Australian Human Monkeypox Treatment Guidelines

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Australian Human Monkeypox[1] Treatment Guidelines

Including the management of Vaccinia virus vaccine complications

Executive summary

Guiding principles

- In the current phase of the Australian monkeypox outbreak[2], seek expert guidance for clinical management of human monkeypox from an infectious diseases or sexual health physician. Because most infections are mild in the current outbreak, most patients will not require antiviral treatment. However, patients requiring antiviral treatment for monkeypox should have it initiated in consultation with an infectious diseases physician and/or a sexual health physician involved in case management.
- Patients with monkeypox requiring hospital admission should ideally be managed in a centre with a suitable level of biocontainment care capability[3] such as a designated High Consequence Infectious Diseases (HCID) facility wherever possible. Such facilities can make the most of dedicated trained personnel in managing HCID.
- In patients who do not require admission to hospital, management should be coordinated with the patient's primary medical practitioner, with input from relevant specialists and public health units.
- Available treatment options remain investigational. It is important to carefully consider the benefits and risks before initiating treatment in individual patients.
- Consultation with an infectious diseases physician is also required for patients with complications following Vaccinia vaccination.

Purpose of guidelines

The purpose of these guidelines is to outline the current therapeutic options for the management of human monkeypox virus[4] infection and vaccine related complications.

These guidelines will be reviewed regularly as the monkeypox situation evolves and as therapeutic options change.

[1] This guidance document also includes the management of infections associated with Vaccinia virus-based vaccine complications.

[2] If the outbreak becomes prolonged, clinical management and treatment initiation by primary care medical practitioners (SHPs and GPs) may become routine.

[3] For hospitalised patients, end to end patient management should be coordinated by a hospital incident management team. Biocontainment in a single room may be sufficient in uncomplicated cases. If aerosol generating procedures are undertaken, a single room with negative pressure may be required. A positive pressure room should not be used.

[4] Monkeypox is caused by viruses (e.g., monkeypox viruses) in the species *Monkeypox virus* within the genus *Orthopoxvirus*. Taxonomic constructs follow the traditional binomial approach with genus and species epithets italicised. Virus names are not italicised. Zerbini, F. M., et al. (2022).

Scope

- This guidance focuses on the off-label treatment options for patients with confirmed monkeypox virus infection or complications related to replication-competent vaccinia virus vaccines (e.g., ACAM2000™).
- This guidance further provides pharmacological options for post-exposure prophylaxis (PEP) in those at risk of severe complications following monkeypox exposure (e.g., severely immunocompromised).
- This guidance does not elaborate on the diagnostic work up and clinical management of patients prior to the confirmation of monkeypox virus infection or vaccine related complications.
- For further information on diagnostic workflow: *Public Health Laboratory Network (PHLN) Laboratory Case Definition*.
- For further information on vaccination *https://health.gov.au/resources/publications/atagi-clinical-guidance-on-vaccination-against-monkeypox*
- For further information on infection prevention and control guidance for hospital and hospital in the home *https://health.gov.au/resources/publications/iceg-interim-guidance-on-monkeypox-for-health-workers*
- For further information on public health response guidance *https://health.gov.au/resources/publications/cdna-monkeypox-virus-infection-case-and-contact-management-guidelines*

Treatment of symptomatic infection

- Monkeypox is generally a self-limited infection. Most cases will not require specific treatment other than supportive management or treatment of complications (e.g., antibiotics for secondary cellulitis).
- Antiviral therapy should be initiated in consultation with an infectious diseases and/or sexual health physician[5].
- Patients admitted to a hospital should be managed in a centre with suitable biocontainment care capability[6].
- In clinically well patients, outpatient management is recommended along with shared care with the patient's primary medical practitioner.
- Tecovirimat is the preferred treatment for severe monkeypox virus infection.

Management of complications associated with Vaccinia vaccination

- Treatment may be required for those with complications following vaccination with a replication-competent vaccinia vaccine.
- Vaccinia Immunoglobulin (VIG) is the preferred treatment for Vaccinia vaccine complications.

[5] If the outbreak becomes prolonged, clinical management and treatment initiation by primary care medical practitioners (SHPs and GPs) may become routine.
[6] End to end patient management should be coordinated by a hospital incident management team.

- Information on serious adverse events associated with Vaccinia vaccination can be found in the ATAGI monkeypox vaccination guidance. *https://health.gov.au/resources/publications/atagi-clinical-guidance-on-vaccination-against-monkeypox*

Post-exposure prophylaxis

- Evidence for the use of antiviral agents is limited.
- Antiviral agents may be used for PEP and this guideline should be read in conjunction with advice from ATAGI on the use of vaccines for monkeypox. *https://health.gov.au/resources/publications/iceg-interim-guidance-on-monkeypox-for-health-workers*
- Identifying candidates for PEP will be aided by referring to CDNA's monkeypox national guidelines for public health units. *https://health.gov.au/resources/publications/cdna-monkeypox-virus-infection-case-and-contact-management-guidelines*

Treatment options

Current therapeutic options for human monkeypox in Australia include:

- Tecovirimat
- VIG

If expert clinical judgement determines a patient requires specific treatment for monkeypox, the preferred first option for drug treatment is tecovirimat. If tecovirimat is unavailable, VIG is the next preferred option.

If the patient requires treatment for complications following vaccination with a replication-competent vaccinia vaccine, VIG is the preferred option.

- **Tecovirimat**, which is held in the National Medical Stockpile (NMS) is not approved for the treatment of human monkeypox by the Therapeutic Goods Administration (TGA)[7]. It appears to be well tolerated and active *in vitro* against orthopoxviruses. It is highly efficacious as PEP and treatment in animal models. See appendix for further details.
- **VIG** is held in the NMS in limited quantities. It is used alone or in combination with antivirals for the treatment of Vaccinia related complications.

Other treatments with potential activity

- **Cidofovir**, which is currently TGA registered and used in Australia for the treatment of human cytomegalovirus (CMV) infections, other human herpesvirus, and adenovirus infections in immunocompromised patients. Cidofovir should be carefully considered for the treatment of monkeypox virus infection to preserve supply, particularly for patients with difficult to treat CMV disease and other viral infections in those that have undergone solid organ or hematopoietic stem cell transplantation. The significant adverse events profile especially nephrotoxicity and myelosuppression may outweigh the benefit.

[7] The Therapeutic Goods Administration has granted an emergency exemption for the medicine Tecovirimat for use in Australia against monkeypox.

- **Brincidofovir** which is not available in Australia and not registered by the TGA. Access is only available to those enrolled in a clinical trial.

Indications for use

Treatment of confirmed monkeypox virus infection

https://health.gov.au/resources/publications/cdna-monkeypox-virus-infection-case-and-contact-management-guidelines

- Tecovirimat for 14 days is the preferred treatment of monkeypox virus infection when treatment is deemed necessary.
- Those who should be considered for treatment may include:
    - Those with severe disease (e.g., haemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalisation)
    - Those who may be at high risk of severe disease:
        - Those who are immunocompromised (e.g., acquired immune deficiency syndrome with CD4 count <200 cells/µL[8], leukaemia, lymphoma, generalised malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, tumour necrosis factor inhibitors, high-dose corticosteroids, hematopoietic stem cell transplant recipient <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component)
        - Paediatric populations, particularly patients younger than 8 years of age
        - Persons who are pregnant or breastfeeding
        - Those with one or more complications (e.g., secondary bacterial skin infection; gastroenteritis with severe nausea/vomiting, diarrhoea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities). Other complications include aberrant infections that include its accidental implantation in eyes, mouth, or other anatomical areas where monkeypox might constitute a special hazard (e.g., the risk of secondary bacterial infection and Fournier's gangrene in relevant sites where the risk of complicated skin and soft tissue infections are high).
- Early treatment in immunocompromised and other risk groups, e.g., children and pregnant patients. In pregnant patients, VIG may be preferred over Tecovirimat. In very young children, consider treatment for confirmed infection with serious or progressive infection. Consult an infectious diseases paediatrician for management of paediatric infections.

[8] This threshold of 200 cells/µL represents a live vaccine cut-off between a moderate and severe definition of immunocompromise in a setting of HIV infection. This threshold will also balance antiviral supply.

Treatment of vaccine related complications

- VIG is preferred for the treatment of complications associated with replication-competent Vaccinia vaccination (ACAM2000™). Large doses of VIG may be required.
- Information on serious adverse events associated with Vaccinia vaccination can be found in the ATAGI monkeypox vaccination guidance. *https://health.gov.au/resources/publications/atagi-clinical-guidance-on-vaccination-against-monkeypox*
- Established indications for VIG following vaccination include:(Cono, Casey, & Bell, 2003)
    - Eczema vaccinatum, which involves widespread pustular/erosive lesions from the vaccinia virus, occurring particularly in areas affected by eczema/atopic dermatitis.
    - Generalised vaccinia which results from viraemia and presents with a generalised vaccinia virus rash and can be accompanied by fever, myalgia, and headache; but is self-limiting in immunocompetent hosts.
    - Progressive vaccinia, which presents with delayed/absent local wound healing and widespread lesions emanating from the inoculation site that can become necrotic. The risk is highest in people with severe immunocompromise, particularly those with defective cell-mediated immunity.
- Post-vaccination conditions where the role of treatment is uncertain include
    - Accidental autoinoculation to sensitive sites, particularly the eye
    - Postvaccinial central nervous system disease (postvaccinial encephalopathy (PVE) and postvaccinial encephalomyelitis (or encephalitis) (PVEM))
    - Post-exposure prophylaxis in pregnancy to prevent fetal vaccinia

The evidence for treatment with VIG is limited in these situations. The pathophysiology is unclear and limited clinical experience from past suggests the VIG may not cause harm. Consultation with an infectious diseases physician is imperative.(Aragón, Ulrich, Fernyak, & Rutherford, 2003; Hopkins & Lane, 2004; Melekhin, Karem, Damon, & Bloch, 2009; Van Dam et al., 2009)

Post-exposure prophylaxis following a significant monkeypox exposure in an individual at high-risk of complications

- Under guidance of an infectious diseases physician. Dose and duration of treatment in appendix
- PEP with Tecovirimat in high-risk, immunocompromised persons
- PEP using VIG for inadvertent vaccination in pregnancy
- This guideline should be read in conjunction with advice from ATAGI on the use of vaccines for monkeypox virus infection *https://health.gov.au/resources/publications/atagi-clinical-guidance-on-vaccination-against-monkeypox*
- Identifying candidates for PEP will be aided by referring to CDNA's monkeypox national guidelines for public health units.

https://health.gov.au/resources/publications/cdna-monkeypox-virus-infection-case-and-contact-management-guidelines

Drug combinations

Caution should be exercised when considering combining an antiviral agent and a competent virus vaccine, e.g., ACAM2000™. Little human evidence is available on whether combination therapy is superior to antiviral agent alone. The antiviral agent may reduce the activity of replicating vaccines. There is animal evidence that Tecovirimat when used with ACAM2000™ may ameliorate adverse events associated with ACAM2000™.(Berhanu et al., 2010; Douglas W. Grosenbach et al., 2008; Russo et al., 2020)

Accessing the National Medical Stockpile

Any request to access treatments held by the NMS must be made from a state or territory Chief Health Officer (or authorised delegate) on the official NMS request form and emailed to the NMS via stockpile.ops@health.gov.au. On receipt of this request, the NMS will seek approval from the Chief Medical Officer to the deployment of the treatments.

Appendix

Tecovirimat (FDA, 2022; Russo et al., 2018; Russo et al., 2021)

Other names	ST-246, Tpoxx®
Dose	200 mg capsules Adult 600 mg bd PO for 14 days; paediatric 13–25 kg: 200 mg bd, 25–40 kg: 400 mg bd, >40 kg: 600 mg bd, with high fat meal No dose adjustments for renal/hepatic failure
Regulatory history	Approved by the FDA for treatment of human smallpox disease Not TGA registered
Mechanism of action	Antiviral drug that inhibits the orthopoxvirus VP37 envelope wrapping protein. Prevents the formation of egress competent enveloped virions necessary for cell-to-cell and long-range dissemination of virus.
Clinical pharmacology	Resistance: mutations in target VP37. Treatment emergent resistance reported.(Lederman et al., 2012) Peak serum concentration of tecovirimat under fed conditions is up to 50% higher than under fasting conditions.
Efficacy	Efficacy based on animal studies (95% vs 5% mortality in non-human primates), may be less effective in immunocompromised and if given >6 days after challenge (noting incubation period in animal models are much shorter than in humans so day 4 is approximately the onset of lesions) Potential utility as post-exposure prophylaxis based on animal models, but duration of treatment unclear
Safety	Phase 1 study in humans (n=449, n=359 received active drug) - no safety signals. One fatal AE (PE) not related.(D. W. Grosenbach et al., 2018) Pregnancy - animal studies - no toxicity. Detectable in breast milk. Common side effects include headache, nausea, abdominal pain, and vomiting.
Practice points	Interactions: repaglinide (hypoglycaemia) For patients who have trouble swallowing capsules; capsules can be administered by carefully opening the capsule and mixing the entire contents in 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt). The entire mixture should be administered within 30 minutes of its preparation.

Vaccinia immune globulin (VIG) (CDC, 2022; FDA, 2018)

Other names	Vaccinia Immune Globulin Intravenous (Human)
Proposed dose	Dose of 6000 Units/kg intravenous. Consider higher doses where the patient does not respond to the initial dose. Multiple and repeated treatments may be required.
Regulatory history	Not TGA registered. Indications include: - Eczema vaccinatum - Progressive vaccinia - Severe generalised vaccinia

	- Vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions - Aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard. VIG is not considered to be effective in the treatment of postvaccinial encephalitis
Clinical pharmacology	VIG provides passive immunity for individuals with complications to vaccinia virus vaccination. The exact mechanism of action is not known After intravenous administration of 6000 Units per kg to 31 healthy subjects in a double-blind study, the peak plasma concentration was achieved within 2 hours. The half-life of VIG was 30 days (range of 13 to 67 days)
Efficacy	Clinical studies suggest reduced pox reaction and erythema area following VIG administration.
Safety	Contraindications: - isolated vaccinia keratitis (Altmann S, Brandt CR, Murphy CJ, et al. 2011) - anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immune globulin preparations - IgA-deficient patients with antibodies against IgA and a history of IgA hypersensitivity, as it contains trace amounts of IgA. Precautions: VIG administration is associated with aseptic meningitis syndrome, transfusion-related acute lung injury, acute renal dysfunction/failure, thrombosis, aseptic meningitis, and haemolysis. Common adverse reactions in clinical trials (>10%) include headache, nausea, rigors, and dizziness.
Practice points	Product may be stored frozen at or below –15 °C or refrigerated at 2–8°C. Bring VIG vials to room temperature prior to dosing. Administer 6000 U/kg intravenously through a dedicated intravenous line with the infusion rate of no greater than 2 mL/min. Blood glucose measurement in patients receiving VIG must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose contained in VIG. Glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dyeoxidoreductase method (monitor and test strips) must not be used for blood glucose testing in patients receiving VIG, since maltose in VIG products has been shown to give falsely high blood glucose levels in these testing systems.

Cidofovir (Stittelaar et al., 2006; TGA, 2019)

Other names	Vistide; EMPOVIR
Proposed dose	5 mg/kg body weight, intravenous <u>Induction treatment:</u> Intravenous infusion at a constant rate over 1 hr administered once weekly for two consecutive weeks.

	Maintenance treatment: Beginning two weeks after the completion of induction treatment, intravenous infusion at a constant rate over 1 hour administered once every two weeks.
Regulatory history	Approved by the TGA for the treatment of CMV infection in adults with acquired immunodeficiency syndrome
Clinical pharmacology	Inhibits viral DNA synthesis in CMV Half-life elimination: 2.6 hours Excretion: urine
Efficacy	No clinical data regarding efficacy against monkeypox in humans Significant adverse events, including nephrotoxicity (kidney failure is cited as a common adverse effect in the PI) In vitro activity against monkeypox and has been shown to be effective against lethal challenge in animal models
Safety	Contraindications: renal impairment; concomitant administration of cidofovir and potentially nephrotoxic agents (e.g., NSAIDs) Precautions: dose-dependent nephrotoxicity; uveitis and/or iritis; decreased intraocular pressure/ocular hypotony; neutropenia Pregnancy category D (do not use) Common adverse events include renal failure, neutropaenia, iritis, uveitis, ocular hypotony, nausea, vomiting, diarrhoea, asthenia, fever, alopecia, and rash
Practice points	Closely monitor renal function With a syringe, transfer the appropriate dose of Cidofovir (5 mg/kg body weight) from the vial to an infusion bag containing 100 mL 0.9% (normal) saline solution, and mix thoroughly. The entire volume should be infused intravenously into the patient (adult aged 18 years or older) at a constant rate over a period of 1 hour by use of a 2 standard infusion pump. Store at a temperature below 25 °C. Do not refrigerate or freeze. Infusion admixtures may be stored temporarily for up to 24 hours in a refrigerator (2–8 °C) when reconstitution is performed under aseptic conditions. Administration of Probenecid 2 g *po* 3 hours before Cidofovir, and 1 g 2–8 hours post Cidofovir is recommended for most indications to increase blood levels. Probenecid may interact with several other medications. If probenecid cannot be administered the pharmacokinetics of Cidofovir may be less reliable.

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