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REVIEW

Monkeypox: A review of data essential in primary care

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Abstract

Monkeypox is known to be endemic in Africa, but recently, the unusually increasing number of cases of monkeypox in non-endemic countries has caught the attention of the world. The World Health Organization has declared the monkeypox outbreak a public health emergency. The spread pattern is unlikely associated with the previous outbreak outside of Africa, which is related to travelling or contact with exotic animals. The current outbreak is linked to sexual history and presents with atypical localised genital eruptions with an unpredictable onset of viral prodromal symptoms. Although the monkeypox virus is not easily transmittable compared with severe acute respiratory syndrome coronavirus 2, anyone who has been in close contact with a patient with monkeypox is at risk. Most patients will present to a primary care centre for assessment and treatment; therefore, it is important to increase awareness of the infection among primary care providers for early recognition of monkeypox, containment of the outbreak and prevention of healthcare-associated infection. A physician who suspects any patient with monkeypox should notify local or state health authorities immediately.

Introduction

Monkeypox is a zoonotic disease caused by the monkeypox virus, which belongs to the orthopoxvirus in the *Poxviridae* family. The monkeypox virus was first identified in 1958 when research monkeys became ill.[1] In 1970, the first case of infection with the monkeypox virus in humans was found in the Democratic Republic of the Congo when a child was initially suspected of having smallpox. The illness subsequently spread to several nations in central and western Africa and became endemic.[2] Two distinct clades have been identified: the Congo Basin clade (Clade I) and the West African clade (Clade II). The case fatality ratio for monkeypox in Africa is 10% for the Congo Basin clade, with the highest rates occurring in children and individuals without vaccination.[3] Immunity protection against the monkeypox virus was previously achieved with smallpox vaccination. Subsequently, owing to waning immunity and lack of vaccination efforts, monkeypox has emerged as the most prevalent orthopoxvirus after smallpox eradication.[4]

Since May 2022, monkeypox has been reported in a few non-endemic countries such as Austria, Belgium, France, Germany, Italy, Portugal, Spain and Sweden. Most cases have no direct travel links to an endemic area.[5] Subsequently, numerous monkeypox cases and clusters have been reported simultaneously in non-endemic and endemic countries across vast geographical regions. On 23 July 2022, the World Health Organization (WHO) declared the global monkeypox outbreak as a public health emergency of international concern. From January to October 2022, about 77,000 cases of monkeypox and 36 deaths across 109 countries have been reported to the WHO, with more than 65% of cases reported from American regions and 32% of cases from European regions.[6] Several monkeypox-related deaths reported were due to complications, such as encephalitis, and mainly occurred among immunocompromised patients.[7] In the current outbreak, most cases reported are among young men, with the transmission through skin and mucosal contacts during sexual activities; the most commonly reported sexual orientation is men who have sex with men (MSM) in connected social and sexual networks. According to some preliminary studies, the reproductive number (R0) is 0.8, and among MSM, the R0 is above 1. The R0 is the average number of individuals infected with monkeypox who can pass the virus to someone else.[8] A higher prevalence of human immunodeficiency virus infection has been reported among patients with monkeypox.[6] Cases are expected to continue to occur in other vulnerable populations and communities.

To date, no monkeypox case has been reported in Malaysia, although nearly all neighbouring countries have recorded cases, with Singapore reporting the highest number at 19, according to the United States (US) Centers for Disease Control and Prevention (CDC).[9] The experience of countries with monkeypox highlights the importance of investing in preparedness, mainly keeping surveillance systems capable of identifying the emergence of infectious diseases. The government also provides regular updates to healthcare workers on the monkeypox situation, including guidelines for recognising suspicious cases and managing confirmed cases.[10] Close contacts of patients with monkeypox have been offered smallpox vaccination as post-exposure prophylaxis.[10] Our country remains at risk of monkeypox importation with the opening of borders. Therefore, it is important to provide information and increase awareness about monkeypox for early recognition and prevention of an outbreak, especially among primary care providers.

Transmission

Monkeypox can be transmitted through contact with skin lesions, bodily fluid or respiratory droplets of infected animals directly or indirectly via contaminated fomites. The infection has been found in many animals, including squirrels, rats, mice and different species of monkeys. Eating inadequately cooked meat of infected animals is also a possible risk factor.[11] Historically, monkeypox does not spread easily between people but may occur as herd immunity to orthopoxviruses decreases.[12] Human-to-human transmission can result through direct contact with skin or mucosal lesions (oral, pharyngeal, ocular, genital and anal) or respiratory secretions of an infected person and contaminated objects. Transmission via droplet respiratory particles usually requires prolonged face-to-face contact, making household members, healthcare workers and other close contacts of active cases at a higher risk.[13] Infections among healthcare workers have been documented, suggesting transmission of monkeypox through contact with contaminated bedding or through an accidentally contaminated needle stick injury.[3,14] Transmission can also occur via the placenta from the mother to the baby, which can lead to congenital monkeypox, or via close contact during and after delivery.[15] In the current outbreak, the temporal association between sexual intercourse, increased inguinal lymphadenopathy and recurrence of rashes suggests a genital reservoir of the monkeypox virus, as reported with many other emerging viruses; however, this theory warrants more research in a larger cohort of patients.[16]

Clinical features

Monkeypox has clinical symptoms that are quite similar to those of smallpox, but which are milder. The incubation period of monkeypox is usually from 6 to 13 days but can range from 5 to 21 days.[15]

Classic monkeypox infection can be divided into two stages: prodromal stage and rash stage. In the prodromal stage, which can last between 1 and 4 days, the symptoms include fever (temperature of >38.5°C), headache, sore throat, myalgia, fatigue, and lymphadenopathy. Lymphadenopathy is a key differentiating feature of monkeypox from other diseases, such as smallpox, chickenpox or measles.[15] Lymph node swelling may occur on the bilateral or unilateral side of the submandibular, cervical, axillary or inguinal region.[17] Within 1 to 3 days after the onset of fever, the rash stage begins. Rashes appear first on the face and spread to the extremities (arms and legs) (**Figure 1**), including the palms and soles. They vary in size and evolve progressively from macules to papules, vesicles (**Figure 2**), pustules (**Figure 3**), crusts and scabs, which eventually fall off during healing. The rashes usually concentrate more on the face (95%), palms (**Figure 4**) and soles of the feet (75%) than on the trunk, which can be described as centrifugal distribution. Skin lesions are often at the same stage of development (monomorphic). This disease may also affect the oral mucus membranes, genitalia, conjunctiva and cornea.[15]

In the current global outbreak, the clinical features of monkeypox differ from those of the previous reported classic cases. Patients are exhibiting more mucosal lesions, which localise in the genital or perineal/perianal region as well as on the eyes and in the mouth.[18] The rashes may be confined to only a few lesions, not always appear on the palm and sole and appear at different stages of evolution. Notably, the rashes may develop prior to the development of typical prodromal symptoms, such as fever and fatigue. Anorectal pain and bleeding have also been frequently reported in the current outbreak.[7,18] This makes the diagnosis challenging; a high index of suspicion of monkeypox is required in the current outbreak.

Figure 1. Monkeypox lesions (Public Health Image Library #2329).

Figure 2. Vesicle (https://www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates).

Figure 3. Umbilicated pustule (https://www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates).

Figure 4. Maculopapular lesions on the palms of a patient with monkeypox (Public Health Image Library #12761).

Monkeypox is usually a self-limiting disease with symptoms lasting from 2 to 4 weeks. Infected individuals may be contagious from 1 day before the rashes appear and up to 21 days after the initial symptoms or until all skin lesions have formed scabs or fallen off and no other symptoms are present.[11]

Severe cases occur more commonly among children, pregnant women and immunodeficient individuals. The complications of monkeypox can include secondary skin infections, bronchopneumonia, sepsis, encephalitis and keratitis with possible loss of vision.[11]

Differential diagnosis

Patients commonly present with rashes in primary care settings, and there are many possible diagnoses, such as chickenpox, hand–foot–mouth disease, measles, scabies and syphilis (**Table 1**). History of recent travel to endemic areas, interaction with imported wild animals and contact with an infected patient could help establish a differential diagnosis, but clinical features are also important. The main clinical diagnostic problem is the differentiation of human monkeypox from chickenpox, as both have some similar features in terms of appearance (**Table 2**).[19,20] If a patient presents with an acute genital eruption, monkeypox, syphilis, lymphogranuloma venereum, chancroid and granuloma inguinale should be considered as differential diagnoses.[21]

Table 1. Differential diagnosis.

• Chickenpox
• Hand–foot–mouth disease
• Measles
• Molluscum contagiosum
• Scabies
• Yaws
• Syphilis
• Bacterial skin infections
• Drug-associated allergies

Table 2. Characteristics of monkeypox, chickenpox, hand–foot–mouth disease (HFMD) and measles.

Characteristics	Monkeypox	Chickenpox	HFMD	Measles
Incubation period	5–21 days	10–21 days	3–6 days	10–15 days
Prodromal period	1–4 days	0–2 days	2–3 days	2–4 days
Rash period	14–28 days	10–21 days	5–10 days	4–6 days
Fever	Yes (38.5–40.5°C)	Yes (up to 38.8°C)	Yes (up to 38.3°C)	Yes (up to 40.5°C)
Lymphadenopathy	Yes	No	No	No
Lesion on the palms or soles	Yes	Rare	Yes	Rare
Lesion appearance	Firm/rubbery and deep vesicles, well-circumscribed, umbilicated	Superficial vesicles, surrounded by irregular erythema ('dew drop on rose petal')	Small vesicles (2–8 mm), elongated on an erythematous base (**Figure 6**)	Maculopapular rash (non-vesicular rash)
Lesion distribution	Generalised with centrifugal distribution	Generalised with centripetal distribution (**Figure 5**)	Hand, soles, buttock, genitalia	Start on the head and spread, may reach the hands and feet
Lesion progression	Slow, lesions present at the same stage of development on any area (monomorphic)	Rapid, lesions often in multiple stages of development (polymorphic)	Rapid, lesions present in different stages	Rapid, lesions present in different stages
Classic features	Lymph node swelling	Itchy rash	Oral ulcers	Koplik spots

Figure 5. Vesicular lesions with a centripetal distribution in a patient with chickenpox (Public Health Image Library #2882).

Figure 6. Elongated vesicular lesions in a patient with hand–foot–mouth disease (used with permission from the Mayo Foundation for Medical Education and Research).

Case definition

The WHO developed interim guidelines of surveillance case definitions for the current monkeypox outbreak (**Table 3**).[7]

Table 3. Case definition for suspected/probable/confirmed cases of monkeypox.

Suspected case
i) A person who is a contact of a probable or confirmed monkeypox case within 21 days before the onset of signs or symptoms AND presents with any of the following: • acute onset of fever (>38.5°C) • headache • myalgia • back pain • profound weakness or fatigue OR
ii) A person presenting with an unexplained acute skin rash, mucosal lesion or lymphadenopathy since 1 January 2022 (Skin rashes may include single or multiple lesions in the anogenital region or elsewhere on the body. Mucosal lesions may consist of single or multiple oral, conjunctival, urethral, penile, vaginal or anorectal lesions. Anorectal lesions may also manifest as anorectal inflammation [proctitis], pain and/or bleeding).

Table 3. Continue

Suspected case
AND for which the following common causes of acute rash do not fully explain the clinical picture: varicella zoster infection, herpes zoster infection, measles, herpes simplex infection, bacterial skin infection, disseminated gonococcal infection, primary or secondary syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, molluscum contagiosum and allergic reaction (e.g. to plants) as well as any other locally relevant common causes of papular or vesicular rash. **Note:** It is not necessary to obtain negative laboratory results for the listed common causes of rash illness to classify a case as suspected.
Probable case
A person presenting with an unexplained acute skin rash, mucosal lesion or lymphadenopathy AND meeting one or more of the following: • has an epidemiological link to a probable or confirmed case of monkeypox within 21 days before symptom onset • identifies as gay, bisexual or other man who has sex with a man • has had multiple and/or casual sexual partners within 21 days before symptom onset • has detectable levels of anti-OPXV IgM antibody (from 4 to 56 days after rash onset) or a four-fold rise in the IgG antibody titre based on acute (up to days 5–7) and convalescent (day 21 onwards) samples in the absence of a recent smallpox/monkeypox vaccination or other known exposure to OPXV • has a positive test result for OPXV infection (e.g. OPXV-specific PCR without monkeypox virus-specific PCR or sequencing)
Confirmed case
A person with laboratory-confirmed monkeypox virus infection based on detection of unique sequences of viral DNA via real-time PCR and/or sequencing

* OPXV: orthopoxvirus, IgM: immunoglobulin M, PCR: polymerase chain reaction, DNA: deoxyribonucleic acid

A suspected monkeypox case should be notified to local public health authorities immediately. Probable and confirmed cases should be reported to the WHO through National International Health Regulations Focal Points.[6]

Laboratory testing

If monkeypox is suspected, it should be confirmed with polymerase chain reaction (PCR) testing.[22] Antibody and antigen detection methods are not recommended for diagnosis, as they cross-react with other orthopoxviruses. Blood tests are usually inconclusive because of the short duration of viraemia in the early course of infection.[22] The correct timing of sampling depends on the onset of clinical signs, and the stage of infection is important for interpreting the results and establishing an accurate diagnosis. Optimal diagnostic samples for monkeypox are obtained from the skin or mucosal lesions including the roof or fluid from vesicles, pustules or lesion crusts. In the absence of skin or mucosal lesions, PCR testing can be conducted on an oropharyngeal, rectal or anal swab. However, a negative result is not enough to exclude the infection.[22]

Vesicular swabs of lesions with exudates or crusts need to be stored in a dry, sterile tube and kept under a cold temperature (2–8°C) during transportation. Samples should be safely handled with additional precautions, and healthcare personnel are advised to wear recommended personal protective equipment (PPE; e.g. disposable gown, gloves, N95 mask, eye protector and headgear) and follow other infectious disease control protocols.[10] Hand hygiene procedures before and after sample collection are crucial.

Management of monkeypox

The main principle of the management of monkeypox is providing supportive care, preventing complications and controlling the outbreak.

Many patients with monkeypox have mild infections and will recover without medical intervention.[21] Infected patients should be isolated and follow infectious control precautions until all skin lesions have dried and fallen off. During isolation, supportive care, such as adequate hydration and nutritional support, antipyretics use, pain control and psychosocial support, should be given. Patients must be advised to avoid scratching and picking their skin lesions to prevent secondary skin infections. Topical antiseptics can be applied

onto excoriated skin lesions, and any skin infection or sepsis must be observed closely. Secondary skin infections should be treated with an antibiotic. For anorectal or genital lesions, warm sitz baths or topical lidocaine may be offered for symptomatic relief.[21]

Antivirals such as tecovirimat and brincidofovir have been approved for the treatment of smallpox based on animal models as well as dose and safety trials in healthy individuals but are also predicted to be effective against monkeypox. Tecovirimat, an inhibitor of orthopoxvirus VP37 envelope wrapping protein, is licensed by the European Medicines Agency for treating monkeypox but has not yet been approved by the US Food and Drug Administration.[23] A clinical trial of its efficacy during the latest monkeypox outbreak is currently underway. In another report, tecovirimat is well tolerated, and a shorter duration is required for improvement.[24] Nonetheless, the US CDC suggests tecovirimat use in patients with severe disease (haemorrhagic disease or encephalitis), those at risk of severe disease (immunocompromised patients, pregnant women and children) and those with infection in sites with severe pain, infection in sites that might result in serious sequelae (e.g. scarring or stricture) or infection of the eyes.[23] Brincidofovir, another potential antiviral agent, has not been found to have any convincing therapeutic benefit and is linked with adverse effects on the liver.[16] Vaccinia immunoglobulin is still under clinical research. Trifluridine eye drops or ointments are used off-label in patients with ocular lesions.[21]

Management of close contacts

Contact tracing is also an important public health measure for controlling the spread of monkeypox. It can help individuals with a higher risk of developing severe disease identify their exposure more rapidly, monitor their health status and seek medical care if they become symptomatic.

Close contacts are defined as individuals who have an exposure to a probable or confirmed case of monkeypox at any time from the beginning of the first symptoms until all scabs have fallen off. They include those who have face-to-face exposure without proper PPE, direct skin-to skin or skin-to-mucosal physical contact, contact with contaminated materials, such as bedding or clothing, and prolonged face-to-face respiratory exposure in close proximity.[7] Close contacts should be under observation and surveillance for any symptoms for up to 21 days because of the incubation period of monkeypox.[6] Those who develop any symptoms but not rashes should be isolated and monitored for any signs of rash for the following 7 days. If no rash occurs, the contacts can return for surveillance for a remainder of 21 days.[7] If the contacts develop a rash, a test to confirm monkeypox should be conducted. Contacts should regularly practice hand hygiene and respiratory etiquette and should not donate blood, cells, tissue, organs, breast milk or semen while they are under symptom surveillance.[21] Options for monitoring by public health authorities are dependent on available resources.

Vaccination

Vaccination against smallpox is reported to be at least 85% effective in preventing monkeypox. Protective immunity from smallpox vaccination is limited to those people born before 1980, but protection may have waned over time.[15] The first-generation smallpox vaccines are no longer available to the general public. Development of a new and safer (second- and in particular third-generation) vaccine for smallpox may be useful for monkeypox.[21] At present, smallpox vaccine options that have been approved for off-label or compassionate use for pre-exposure or post-exposure preventive vaccination of monkeypox include modified vaccinia Ankara-Bavarian Nordic (MVA-BN), LC16 and ACAM2000.[7] ACAM2000 is a second-generation and replication-competent vaccine, which consists of live vaccinia virus that offers cross-protection when administered for the prevention of infectious diseases due to other orthopoxviruses (e.g. smallpox, monkeypox and cowpox). However, it is associated with serious adverse effects, such as myopericarditis/pericarditis, and is contraindicated for immunocompromised individuals, pregnant women, breastfeeding women, patients with atopic dermatitis and children. Third-generation vaccines that are minimally replicating (e.g. LC16) and non-replicating (e.g. MVA-BN) consist of live attenuated vaccinia virus with improved safety profiles.[7] As there are still limited data on these vaccines, the reactogenicity as well as the safety of the vaccines should be considered.[25]

Based on the WHO interim recommendation on 19 August 2022, post-exposure prophylaxis with an appropriate second- or third-generation vaccine is recommended for selected close contacts based on the risk of exposure to monkeypox and must be given within 4 days from the date of exposure to prevent the

onset of the disease. Meanwhile, pre-exposure prophylaxis vaccine is recommended for groups at a high risk of exposure to monkeypox, such as healthcare workers, laboratory personnel or anyone with an occupational or personal risk.[7] National health authorities must ensure that information regarding vaccine products, including the administration, storage and relevant procedures, is provided to healthcare personnel. At present, mass vaccination against monkeypox is not recommended.[15]

Infection prevention and control

Education of the public and healthcare workers in preventing outbreak is of utmost importance. Healthcare workers should be protected with appropriate PPE and strengthened infection prevention and control practices when handling monkeypox cases. Infection among healthcare workers who cared for patients with monkeypox has been reported previously, suggesting a possible breach in infection prevention and control measures.[7] Healthcare workers who have occupational exposures, such as needle stick injuries or contact with monkeypox cases while not wearing appropriate PPE or contaminated materials, should notify infection control, occupational health and public health authorities, so that the potential infection can be assessed and managed. They do not need to be excluded from work duty if they are asymptomatic but should actively monitor for symptoms for 21 days following the exposure and should not handle vulnerable patients during this period.[7]

The spread of an infectious disease results from the interaction of an agent (e.g. virus), a susceptible host and an environmental factor that provides opportunities for transmission.[26] As a result of globalisation and environmental factors, monkeypox poses a greater threat to previously unaffected countries.[27] Therefore, increasing awareness of the risk factors as well as educating the public about the measures they can take to reduce exposure to the virus is the main preventive strategy for monkeypox. The public is advised to maintain good personal hygiene, particularly frequent handwashing and avoiding high-risk sexual activity. Targeted interventions are required in communities with a high proportion of MSM to prevent further transmission while avoiding stigmatisation. Travellers to monkeypox-affected countries must be given health alerts regarding monkeypox through MySejahtera and monitor their symptoms for 21 days from the date of arrival in Malaysia.[28] In addition, unprotected contact with wild animals that are possible monkeypox reservoirs must be avoided. All foods containing animal meats or parts must be thoroughly cooked before eating.[15] Living in the forest or recently deforested areas is also a risk factor for zoonotic transmission of the monkeypox virus.[27] Some counties have established regulations restricting the importation of rodents and non-human primates that are potentially infected with monkeypox.[15]

Conclusion

All primary care providers should be alert for monkeypox cases and notify their local or state health authorities immediately. Early recognition of monkeypox on anyone with the characteristic rash with or without a history of travel or contact with someone with a rash is important. Although the current outbreak has demonstrated that many patients do not develop the characteristic clinical signs, detailed travel and sexual history-taking as well as a high index of suspicion is important to detect monkeypox cases. The mainstay management is rapid isolation and contact tracing for outbreak control. The identification of contacts requires carefully designed communication strategies to be effective and to avoid stigmatisation. Healthcare workers should adhere to infection prevention and control measures when handling monkeypox cases or specimens to help prevent secondary transmission.

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Author contributions

Conceptualization: Ng YY, Azidah AK; Writing-original draft preparation: Ng YY; Writing-review & editing: Ng YY, Azidah AK; Approval of final manuscript: Ng YY, Azidah AK.

Conflicts of interest

The authors declare no conflicts of interest.

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How does this paper make a difference in general practice?

- This review is designed to improve the clinical knowledge of primary care providers in monkeypox.
- This paper describes the current global outbreak of monkeypox, typical and atypical clinical features, management of patients and close contacts, and infection prevention and control of monkeypox.

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