American Association of Tissue Banks®

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Physicians Council Provides Information on Monkeypox Virus (MPXV)

Introduction

In May 2022, clusters of monkeypox cases appeared in several countries where it is not endemic. On July 23, 2022, the World Health Organization declared monkeypox to be a public health emergency of international concern. The United States (US) Secretary of Health and Human Services announced on August 4, 2022, that he will declare the ongoing spread of monkeypox virus in the United States a Public Health Emergency. As of August 12, 2022, CDC reports there have been 11,177 confirmed monkeypox/orthopoxvirus cases in the US and 31,799 cases worldwide (31,424 reported from countries that have not historically reported monkeypox). At least five US cases have been reported to be in children.

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Monkeypox virus (MPXV)

MPXV is an enveloped double-stranded DNA virus that belongs to the *Orthopoxvirus* genus of the *Poxviridae* family. There are two distinct genetic clades of the monkeypox virus: the central African (Congo Basin) clade and the west African clade. The Congo Basin clade has historically caused more severe disease and was thought to be more transmissible. Preliminary data from polymerase chain reaction (PCR) assays indicate that the monkeypox virus genes detected belong to the West African clade. Various animal species have been identified as susceptible to monkeypox virus.

Prior Outbreaks

Human monkeypox is a viral zoonosis that was first identified in humans in 1970 in the Democratic Republic of the Congo in a 9-month-old boy in a region where smallpox had been eliminated in 1968. Since 1970, human cases of monkeypox have been reported in 11 African countries. In 2003, the first monkeypox outbreak outside of Africa was in the United States of America and was linked to contact with infected pet prairie dogs. Monkeypox has also been reported in travelers from Nigeria to Israel in September 2018, to the United Kingdom in September 2018, December 2019, May 2021 and May 2022, to Singapore in May 2019, and to the United States in July and November 2021.

Transmission

Animal-to-human transmission can occur from direct contact with the blood, body fluids, or cutaneous or mucosal lesions of infected animals. The natural reservoir of monkeypox has not yet been identified,

though rodents are the most likely.

Human-to-human transmission can result from close contact with respiratory secretions, skin lesions of an infected person or recently contaminated objects. Transmission via droplet respiratory particles usually requires prolonged face-to-face contact, which puts health workers, household members and other close contacts of active cases at greater risk. Transmission of monkeypox between people was relatively rare in the past, and the virus normally jumped from animals to humans. Prior to the 2022 outbreak, the longest documented chain of transmission in a community was 9 successive person-to-person infections (not including the current worldwide outbreak). *However, monkeypox is now spreading more efficiently between people.*

Transmission can also occur via the placenta from mother to fetus (vertical transmission which can lead to congenital monkeypox) or during close contact during and after birth. While close physical contact is a well-known risk factor for transmission, it is unclear at this time if monkeypox can be transmitted specifically through sexual transmission routes.

Currently, MPXV is primarily spreading through skin-to-skin contact during sex. The majority of transmission has occurred in MSM to date. Lewis, the WHO's monkeypox expert, said 99% of cases reported outside Africa are among men and 98% of infections are among men who have sex with men, primarily those who have had multiple, recent anonymous or new sexual partners. The virus has been detected outside of MSM, while transmission has been low so far; notably five cases are currently reported in children in the United States.

Signs and symptoms

Incubation period:

- Incubation period is roughly 3-17 days
- A person does not have symptoms and may feel fine
- People are not considered contagious during this period

Prodromal phase:

- The first symptoms include fever, malaise, headache, sometimes sore throat and cough, and lymphadenopathy (swollen lymph nodes)
- Fever and other prodromal symptoms (e.g., chills, lymphadenopathy, malaise, myalgias, or headache) can occur before rash but may occur after rash or not be present at all
- People may be contagious during this period

Rash: Following the prodrome, lesions will develop in the skin and mucosal sites (including mouth, anus, vagina) within 1–3 days of appearance of fever. Classically, the rash from MPXV tends to be more concentrated on the face and extremities rather than on the trunk. It affects the face, and palms of the hands and soles of the feet. Also affected are oral mucous membranes, genitalia, and ocular tissues, including the conjunctivae and the cornea.

The rash typically evolves sequentially from macules (lesions with a flat base) to papules (slightly raised firm lesions), vesicles (lesions filled with clear fluid), pustules (lesions filled with yellowish fluid), and crusts which dry up and fall off. The number of lesions varies from a few to several thousand. In severe cases, lesions can coalesce until large sections of skin slough off.

Rash resolved: Pitted scars and/or areas of lighter or darker skin may remain after scabs have fallen off. Once all scabs have spontaneously fallen off a person is no longer contagious.

The clinical presentation of monkeypox cases associated with this outbreak has been atypical as compared to previously documented reports: many cases in newly affected areas are not presenting with the classically described clinical picture for monkeypox (fever, swollen lymph nodes, followed by centrifugal rash).

Atypical features described include presentation of only a few or *even just a single lesion*, absence of skin lesions in some cases, with anal pain and bleeding, lesions in the genital or perineal/perianal area which do not spread further, lesions appearing at different (asynchronous) stages of development, absence of prodromal period (i.e., the appearance of lesions before the onset of fever, malaise and other constitutional symptoms).

According to CDC, the clinical presentation of monkeypox may be similar to some STIs, such as syphilis, herpes, lymphogranuloma venereum (LGV), or other etiologies of proctitis. The search for lesions consistent with monkeypox should be performed even if lesions consistent with those from more common infections (e.g., varicella zoster, syphilis, herpes) are observed; this is particularly important when evaluating patients who have epidemiologic risk factors for monkeypox.

Clinical course: Monkeypox is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Severe cases occur more commonly among children and are related to the extent of virus exposure, patient health status and nature of complications. Underlying immune deficiencies may lead to worse outcomes. The severity of illness can depend upon the initial health of the individual, the route of exposure, and the strain/clade of the infecting virus.

Complications of monkeypox can include secondary infections, bronchopneumonia, sepsis, encephalitis, and infection of the cornea with ensuing loss of vision.

The case fatality ratio of monkeypox has historically ranged from 0 to 11 % in the general population and has been higher among young children. In recent times, the case fatality ratio has been around 3–6%. No deaths have been reported globally from the current outbreak.

Diagnosis

Laboratory testing:

Confirmation of monkeypox depends on the type and quality of the specimen and the type of laboratory test. Optimal diagnostic samples for monkeypox are from skin lesions – the roof or fluid from vesicles and pustules, and dry crusts. Biopsy also could be done. Polymerase chain reaction (PCR) testing of skin lesion samples is the preferred laboratory test given its accuracy and sensitivity. Lesion samples must be stored in a dry, sterile tube (no viral transport media) and kept cold.

PCR blood tests are usually inconclusive because of the short duration of viremia relative to the timing of specimen collection after symptoms begin and should not be routinely collected from patients.

As orthopoxviruses are serologically cross-reactive, antigen and antibody detection methods do not provide monkeypox-specific confirmation. Serology and antigen detection methods are therefore not recommended for diagnosis or case investigation where resources are limited. Additionally, recent or remote vaccination with a vaccinia-based vaccine (e.g. anyone vaccinated before smallpox eradication, or

more recently vaccinated due to higher risk such as orthopoxvirus laboratory personnel) might lead to false positive results.

Treatment
Many people infected with monkeypox virus have a mild, self-limiting disease course in the absence of specific therapy. However, the prognosis for monkeypox depends on multiple factors, such as previous vaccination status, initial health status, concurrent illnesses, and comorbidities among others.

Currently there is no treatment approved specifically for monkeypox virus infections. However, antivirals developed for use in patients with smallpox may prove beneficial against monkeypox.

The following medical countermeasures are currently available from the Strategic National Stockpile (SNS) as options for the treatment of monkeypox:

- **Tecovirimat** (also known as TPOXX, ST-246)
- **Vaccinia Immune Globulin Intravenous** (VIGIV)
- **Cidofovir** (also known as Vistide)
- **Brincidofovir** (also known as CMX001 or Tembexa)

Monkeypox Vaccines
Two vaccines may be used for the prevention of monkeypox infection in the United States**:**

JYNNEOS vaccine (FDA-licensed for the prevention of MPXV infection)
- JYNNEOS is replication-deficient modified vaccinia Ankara that *does not replicate efficiently in human cells*.
- It is administered as two injections 28 days apart.
- The immune response takes 14 days after the second dose for maximal development.
- According to CDC, there is no visible "take" and as a result, no risk for spread to other parts of the body or other people.

ACAM2000 vaccine (FDA-licensed to prevent smallpox, available against MPXV under an Expanded Access Investigational New Drug application)
- ACAM2000 contains a live *Vaccinia virus* that is replication competent.
- It is administered as one percutaneous dose via multiple puncture technique with a bifurcated needle.
- The immune response takes 4 weeks for maximal development.
- Following a successful inoculation, a lesion (known as a "take") will develop at the site of the vaccination; the lesion may take up to 6 weeks or more to heal.

A. Current Donor Data Collected:
Current donor screening questions in the UDRAI that could obtain information about risk factors for MPXV exposure or infection:
- Q4 and b: Asks about most recent visit to medical provider or visits to medical facility
    - Asks why they were seen – people typically resolve MPXV within 4 weeks or so, and it is the month prior to death that is most important to evaluate
- 5a: Did she/he take any prescription medication recently or on a regular basis

    - Some individuals are being treated for MPXV with antivirals that we are not accustomed to seeing
- Q6: Did they recently have fever, …, swollen lymph nodes, … a rash, sores in the mouth or on skin, …?
    - Not everyone has prodrome in current outbreak
    - Rash characteristics in current outbreak could lead to gaps in historian knowledge
- Q8: Did she/he know anyone who had a smallpox vaccination?
    - ACAM2000 vaccine is approved for use to prevent smallpox, and is therefore a smallpox vaccination – it is being used under expanded access for monkeypox prevention
    - There should be awareness that the individual responding to the questions may not make the link between a vaccination now for monkeypox is "a smallpox vaccination"
    - If donor were exposed to ACAM 2000 vaccine, donor exclusion criteria apply regardless of the reason for the vaccination
- Q10: In past 12 months was she/he bitten or scratched by any pet, stray, farm, or wild animal?
    - Less related to current outbreak, but along with travel history is the more common way one would otherwise be exposed to MPXV
- Q 12: In the past 12 months did she/he have any shots or immunizations…?
    - Some people are being vaccinated – both pre or post-exposure
- Q 15: In the past 12 months, did she/he come into contact with someone else's blood? Q17: accidental needle-stick
    - Blood exposure to someone infected could transmit MPXV if they are in the (brief) viremic phase, although not most common/expected route
- Q18: In the past 12 months did she/he have a sexually transmitted infection…What was it?
    - MPXV may or may not be a response, but could consider recent STI as something to raise index of suspicion, IF historian is aware
- Q26: Did she/he ever travel or live outside the US or Canada?
    - Most sources talk about considering travel history as part of clinical assessment, there are emerging trends, could raise index of suspicion if in area with a lot of cases, but for MPXV "a lot" is a relative term
- Q45: Are there other medical conditions you are aware of that we have not discussed?

Physical examination:

- Rashes
- Lymphadenopathy

B. Information Provided by Other Organizations:

- Centers for Disease Control and Prevention. Monkeypox. Last reviewed [at CDC] July 29, 2022.
- Eye Bank Association of America (EBAA). Monkeypox Information Alert. July 6, 2022.
- European Centers for Disease Control (ECDC). Fact Sheet for Health Professionals on Monkeypox. June 14, 2022.
- World Health Organization. Monkeypox. July 12, 2022.

- Organ Procurement and Transplantation Network. Information regarding increase in worldwide cases of monkeypox. May 27, 2022.
- The NOTIFY MPHO Safety Group position statement: Monkeypox and MPHO Safety

C. Summary and Recommendations:

On July 23, 2022, a public health emergency of international concern (PHEIC) was declared by the WHO. As of August 2022, thousands of confirmed MPX cases in dozens of countries have been reported. Many cases involve men who have sex with men, confirming that MPX may be spread by close contact during sexual activity. There has been no reported transmission via (deceased or living donor) tissue or ocular transplantation thus far. Animal studies and studies of the recent human cases show presence of the pathogen in human tissues and body fluids (See refs. Antinori, Adler, Noe).

- At present, there has been no guidance or recommendations provided by the FDA regarding HCT/P donor screening and testing for monkeypox, which is not currently a relevant communicable disease agent or disease.
- The Eye Bank Association of America (EBAA) recently recommended deferral of potential ocular tissue donation if the donor has history of a new rash with characteristic features of MPX, close contact with a confirmed case of MPX, and/or positivity for Orthopox virus or MPX virus within 21 days of death.
- The ECDC cautions that a very meticulous donor history should be performed to identify any recent travel or exposure to human or animal MPX. It also recommends that an asymptomatic donor with a history of exposure should be deferred for a minimum of 21 days. Even after this period, careful physical assessment of the donor should take place to rule out any signs of infection.
- The Notify MPHO safety group suggests that individuals diagnosed with monkeypox should not be eligible to donate during the clinical course of the disease and for two weeks after the end of the symptoms and disappearance of crusted vesicular lesions. If the illness required hospitalization, the length of deferral is recommended to be longer (up to three months). Close contacts are recommended to be excluded from donation for the period of maximal or double average incubation from the date of exposure.

The tissue establishment's medical director is responsible for evaluating donors for the possibility of communicable disease transmission via HCT/Ps; this is an emerging infectious disease that has a brief viremic phase and the virus disseminates systemically. The MPX virus can be found both intracellularly and extracellularly in many tissue types. A thorough medical and social history is crucial. As with many infectious diseases, the most vulnerable tissues include those that are minimally processed, including fresh grafts, live cells, stem cells, and those containing live cells. Tissues that are decellularized and terminally sterilized by a validated process carry the least risk of transmission.

Risk factors for exposure to MPXV:

- Direct contact with MPXV-infected individuals, including household & healthcare exposure (without proper PPE)
    - Direct contact includes extended, close, face-to-face, sexual, & fomite contact as well as direct contact with skin lesions
- Those with multiple sexual partners
- Those working at laboratories that handle MPX virus or MPX virus-positive specimens
- Those who slaughter wild game in an endemic region
- Those working at large animal breeding facilities

Individuals at risk for MPX complications:

- Immunocompromised
- Those who are pregnant or breast-feeding
- Young children (<8)
- Those with a history of atopic dermatitis, eczema, or active exfoliative conditions
- Those with multiple comorbidities

Currently, AATB is unaware of any MPXV testing recommendations.

- FDA advises that only swab samples taken directly from a lesion (rash or growth) when testing for the monkeypox virus. Testing samples not taken from a lesion may lead to false test results.
- The CDC's FDA-cleared non-variola orthopoxvirus test can detect monkeypox from a lesion sample. This assay is available at many laboratories throughout the country.
- Lab-developed assays may also be available, which must be validated by the laboratory.
    - Whole genome sequencing is the gold standard for distinguishing between the different Orthopox viruses.
- Enzyme-linked immunosorbent assay (ELISA) can detect specific IgM and IgG antibodies in the serum of MPX patients after 5 and 8 days of infection, respectively. The specificity is reduced due to cross-reactivity between the MPX virus and other poxviruses. These tests are not suitable for deceased donor testing.

D. Conclusion

AATB will continue to monitor the MPX outbreak and global guidance as it becomes available.

If you have questions, please contact Dr. Melissa Greenwald, greenwaldm@aatb.org.

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