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Pharmacological Prevention and Treatment of Monkeypox

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Introduction

Human monkeypox infection (hMPXV) is caused by the monkeypox virus. This double-stranded DNA virus is categorized in the same *Orthopoxvirus* genus as the smallpox (Variola) virus.[1] Pox viruses all elicit cross-reactive humoral and cellular immune responses.[2] Monkeypox was first identified in the 1950's in macaque research monkeys. In 1970, human cases were identified in the Democratic Republic of Congo.[2] There are two genetic clades for hMPXV based on location origin, with a historic fatality rate of 10.6% for clade I and 3.6% for the less virulent clade II.[2]

Spread of clade II hMPXV outside of endemic African nations was identified in early 2022. The World Health Organization declared the global spread of hMPXV a public health emergency of international concern in July 2022. Spread is generally through to close or intimate skin-to-skin contact (including sex), contact with respiratory secretions, and contact with objects, fabrics, and surfaces used by someone with monkeypox.[3] Most cases have occurred in gay, bisexual, and other men or have sex with men, though any patient with exposure, regardless of sexual or gender identity, is at risk of acquisition.[4]

The incubation period of hMPXV ranges from 5 to 21 days, while the disease itself can remain symptomatic for 2 to 4 weeks. The key sign is rash which may be painful or itchy, though other generalized viral symptoms (e.g. fever, chills, swollen lymph nodes) may also occur. Children and those with underlying immune deficiencies may have more severe cases with worse outcomes.[5] Over 235 total cases (confirmed and presumptive) have been identified in Oregon as of Oct 26th, with two pediatric patients.[6]

Vaccination

It is estimated that the smallpox vaccine may provide up to 85% efficacy against hMPXV infection, though this is based on historical data from the 1980s.[1] It is unknown if vaccine efficacy may wane over time for those vaccinated prior to smallpox eradication, and the current hMPXV may have mutations affecting its susceptibility to preexisting immunity. Human studies of vaccine efficacy for hMPXV are lacking.

After exposure to hMPXV, the Centers for Disease Control and Prevention (CDC) recommends vaccination within 4 days to prevent disease. Vaccination between days 4 to14 may not prevent disease, but may reduce the symptom severity.[4]

JYNNEOS (modified vaccinia Ankara vaccine) was Food and Drug Administration (FDA) approved in 2019 for prevention of smallpox and hMPXV in adults 18 years and older determined to be at high risk.[7] The vaccine was originally approved as a subcutaneous (SC) injection. In August 2022, JYNNEOS was granted an emergency use authorization (EUA) for intradermal injection of those at high-risk for hMPXV infection. Intradermal administration allows for a smaller injection volume and effectively increased the amount of vaccine doses five-fold. This was based on existing data showing intradermal administration at one-fifth the SC dose elicited a similar immune response. Additionally, the EUA allows for subcutaneous administration for those under 18 years of age. Two doses should be given 4 weeks apart. Data are not available to show effectiveness after a single dose. A patient is considered vaccinated 2 weeks after the second vaccine dose.[4,8] Severe adverse events are rare. Common side effects are primarily associated with local injection site pain and discomfort.[9] To obtain the JYNNEOS vaccine, Oregon Health Authority has guidance on eligibility[6] and access to a vaccine locator.[10]

ACAM2000 live virus vaccine is FDA approved for prevention of smallpox for those at high risk of infection.[11] An Expanded Access Investigational New Drug (EA-IND) Application allows for its use for the prevention of hMPXV in those 1 year and older.[4] It is given percutaneously via a bifurcated needle as a single dose with peak immunity at ~4 weeks. Significant adverse events of myopericarditis/pericarditis and vaccinia virus transmission are possible.[4,11] This second-generation smallpox vaccine will leave a scar similar to the now discontinued, first generation "DRYVAX" vaccine used historically in smallpox eradication efforts. ACAM2000 has a number of contraindications which should be carefully assessed. These include patients living with HIV (regardless of immune status) and atopic dermatitis.[11] Currently ACAM2000 is part of the Strategic National Stockpile (SNS) and only available to military personnel and laboratory workers who work with certain pox viruses, or through expanded access (compassionate use).[4]

Treatment

Pharmacologic options are limited, as no agents are currently approved specifically for hMPXV treatment. Herbal supplements are not recommended. The CDC recommends that those with high-risk disease manifestations or with

higher risk for severe disease should be considered for treatment (Table 1).[4]

Table 1. Patient Characteristics for Prioritized Antiviral Treatment[4]

Clinical Manifestations	• Severe disease (e.g. infected or bleeding lesions, hospitalization, periorbital infections, hemorrhagic disease) • Lesion anatomic location at risk of scarring or strictures (e.g. pharynx, penile foreskin, vulva, rectum)
Risk for Severe Disease	• Severely immunocompromised conditions • Pediatrics, especially less than 8 years of age • Pregnant or breastfeeding • Preexisting condition affecting skin integrity (e.g. atopic dermatitis, severe acne)

Tecovirimat (TPOXX) is Food and Drug Administration approved for use in human smallpox in adults and children weighing at least 3 kg.[12] Given the unique circumstances and ethics of studying a treatment for the eradicated disease of smallpox, tecovirimat efficacy was assessed using primate (monkeypox) and rabbit (rabbitpox) models in line with the FDA Animal Efficacy Rule.[13] Pharmacokinetics and safety were separately tested in over 400 healthy adult volunteers. Headache was the most common adverse event. Pediatric dosing was based on pharmacokinetic simulations to provide comparable exposure to that of adults.[12] Use in hMPXV is considered experimental and current evidence in humans is limited to sources such as case reports and retrospective cohorts.[14-16] Initial data from patients treated with tecovirimat during this hMPXV outbreak show few adverse events.[16] This medication is currently available through the national stockpile and prepositioned supplies. Providers requesting TPOXX must obtain it through the OHA.[17]

Vaccinia Immune Globulin Intravenous (VIGIV) is licensed by the FDA for complications due to vaccinia (smallpox) vaccination.[18] Post-exposure prophylaxis for hMPXV with VIGIV may be considered in those at risk of severe disease where vaccination is contraindicated, such as severe immunodeficiency in T-cell function.[4] Data are not available for effectiveness of treatment of hMPXV. Use may be considered in severe cases after weighing risk and benefit. Adverse events are similar to other IVIG products.[18]

Two other antivirals, cidofovir and brincidofovir, have *in vitro* and animal data to show effectiveness against orthopoxviruses, but not human data specific to hMPXV. Cidofovir is commercially available for treatment of cytomegalovirus retinitis, though severe renal toxicity is a known adverse effect of this product. Additionally, an expanded access protocol allows for use from the SNS. Brincidofovir, FDA approved for treatment of smallpox, may have a preferred safety profile over cidofovir, but does not yet have an EA-IND for use and is not available from the SNS.[4]

- Pharmacologic prevention and treatment options for hMPXV are derived from therapies for smallpox.
- Therapeutic recommendations may change as effectiveness and safety data become available from use in humans for hMPXV.

Conclusion

The hMPXV outbreak is evolving. Current pharmacologic treatment recommendations include prevention of disease through vaccination of people at high risk of exposure, and post-exposure prophylaxis immediately after known exposure. Antiviral treatment should be considered in patients exhibiting certain significant disease manifestations, as well at patients at higher risk of developing severe disease. Evidence supporting vaccines and antiviral treatments are primarily based on historic smallpox data, animal models, and pharmacokinetic data. Recommendations may evolve over time as real-world data for use of these agents in hMPXV become available through case reports and randomized trials.

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