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# Mpox: A rapidly evolving disease

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## Abstract

The 2022 mpox outbreak has rapidly emerged onto the global medical scene while the world continues to grapple with the COVID-19 pandemic. Unlike COVID-19, however, most patients with mpox present with skin findings, the evolving clinical presentation of which may be mistaken for other common skin diseases, particularly sexually transmitted infections. In this review, we provide an overview of the evolution of mpox skin findings from its initial description in humans in 1970 to the present-day multi-national outbreak.

## Introduction

The 2022 multi-national mpox outbreak is a public health emergency that poses a particular challenge to dermatologists. Mpox was first reported in humans in 1970 and nearly all affected individuals presented with cutaneous findings. However, before 2022, few clinicians, including dermatologists, had encountered a case. Furthermore, much of the prevailing information is based on a limited outbreak in the United States in 2003[1] and ongoing experience in endemic areas of the Congo Basin and West Africa.[2] The current multi-national outbreak in mpox cases differs in important ways from the disease in endemic areas, including clinical presentation, epidemiology (both transmission and demographics), and mortality. In this review, we provide a comprehensive overview of the clinical aspects of mpox for dermatologists with a specific focus on differential diagnosis, the current classification system for differentiating the disease presentations, and the epidemiologic and public health education considerations crucial to understanding and controlling this emerging disease.

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## A brief history of mpox and MPXV

Until 2022, mpox was largely associated with sporadic individual cases and scattered small outbreaks in countries in several tropical African countries. Two clinical forms of the disease were recognized, a more virulent Central African form and a less virulent West African form. Because of these clinical differences, the two forms were originally designated by geography. For decades, mpox was largely confined to the two endemic areas in Africa, although, on rare occasions, mpox was diagnosed elsewhere in travelers who had recently been in endemic areas.

In 2003, a small, self-contained outbreak in the United States arose from an infected Gambian giant rat that had been co-housed with prairie dogs, a native North American rodent. The prairie dogs were infected and subsequently transmitted the disease to dozens of humans.[1] Cases of human-to-human transmission did not occur in the 2003 outbreak.[3] Until the 2003 outbreak of mpox, much of what we know about the disease came from endemic cases, which also arose primarily from contact with infected animals, often a rodent that had been caught, prepared, and consumed as bushmeat.[4]

In May 2022, hundreds of mpox cases were diagnosed in non-endemic countries around the globe, without a concurrent increase in cases in endemic areas. It was quickly determined that the disease was spreading via direct person-to-person transmission—and doing so at an alarming rate. It was also soon clear that the multi-national outbreak had important clinical and epidemiologic differences from the endemic disease. On July 23, 2022, the World Health Organization (WHO) declared the mpox situation a Public Health Emergency of International Concern, the highest threat level assigned to any disease.

Monkeypox virus (MPXV) was first identified in 1957 among a shipment of laboratory monkeys, specifically fish-eating macaques, in Denmark, leading to the common name of monkeypox (now mpox). The clinical appearance of the disease in monkeys resembled smallpox, however smallpox had never been identified in any animal other than humans. Subsequent investigation confirmed that MPXV was a closely related orthopoxvirus to smallpox virus.[5] The first cases of human mpox were detected 13 years later in the Democratic Republic of the Congo (DRC). At that time, most people in endemic areas had been vaccinated against smallpox. However, once the global smallpox vaccination campaign eradicated the disease, vaccination ceased. Over the next several decades, scattered individual cases and sporadic small outbreaks of mpox in the two endemic areas continued to occur, and the possibility of waning smallpox immunity at the individual or community level raised the specter of an emergence of mpox or other orthopox zoonosis. A comparison of similarities between smallpox and mpox is provide in eTable 1. A recent review provides additional history of mpox from its first discovery to modern day.[6]

## Current nomenclature

In November 2022, the WHO announced the adoption of mpox as the preferred term for monkeypox. ‘Mpox’ is encouraged in health communications, although both names will be considered valid until late 2023. The International Classification of Disease has adopted

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mpox in the online version of ICD-10 and it will be used in the 2023 release of ICD-11. The virus is currently still termed monkeypox virus (MPXV), but that terminology will be reviewed in 2023 by the International Committee on the Taxonomy of Viruses.

Based on WHO guidelines,[4] mpox has been subclassified into genomic variants--Clade I, IIa, and IIb--named in the order of appearance. Before 2019, the overwhelming majority of mpox cases were Clade I disease located in Central Africa. Only a few hundred cases of Clade IIa disease have been reported, all from Western Africa.[7] Although probably in circulation since 2017, Clade IIb emerged as the cause of the 2022 multi-national outbreak. The current cases do not involve transmission from an animal reservoir; most cases occur outside of Africa; and most arise from person-to-person contact.[4] Furthermore, to date, most Clade IIb infections have been reported among men who have sex with men (MSM).[8] Within Clade IIb, genomic variants continue to evolve; these are named hMPXV1 virus with subordinate lineages designated A, A.1, A1.1, B.1, etc. based on mutations, such as the APOBEC3 protein.[9]

## Cutaneous signs and symptoms of mpox infection

Mpox is a systemic disease that presents with skin lesions in most patients. Because the clinical suspicion of mpox as well as diagnostic testing is usually based on cutaneous aspects of the disease and not on other organ systems, this section will focus on mucocutaneous signs and symptoms. Systemic manifestations are discussed in greater detail in Table 1.

An oral enanthem often appears during the final days of the prodrome. Cutaneous lesions of mpox infection first appear when the prodrome transitions to the eruptive phase. Lesions classically evolve in an orderly progression from subtle erythematous macules to papules to vesicles to characteristic deep-seated dome-shaped pustules. Individual lesions often develop central umbilication (‘doughnut’ lesions), which is then followed by crust/eschar formation and finally desquamation. Lesions develop together in similar stages (synchronous evolution) with the greatest density of lesions on the head and extremities, and lower density on central areas of the body (Figure 1).[10] Lymphadenopathy is a hallmark feature of classic mpox infection that can be easily assessed during the skin exam and most commonly involves the cervical and submandibular nodes. Together with skin lesions, lymphadenopathy is present in almost all patients with Clade I disease. Other associated systemic features include fever, headache, backache, myalgia, and fatigue.

This ‘typical’ constellation of findings, however, differs markedly from most mpox cases in the current multi-national outbreak (Table 1). Clade IIb disease typically presents with localized lesions on the head, genital or perianal areas acquired through direct skin-to-skin contact. Skin lesions may present in different phases of evolution and may be smaller in size with a non-specific appearance (Figure 2). In contrast to Clade I infections, lymphadenopathy is a less consistent feature and prodromal symptoms may be mild or absent. Mortality—a major concern in pediatric Clade I infections, is extremely rare with Clade IIb disease.[11] According to the WHO, among 77,264 cases during the current outbreak, only 36 deaths have been reported.[12]

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It is not yet clear if the observed clinical differences between Clade I, IIa, and IIb infections (e.g. mortality of ~10% vs 1–3% vs <0.05%, respectively)[7] are due to inherent biological differences between the viral Clades (e.g. 10-fold increase in mutation rate of newer strains),[9] clinical characteristics (e.g. duration of viremia),[13] source of infection (e.g. zoonotic vs human), mode of transmission (e.g. respiratory vs skin and/or mucosal contact) or patient comorbidities. Malnutrition likely plays a major role in Clade I mortality—in a US Army observational mpox study in the DRC, the median serum albumin level of the study population was 2.75 g/dL (normal >3.3 g/dL) and hypoalbuminemia was associated with severe disease.[10]

## Cutaneous assessment

In the past, the WHO has used lesion count as a biomarker of disease severity based on prior experience with Clade I disease.[14] Skin lesion count was also applied to the first outbreak outside of Africa in 2003.[13] In the DRC outbreaks, disease severity correlated with peak lesion counts: the mildest (Level 1) cases had a mean peak lesion count of hands and total body of 19 and 223 lesions, respectively, compared to 222 hand and 3879 total body lesions in lethal cases. For this reason, the primary outcome for the PALM007 randomized controlled trial of tecovirimat in the DRC will require manual lesion counts for all patients (NCT05559099). As this is a time-consuming and tedious effort, methods are being explored to automate this task with artificial intelligence analysis of total body photographs.[15]

By contrast, Clade IIb disease typically presents with fewer than 10 lesions over the entire body.[16] Although less time-consuming to monitor by manual counts, significant challenges remain to assess patients and collect data on Clade IIb disease. Clinical and prognostic tools are needed, such as a standardized system of cutaneous disease severity and common agreement on lesion ‘resolution’. Clinical assessment will likely evolve rapidly as results become available from recently launched clinical trials and observational studies using an array of clinical endpoints (e.g. resolution of pustules vs. crust formation vs. desquamation and re-epithelialization).[17] Dermatologists are encouraged to contribute to the American Academy of Dermatology Monkeypox Registry in order to share information regarding mpox patients (https://www.aad.org/member/clinical-quality/clinical-care/monkeypox/registry). Clinicians should also follow the reporting guidelines of their local and state health departments. Adverse effects from the smallpox/mpox vaccine may be entered into the AAD’s Monkeypox Registry, but should also be reported to the Vaccine Adverse Event Reporting System (https://vaers.hhs.gov/).

## Transmission and infectivity

The potential infectivity of cutaneous mpox lesions in differing stages of evolution is a major gap in knowledge. By comparison, herpes zoster skin lesions are usually considered of low infectivity once all lesions have formed crusts, even though viral DNA is still recoverable by PCR at this stage.[18] In contrast, crusts associated with smallpox skin lesions were considered highly infectious until complete re-epithelialization occurred. Similarly, crusts of mpox lesions contain significant virus, the infectivity of which is currently under investigation. The CDC recommends PCR testing for MPVX by swabbing the surface of the

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lesions with a synthetic swab or by collecting crust material.[19] Unroofing or aspiration of lesions is not recommended due to the risks for sharps injury, and several cases of occupational needlestick injuries leading to mpox infection have reported.[20,21] Other unexpected types of transmission have been reported. For example, poor hygiene practices/instrument cleaning was associated with 20 mpox cases arising from a Spanish tattoo and piercing establishment. Most skin lesions developed at the site of piercing or tattooing.[22] All affected individuals were unaware of other possible mpox exposure. Numerous surface areas at the establishment were sampled and positive for MPXV, including work tables, chairs, sharps, tweezers and scissor tips.

## Differential diagnosis

The distribution of lesions in mpox Clade I resembles smallpox, as outlined earlier (Figure 1). By contrast, the distribution of lesions in the current multi-national outbreak (Clade IIb) presents with focal areas of involvement, most commonly the genital, perianal, and oral regions. The often polymorphous nature of Clade IIb lesions may resemble other conditions (Figure 3). Oral/perioral lesions seen may be confused with herpes simplex infection (ulcers), syphilis (chancriform papules) and oral candidiasis (pseudomembranous plaques). Genital ulcers are common in Clade IIb infection, so herpes simplex and syphilis should be considered as well as chancroid. The umbilicated lesions may resemble molluscum contagiosum or cutaneous cryptococcosis, histoplasmosis, and talaromycosis. Hypertrophic and verrucous mpox lesions, similar to that seen in the immunocompromised setting due to chronic HSV, have been reported.[23,24] Inflammatory diseases such as Behcet's disease should be considered in individuals presenting with oral and genital ulcers. The incidence of several sexually transmitted infections (STI) has been increasing over the past several years, and co-existence of mpox with other STI, including syphilis, chlamydia, gonorrhea, lymphogranuloma venereum and HIV, should be considered in all patients presenting with genital involvement. However, lymphogranuloma venereum and chancroid are exceptionally rare in the United States.

## Epidemiology of Clade IIb infection

As of Dec 22, 2023, almost all of the 83,424 cases in the current multinational mpox outbreak have been Clade IIb.[25] As mentioned previously, the MSM population has been most significantly impacted by the 2022 outbreak of Clade IIb mpox. Infection may occur by respiratory secretions during prolonged close contact or by direct contact with skin lesions or body fluids. Therefore, mpox is a 'sexually transmissible' condition. This has important epidemiologic implications, particularly in the MSM population, and underscore the importance of sexual health clinics and community outreach to effectively combat the disease.[26] Co-infection with HIV has been reported in 26–52% of patients with mpox in the MSM population.[27] Among 528 mpox cases described from 16 countries between April-June 2022, 57% of HIV-negative (or status unknown) patients were taking preexposure HIV prophylaxis (PrEP). An association was also seen with increased number of sexual partners, and prior STIs, underscoring the importance of eliciting a sexual history.[16]

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Current understanding of the impact of HIV on the natural history of mpox is rapidly evolving. In a 2017 Nigerian outbreak, 4 of the 7 deaths in a series of 122 patients occurred in individuals with uncontrolled HIV, although the overall proportion of patients with HIV was unclear.[28] During the 2022 outbreak, among a series of 57 patients hospitalized with severe manifestations of mpox, most (95%) were male, 82% had HIV infection, and 68% were non-Hispanic Black.[24] 23% of patients experienced homelessness and a delay in diagnosis and treatment initiation was identified as a factor in the cohort. Five of the twelve fatalities were related to mpox infection. In contrast, the GeoSentinel global surveillance system (29 countries) found a greater rash burden in patients with HIV but did not detect a difference in the proportion of men with severe illness by HIV status.[29]

## Cutaneous management

Wound management is important to prevent secondary bacterial infection, hasten resolution and minimize scarring. As yet, there are no evidence-based clinical studies evaluating the management of cutaneous mpox. We recommend gentle skin cleansing and keeping lesions moist with regular application of petrolatum. The rate of wound healing and scarring varies between patients and based on the site of involvement (eFigure 1). In our experience, genital lesions generally heal well with post-inflammatory pigment alteration and minimal scarring, despite often dramatic ulcer formation. If lesions become impetiginized, bacterial culture and appropriate topical or oral antibiotics should be initiated with monitoring for cellulitis (eFigure 2). For areas of slowly healing ulceration, the use of a hydrocolloid dressing may be helpful.

## Vaccination and systemic management

There are no FDA approved treatments for mpox, although tecovirimat (approved for smallpox) is currently used under the expanded access investigational new drug program and in clinical trials.

ACAM2000 and JYNNEOS are the two vaccines approved by the FDA for prevention of smallpox that are currently available for prevention of mpox. Both vaccines use live, attenuated vaccinia virus strains to develop neutralizing antibodies to smallpox. However, JYNNEOS uses a non-replicating strain of vaccinia, which greatly reduces the number of contraindications for vaccination and greatly reduces the risk of an adverse vaccine-related event. The JYNNEOS vaccine is administered in a two-dose series, 28 days apart, with full protection presumed 14 days after the 2$^{nd}$ dose.

ACAM2000 is administered as a single dose but uses but requires multiple jabs with a specialized bifurcated needle to induce a skin lesion or ‘take’ at the injection site. This skin lesion is necessary for proper immunity to develop, but also creates a risk of vaccinia virus spreading to other body sites, particularly in the setting of atopic dermatitis (eczema vaccinatum). ACAM2000 should not be administered to patients with current or previous history of atopic dermatitis, Darier’s disease, or widespread areas of raw, open, or eroded skin.[30] People vaccinated with ACAM2000 vaccine must also take care to avoid inadvertent spread of the live virus to any household members or other contacts with these risk factors.

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In addition, significant systemic risks have been associated with this vaccine, including myocarditis.

The FDA approved JYNNEOS for subcutaneous administration, however the CDC issued Interim Guidance recommending an alternative regimen with intradermal administration. Most recipients of the JYNNEOS vaccine, administered by either route, experience injection site reactions (specifically pain, redness, and swelling) after both the first and second vaccinations. The *incidence* of local adverse events is irrespective of the vaccine recipient's HIV status or prior smallpox vaccination status.[31] The *intensity* of the reaction, however, is generally greater with the intradermal route, despite its use of only one-tenth of the amount of vaccine. Induration and mild hyperpigmentation may persist for several months after intradermal administration. The CDC recommends using subcutaneous administration in individuals at risk for keloid formation.[32]

The incidence of mpox in males aged 18–49 eligible for JYNNEOS vaccination was 14-fold higher among unvaccinated males compared to those with a first vaccine dose 14 days earlier.[33] Therefore, the CDC recommends that pre-exposure vaccination may be offered to individuals at increased risk, as well as after exposures.[34]

A recent systematic review of 14 guidelines worldwide identified discrepancies in mpox management recommendations, including whether cidofovir (7/14), tecovirimat (4/14) or brincidofovir (1/14) should be initiated. Lack of consistent guidance was also noted for post-exposure prophylaxis and vulnerable populations, such as children, pregnant women and the immunocompromised population. The authors emphasize the need for a 'living guideline' framework, such as the current CDC indications and access guide for tecovirimat[35] to rapidly adjust recommendations as new evidence for clinical management of mpox emerges.[36]

## Conclusions

Control of the multi-national mpox outbreak requires a collaborative approach between Dermatology, Infectious Disease specialists, sexual health clinics, epidemiologists and public health experts, as well as outreach to patient populations at greatest risk of infection. The evolution of clinical presentation from the first recorded case of mpox 52 years ago to modern day disease serves as another important reminder that infectious diseases may evolve rapidly, and individual and collective vigilance is needed to rapidly identify and mitigate future emerging infectious diseases.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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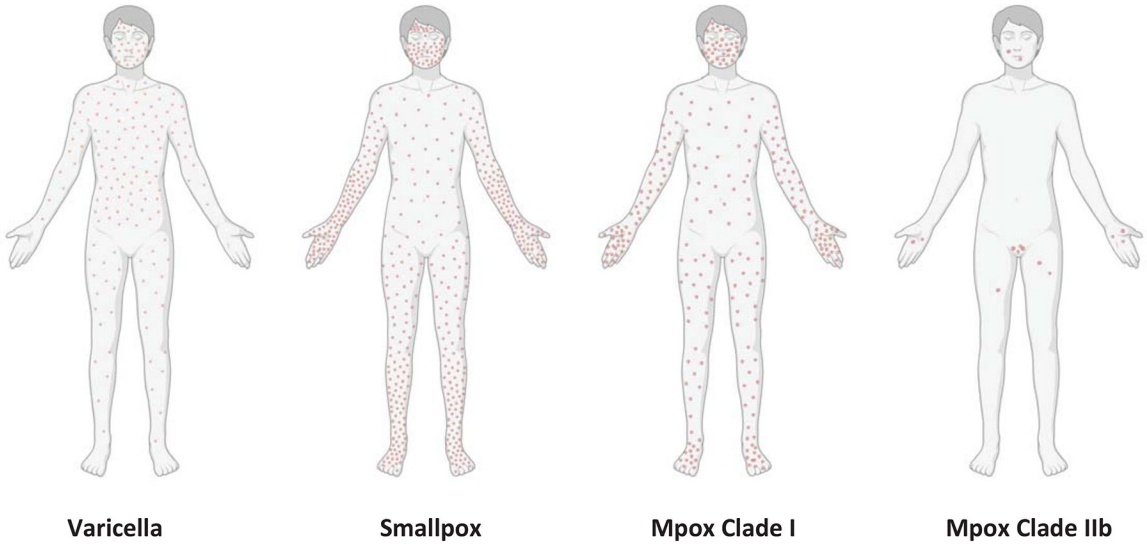


**Figure 1. Distribution of skin lesions in primary varicella, smallpox and mpox Clade I and Clade IIb**

Primary varicella is characterized by a central predominance of lesions. In contrast, smallpox and mpox Clade I favor an acral predominance. Hundreds to thousands of lesions may develop. In contrast, Clade IIb mpox is characterized by a limited number of lesions (typically < 10) that vary in location—many cases have a facial, genital and/or perianal predominance. Clade IIa distribution not shown due to paucity of cases. Created with BioRender.com

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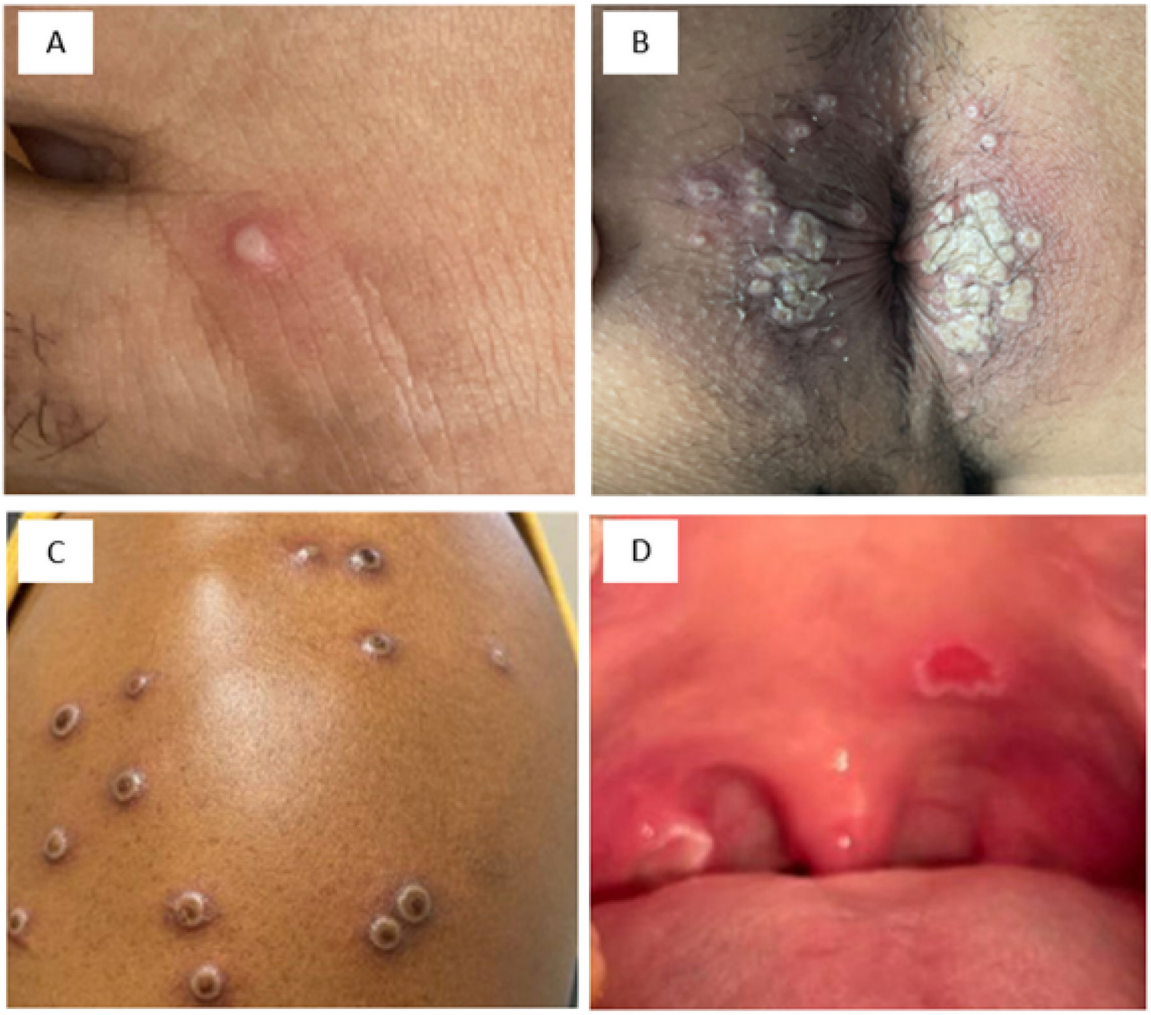


**Figure 2. The Spectrum of Mpox Skin and Mucosal Disease.**

A, Pustule. A firm dome-shaped lesion with an opalescent surface. B, 'Kissing' pseudopustular perianal lesions, coalescing into flat-topped plaques that resemble condyloma lata. C, Pseudopustular 'doughnut' lesions with central crust. Note the strikingly uniform morphological characteristics seen with synchronous evolution of lesions. D, oral ulcer on soft palatal mucosa.

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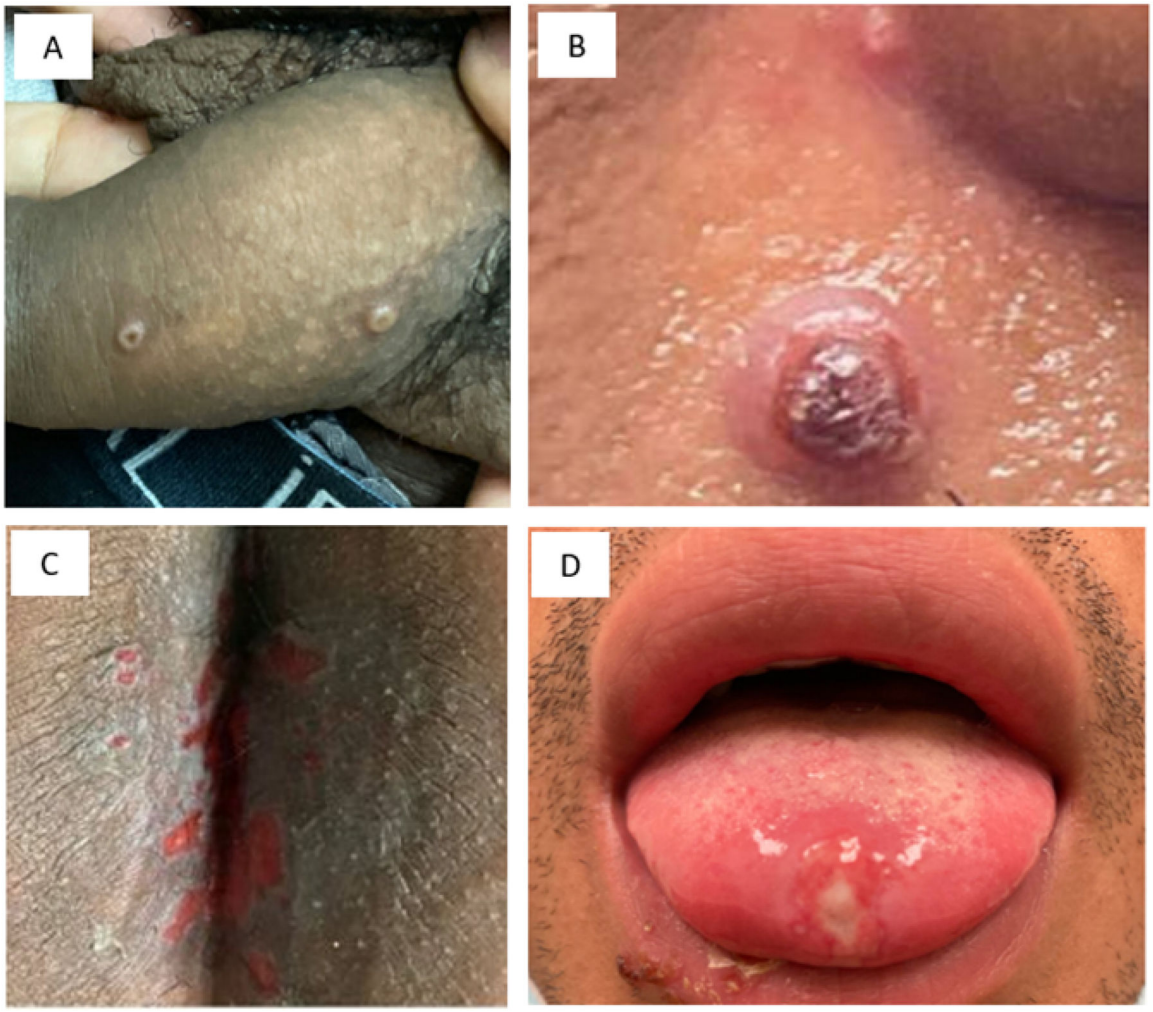


**Figure 3. Mpox Mimics Other Skin Conditions.**

A, Molluscifform papules. B, Keratoacanthoma-like facial nodule. C, Perianal ulcers mimicking herpes simplex virus. D, Chancriform tongue papule.

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**Table 1.**

Differential Diagnosis of Mpox

| Illness | Incubation/ prodrome | Patient clinical appearance | Morphology | Lesion distribution | Lesion evolution | Lab testing |
|---|---|---|---|---|---|---|
| **Mpox Clade I (formerly Central African or Congo Basin Clade)** | Incubation: 3–17 days<br>Prodrome: 1–4 days. Fever, headache, backache, malaise, lymphadenopathy, sore throat, flu-like symptoms, arthralgia. Enanthem of oral mucosa appears in late prodrome. | Ill to toxic. Respiratory symptoms are common. Lymphadenopathy common. Most commonly cervical and submandibular. Often firm & tender.<br>Mortality ~10% in endemic areas (in unvaccinated individuals). | Early vesicular stage may resemble varicella (“dew drop on rose petal”).<br>Pustular stage is usually firm, deep-seated, white/ opalescent, dome-shaped papules, “Pearls of pus.”<br>Umbilicated pustules have characteristic shape, resembling doughnuts or ‘Cheerios’ cereal.<br>Lesions heal with scarring. | Starts with centrifugal (acral) distribution. Most prominent on face, hands, & feet.<br>Nearly always on palms and soles. Tight skin limits elevation of lesions on these surfaces. May appear as uniform “donut-like” papules.<br>May become generalized, although density of lesions is usually much lower centrally on the torso and proximal extremities. | Subtle macules evolve synchronously into papules → vesicles → deep-seated dome-shaped pustules → umbilicated or necrotic pustules → crusts over 2–3 weeks.<br>Lesions are monomorphic at any point in time.<br>Several stages may be present simultaneously in <5% of cases. | PCR of lesional material.<br>Cultures are not available for routine clinical use.<br>No commercially available blood or serologic tests.<br>Formalin-fixed skin biopsy material can be tested at CDC.<br>In US, contact state health dept first.[1] |
| **Mpox Clade IIa (formerly West African Clade)** | Incubation: 3–17 days.<br>Prodrome: 1–4 days. Resembles Clade I prodrome but typically milder. | Varies. Usually milder than Clade I. Ranges from flu-like symptoms to toxic illness.<br>Lymphadenopathy common.<br>Mortality 1–3% in endemic areas (in unvaccinated individuals). | | | | |
| **Mpox Clade IIb (the current multi-national outbreak)** | Incubation: 3–17 days.<br>Prodrome: 1–4 days. Prodromal symptoms vary from a Clade IIa-like prodrome to very mild flu-like symptoms to being entirely asymptomatic.<br>Oral enanthem may be present during prodrome. | Varies. Usually milder illness than Clade IIa. Patients often asymptomatic or may have minor flu-like symptoms. Rarely toxic.<br>Deeper lesions may heal with scarring.<br>Perianal and genital lesions may lead to scarring and strictures.<br>Lymphadenopathy is common.<br>Mortality <0.05% (unvaccinated individuals). | Early vesicles may resemble varicella.<br>Some surfaces (eg, penis) may ulcerate early in disease course.<br>Oral, oropharyngeal, genital, perianal, rectal lesions in MSM, at site of viral exposure and transmission.<br>Verrucous/ hypertrophic lesions or expanding necrotic ulcers in severely immunocompromised. | Genital, anal & perianal, intraoral lesions in MSM.<br>Initial lesions at site of inoculation if acquired from skin-to-skin contact,<br>In patients with few lesions, palms & soles may be spared.<br>If >100 lesions, may resemble Clade II mpox with acral (palms/soles) involvement. | Morphology varies during course of disease; however, lesions are monomorphic at any point in time.<br>When only a few lesions present, evolution of lesions may not be as apparent, or several stages may be present simultaneously. | |
| **Molluscum contagiosum (in immunosuppressed patients)** | Incubation: 2–7 weeks<br>None | Depends on overall health. Molluscum alone will not make the person fell ill. Severely immunocompromised individuals with a concomitant febrile illness may appear ill to toxic. | 2–5mm papules. Skin-colored to pink. Translucent, pearly, opalescent surface.<br>Apex of many lesions appears umbilicated or as a smooth white dot.<br>The edges of heavily involved surfaces often have several lesions with typical molluscum features described above. | Genitals and suprapubic areas in sexually active persons.<br>May approach mucosa on face, involving keratinized vermilion of lips or lash lines on eyelids, but no intraoral lesions.<br>May be generalized in the immunocompromised. | Minute, skin-colored papules, evolve to domed, umbilicated firm, white pseudo-pustular lesions.<br>May coalesce into plaques with irregularly mamillated surface. Innumerable lesions, particularly on the face in immunocompromised setting | Diagnosis usually made clinically.<br>Skin biopsy or “bedside scrape-and-examine” test using Wright-Giemsa stain. |

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| Illness | Incubation/ prodrome | Patient clinical appearance | Morphology | Lesion distribution | Lesion evolution | Lab testing |
|---|---|---|---|---|---|---|
| **Varicella** | Incubation: usually 14–16 days. May range from 10–21 days).<br>Prodrome is rare in children; occasionally present in adults but brief (<2 days). | Usually uncomfortable, mild fever, pruritus<br>Recent exposure to chickenpox or shingles, 10–21 days before rash. No history of prior varicella or varicella vaccination.<br>Many systemic complications, particularly in newborns or immunocompromised patients. | Discrete superficial vesicles on erythematous base “dew drop on rose petal.”<br>250–500 lesions in unvaccinated.<br><50 lesions in “breakthrough” varicella. | Disseminated with greatest concentration on trunk, occasionally on face.<br>Rare on palms & soles. | Rapid evolution. Individual lesions evolve quickly from macules to papules then vesicles then crusts.<br>Lesions are in different stages at the same time. | PCR of vesicular fluid or lesional material,<br>DFA, Tzanck |
| **Disseminated zoster** | No incubation period; affected patients were previously infected with varicella.<br>No prodrome | Patients are often ill from underlying immunosuppressive state.<br>Pain may be severe and persistent beyond healing of lesions. | Primary dermatome(s) often remains evident, but there are abundant, widely scattered, non-clustered varicelliform vesicles scattered widely. | Usually begins in single dermatome. May evolve to resemble varicella.<br>Often on palms & soles. | Rapid. Usually vesicles, pustules, crusts present.<br>Lesions usually more uniform than in varicella. | PCR of vesicular fluid or lesional material.<br>DFA, Tzanck. |
| **Eczema herpeticum (Kaposi varicelliform eruption) due to HSV1 or HSV2** | Incubation: 2–14 days<br>HSV may be the patient’s own virus or may be transmitted via direct contact with someone shedding live HSV, including from an asymptomatic cold sore. | Children > adolescents. Rare in adults. Children usually very uncomfortable, febrile and underlying eczema is extremely pruritic.<br>If eczema herpeticum due to primary HSV1 or HSV2, patients can be very ill.<br>Most common predisposing condition is severe atopic dermatitis. | Innumerable uniform 1–2mm diameter papules that evolve into fragile vesicles that easily become unroofed, leaving hundreds of minute (~1mm diameter) punched-out or crusted erosions. | Most abundant on face and on areas with active, poorly controlled atopic dermatitis.<br>Rare on palms & soles. | Rapid. Usually progresses through all stages in < week.<br>Lesions are generally uniform on all parts of the body. | PCR of vesicular fluid or lesional material.<br>DFA, Tzanck.<br>Viral culture |
| **Hand, foot, & mouth disease. Coxsackie A6 and A16** | Incubation: 3–6 days<br>Prodrome: None | Mildly uncomfortable.<br>Several variants based on geographic serotypes.<br>Children with atopic dermatitis may develop eczema coxsackium. | Exanthem: Thin-walled vesicles arise from macules or macule-papules. Fairly flat, flaccid vesicles, quickly rupture and form superficial ulcers with grey-yellow base & red rim, then acquire red-brown flaky-paint appearance as they heal.<br>Resolves in 3–4d. | Involves both volar & dorsal surfaces of hands & feet.<br>Mouth lesions involve anterior oral mucosa (not posterior oropharynx). Now common on perioral skin as well. | Exanthem: macules, papules → thin-walled vesicles with clear fluid.<br>Oral/peri-oral red macules progress to vesicles, grey/yellow erosions.<br>Onychomadesis 1–3m after infection in some children. | Clinical diagnosis.<br>PCR swab of nasopharynx or opened lesion.<br>RT-PC) assay and culture. |
| **Secondary syphilis, variant on anogenital surfaces** | Patients may be co-infected with mpox. Both can produce lesions on palms/soles, genitalia, and perianal skin.<br>Incubation roughly 3 wks after exposure, can vary from 10–90d. Secondary syphilis begins | Secondary syphilis has innumerable signs and symptoms, many of which are non-specific, such as pharyngitis, malaise, low grade fever, and generalized lymphadenopathy.<br>Among MSM, the behavioral epidemiology of acquiring mpox also applies to syphilis. Many MSM patients with mpox have concurrent syphilis.<br>Lesions of secondary syphilis. and mpox may appear on the same mucocutaneous surfaces, specifically the penis, scrotum, anal & perianal, and oral mucosa. A solitary mpox lesion may resemble as a residual primary syphilitic chancre.<br>Most common cutaneous finding is widespread papulosquamous eruption. This varies widely, however, ranging from no skin findings to necrotizing pustules (malignant syphilis). On palms & soles, lesions typically red-brown, slightly scaly, barely elevated papules.<br>Mucosal and mucocutaneous lesions include condyloma lata and mucous patches. A chancre may be present at or near a bodily orifice where disease was acquired (intraoral, perioral, genitalia, anal or perianal). | | | | Consider treponemal test (eg, FTA-ABS) in all MSM undergoing mpox evaluation. |

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| Illness | Incubation/ prodrome | Patient clinical appearance | Morphology | Lesion distribution | Lesion evolution | Lab testing |
|---|---|---|---|---|---|---|
| | roughly 1–2m later. Prodrome: malaise, splenomegaly, headache, arthralgias. | Exanthem of secondary syphilis may resolve spontaneously in 3–12 weeks, although the individual is still infected, similar to early latent syphilis. | | | | |

[1] https://www.cdc.gov/poxvirus/monkeypox/clinicians/prep-collection-specimens/biopsies.html