Table 2. Selected differentials of current monkeypox outbreak[22,24,25,29]

Clinical differentials	Cutaneous features	Common extracutaneous features	Potential differentiating features	Potential confounding features	Laboratory tests (including point-of-care tests)
Monkeypox (current outbreak)	• Lesions at same stage of development, localised or generalised, frequently genital distribution • Sequential development from macules to papules to vesicles to pustules to scabs over 2–4 weeks • Papulovesicular/pustular stage consists of deep-seated discrete or grouped lesions, often with umbilication	• Tender lymphadenopathy • Viral prodrome-like symptoms may occur before, together or after onset of rash • May have anal discomfort	• Lesions were classically described to be at the same stage of development, although asynchronous lesions have been reported in the current outbreak • Epidemiologic risk factors in terms of travel, sexual history, and contact with dead/live African endemic exotic species	• Sequence of symptom onset is variable • Cases may not have relevant exposure history • May be clinically indistinguishable from less common presentations of SARS-CoV-2 infection or secondary syphilis, or atypical presentations of the other listed differentials	• Lesional swab for MPXV PCR • Consider opportunistic screening for other STIs, including syphilis (such as POC testing with RPR) and HIV (POC)
Herpes simplex	• Grouped vesicles on an erythematous base that may coalesce into bullae/erosions with scalloped borders • Can range from asymptomatic to excruciatingly painful	• Viral prodrome before onset of lesions • May be associated with regional lymphadenopathy	• Characteristically grouped lesions with scalloped border on erythematous base, unlike monkeypox lesions which can be discrete	• Similar sexual epidemiologic risk factor to monkeypox • Monkeypox may also have grouped vesicles on an erythematous base indistinguishable from HSV	• Lesional swab for Tzanck smear (POC) • Lesional swab for HSV PCR
Disseminated gonococcal disease	• Acral distribution of petechial or pustular eruptions	• Milky white or purulent discharge from exposed infected areas e.g. urethra, rectum, vagina, oropharynx • Fever • Arthralgia • Oligoarticular septic arthritis • May have complications such as perihepatitis, meningitis, pelvic inflammatory disease, endocarditis	• Genital discharge is not a feature of monkeypox • Swollen and tender oligoarthritis if septic gonococcal arthritis • Pustules do not demonstrate umbilication	• Similar sexual epidemiologic risk factor to monkeypox • Gram stain of pustules is not sufficiently sensitive to rule out gonococcal infection	• *Neisseria gonorrhoeae* PCR from relevant sites • *Neiserria gonorrhoeae* culture
Lymphogranuloma venereum (LGV)	• Causative organism: the L1, L2 and L3 serovars of *Chlamydia trachomatis* • Primary lesion seen in up to half of cases (1st stage of LGV) — herpetiform lesion that spontaneously resolves without scarring	• Constitutional symptoms are rare • Inguinal syndrome (second stage of LGV): suppurative unilateral inguinal lymphadenopathy with overlying erythema • Anogenito-rectal syndrome (3rd stage of LGV): proctocolitis, perirectal abscesses, urogenital fistulas	• Inguinal lymphadenopathy can be suppurative in LGV • LGV does not usually have multiple vesicles/pustules	• Similar sexual epidemiologic risk factor to monkeypox • Both LGV and monkeypox may cause tender lymphadenopathy • Monkeypox may rarely have no rash or only a single lesion	• Serological tests i.e. LGV complement fixation test • Culture from lymph node aspiration • *Chlamydia trachomatis* PCR from urine as well as other clinical sites as appropriate
Chancroid	• Causative organism: *Haemophilus ducreyi* • Single to multiple painful, purulent and deep genital ulcers with well-defined soft undermined edges	• Painful suppurative inguinal lymphadenopathy (buboes) • Scarring from recurrent buboes may result in urogenital or rectal fistulas	• Inguinal lymphadenopathy can be suppurative in chancroid • Ulcers in chancroid tend to be larger and deeper compared to the shallower erosions of ruptured vesicles and pustules in monkeypox	• Similar sexual epidemiologic risk factor to monkeypox • Both chancroid and monkeypox may cause tender lymphadenopathy	• Smear for direct microscopy (POC, although poor sensitivity) • Culture of smear from ulcer/aspirate from buboes • Smear for PCR

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Granuloma inguinale	• Causative organism: *Klebsiella granulomatis* • Beefy vascular ulcers that began as small papules/nodules which slowly enlarged and ulcerated over weeks to months • Associated with odorous exudate • Subcutaneous granulomas (pseudobuboes) may be present	• Secondary dissemination may lead to involvement of any internal organ or bone	• Granuloma inguinale usually does not have regional lymphadenopathy, while lymphadenopathy is a common feature of monkeypox • Ulcers of granuloma inguinale are large, vascular, and foul smelling, unlike smaller lesions characteristic of monkeypox	• Similar sexual epidemiologic risk factor to monkeypox • Early stage of granuloma inguinale may be mistaken for monkeypox especially when lesions are still small and have not developed the characteristic beefy appearance	• Tissue smear from ulcer for intra-cellular Donovan bodies within histiocytes (not available at all institutions) • Biopsy of ulcer • Culture is difficult with no commercially available PCR
Primary syphilis	• Usually a single painless papule, which may develop into a well-circumscribed surface ulceration that is firm on palpation	• Regional lymphadenopathy	• Primary syphilis is frequently asymptomatic, whereas monkeypox usually has associated prodromal symptoms and tender cutaneous lesions	• Similar sexual epidemiologic risk factor to monkeypox • Chancres may infrequently be multiple and may mimic atypical monkeypox presentations that have few cutaneous lesions	• Lesional smear for darkfield microscopy (POC) • Non-treponemal tests e.g. RPR (POC) • Treponemal tests e.g. TPHA, TPAb • Consider opportunistic screening for other STIs as well, including HIV (POC)
Pustular secondary syphilis	• Miliary pustular syphilis: perifollicular pustules approximately 3–5mm diameter • Acneiform syphilis: acneiform papules and pustules on the face • Varioliform syphilis: umbilicated erythematous infiltrated papules and pustules with superficial erosions • Impetiginoid syphilis and ecthymiform syphilis have lesions similar to impetigo and ecthyma, respectively • Rupoid syphilis: papules and pustules with overlying thick hyperkeratotic crusts resembling oyster shells	• Prodromal symptoms • Lymphadenopathy	• Pustular secondary syphilis is a very rare presentation of syphilis. It is far more common for the rash of secondary syphilis to be a papulosquamous eruption. • There may be a history suggestive of previous primary syphilis	• Similar sexual epidemiologic risk factor to monkeypox • Cutaneous features and prodrome-like symptoms can be indistinguishable from monkeypox	• See above
Varicella zoster	• "Dew drops on a rose petal" appearance, describing clear 1–3mm vesicles with a narrow erythematous halo • Lesions at varying stages concurrently • Cephalocaudal spread • Usually spares distal limbs and lower limbs • Oral enanthem	• Mild viral prodrome • More severe presentation and higher risk of extracutaneous complications in adolescents and adults compared to children	• Lesions are at varying stages concurrently • No previous varicella vaccination or varicella zoster infection	• Generalised vesicular eruption, +/- umbilication may be difficult to differentiate from classic monkeypox eruption	• Lesional swab for Tzanck smear (POC) • Lesional swab for varicella zoster virus PCR

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Herpes zoster	• Grouped vesicles that may coalesce into bullae/erosions with scalloped borders • Dermatomal distribution • May be preceded by hyperaesthesia/ hyperalgesia in the corresponding dermatome	• Neuropathic symptoms in the associated dermatome (may persist as postherpetic neuralgia)	• Dermatomal in nature • Does not cross midline • History of previous varicella zoster infection	• Disseminated zoster is not confined to the dermatome • Genital zoster is uncommon	• Lesional swab for Tzanck smear (POC) • Lesional swab for herpes zoster virus PCR
Hand-foot-mouth disease	• Acral erythematous vesicles with oral stomatitis • May become generalised, involving the face, perioral areas, trunk, buttocks and extremities	• Mild prodrome • Neurologic, cardiopulmonary complications, and death may occur in young children with hand-foot-mouth disease due to enterovirus 71 infection	• Usually affects young children • Oropharyngeal lesions are frequent, occurring on the tongue, buccal mucosae, palate, uvula, tonsillar pillars • Lesions may be more prominent in areas of pre-existing eczematous dermatitis (eczema coxsackium)	• Generalised vesicular eruption may be difficult to differentiate from classic monkeypox eruption	• Usually a clinical diagnosis • Swabs for cell culture or PCR for enterovirus or coxsackievirus can be done if aetiologic confirmation is necessary
Impetigo	• Early lesions begin as a single 2–4mm erythematous macule that quickly evolves into a short-lived vesicle or pustule • Late lesions present as superficial erosions with "honey yellow" crust, and direct extension of the infection to the surrounding skin • The less common bullous variant that presents with small vesicles, which then enlarge into superficial bullae (initially 1–2cm, later up to 5cm in diameter); with a collarette of scale after rupture	• May also have systemic symptoms like fever, weakness and mild lymphadenopathy	• More common in children • Predilection for face (around the nose or mouth) and extremities • Golden crusting is typical	• Less common bullous variant may also affect trunk, buttocks and genitals	• Swab lesions for pyogenic culture
Insect bites and insect bite reactions	• Pruritic urticated papules (usually 2–8mm) that may progress to vesiculobullae or persistent prurigo nodularis-like lesions • May develop papular urticaria, a hypersensitivity reaction to the initial bite(s) that can be localised to sites of bites or generalised	• May not have prodomal symptoms • Rarely associated with anaphylaxis	• Papules may have visible punctum • Patterns of eruption tend to correlate with exposure or exposed areas • History of outdoor exposures, pets, work and hobbies	• Patients may also have a travel history • Secondary infection (e.g. Staphylococcal) may appear more pustular	• Parasite smear may sometimes, but not often, yield arthropod parts (POC) • Swab lesions for pyogenic culture for secondary bacterial infection

HIV: human immunodeficiency virus; HSV: herpes simplex virus; LGV: lymphogranuloma venereum; MXPX: monkeypox virus; PCR: polymerase chain reaction; POC: point of care; RPR: rapid plasma regain; STI: sexually transmitted infection; TPAb: *Treponema pallidum* antibody; TPHA: *Treponema pallidum* haemagglutination
Superscript numbers: Refer to REFERENCES