Monkeypox treatment recommendations SSI/FCSTI

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- The present guideline is an ongoing process by a collaborative group of experts from SSI and FCSTI, and will adapt to accumulated knowledge.
- Inclusion of patients into clinical trials and/or observational studies is encouraged in all care and treatment sites as current data in human are scarce.
- Current recommendations take into account the limited availability of antiviral drugs in Switzerland.
- This document will mainly focus on available antiviral therapy against monkeypox disease. It also aims to increase awareness regarding precautions to take after the resolution of acute disease in order to limit the risk of further transmission as well as testing for sexually transmitted diseases when appropriate. Note that case management should also include close follow-up (virtual or in person) of the patient by health care professionals, including psychological support.
- Currently, the majority of affected patients are men having sex with men. Individuals of this population, as well as other vulnerable individuals, may face stigma. Awareness of this fact is crucial while caring for these patients in order to create trust which lays the foundation for a successful treatment outcome.

1. Summary of evidence for available antiviral treatments

Few drugs have been shown to be effective *in vivo* and in animal models against orthopoxvirus infection(1,2).

- Tecovirimat, a direct antiviral treatment acting as an egress inhibitor against orthopoxviruses is validated under exceptional circumstances by the EMA for the treatment of orthopoxviruses, including monkeypox. The drug has already been registered in some countries for this indication. It showed an *in vitro* efficacy in the nanomolar range against the circulating B.1 strain of Monkeypoxvirus implicated in the 2022 outbreak(3).

- Other direct antiviral treatments include:
    - cidofovir and brincidofovir, an oral prodrug of cidofovir, both direct antivirals acting as DNA polymerase inhibitors. Brincidofovir is approved by the FDA against smallpox (not monkeypox)(4)
    - the vaccinia immune globulins, used in treatment of smallpox vaccine complications, for which no data in treatment of monkeypox complications exist.

Tecovirimat and cidofovir showed encouraging results against monkeypox disease in lethal non-human primate animal models, by preventing death when administered after inoculation(5,6). The evidence in humans is very limited with only few case reports and/or case series of treatment with tecovirimat and/or cidofovir/brincidofovir during monkeypox infection (7–9)

Neither brincidofovir nor tecovirimat are licensed in Switzerland. Tecovirimat is available in Switzerland as compassionate use and/or within the MOSAIC cohort (see below). IV cidofovir is licensed and available in Switzerland (off label for monkeypox), for the treatment of CMV retinitis.

We suggest prioritizing oral tecovirimat when considering antiviral treatment in some clinical situations described below.

2. Case management and indication for antiviral therapy

Most patients suffer from a mild to moderate disease and can be managed with symptomatic treatment, which can include pain killers (such as paracetamol, tramadol and/or codein), local anesthetics (such as lidocaine), local and/or oral antiseptics (such as chlorhexidine), or anti-histamines. In severe proctitis, sulfasalazin enemas can be added. Cream such as "badigeon blanc" can be used on cutaneous lesions only (not mucosal), and disinfection should be applied daily.

One animal study performed in dogs, suggested an increased rate of complications after NSAID treatment(10). In the absence of human clinical data, NSAIDS should be used with caution.

Patients should be advised to reduce their contacts and informed of the transmission modes, in order to reduce further transmission.

As the symptomatology can quickly evolve over time, the need for a specific antiviral treatment should be regularly reassessed.

Young children and immunocompromised are known to be at increased risk for severe outcomes from monkeypox disease. In pregnant women, vertical transmission has been described, associated with miscarriage and/or fetal loss with documented fetal infection (11).

Indirect data originating from other poxviruses may suggest that individuals with history of atopic dermatitis and/or eczema may also be at increased risk for severe disease.

Health care providers are invited to refer to Swissnoso guidelines for infection prevention control (IPC) measures when taking care of the patient.

With regards to the current limitations of the drugs in terms of availability in Switzerland and/or route of administration, a treatment course can be considered in the following situations (low level of evidence):

1. **Patients at high risk for severe disease**, such as
    a. immunocompromised individuals (transplant patients, patients with HIV infection and CD4 cell count below 200 CD4/mm^3, on immunosuppressive drugs),
    b. pregnant women and children (especially below 8 years-old). A gynecologist/obstetrician as well as pediatric infectious disease specialist should always be consulted in such situations.
2. **Patients with a severe disease presentation** for example:
    a. Patients presenting with more than 100 lesions (severe) or more than 250 lesions (very severe).
    b. Patients with lesions leading to functional inability (throat or genital mucosal lesion, eyes) or uncontrollable discomfort (uncontrolled pain on opoids).
3. **Patients hospitalized with organ dysfunction** (encephalitis, myocarditis, sepsis) or hemorrhagic lesions, or evocative form of vasculitis (purpura).

The first line of treatment is oral tecovirimat due to its better *in vitro* performance and better risk profile when compared to other direct antivirals.

Tecovirimat is currently available in Switzerland for compassionate use and/or within the MOSAIC study. Access to tecovirimat in Switzerland is currently restricted within the framework of a collegial and multidisciplinary decision in a validation committee.

Access to tecovirimat: patient's consent, validation committee, and clinical outcome forms are appended to this document or available on request (laeticia.guiraud@hcuge.ch, alexandra.calmy@hcuge.ch, matthias.cavassini@chuv.ch, jan.fehr@uzh.ch).

Cidofovir should be used as an alternative treatment only if tecovirimat is not available and/or contra-indicated, in exceptional circumstances.

Topical cidofovir (off-label in Switzerland) can be proposed in case of a large/extensive lesion(s) on the face and/or the genitals, based on reports from efficacy in immunocompromised individuals presenting with other poxviruses(12,13).

Vaccinia immune globulin is currently only available upon specific request by name in Switzerland and may be discussed in patients in whom cidofovir and/or tecovirimat are contra-indicated (very low level of evidence). A request can be sent by the treating physician to medicalinformation@ebsi.com; learoydt@ebsi.com; cochraneL@ebsi.com to request the treatment.

Other local and/or general complications of monkeypox disease:
Any specific complication should prompt a referral to the specialist:

- Any eye complications such as keratitis/conjunctivitis should be evaluated by an ophthalmologist. Trifluridin eye drops (not licensed in Switzerland, available in neighbor European countries) may be considered for their *in vitro* activity against poxviruses(14).
- Encephalitis will require multidisciplinary case-management with neurologists.
- Cardiologists should be involved in cases of myocarditis.

2. Timing of administration and treatment regimens

Timing of administration: clinical trials are ongoing to gather information on the ideal treatment timing. Animal data originating from non-human primates have shown a decrease in symptomatology and in viral kinetics when the treatment was administered within 5 days after experimental inoculation (5,6). Based on the known physiopathology of monkeypox disease, treatment should be initiated as soon as possible after diagnostic confirmation in an immunocompromised host and/or in case of severe disease.

Treatment duration for monkeypox disease has not been assessed precisely.

Treatment and Duration	Route	Dose	Precaution for use and contra-indications	Additional remark
Tecovirimat First choice antiviral against MPX Duration: 14 days and/or until lesions recovery, whatever happens first	Oral	Adults and children > 40kg: 600 mg bid Children 25-40 kg: 400 mg bid Children 13-25 kg: 200 mg bid NOT INDICATED for children < 13 kg	To be taken with a lipid-rich meal No adaptation for renal or hepatic disease Drug-Drug interactions to consider (repaglinide, risk of hypoglycemia, midazolam, interactions with some HIV treatments (https://hiv-druginteractions.org/checker) Only limited animal data are available regarding tecovirimat use during pregnancy, these data did not showed any embryogenic nor teratogenic effects. Use in children should be discussed with the patient and/or the representative as well as the treating pediatric infectious disease specialist.	Can be given by naso-gastric tube (capsule can be opened) or mixed with water or milk for patients with difficulty in swallowing Monitoring of renal function is recommended in pediatric patients < 2 years of age, given theoretical concerns that renal immaturity in young pediatric patients may result in higher exposure of hydroxypropyl-β-cyclodextrin, an ingredient in IV tecovirimat.
	IV	Depending on body weight Administration over 6 hours 3-35 kg: 6 mg/kg bid 35-120 kg: 200 mg bid >120 kg: 300 mg bid		IV form not available in Switzerland
Cidofovir Only in specific cases not suitable for oral use or with clear contre-indications to tecovirimat	IV	5 mg/kg once a week, with oral probenecid	High renal toxicity. Serum creatinine and urine protein must be checked before each dose administration. No use during pregnancy unless critically ill and other therapy options not available Use in children should be discussed with the patient and/or the representative as well as the treating pediatric infectious disease specialist.	Refer to https://swissmedicinfo.ch/ In absence of available evidence on treatment duration we recommend a once weekly dose for 2 weeks. Depending on the clinical evolution the treatment can then be extended once every 2 weeks until clinical recovery (Recommendation based on no evidence)
	Topical	Cream or gel 1%		To be prepared by a pharmacist

All patients should be encouraged to be included in observational cohorts or clinical trials to help better understand the disease. In Switzerland, the Mosaic cohort is implemented and all patients with a documented MPXV disease should be encouraged to participate.
Pregnant women should be encouraged to be included in the POXPREG cohort (Registry on Monkeypox and pregnancy, contact: poxpreg@chuv.ch).

3. Antibiotic therapy

During the natural course of monkeypox disease, mild erythema frequently surrounds vesicular, popular, or umbilicated lesions, and usually doesn't require antibiotics.
Antibiotic therapy is indicated only in cases of secondary bacterial superinfection of skin lesions and/or abscess in association with appropriate drainage.

4. Other considerations:

Ensure appropriate follow-up even in cases of isolation. Telemedicine may be used. Mental health status should be assessed by the treating physician in all patients, and patients should be referred to a specialist in case of need.

Testing and treatment of concomitant STI:
In one large case series of patients infected by MPXV, who acquired their disease through sexual activity, concomitant sexually transmitted infections have been reported in up to 30% of the cases(15).

HIV test should be done in all cases of MPXV infection when the HIV status is not documented. Recent case series have shown that 30-40% of patients were people living with HIV and 60% were on HIV PrEP.

STI empiric treatment may be considered when appropriate sampling cannot be conducted due to laboratory biosafety reasons, in case of urethral, ano-rectal or ulcerative muco-genital lesions.

Precautions after resolution of acute disease:
Monkeypox virus DNA has been retrieved from semen during acute disease and up to 54 days after the beginning of the symptoms, at high CT values(16), and has been shown to cause a cytopathic effect in inoculated cells up to 6 days after symptoms onset(17). Attempts so far to grow the virus from semen samples collected more than one week after the beginning of symptoms have failed(18). While higher viral loads usually correlate with the presence of infectious virus(19), no large case series and/or longitudinal follow-up allows for a definitive answer to the question of whether semen can remain infectious after the resolution of skin lesions.
Although data regarding persistent viral detection in semen and potential transmission is very scarce, we recommend the use of condoms during sex for 8 weeks after complete recovery.
This recommendation will regularly be updated with more data becoming available.

5. Management of contacts

Antiviral therapy is not recommended as PEP for contacts outside of a clinical trial.
Vaccines recommendations are edicted by the Federal Commission for Vaccination; guidance is available here.
Isolation of contacts is not recommended. Contacts should be advised to monitor themselves for 21 days after the contact, and to reduce their contacts and to quickly look for medical care in case of appearance of symptoms.

6. References and link to international recommendations

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International guidance is constantly updated and can be found in following websites:

https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html

https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/monkeypox

https://apps.who.int/iris/rest/bitstreams/1432076/retrieve

7. Appendix