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MPOX AS A NEW GLOBAL THREAT: PATHOLOGY, EPIDEMIOLOGICAL TRENDS, THERAPEUTICS AND CONTROL STRATEGIES

General Medicine

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ABSTRACT

Mpox, formerly known as monkeypox, is a zoonotic viral illness caused by the monkeypox virus, a member of the genus Orthopoxvirus. Endemic to parts of Central and West Africa, mpox primarily affects small rodents, monkeys, and other mammals in these regions. The virus is classified into two distinct clades: clade I (with subclades Ia and Ib) and clade II (with subclades IIa and IIb). Despite global efforts, mpox remains a significant threat, particularly with rising cases in the Democratic Republic of the Congo and other countries linked to clades Ia and Ib. Effective management of mpox includes vaccination, alongside comprehensive public health strategies. Treatment focuses on supportive care for symptoms such as pain and fever, as well as managing nutrition, hydration, skin care, and preventing secondary infections, especially in patients co-infected with HIV. The purpose of this review is to provide readers with a comprehensive overview of the current knowledge on Mpox.

KEYWORDS

Monkeypox virus, JYNNEOS vaccine, Tecovirimat, Brincidofovir, Cidofovir, Mpox treatment

INTRODUCTION:

Mpox, previously known as monkeypox, is a zoonotic disease caused by the Mpox virus, which can infect both humans and various animals. The virus was first identified in monkeys in 1958 and has since been found in several animal species. The initial human case was reported in 1970 in the Republic of Congo, a country in Central Africa. Mpox has primarily circulated in Central and West Africa, spreading among animals (mainly primates and rodents), from animals to humans, and through human-to-human contact.

In recent years, factors such as globalization, increased travel, and international trade have facilitated the spread of Mpox beyond its traditional regions, leading to outbreaks in different parts of the world. A significant global outbreak occurred in 2022, prompting international concern. However, in May 2023, the World Health Organization declared that Mpox outbreaks no longer represented a Public Health Emergency of International Concern. Despite this, some regions, especially in Asia, have seen a rise in cases due to the virus's rapid evolution and increased global travel[1].

Viral Morphology & Life cycle:

The virus is characterized by a brick-shaped or oval structure, measuring approximately 200–250 nm in diameter. Its genome is composed of linear, double-stranded DNA, which is about 197 kb in length and encodes around 180 proteins. The Mpox virus also has a dumbbell-shaped nucleocapsid surrounded by ovoid particles containing lipids. The genomic structure of the Mpox virus is similar to that of other orthopoxviruses. It features a highly conserved central core region, along with variable regions at both the left and right ends of the genome, and a tandemly repeated inverted terminal repeat. The central core region of the Mpox virus shares more than 90% sequence similarity with other orthopoxviruses, particularly within the open reading frame (ORF) between C10L and A25R. Species- and strain-specific characteristics of orthopoxviruses are typically found in the variable regions at the ends of their genomes[2].

The infection and replication of the Mpox virus can be divided into three main stages: **Virus Invasion:** The virus enters the host cells through attachment and fusion with the cell membrane. **Virus Replication and Synthesis:** Once inside, the virus begins to replicate its DNA and synthesize proteins necessary for the formation of new viral particles. **Virus Assembly, Maturation, and Release:** Newly formed viral particles are assembled, undergo maturation, and are then released from the host cell to infect other cells.

Transmission:

The natural hosts of the Mpox virus include various rodents and primates found in Central Africa. Early human infections are typically associated with direct contact with infected animals, such as exposure to their mucous membranes, bodily fluids, or tissues, or through the consumption of undercooked meat. Transmission can also occur through bites or scratches from infected animals. Human-to-human transmission mainly happens through direct contact with respiratory droplets from an infected person. Additionally, the virus can be transmitted from an infected mother to her newborn during childbirth.

The recent outbreak of Mpox has been the largest epidemic reported outside of Africa, differing significantly from previous outbreaks. In the past, Mpox cases were typically linked to contact with infected animals or travel to regions where the virus is endemic. However, the current outbreak has primarily been associated with sexual contact rather than exposure to infected animals or travel. Over the last two years, most reported cases have occurred among homosexual or bisexual men. A study found that 98% of the cases were among homosexual or bisexual males, with 41% also being co-infected with HIV. Additionally, 73% of the lesions observed in these cases were located in the anal and genital regions. The incubation period for Mpox is typically between 7 to 14 days, with symptoms lasting from 14 to 21 days. This extended incubation period can make timely diagnosis challenging, potentially delaying medical intervention and increasing the risk of further transmission[3].

Pathogenesis:

Mpox is generally a self-limiting disease, but the severity of the infection can vary depending on several factors, such as the specific viral strain, the individual's immune status, and any potential complications that may develop. Common early symptoms of Mpox infection include pain, fever, fatigue, and lymphadenopathy, with significant swelling often observed in the inguinal lymph nodes. This lymph node enlargement can help differentiate Mpox from other orthopoxvirus infections.

Understanding the modes of transmission is crucial for developing effective measures to control Mpox. The virus enters the body through mucous membranes (such as those in the eyes, respiratory tract, mouth, urethra, and rectum) or through broken skin when exposed to the respiratory secretions or bodily fluids of an infected person. It then spreads throughout the body via tissue-resident immune cells and draining lymph nodes. This phase, known as the latent period, usually lasts up to two weeks, during which individuals are typically asymptomatic and show no visible lesions.

Following the latent period, infected individuals begin to exhibit early symptoms, including fever, chills, headache, muscle pain, and lymphadenopathy. These initial symptoms, known as the prodromal phase, typically last for about three days. After this phase, a rash develops, usually starting on the head and face and gradually spreading to the rest of the body. The rash progresses through different stages, from papules to vesicles and pustules, before eventually forming crusts that heal and leave scars. This rash phase generally lasts between 2 to 4 weeks.

In the current outbreak among men who have sex with men (MSM), some atypical clinical signs have been noted, such as rashes appearing

primarily around the genital or anal area and then spreading to other parts of the body. Severe cases of Mpox can lead to complications like hemorrhagic disease, necrosis, obstructive disease, inflammation of vital organs, and septicemia.

Individuals with weakened immune systems, such as children, older adults, HIV patients, and those on immunosuppressive medications, are at a higher risk of severe manifestations. Additionally, immunocompromised individuals are more likely to facilitate the virus's adaptation to human hosts, contributing to its widespread transmission[4].

Laboratory testing

The laboratory diagnosis of mpox is predominantly based on the direct demonstration of the Orthopoxvirus monkeypox (MPXV) in a clinical specimen. Real-time polymerase chain reaction (real-time PCR) on skin lesion materials (e.g. swabs, exudate, or lesion crusts) are used most frequently. Viral throat swabs can be used for highrisk contacts of confirmed or high-probable cases who have developed systemic symptoms but do not have a rash or lesions that can be sampled. Several real-time PCR assays for the specific detection of MPXV, or for generic orthopoxvirus detection are available. Over 80 MPXV laboratory tests are CE-validated, mostly based on PCR. Mpox laboratory diagnostics are well established in several laboratories. Identification of the genetic clade of MPXV is mainly based on the determination and analysis of the partial genome sequences of the detected virus; however, clade-specific real-time PCR assays are also used for this purpose in some laboratories[5].

Recent studies revealed that a novel clade I MPXV which was detected in the current mpox outbreak in DRC has a deletion in and surrounding the OPG032 gene. This mutation may result in false negative test results for certain real-time PCR assays to discriminate between clade I and clade II MPXV strains. However, validated assays are available for the detection of the new clade Ib variant. Mpox diagnostic laboratories in the EU/EEA have been alerted through the EVD-LabNet about this finding and were advised to use molecular assays which are able to detect this mutant strain. The timely detection of the potential emergence of clade I MPXV in the EU/EEA requires molecular identification of viruses detected in diagnostic specimens. Therefore, nucleotide sequencing and sharing sequence information through public databases (e.g., GISAID) remains an essential component to monitor the mpox epidemiological situation in Europe and globally.

Management of Patients with an Monkeypox Virus (MPXV) Exposure:

In general, asymptomatic patients in healthcare facilities who have been exposed to the monkeypox virus (MPXV) do not need to be isolated but should be closely monitored. This monitoring should include daily assessments for signs and symptoms of mpox, with a thorough skin examination for at least 21 days following their last exposure. Postexposure risk assessment and management should be adapted based on whether the exposure occurred in the community or healthcare setting[6].

During the 21-day monitoring period:

- **If a rash develops**, patients should be placed under empiric isolation precautions for mpox until the rash is evaluated and tested, if indicated. Isolation can be discontinued if test results are negative.
- **If other symptoms of mpox occur without a rash**, patients should be placed under empiric isolation precautions for 5 days after the onset of symptoms. If no new symptoms develop and no rashes or lesions are found after 5 days, isolation can be discontinued.
- **If symptoms resolve and mpox is ruled out**, isolation precautions may be ended before the 5-day period is complete.
- **If new symptoms appear at any point**, isolation should be reinstated, and a new 5-day isolation period should begin.

For patients who cannot communicate symptom onset (e.g., newborns or those with delirium), isolation precautions should be considered during healthcare visits until the patient can report symptoms or for up to 21 days post-exposure. Inpatient decisions on isolation should consider the risk of mpox transmission to other vulnerable patients, the likelihood of infection based on exposure, and other relevant factors.

EU/EEA guidelines for detecting cases and preventing secondary transmission: Raising awareness among clinicians and other health professionals about possible travel-associated mpox cases caused by MPXV clade I, including the possibility of different clinical presentations, transmission through sexual and non-sexual routes and different groups affected than in previous outbreaks. Ensuring effective surveillance, laboratory testing (including molecular clade identification), epidemiological investigation and contact tracing capacities. Importation of MPXV clade I infections, or notable mpox events (outbreaks related to mass gathering events or other specific settings, re-infections among cases, rise in cases among women, children or other risk groups) should be promptly reported via EpiPulse and/or EWRS. All mpox cases should be reported to the European Surveillance System (TESSy). Providing advice to travellers to affected areas on national guidance for vaccination against mpox prior to travelling. Rapidly isolating any suspected cases until proven negative and, if positive, until symptom resolution. Implementing contact tracing and testing close contacts of confirmed cases following ECDC testing protocols. Providing travel advice to people visiting or returning from countries with confirmed MPXV clade I outbreaks. Continuing risk communication activities and working with civil society organisations to engage population groups at higher risk of infection[7].

Therapeutics:

Currently, there is no specific treatment approved for Mpox virus (MPXV) infections. For most patients with Mpox who have a healthy immune system and no skin conditions, supportive care and pain management are typically sufficient to help them recover without the need for medical treatment. However, some patients can develop severe complications from Mpox, including: Ocular infections, Neurologic complications, Myopericarditis, Complications from mucosal lesions (oral, rectal, genital, and urethral), Complications due to uncontrolled viral spread, especially in individuals with moderate or severe immunosuppression, such as those with advanced HIV infection. Patients who are severely immunocompromised or have certain skin conditions, like eczema, are at a higher risk for uncontrolled viral spread, which can result in severe manifestations of Mpox that may be life-threatening.

Tecovirimat (TPOXX, ST-246)

Tecovirimat is a novel antiviral that was made available for treatment of certain patients with mpox under the CDC-held Expanded Access-Investigational New Drug (EA-IND) protocol during the global outbreak of mpox that began in 2022. Data from one study have recently been released, but more information is needed to determine tecovirimat's effectiveness in treating mpox infection in people. Based on the animal efficacy data that showed survival benefit over placebo in lethal animal models, it may be reasonable to anticipate tecovirimat may provide benefit in treating some people with disease caused by orthopoxviruses, including the virus that causes mpox. However, whether and how the efficacy in animals may translate to humans with active disease, the patients who might benefit from tecovirimat, and what specific clinical benefits might occur with tecovirimat are unknown currently. There are ongoing clinical trials to determine the efficacy and safety of tecovirimat in people with mpox[8].

Brincidofovir (CMX001 or Tembexa)

Brincidofovir is a prodrug of cidofovir that is approved by the FDA for the treatment of human smallpox disease in adult and pediatric patients, including neonates. Data are not available on the effectiveness of brincidofovir in treating MPXV infection in people. However, it has shown to be effective against orthopoxviruses in in vitro and animal studies. Brincidofovir should not be used simultaneously with cidofovir.

Cidofovir

Cidofovir is an antiviral medication that is approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with Acquired Immunodeficiency Syndrome (AIDS), and is commercially available as an injection. Data are not available on the effectiveness of cidofovir in treatment of MPXV infection in people. However, it has shown to be effective against orthopoxviruses in in vitro and animal studies. It is unknown whether a person with severe mpox infection will benefit from treatment with cidofovir, although its use may be considered in such instances. Brincidofovir (a prodrug of cidofovir) may have an improved safety profile over cidofovir. Serious renal toxicity or other adverse events have not been observed during

treatment of cytomegalovirus infections with brincidofovir as compared to treatment using cidofovir. Cidofovir should not be used simultaneously with brincidofovir. Clinicians can switch patients between IV cidofovir and brincidofovir right away without a drug holiday. Nearly all patients who receive cidofovir for mpox are severely immunocompromised and require cidofovir in combination with tecovirimat.

Vaccinia Immune Globulin Intravenous (VIGIV)

VIGIV is licensed by FDA for the treatment of complications due to vaccinia vaccination. However, it is not approved for treatment of mpox. Data are not available on the effectiveness of VIGIV in treatment of MPXV virus infection in people. Use of VIGIV has no proven benefit in the treatment of mpox and it is unknown whether a person with severe mpox infection will benefit from treatment with VIGIV. However, healthcare providers may consider its use in severe cases in which the development of a robust antibody response may be impaired.

VIGIV can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox or mpox vaccination following exposure to MPXV is contraindicated. Patients who receive VIGIV typically are concomitantly receiving both tecovirimat and either brincidofovir or cidofovir.

Immunotherapy in Mpox

Mpox virus-induced immunopathology leads to adverse outcomes in clinical, and immunotherapy for Mpox has the potential to reduce severe cases. Antibody-based therapeutics, immune cell, Immune effector molecules, and Modulation of cellular signal transduction are potential immunotherapies. Combination antiviral drugs with immunotherapy may be more effective and provide greater clinical benefit than single antiviral therapy alone.

Vaccination

JYNNEOS is a 2-dose vaccine developed to protect against mpox and smallpox. People need to get both doses of the vaccine for the best protection against mpox. The second dose should be given 4 weeks after the first dose. However, if it has been longer than 4 weeks since you got the first dose, get the 2nd dose as soon as possible. Vaccination is an important tool in stopping the spread of mpox. People who are vaccinated should continue to avoid close, skin-to-skin contact with someone who has mpox.

While it is possible for people who have recovered from mpox to get mpox again, it's very rare. According to unpublished CDC data, a reinfection has occurred in less than 0.1% of people in the United States who previously had mpox. Also, the second time they got mpox, the illness was generally milder than the first time. Because of this, people who have recovered from mpox are not recommended to receive JYNNEOS vaccine doses at this time[9].

Challenges

With the global cessation of smallpox vaccination, the number of individuals with cross-immunity against the Mpox virus has significantly decreased, making Mpox a potential bioterrorism threat. Although a few anti-Mpox drugs, such as Tecovirimat, have proven effective, relying solely on them is not advisable. Despite being a DNA virus, the Mpox virus shows considerably high genomic variability due to increased nucleotide polymorphism. Rapid population movement and international travel have further facilitated the spread of the Mpox virus, increasing the likelihood of mutation. These factors contribute to greater genetic diversity, drug resistance, and the emergence of multidrug-resistant strains of the Mpox virus.

Moreover, currently available drugs have limitations that affect their clinical use. For example, Cidofovir has low bioavailability and poses a risk of renal damage, while both Cidofovir and Brincidofovir can potentially harm hematopoietic and liver functions. Therefore, there is an urgent need to develop new anti-Mpox virus drugs.

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