibit a brick-shaped or ovoid structure, measuring approximately 200–400 nm in size [20]. Poxviruses possess the largest and most complex DNA genome among animal viruses, comprising four main components: the core, lateral bodies, outer membrane, and lipoprotein envelope [20-22]. The core contains the viral double-stranded DNA (dsDNA) and associated protofibrils. The monkeypox virus genome is approximately 197 kb in length, comprising a conserved central region flanked by two variable terminal regions [23,24]. Most genes associated with virulence are located at the terminal regions of the genome [25]. The terminal genes contribute to immune evasion by interacting with host antigens, whereas genes involved in replication, transcription, assembly, and release are located in the central genomic region [26,27]. Poxviruses are known to produce two forms of virions—extracellular virions (EVs) and mature virions (MVs)—which display distinct surface epitopes [28]. The mechanism by which the virus enters the cell is different depending on the form of infection [27,28]. Following attachment to the host cell surface, the virus fuses with the cell membrane through its envelope proteins (L1, F9,

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A28, L5, and H2), which are essential for viral entry. Subsequently, viral components containing transcriptional initiators are released into the cytoplasm. Viral DNA replication occurs entirely in the cytoplasm, where most of the newly synthesised virions remain as intracellular mature particles, while a smaller proportion are released and facilitate cell-to-cell viral transmission [20,27,29].

Viral replication follows, after an incubation period of approximately seven to fourteen days [6]. The virus is disseminated from the skin to local lymph nodes in primary viraemia and then to distant lymphoid tissues and organs via secondary viraemia [3,11]. During the prodromal phase, the viral particles reach tertiary organs like the skin, lungs, eyes, and gastrointestinal tract [10,30]. During this phase, in which most patients develop non-specific symptoms, the immune response may be turned on: fever, lymphadenopathy, and myalgia are common manifestations [5,6,31]. Lymph nodes, especially those in the submandibular, cervical, and inguinal regions, may become enlarged, and individuals in this phase are thought to be most contagious [3,4,32].

MPXV, a member of the genus Orthopoxvirus, has been reported to exhibit various sophisticated strategies of immune evasion to successfully infect and persist within the host [33,34]. These include suppression of innate immunity, interference with adaptive immune responses, modulation of apoptosis, and disruption of the complement system [26,34]. The following section outlines these mechanisms of immune escape and their impact on host immunity.

3.1. Innate immunity escape mechanism

First, the inhibition of the DNA sensing system. By using various proteins, the monkeypox virus can inhibit the DNA sensing system of the host, preventing host cells from initiating recognition and responses against viral invasion [34]. The main strategies involved in this context are impairing the cGAS-STING pathway and inhibiting DNA-dependent protein kinase (DNA-PK) [35]. It uses its F14 protein to resemble the p65 subunit of NF-κB, which suppresses pathway activation and blocks antiviral gene expression [36]. Meanwhile, the C16 protein encoded by monkeypox virus binds with the Ku heterodimer, which blocks DNA-PK from recognizing viral DNA and escapes the induction of innate immune responses [37].

Indeed, it has also been shown to interfere with inflammatory signalling pathways by inhibiting the NF-κB pathway [34]. IFN signalling interference by the monkeypox virus includes the use of its B19 protein to block IFN binding to its receptor and, thereby, prevent an antiviral state [38,39]. This has indeed been demonstrated to weaken the host inflammatory response [34].

3.2. Apoptosis escape

The monkeypox virus evades apoptosis in host cells by employing various strategies, including the following: BCL-2-like proteins: Monkeypox virus encodes a variety of BCL-2-like proteins (e.g., A47, B13, C6, D11) that inhibit apoptotic signalling pathways and allow infected cells to survive for a longer period of time [34]. Influence on Natural Killer (NK) Cell Activation Monkeypox virus is able to affect NK cell function in the following ways: Inhibiting NKG2D receptors: Monkeypox virus secretes MHC class I-like protein (OMCP), which binds to NKG2D receptors on NK cells and prevents them from recognising infected cells, thereby evading immune clearance [40].

3.3. Affects the complement system

The monkeypox virus modulates the host complement system to evade immune clearance [41]. The Central African clade (Clade I) encodes MOPICE (Monkeypox virus inhibitor of complement

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enzymes), a viral complement control protein that functionally mimics host regulators such as CD46 and CD55 [42]. MOPICE acts by promoting the inactivation of C3b and C4b, thereby disrupting C3/C5 convertase formation and preventing complement-mediated opsonization and lysis [43]. In contrast, the West African clade (Clade II) lacks the MOPICE gene, which may contribute to its comparatively lower virulence [42]. Another homologous protein, VCP (Vaccinia virus complement control protein), encoded by the vaccinia virus, exhibits structural similarity to MOPICE and serves as a cofactor for the factor I–mediated proteolytic cleavage of C3b and C4b, thereby blocking complement activation [44]. Collectively, the expression of such soluble complement inhibitors represents a conserved immune evasion strategy among Orthopoxvirus, albeit with clade-specific variations in the genes employed [45].

3.4. Impact of immune escape

Discernibly shaping the pathogenesis interplay betwixt host and pathogen, MPXV's adeptness at manipulating immunity significantly governs ailment trajectory along with resultant clinical effects [46]. At the core of this engagement lies viral expression of immunomodulatory proteome arrays disassembling signalling pathways requisite for initiating early antiviral counteraction [47]. Paradigmatic viral genetic outputs embodied by B19 protein impede type I interferon receptor interaction,F14 subverts NF-B pathway through mimetic action upon p65 component, whilst the OMCP ligand engages NKG2D receptors atop NK cells, diminishing their infected cellular recognition capabilities [48]. These cumulative evasive mechanisms permit prolific viral replication, systemic dissemination, neutralizing indelible portions across innate-adaptive immunological continuums efficaciously [46].

Severe clinical manifestations of viral immune escape present prominently within the demographic of immunodeficient individuals. Amongst those diagnosed with advanced human immunodeficiency virus (HIV),engaged in treatment for malignancies, or recipients of organ transplantation necessitating ongoing immunosuppressive regimes, a heightened susceptibility to grave and atypically protracted presentations of mpox disease emerges [49]. Observed herein is a tendency toward secondary bacterial superinfection alongside extended recuperation intervals within this contingent, reflecting the critical implications inherent in MPXV's evasive stratagems vis-à-vis host immunity [50].

Within an immunological context, perturbations induced by MPXV on B-cell operability—particularly its activation alongside antibody maturation—evoke theoretical apprehensions regarding potential compromises inflicted upon vaccine-induced immunity [51]. Evidence rooted in empirical observation nonetheless illustrates that vaccines such as JYNNEOS coupled with ACAM2000 retain substantial protective efficacy against mpox pathogens [52]. Given these findings, it becomes apparent that ongoing vigilance via genomic scrutiny remains crucial. Such measures would ensure swift identification of any genomic alterations within the virus that could potentiate increased evasion from immune defences, augment virulence factors, or decrement current vaccine effectiveness in future contexts [53].

Although there is no evidence supporting persistent or latent infection with MPXV at this time, suppression of both innate and adaptive immune responses by the virus can temporarily induce an immunosuppressive state [54]. This transitory weakening in immune function might delay viral clearance, particularly in persons with a background of immune deficiencies, and thus further complicate the disease management and recovery process [55].

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4. Disease diagnosis and prevention

The pathological features of monkeypox are mainly characterised by lesions on the skin and mucous membranes. Histopathological examination has shown necrosis, inflammatory cell infiltration, and vasodilatation with congestion in the epidermis and dermis [30,56]. In infected tissues, a large number of viral inclusion bodies are usually observed. These inclusion bodies are round or oval, and their diameters range from 10 to 20 micrometres [57]. Pathological examination helps conduct a differential diagnosis of monkeypox, distinguishing it from other vesicular or pustular skin diseases.

Diagnosis can also be based on clinical history, including travel history and characteristic symptoms such as fever, myalgia, lymphadenopathy, and rash, combined with laboratory testing. According to the World Health Organization, RT-PCR is the preferred approach for confirming acute infection in cases of monkeypox [58]. Serological methods that detect IgM and IgG antibodies can be helpful when virological samples are not available. IgM antibodies appear very shortly after the rash first appears, peak in approximately two weeks, and decline within a year, while IgG antibodies peak at approximately six weeks and may remain detectable for several decades [59]. Electron microscopy may also prove useful as a supplemental diagnostic modality, though its application is limited by the complexity and time-consuming nature of specimen preparation [60].

A multifaceted stratagem constitutes the essence of monkeypox transmission prevention, wherein the intricacies of immunization, meticulous personal sanitation ordinances, and public health directives at communal echelons delineate the quintessential tactics of intervention [61]. Immunoprophylaxis emerges as a pivotal deterrent instrument by engendering an orchestrated immune system response conducive to mitigating susceptibility to MPXV exposure [62]. Concomitantly, adherence to exemplary hygienic edicts—such as assiduous hand sanitization and eschewal of tactile acquaintance with individuals bearing infection or possible affliction—assumes a paramount function, it is discerned in circumscribing inter-human viral propagation and attenuating prospects for pervasive societal outbreaks [1].

At the community level, preventive measures should focus on early case detection, prompt isolation of infected individuals, environmental sanitation, and disinfection to interrupt transmission chains and control outbreaks [63]. In summary, optimal prevention of monkeypox requires an integrated approach combining vaccination with non-pharmaceutical interventions to achieve the greatest public health impact.

5. Differential diagnosis

Monkeypox requires careful differential diagnosis because its clinical presentation may resemble several other viral exanthematous diseases [1,10].

Primarily, it should be distinguished from chickenpox (varicella). Monkeypox typically has a longer course lasting approximately two to three weeks, whereas chickenpox resolves within about one week [6,10]. In monkeypox, lesions often progress synchronously through macules, papules, vesicles, and pustules, while in chickenpox, lesions appear in multiple stages simultaneously [6,10]. Moreover, monkeypox lesions usually first appear on the face, neck, and chest before spreading centrifugally to the rest of the body, whereas the distribution of chickenpox lesions is more scattered and centripetal [1,10].

Monkeypox must also be differentiated from other viral skin diseases such as smallpox and hand, foot and mouth disease (HFMD) [9]. The rash of smallpox consists of granular papules and pustules that are more uniformly distributed and accompanied by pronounced systemic toxicity [64]. By

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contrast, HFMD primarily affects the hands, feet, and oral mucosa, presenting as erythematous macules and vesicles [65].

Accurate differential diagnosis depends on detailed clinical observation of rash morphology and distribution, together with evaluation of systemic symptoms and relevant exposure history [10,61,66]. Correct identification is essential for appropriate treatment and effective infection control [1,6,61].

6. Disease treatment

6.1. General treatment and supportive therapy

The primary treatment for monkeypox is symptomatic and supportive care [6,9,10]. Patients should receive adequate rest, hydration, and nutritional support. Antipyretics may be used to control fever, while analgesics help alleviate pain and discomfort [6,9,10]. Respiratory complications such as bronchopneumonia or sepsis require appropriate antibiotic prophylaxis, non-invasive ventilation, and other interventions as clinically indicated [10,30,67].

For gastrointestinal complications, oral or intravenous antiemetic and antidiarrheal therapy may be administered, together with rehydration therapy [6,9,31]. In patients with secondary skin infections, wound care, incision and drainage, and antibiotic therapy are essential (Cheema et al., 2022; Thornhill et al., 2022) [5,10]. These measures aim to relieve symptoms, prevent secondary bacterial infections, and promote recovery [6,9].

6.2. Antiviral therapy

There is currently no specific antiviral treatment approved exclusively for monkeypox; however, certain antivirals developed for smallpox have shown efficacy against MPXV [6,9].Tecovirimat, first identified in 2005 as an inhibitor of extracellular virus formation, targets the VP37 membrane protein, thereby preventing the release of enveloped viral particles from infected cells [68,69]. In clinical reports, treatment with tecovirimat has been associated with reduced viral shedding and a shorter duration of illness compared to untreated cases [6,70]. Successful outcomes have also been documented in patients co-infected with MPXV and HIV [5,10].

Brincidofovir belongs to the class of acyclic nucleotide phosphonates and acts by inhibiting orthopoxviral DNA polymerase, thus preventing viral DNA replication [71,72]. It also binds directly to viral DNA strands, further impairing replication and transmission [73,74]. Owing to potential adverse effects, these antiviral agents are generally reserved for severe or high-risk cases [9,10,31]. As summarised in Table 1, tecovirimat and brincidofovir remain the principal antiviral options, with ongoing clinical trials evaluating their safety and efficacy.

6.3. Vaccination

In addition to antiviral drugs, vaccination plays a critical role in mpox prevention (see Table 1 for trial information and dosing schedules).

Two vaccines—ACAM2000 and JYNNEOS—have been authorised for pre-exposure prophylaxis against Orthopoxvirus infections [9]. These may also be used post-exposure (up to four days after contact) to reduce infection risk and disease severity [75,76].

ACAM2000 is a second-generation live attenuated vaccinia-based vaccine that can cause serious side effects [77-79]. It is contraindicated in immunocompromised individuals, patients with eczema, those with underlying cardiac disease, and pregnant women [80].

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JYNNEOS is a third generation, highly attenuated vaccinia-based vaccine with an improved safety profile [81,82]. In animal models, two doses of JYNNEOS provided strong protection against severe and fatal disease, whereas a single dose was less effective in preventing severe outcomes [83].

6.4. Individualized therapy and prognosis

Due to the potential side effects of antiviral drugs and vaccines, treatment selection should be individualized according to disease severity and patient condition [6,10]. Enhancing host immunity through proper nutrition, rest, and management of comorbidities contributes to faster recovery [9]. Patients with mild disease generally require only symptomatic care and observation, while those with severe systemic symptoms—such as high fever, severe rash, or myalgia—should receive both supportive and antiviral therapy as appropriate [5,10].

An integrated treatment approach combining pharmacological therapy and supportive care remains the cornerstone of effective monkeypox management [6,9].

Table 1. Antiviral agents and vaccines for mpox: mechanisms, approval status, key trials, and dosing

Drug Name	Mechanism of Action	FDA Approval status	Clinical Trial ID	Dosage and Administration
Tecovirimat	Inhibits VP37 protein, preventing viral release from cells	Approved for smallpox and monkeypox	NCT05380752 (for people infected with Orthopoxvirus) NCT02080767 (for people infected with Orthopoxvirus) NCT02474589 (for people infected with Orthopoxvirus) NCT03972111 (for people infected with smallpox)	Oral, once daily for 14 days
Brincidofovir	Interferes with viral DNA polymerase, inhibiting DNA replication	Approved for smallpox, experimental use for monkeypox	NCT0114318 (for people infected with double-stranded DNA viruses)	Oral, once weekly for 2-3 weeks
ACAM2000	Live-attenuated vaccinia vaccine, induces immune response against poxviruses	Approved for smallpox, but with risk of adverse effects	NCT01158157 (for people infected with smallpox) NCT01913353 (for people infected with smallpox)	Subcutaneous injection, single dose, may cause local reactions
JYNNEOS	Modified vaccinia virus vaccine, enhances immune safety	Approved, high safety, suitable for high-risk populations	NCT00914732 (for people infected with smallpox) NCT02977715 (for people infected with smallpox)	Two-dose regimen, 28-day interval, enhances immune tolerance

7. Conclusion

Monkeypox is an emerging zoonotic infectious disease caused by the monkeypox virus (MPXV), a double-stranded DNA virus belonging to the Orthopoxvirus genus [1,7,18]. Its increasing global incidence highlights the growing threat posed by re-emerging viral infections to public health systems [1,5]. The complex pathogenesis of MPXV is characterised by intricate immune evasion strategies, including suppression of innate and adaptive immune responses, modulation of apoptosis, and inhibition of interferon signalling [34,84]. These mechanisms enable viral persistence, systemic

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dissemination, and severe disease manifestations, particularly in immunocompromised individuals [6,10].

The elucidation of monkeypox persistently predicate upon molecular substantiation through polymerase chain reaction (PCR),while serological interrogatives and histopathological scrutiny retain auxiliary pertinence under clinical requisition [85]. Despite the nonexistence of universally endorsed antiviral agents for mpox-specific application, pharmaceuticals like tecovirimat and brincidofovir exhibit nascent efficacy in ameliorating disease gravamen and forestalling complications within select cohorts [6,9]. Consequently, supportive therapeutics comprise the substratum of therapeutic governance, addressing analgesic adequacy, optimization of hydration and alimentary support, inhibitory measures against secondary bacterial incursions, alongside scrupulous surveillance fostering unperturbed convalescence [10,31]. Persistent is the role of vaccination, occupying its central preventative forte; ACAM2000 and JYNNEOS proffer orthologous protection vis-à-vis Orthopoxvirus infections. Nevertheless, administration necessitates individuation, accommodating safety prerogatives, comorbidity considerations, and distinctive contraindications within populations of heightened susceptibility [9,75,86].

Prospective governance over monkeypox necessitates reinforced early diagnostic accuracy, expeditious sequestration of authenticated cases, coupled with anticipatory vaccination regimens targeting high-risk cohorts effectively interruptive of transmission pathways [1,5]. Augmented investment into robust public health oversight and capacitated laboratory diagnostics embodies essential facilitative measures for swift outbreak recognition and curtailment [3,12,61]. Furthermore, ongoing scholarly exploration regarding viral pathogenesis, immunological manipulation phenomena, along with molecular progression schemata will be instrumental for judicious creation of targeted therapeutics and evolutionarily advanced inoculants [7,34]. Ultimately, anticipation of epidemic diminution and fortification against incipient Orthopoxvirus menaces mandates a collaborative, multilateral, and internationally consistent response synthesizing elements of medical practice, population-wide health strategies, virological sciences, and policy legislation across health domains [87-89].

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