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ORIGINAL ARTICLE

Monkeypox Virus Infection: Donor and Candidate Evaluation for Solid Organ Transplantation

Wanessa Trindade Clemente[1,*], Raquel Stucchi[2], Daniel Wagner Santos[3], Edson Abdala[4], Ligia Pierrotti[4], Guilherme Santoro-Lopes[5]

1. Universidade Federal de Minas Gerais – Faculdade de Medicina – Departamento de Propedêutica Complementar – Belo Horizonte/MG – Brazil 2. Universidade Estadual de Campinas – Campinas/SP- Brazi 3. Universidade Federal do Maranhão – Hospital Universitário Presidente Dutra – São Luís (MA) – Brazil. 1 4. Universidade de São Paulo – São Paulo/SP – Brazil 5. Universidade Federal do Rio de Janeiro – Rio de Janeiro/RJ – Brazil.

*Corresponding author: wanclemente@yahoo.com.br

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ABSTRACT

Contextualization: Since May 2022, cases of monkeypox (mpox) have been reported in several countries, with evidence of community transmission. In the current scenario, transmission has been identified in different continents, related to the local spread of the virus by intimate inter-human contact. **Objective:** The purpose of this article is to inform the transplant community about the possible implications of the disease for the population of transplant recipients and their donors. **Method:** This article presents guidelines for adapting the evaluation of donors and candidates for organ transplants, bearing in mind the potential risks resulting from the emergence of mpox in our midst. It is important to consider that this document reflects the opinion of specialists given the scarce evidence currently available. **Results and Conclusions:** Donor assessment and management recommendations are based on the potential risk of monkeypox vírus (MPXV) transmission. The risk of transmission by transplantation is estimated to be low, taking into account the uncertainty about the duration of viremia in patients with mpox and the presence of viable virus in cells and tissues. It is recommended, however, that the physicians responsible for the patient are alert to evidence of infection and that they activate or notify the institutions in case there are indications of transmission through the transplant.

Keywords: Monkeypox; Infection in transplants; Diseases transmitted by the donor.

Infecção por Vírus Monkeypox: Avaliação do Doador e do Candidato ao Transplante de Órgãos Sólidos

RESUMO

Contextualização: Desde maio de 2022, casos de monkeypox (varíola dos macacos ou mpox) foram relatados em vários países, com evidências de transmissão comunitária. No cenário atual, temos transmissão identificada em diferentes continentes, relacionada com disseminação local do vírus por contato íntimo inter-humano. **Objetivo:** O objetivo desse artigo é informar a comunidade transplantadora sobre as eventuais implicações da doença para a população de receptores de transplantes e seus doadores. **Método:** Nesse artigo apresenta-se as orientações para adequar a avaliação de doadores e de candidatos a transplantes de órgãos, tendo em vista os riscos potenciais decorrentes da emergência de mpox em nosso meio. É importante considerar que este documento reflete a opinião de especialistas diante das escassas evidências atualmente disponíveis. **Resultados e Conclusões:** As recomendações de manejo e avaliação do doador baseiam-se no risco potencial da transmissão do vírus monkeypox (MPXV). Estima-se que o risco de transmissão pelo transplante seja baixo, levando-se em conta a incerteza sobre a duração da viremia em pacientes com mpox e a presença de vírus viável em células e tecidos. Recomenda-se, no entanto, que os médicos responsáveis pelo paciente estejam alerta para as evidências de infecção e que acionem ou notifiquem as instituições caso haja indícios de transmissão pelo transplante.

Descritores: Monkeypox; Infecção em transplantes; Doenças transmitidas pelo doador.

INTRODUCTION

Since May 2022, cases of monkeypox (mpox) have been reported in several countries, with evidence of community transmission.[1] Several reported cases were not directly related to travel to an endemic area of the disease. Until then, the occurrence of the disease in non-endemic countries was generally of an imported nature and associated with travel to endemic areas or resulting from contact with animals from such areas. In the current scenario, we have a different epidemiological pattern, with transmission identified on different continents, related to local spread of the virus through intimate inter-human contact, predominantly among individuals who self-identify as men who have sex with men (MSM) and report multiple sexual partners. Thus, on July 23, 2022, the World Health Organization (WHO) recognized this outbreak as a Public Health Emergency of International Concern, considering the increase in cases in non-endemic areas.[2] As of February 17, 2023, 86,017 cases have been reported in 103 countries.[1] Until the same date, 10,825 cases were confirmed in Brazil, registering 15 deaths.[3] The case definitions proposed by the WHO and adapted by the Brazilian Ministry of Health to guide the recognition and reporting of cases are described in Table 1.[4,5]

Table 1. Definitions of monkeypox cases

Category	WHO definition	Definition of the Brazilian Ministry of Health[a]
Suspect Case	A person who had contact[b] with a probable or confirmed case of mpox within the 21 days before the onset of signs or symptoms and who has any of the following symptoms: acute onset of fever (>38.5°C), headache, myalgia (muscle pain/body aches), back pain, profound weakness or fatigue OR A person who, as of January 1, 2022, has presented with an unexplained acute skin rash, mucosal lesions or lymph node enlargement. The rash can include single or multiple lesions in the anogenital region or anywhere else on the body. Mucosal lesions can be single or multiple, oral, conjunctival, urethral, penile, vaginal or anorectal. Anorectal lesions may also manifest as anorectal inflammation (proctitis), pain and/or bleeding. AND In which the clinical picture is not fully explained by other common causes of acute rash listed below among the possible differential diagnoses.	Individual of any age who, as of March 15, 2022, presents with a sudden onset of an acute rash suggestive of mpox, single or multiple, on any part of the body (including the genital region), with or without adenomegaly or a report of fever AND History of intimate contact with a stranger(s) and/or casual partner(s) in the last 21 days before the onset of signs and symptoms OR Have an epidemiological link[b] with a suspect, probable or confirmed case of mpox in the 21 days before the onset of signs and symptoms OR History of travel to an endemic country or one with confirmed cases of mpox in the 21 days before the onset of signs and symptoms OR Have an epidemiological link[b] with people with a history of travel to an endemic country or country with confirmed cases of monkeypox since March 15, 2022, in the 21 days before the onset of signs and symptoms.
Probable Case	An individual who meets the definition of a suspect case but without laboratory confirmation of infection by a specific molecular test for MPXV and who presents one or more of the following criteria: •Have an epidemiological link[b] with a probable or confirmed case of mpox in the 21 days before the onset of symptoms; • Identifies as a man who has sex with men; • Had multiple and/or casual sex partners in the 21 days before the onset of symptoms. • Has detectable levels of anti-orthopoxvirus (OPXV) IgM antibody (within 4 to 56 days after rash onset) or a four-fold increase in IgG antibody titer in the absence of recent smallpox/mpox vaccination or other exposure known to OPXV. •Has a positive test result for OPXV infection not specific for MPXV.	suspect case, submitted to clinical and epidemiological investigation AND that developed a clinical picture compatible with mpox, but without the possibility of laboratory confirmation by real-time PCR and/or sequencing.
Confirmed Case	An individual who meets the suspect case definition and who is laboratory confirmed by MPXV-specific molecular testing (real-time PCR or sequencing).	Suspect case, submitted to clinical and epidemiological investigation AND that had a clinical picture compatible with mpox AND had laboratory confirmation by real-time PCR and/or sequencing.

Continua...

Table 1. Continuation.

Category	WHO definition	Definition of the Brazilian Ministry of Health[a]
Discarded case	An individual who meets the definition of a suspect case with a "Negative/Not Detectable" laboratory test result/report for mpox by molecular diagnosis (Real-Time PCR and/or Sequencing) OR a suspect case in which, during clinical, epidemiological and another compatible disease was diagnosed [c] with the picture presented by the patient. However, laboratory diagnosis of a sexually transmitted infection does not rule out the possibility of co-infection with MPXV.	An individual who meets the definition of a suspect case with a "Negative/Not Detectable" laboratory test result/report for MPXV by molecular diagnosis (real-time PCR and/or sequencing) OR A suspect case that during the clinical, epidemiological and laboratory investigation was diagnosed as another disease compatible with the observed condition [c] except STI.

[a] Any individual who fits the definition of a suspected or probable case of mpox by the Brazilian Ministry of Health must be immediately notified and must undergo a laboratory test for diagnostic confirmation, using the RT-PCR method for detecting viral DNA in the mucocutaneous lesion material[23] [b] Contact (epidemiological link) is characterized by the history of exposure to a potentially transmitting individual in any of the following situations: close and prolonged contact without respiratory protection; direct physical contact, including sexual contact; contact with contaminated materials such as clothing or bedding. The risk of transmission is present from the onset of the first symptoms of the case until the complete healing of the lesions, characterized by the formation of a new layer of skin after the peeling of the crusts. [c] The differential diagnosis of mpox includes chickenpox, herpes zoster, measles, herpes simplex, Zika, dengue fever, Chikungunya, Staphylococcus spp. bacterial skin infections, scabies, disseminated gonococcal infection, primary or secondary syphilis, chancroid, lymphogranuloma venereum, inguinal granuloma, molluscum contagiosum, allergic reaction (for example, to plants), among others[1]. mpox: monkeypox; MPXV: Monkeypox virus; OPXV: Orthopoxvirus; STI: sexually transmitted infection.

As with other emerging infections, the potential implications for the organ transplant recipient population are clear and will remain relevant. Although there is a current trend toward reducing the number of new cases of the infection, the possibility of a future resurgence of transmission cannot be ruled out. Despite the scarce investigation in this population, it is reasonable to assume that immunosuppression may worsen the clinical course and prognosis of recipients who acquire the infection after transplantation or within the three weeks preceding surgery. It is also plausible that, as with other viral pathogens, the infection can be transmitted by organ and tissue donation, even after the resolution of the clinical manifestations of the infection in the donor, which is a risk that needs to be considered even in the momentary absence of evidence to confirm this hypothesis. In this sense, the transplant community should be constantly updated regarding mpox screening and clinical management protocols. Transplant recipients should be considered a priority group for prevention and treatment when the latter is indicated.

In this article, we present guidelines to adapt the evaluation of donors and candidates for organ transplants, given the potential risks arising from the emergence of mpox in our environment. Given the current scarce evidence, it is important to consider that this document reflects specialists' opinions. However, revisions to the guidance are expected as knowledge on this topic advances.

Etiology and Epidemiology

Monkeypox virus (MPXV), of the genus *Orthopoxvirus*, is a double-stranded DNA virus, similar to the smallpox virus and *Vaccinia* virus. Two strains are responsible for disease cases in Central and West Africa. The two original genetic lineages: Central Africa (clade 1) and West Africa (clade 2) have different lethality rates.[6] Initial analysis indicated that the genomic sequences of the virus causing the current outbreak are similar to those of the strains circulating in the outbreak that occurred in Nigeria between 2018 and 2019. It is also suggested that the current outbreak could be attributed to another lineage, the so-called clade 3, which would explain the rapid adaptation of the virus to humans.[7]

The virus is traditionally transmitted by contact with infected animals (mainly rodents), whose reservoirs remain unknown. Person-to-person transmission can occur through contact with respiratory droplets or skin lesions, including during sexual activity.[8–10] Also, through indirect contact with personal clothing, contaminated bedding or through the placenta (in pregnancy) and during childbirth.

Another concern is fecal microbiota transplantation, an established treatment for recurrent *Clostridioides difficile* infection. Recently, concern about the possible transmission of the SARS-CoV-2 virus through feces has led to the temporary suspension of the procedure in some countries. In this new context, the concern with the transmission of MPXV through this procedure is justified. The scientific communities still need to determine a recommendation for testing for MPXV in donors involved in microbiota transplantation. However, the questionnaires of signs and symptoms need to be carried out rigorously to avoid adverse events.[11–13]

Clinical Manifestations and Treatment

mpox manifests itself after an incubation period of 5 to 21 days, characterized by cutaneous lesions, initially vesicular, which evolve with central umbilication and formation of crusts and subsequent healing and can occur in any part of the body. The 2022 cases are characterized by mucocutaneous lesions located mainly in the genital and perianal regions, with frequent associated lymph node enlargement.[14,15] Systemic signs and symptoms, such as fever, myalgia and headache, may precede the condition. Some patients may evolve with signs of proctitis, penile edema, or odynophagia as a clinical manifestation of the disease without

necessarily having cutaneous and mucous lesions. In immunocompetent patients, the disease is usually self-limiting, with complete resolution of the lesions within 2 to 4 weeks.[16]The reported lethality rate is around 0.03%, but it can be complicated by secondary bacterial infection, pneumonitis, encephalitis, keratitis, among others.[15] Children under 8 years old, pregnant women and people with immunosuppression may be at greater risk of having more severe symptoms or dying.[17]

Prevention

Concerning prevention, it is worth mentioning the existence, so far, of three vaccines considered by the WHO as appropriate for use: 1) MVA-BN (Jynneos®, Imvamune®), which uses an attenuated and non-replicating strain of the *vaccinia* virus, which can be administered to immunosuppressed patients; 2) ACAM2000, which uses attenuated, replication-competent virus, and therefore cannot be administered to immunosuppressed patients; and 3) LC16, which uses a highly attenuated and minimally replicating viral lineage, and can be administered to immunosuppressed patients. However, the latter is manufactured in Japan to serve the local population, with no intention of increasing production.

mpox vaccine can be given as primary prevention (pre-exposure) to individuals at high risk of exposure. People most at risk of exposure in the current outbreak in many countries are men who have sex with men (MSM), some with multiple sexual partners. Others at risk may include individuals with multiple casual sexual partners, sex workers, healthcare workers at risk of repeated exposure, clinical and/or research laboratory workers who work with *Orthopoxviruses*, and members of the outbreak response team. Preventive post-exposure vaccination (PEPV) is another possible strategy. It is recommended for asymptomatic contact of cases whose first exposure ideally occurred within four days or up to 14 days before.[18–20]

Mpox in Organ Transplant Recipients

The available literature on the clinical presentation and course of mpox in organ transplant recipients is sparse. Recently, Raccagni et al. described a case of mpox in a patient with amyloidosis who underwent a heart transplant in 2018 and subsequent autologous hematopoietic stem cell transplant (HSCT) in 2019, who achieved a complete response to daratumumab treatment in 2021.[21] The patient had received smallpox vaccination in his youth. The patient was on cyclosporine and mycophenolate mofetil when the clinical manifestations appeared. He developed fever and multiple vesicular lesions after recent sexual contact with someone known to have mpox. Upon examination, there were more than 30 painful, vesicular, umbilicated lesions in the genital area, with a single painful, ulcerated lesion on the tongue. There was adenopathy in cervical and inguinal chains. PCR was positive in swabs collected from the oropharynx, secretions from skin lesions, rectal swabs, urine and plasma. Positive viral cultures were obtained from oropharyngeal swabs, skin lesions and urine. Due to the accentuation of the clinical manifestations observed in the first days of evolution, it was decided to reduce the dose of mycophenolate. Although it evolved with clinical improvement, with desquamation of the crusted lesions in the genital area and progressive regression of the ulcer on the tongue on D23 of disease, the genetic material of mpox was still detected in urine and seminal fluid and associated with viral isolation in culture. The PCR collected on D60 after the onset of symptoms was negative.

In another report, Schmalzle et al. describe the case of a 62-year-old man who, five years ago, had undergone a kidney transplant (deceased donor) due to end-stage renal failure resulting from HIV-associated nephropathy.[22] The patient complained of fatigue, chills, severe rectal pain during defecation, mild dyspnoea on exertion, and decreased sense of taste. He reported unprotected anal intercourse with an unknown partner three weeks earlier. On subsequent days, painful inguinal lymph node enlargement and skin eruptions on the face and limbs suggestive of mpox appeared. Molecular tests on samples of respiratory droplets and secretion from skin lesions have demonstrated the occurrence of co-infection with SARS-CoV-2 and MPXV. Faced with the diagnoses, the assistant team decided to suspend azathioprine, maintaining only monotherapy with tacrolimus. On the 12th day of evolution, when the patient had about 50 skin lesions, tecovirimat was started and maintained for 14 days. Although a progressive regression of the cutaneous lesions was observed from the second day of use of the antiviral, the appearance of a new solitary lesion was observed on the sixth day of treatment. It evolved to complete healing of the skin lesions after 41 days. The symptoms previously attributed to COVID-19 disappeared without the need for any therapeutic intervention.

Although it is impossible to draw conclusions based on such limited clinical experience, these reports highlight some already foreseen aspects. For example, the possibility that immunosuppression may be associated with a greater intensity of clinical manifestations justifies doubts regarding its management during the infection. Some additional considerations can be made regarding antiviral therapy. The intravenous formulation of tecovirimat is discouraged in patients with impaired renal function due to the risk of accumulation and nephrotoxicity of the hydroxypropyl-β-cyclodextrin vehicle. Brincidofovir, a lipid conjugate that is an oral prodrug of cidofovir, was conditionally approved in June 2021 in the United States of America for treating smallpox. There are no studies on the efficacy of brincidofovir in the treatment of MPXV virus infection in humans. However, this proved effective against *Orthopoxvirus in vitro* and animal studies. Currently, its use is accepted as an alternative in patients who were not responsive or can not be treated with tecovirimat. In a small case series, three patients with mpox treated with brincidofovir had to discontinue this drug due to hepatotoxicity.[23] *In vitro* and animal studies suggest that cidofovir may be effective in the treatment of

mpox. However, the high incidence of nephrotoxicity demonstrated with its use in the treatment of cytomegalovirus retinopathy in patients with HIV may constitute an important limitation to its use.[24–26]

Evaluation of the Candidate for Organ Transplantation

Given the above, it is advisable to carefully evaluate candidates for transplants to avoid the potential harm of starting immunosuppression in recently infected individuals.

Clinical screening of transplant candidates should include collecting information regarding recent close contact with people or animals with clinically suspected or confirmed diagnosis of MPXV infection, as well as investigation of nonspecific clinical manifestations of infection (fever, myalgia, lymph node enlargement) and skin or mucosal lesions compatible with the disease. If there is clinical suspicion of mpox, it is essential to carry out laboratory investigations to differentiate the occurrence of MPXV infection from other diagnoses (Table 1).[27–29]

Asymptomatic candidates with a history of contact with infected people or animals should be considered unfit for transplantation within 21 days of last known exposure. During this period, they should remain under surveillance for the onset of fever or other manifestations of MPXV infection.

The evaluation of the candidate has been hampered by the absence of data regarding the potential impact of the recent occurrence of mpox on the postoperative evolution of organ transplant recipientes. On the other hand, the retrospective study of a small series of cases showed that it is possible to detect MPXV DNA in blood, urine and respiratory tract samples in the weeks following healing of the cutaneous lesions.[23,30] However, the occurrence of viruses with replicative competence was not investigated in the analyzed clinical samples. Thus, the epidemiological implications of long-term detection of MPXV viral DNA remain unknown.

Considering such gaps in knowledge and weighing the risks and benefits of postponing the transplant, it is proposed that the candidate with a confirmed or probable diagnosis of mpox be inactivated on the transplant list until at least 28 days have elapsed since the start of the clinical manifestations and at least 14 days since healing of all skin lesions.

In situations where there is no urgency to perform the transplant, we suggest postponing the procedure for at least 60 days from the onset of clinical manifestations, maintaining a period of at least two weeks after healing the lesions. In suspected cases that are subsequently discarded, the assessment of immediate suitability for transplantation will take into account the alternative diagnosis that has been established.

General Guidelines in the Context of Donation

The recommendation for donor evaluation is based on the potential risk of MPXV transmission at the time of transplantation, either through the allograft or the blood. However, there are no virus transmission cases by cells, tissues or organs of human origin reported so far. The risk of transmission is estimated to be low, considering the uncertainty about the duration of viremia in patients with mpox and the presence of viable viruses in cells and tissues.[31]

The screening of living and potential deceased donors should include an inquiry about recent exposure to MPXV and the occurrence of clinical manifestations of active infection. Physical examination should seek for of skin and mucosal lesions, including those located in the anogenital regions.

Asymptomatic individuals with a history of contact with confirmed cases must be considered unfit for organ donation for 21 days from the last contact with the confirmed case. As for candidates who urgently need a transplant, the risk-benefit of accepting a deceased donor without manifestations suggestive of MPXV infection but with a history of exposure to MPXV in the previous 21 days must be individually assessed.

In the context of this newly emerging infection, the conduct of donors who have had mpox is the point of greatest divergence in the few documents that formulate recommendations on evaluating organ donors.[32] While part of the documents consider donors suitable from the moment they have presented healing of all skin lesions with re-epithelialization of the affected areas,[30] the British recommendations advice is to consider the donor ready only when eight weeks have elapsed after the clinical cure.[26] The main reason for this divergence concerns the interpretation of the studies by Adler et al..[23] The authors observed in some patients the persistence of positivity in PCR tests in blood samples in the two weeks following the healing of the cutaneous lesions and up to 30 days after the onset of symptoms. They detected MPXV genetic fragments in airway samples for even longer periods in two cases. However, the significance of these findings needs to be clarified, as the study did not use culture assays to assess viral viability in the samples. Because of these aspects, it seems prudent to suggest that individuals infected with MPXV (probable or confirmed) should be excluded from donation for a minimum period of 30 days after the onset of lesions. The exclusion is also valid for at least 14 days after healing the skin lesions (total healing and complete re-epithelialization of the skin). In the case of living donors, we suggest postponing the procedure for at least 60 days after healing the skin lesions. In suspected cases that are later discarded, the assessment regarding immediate suitability for organ donation will take into account the alternative diagnosis that has been established.

CONCLUSIONS

Donor management and evaluation recommendations are based on the potential risk of monkeypox transmission. Due to the scarcity of information in this context, it is recommended that the physicians responsible for the patient remain alert for evidence of infection and notify the responsible administrative bodies in case there is evidence of transmission through transplantation.

CONFLICT OF INTEREST

The authors declares no conflict of interest

AUTHOR'S CONTRIBUTION

All the authors contributed equally in all steps.

DATA AVAILABILITY STATEMENT

All datasets were generated or analyzed in the current study.

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