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Primary HHV-8 infection in immunocompetent children may manifest as fever and maculopapular rash. Among individuals with intact immunity, chronic asymptomatic infection is the rule, and neo plastic disorders generally develop only after subsequent immunocom promise. Immunocompromised persons with primary infection may present with fever, splenomegaly, lymphoid hyperplasia, pancytopenia, or rapid-onset KS. Quantitative analysis of HHV-8 DNA suggests a predominance of latently infected cells in KS lesions and frequent lytic replication in multicentric Castleman disease. The KS-associated herpesvirus inflammatory cytokine syndrome (KICS)—consisting of fever, lymphadenopathy, hepatosplenomegaly, cytopenias, and high levels of HHV-8, human and viral interleukin 6, and human interleukin 10—has been described in some HIV-infected patients and is associ ated with a high mortality rate. Effective antiretroviral therapy for HIV-infected individuals has led to a marked reduction in rates of KS among persons dually infected with HHV-8 and HIV in resource-rich areas. HHV-8 itself is suscep tible in vitro to ganciclovir, foscarnet, and cidofovir. A small, random ized, double-blind, placebo-controlled, crossover trial suggested that oral valganciclovir administered once daily reduced HHV-8 replica tion. However, clinical benefits of valganciclovir or other drugs in HHV-8 infection have not yet been demonstrated. Sirolimus inhibits the progression of dermal KS in kidney transplant recipients while providing effective immunosuppression. Rituximab alone or in combi nation with chemotherapy can lead to a survival of >90% at 5 years in HHV-8–associated multicentric Castleman disease. ■ ■FURTHER READING Cytomegalovirus Avery RK et al: Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: Results from a Phase 3 randomized clinical trial. Clin Infect Dis 75:690, 2022. Chatzakis C et al: The effect of valacyclovir on secondary prevention of congenital cytomegalovirus infection, following primary maternal infection acquired periconceptionally or in the first trimester of pregnancy. An individual data meta-analysis. Am J

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Monkeypox, Molluscum

Contagiosum, and Other Poxvirus Infections POXVIRUSES CHAPTER 201 ■ ■DEFINITION AND ETIOLOGY Poxviruses (Poxviridae) are a family of double-stranded DNA viruses whose genomic structure is generally conserved across subfamilies, genera, and species. The central portion of the genome, which can range up to 200 kb, encodes the open reading frames (ORFs) required for replication or packaging of virions. The left and right ends of the genome encode genes with predicted functions in immune eva sion, host interaction, or unknown roles. The complement of ORFs across different genera is largely responsible for differences in disease manifestations and/or virus host range. Four genera of poxviruses (Orthopoxvirus, Parapoxvirus, Yatapoxvirus, and Molluscipoxvirus) include species that can infect humans. Additionally, a currently unclassified poxvirus has been reported to cause human illness. Table 201-1 identifies these viruses, the majority of which are zoonotic, and lists some of their epidemiologic characteristics. Monkeypox, Molluscum Contagiosum, and Other Poxvirus Infections ■ ■EPIDEMIOLOGY Most poxviruses that infect humans are spread through direct contact; notable exceptions are some species of Orthopoxvirus (i.e., variola and monkeypox viruses [MPXV]). Variola virus (the virus that causes smallpox) is transmitted primarily by close contact and via respira tory secretions. In what seems

to have been a rare circumstance near the end of global efforts to eradicate smallpox, it was reported that variola virus appeared to transmit via aerosol in a German hospital in Meschede. The degree to which potential aerosols had a role in small pox transmission remains debated. There are two geographically, genetically, and clinically distinct clades of MPXV. Clade I (formally Congo Basin clade) is endemic to Central Africa (Democratic Republic of the Congo, Republic of the Congo, Central African Republic, Cameroon, Gabon). Clade II (for mally West African clade) is endemic to West Africa (Nigeria, Liberia, Sierra Leone, Cameroon, Cote d'Ivoire). Clade I MPXV causes a higher proportion of individuals with severe disease than Clade II, which is further subdivided into clade IIa, found endemically in West Africa, and clade IIb, which spread worldwide in 2022, with low levels of virus circulation continuing to date. In endemic areas, MPXV infections historically clustered around rural villages and within households with significant wildlife exposure. Spread to humans is primarily through direct contact (e.g., handling during food preparation) with infected animals leading to percutaneous or permucosal exposure. Human-tohuman spread historically was primarily via close skin-to-skin contact;

TABLE 201-1 Poxviruses Causing Infection in Humans GENUS, SPECIES GEOGRAPHY ZOONOTIC CHARACTERISTICS Orthopoxvirus Variola (smallpox) Eradicated, formerly worldwide Solely a human pathogen Monkeypox Historically endemic to West and Central Africa, but spread worldwide in 2022 Squirrel species, Gambian rats, and dormice implicated as potential reservoir species; other species effective in transmitting disease to humans (pet North American prairie dogs, non-human primates); can be acquired during hunting/preparation of African wildlife for nutritional protein source Cowpox Europe Rodents as reservoir; outbreaks associated with rodent pet trade; cats also effective transmitters of illness; previously, dairy cow teat lesions linked to human cutaneous lesions Vaccinia and vaccinia-like viruses (e.g., buffalopox, Cantagalo, Araçatuba) Europe, India, and South America Rodents suspected as a potential reservoir; localized lesions on cattle or other ruminants (e.g., water buffalo for buffalopox) responsible for most human infections Borealpox (formally known as Alaskapox) United States (Alaska) Northern red-backed voles, squirrels, and shrews suspected as potential reservoir species; potential transmission to humans suspected from contact of above species or pets (e.g., cats, dogs) who were infected PART 5 Infectious Diseases Akhmeta Georgia (country) Woodmice (Apodemus spp.); cows can be infected and possibly transmit to humans. Molluscipoxvirus Molluscum contagiosum Worldwide Thought to be solely a human pathogen; closely related viruses described in other mammals Parapoxvirus Orf Worldwide Handling of infected sheep and goats primarily responsible for transmission to humans Pseudocowpox Worldwide Handling of infected dairy cattle Bovine papular stomatitis Worldwide Handling of infected beef cattle Deerpox U.S. deer herds Handling of infected deer Sealpox Seal/pinniped colonies worldwide Handling of infected pinnipeds Yatapoxvirus Tanapox Africa Possible nonhuman primate reservoir; potential arthropod mediator Unclassified poxvirus NY-014a United States (New York State) Unknown aPossibly an orthopoxvirus. however, spread via respiratory secretions also was believed to occur. After decades without detection of MPXV infections, Nigeria expe rienced a rapid increase in mpox cases in 2017. As routine smallpox vaccination (which provides cross-protection for mpox) ended in 1980, it is unclear what role waning orthopoxvirus immunity played in its reemergence. These cases in Nigeria were unusual in that they occurred in urban centers in persons without known animal con tact. In 2021, eight travel-associated mpox cases in persons who flew from Nigeria were identified in four countries (United States, United Kingdom, Israel, and Singapore), with limited subsequent human-tohuman transmission. In 2022, clade IIb mpox spread globally, with

transmission occurring primarily via close, intimate (e.g., sexual) contact and predominantly affecting gay, bisexual, and other men who have sex with men (MSM). MSM, particularly Black and Hispanic MSM in the United States, remain disproportionately affected by mpox to date. Additionally, up to 50% of those diagnosed with mpox in this outbreak are also living with HIV. Other orthopoxviruses (apart from variola virus) (Table 201-1) are thought to spread only via direct contact or percutaneous/permucosal exposures to infected animals (or humans). The orthopoxvirus infec tions caused by cowpox and the vaccinia-like viruses are typically acquired initially through contact with an infected animal. Humanto-human transmission can also occur via contact with the lesion(s) of the infected human. In Europe, human cowpox infections have been associated with the pet rat trade, and vaccinia-like viruses (e.g., Belo Horizonte, Cantagalo, Araçatuba) are reported in handlers of dairy cattle in South America. Similarly, buffalopox has been reported in inhabitants of the Indian subcontinent exposed to infectious lesions on water buffalo. In the United States, vaccinia, the virus historically known as the substrate for smallpox vaccine, has caused infections in laboratory workers studying the virus. With all orthopoxvirus infec tions, the illness is considered infectious from symptom onset until all lesions have crusted, the crust(s) have separated from the skin, and a fresh layer of healthy skin has formed underneath. The most common poxvirus encountered in practice is molluscum contagiosum virus (MCV), which is a molluscipoxvirus. MCV likely spreads through direct contact with and percutaneous exposure to another infected human. Like variola virus (an orthopoxvirus), MCV is considered to be a pathogen of humans only. Infections are com monly seen in pediatrics where transmission occurs through play activities. In adults, the disease can manifest similarly, but genital involvement also is noted as transmission often occurs through sexual exposure. The epidemiology of tanapox (a yatapoxvirus) is poorly under stood. Simian reservoirs and the potential for an arthropod vector are hypothesized. Rare cases of tanapox have only been seen in the United States from travelers returning from West or Central Africa. Human infections with parapoxviruses occur through direct contact with and percutaneous exposure to lesions developing at the site of contact with an infected animal. ■ ■PATHOGENESIS The pathogenesis of orthopoxvirus infections is thought to involve sys temic spread of disease from the site of virus inoculation to local lymph nodes, lymphoreticular tissue seeding, and finally the development of symptomatic (febrile) viremia and viral skin tropism. Disease severity is affected by the degree to which the innate immune and interferon responses control the initial stages of infection. During illness, patients may experience lymphadenopathy, fever, pain, and malaise. In immu nocompromised persons more severe systemic manifestations are seen. Cases exemplifying this were seen throughout the global mpox outbreak in 2022. Individuals with intact immune systems develop lesions (often at the exposure site) about 1 week after exposure; these lesions progress through specified stages over the next 7–14 days, fol lowed by scabbing and complete resolution by 14–21 days after rash onset. Lesion scabs contain viable virus, and it is only once all lesions scab over, the scabs separate from the skin, and newly formed intact skin forms that the infectious period ends. In contrast, persons with severe immunocompromised states (e.g., advanced HIV [i.e., CD4 T cell count <200 cells/mm3], organ transplantation) can develop severe mpox. In these instances, the spread or growth of MPXV goes unchecked, and systemic spread of disease results in wide dissemina tion of the rash, with large confluent lesions persisting for months and additional organ involvement. Other poxvirus infections—with the possible exception of yatapox virus infection, in which disease pathogenesis is poorly understood— likely involve only local growth of the virus at the site of inoculation or reinoculation. In some immunocompromised hosts, the lesions caused by Parapoxvirus infections can become quite large; such lesions are referred to as “giant orf.”

■ ■CLINICAL MANIFESTATIONS Systemic poxvirus infections (i.e., Variola Virus, Monkeypox Virus [Orthopoxvirus genome] and Tanapox [Yatapoxvirus genome]) Following exposure, both smallpox and mpox have a similar incuba tion period of up to 17 days. Classically, smallpox and mpox present as follows: the first clinical sign is fever, which is followed by rash onset days later. Other prodromal symptoms include malaise, sore throat, and headache. When lymphadenopathy was present during this stage and throughout illness, it was a key differentiating factor between smallpox (absent) and mpox (present) in endemic countries. The rash evolves through classic macular, papular, vesicular, and pustular phases (the last with central umbilication), with each stage lasting 2–3 days and lesions in the same anatomic location typically in the same stage of development. Diffuse, well-circumscribed, centrifugally distributed (i.e., lesions more prominent on the face and extremities, including palms and soles, than on the trunk) lesions are classic. Lesions are typi cally painful as they emerge and subsequently become pruritic during later stages. However, during the emergence of clade IIb mpox in 2022, several clinical manifestations differed from this classic presentation. During the clade IIb outbreak, patients often presented with rash as their first sign or symptom of disease or concurrently or in the absence of prodromal symptoms; lesions were frequently localized, primarily in the anogenital region (Fig. 201-1). The lesions themselves were smaller, fewer in number (often <10), and often in different stages at the same anatomic site. There does not appear to be an increase in disease severity in those without severe immunocompromise (i.e., HIV with CD4 T cell count >200 cells/mL). However, a minority of patients have developed severe manifestations of mpox, many of whom who are severely immunocompromised (e.g., advanced HIV, organ transplanta tion, comparable severe immunocompromise). Severe Mpox Rare severe manifestations of mpox include ocular infection, neurologic complications, myopericarditis, and uncontrolled viral replication in severely immunocompromised patients. Mpoxrelated ocular disease can occur via autoinoculation (i.e., touching a lesion then the eye) or local spread from a nearby lesion. Symptoms include eye pain, redness, vision changes or loss, or periorbital swell ing. Ocular disease can manifest as blepharitis, conjunctivitis, con junctival lesions, keratitis, and vision loss. Neurologic complications include rare reports of encephalitis and myelitis. Patients may have severe headache, neck pain, altered mentation, or focal deficits. Myo pericarditis has been reported in some patients with mpox, including complaints of shortness of breath or palpitations with elevations in car diac biomarkers and electrocardiographic changes. Mucosal complica tions can affect alimentation, urination, or defecation due to painful or obstructive lesions. These can lead to strictures, edema, and severe lymphadenopathy. Complications from uncontrolled viral replication commonly occur in severely immunocompromised persons such as those with advanced HIV or organ transplantation. These patients often develop numerous large, coalescing, or necrotic lesions and can have other organ involvement including the gastrointestinal tract, liver, lungs, and brain, which can manifest as organ dysfunction. These patients may have disease lasting many months in which immune system optimization is crucial to recovery. Most deaths have occurred in the United States, predominantly among people with advanced HIV with CD4 <50 cells/mm3. Tanapox Patients infected with tanapox virus initially present with a very high fever, are often thought to have malaria (given the endemic location), and later develop 1–10 nodular lesions. These nodules are often in anatomic areas not typically covered by clothing. Lesions are seldom filled with fluid and more often contain necrotic tissue. The lesion size peaks around 2 weeks after initial formation, and lesions typically disappear spontaneously within 6 weeks. Other Orthopoxvirus Infections Other orthopoxvirus infec tions are more localized in their presentation, with lesions likely devel oping directly at the site of contact with the virus. Akhmeta, Borealpox (formally known as Alaskapox), vaccinia, vaccinia-like, and

cowpox virus infections are typically associated with a localized rash or lesion

evolving through classical papular, vesicular, and pustular phases. In immunocompromised patients, presentation of these orthopoxvirus infections can be protracted or disseminated and, rarely, lead to death.

Other Poxvirus Infections Individuals infected with other pox viruses that cause localized disease (parapoxviruses and MCV) seldom report a febrile phase and instead experience slow and gradual devel opment of a lesion or lesions. The lesion of molluscum contagiosum has a classic pearly appearance that sometimes umbilicates as it matures (Fig. 201-2). There is little inflammation that surrounds the painless lesions, which persist for months but gradually regress after 6–12 months. Patients with immunocompromised status can have severe and prolonged disease; in patients with uncontrolled HIV and advanced HIV, immune reconstitution is usually sufficient to clear the virus. The rash lesions of parapoxvirus infections begin as ery thematous papules, develop into a “target” lesion, and then become nodular and papilloma-like. “Giant” parapoxvirus infections have been reported in immunocompromised individuals. ■ ■DIFFERENTIAL DIAGNOSIS A patient usually presents to the clinician with nodular or vesicu lopustular lesions. Important elements of the history include travel, occupation (with risk varying dependent on the poxvirus; greater risk is in laboratory workers working with poxviruses, farmers, hunters, and sex workers), animal exposures, lesion evolution, sexual history, and symptom timing with respect to rash onset. Additionally, given the appearance and location, mpox lesions in the anogenital area may resemble common sexually transmitted infections (STIs) such as gon orrhea, chlamydia, or syphilis; up to 10% of patients with mpox may be coinfected with an STI. Other differential diagnoses in poxvirus infec tions include varicella, yaws, papillomavirus infection, herpes simplex virus, and (particularly in parapoxvirus infections) cutaneous anthrax. While the characteristic lesions of poxvirus infection coupled with an indicative exposure history are helpful in narrowing the differential, laboratory testing is needed to confirm the diagnosis. CHAPTER 201 Monkeypox, Molluscum Contagiosum, and Other Poxvirus Infections Currently, the most common laboratory tool for diagnosis of pox virus infection involves nucleic acid (i.e., molecular) testing. Nucleic acid–based diagnostics include polymerase chain reaction (PCR) and sequencing to fully characterize the isolate in some cases. This technol ogy has led to the identification of a number of new poxviruses that can cause human infection, including Akhmeta, Borealpox, and NY-014. Orthopoxvirus molecular testing options drastically expanded during the global 2022 mpox outbreak that was caused by clade IIb MPXV. Prior to the outbreak, only select PCR assays (developed by the Centers for Disease Control and Prevention [CDC] for smallpox prepared ness) were available within a subset of the Public Health Laboratories (PHL) within the Laboratory Response Network. During the 2022 outbreak, CDC and the U.S. Food and Drug Administration (FDA) collaborated to increase testing availability in commercial laboratories within the United States. PCR assays specific to non-variola ortho poxvirus (NVO), orthopoxvirus generic, generic mpox, and mpox clade II are now readily available for testing of most orthopoxviruses. Other countries experienced similar growth in orthopoxvirus testing options. Many laboratories have also introduced multiplex testing options that include both NVO- and MPXV-specific targets. Some laboratories (U.S. Government and PHL) offer mpox clade-specific testing. The orthopoxviruses also grow well in most standard clinical laboratory tissue cultures. The parapoxviruses are difficult to isolate via culture (primary cells are best), and MCV cannot be cultured. Electron microscopy identifies the characteristic large, brick-shaped virus par ticles on negative stain if orthopoxvirus, yatapoxvirus, or MCV is pres ent. Parapoxviruses have an ovoid

structure with crisscross spicules on negative-stain electron microscopy. MCV has a classic appearance, with Henderson-Patterson bodies, on pathologic analysis of a biopsy sample. Serologic assays can demonstrate orthopoxvirus reactivity, but most are unable to distinguish between orthopoxvirus species because of their broad antigenic similarity. Efforts in serology tests during the mpox outbreak are ongoing in order to differentiate infection from vaccination.

PART 5 Infectious Diseases A D B E C F FIGURE 201-1 Mpox lesions. A–D. Standard lesions seen in mpox. Notice the well-circumscribed nature of the lesions even on mucosal surfaces; many of the lesions display the central umbilication unique to poxviruses, which often develop in later stages of illness. E and F. Severe mpox manifestations in a patient with advanced HIV. Notice the large coalescing lesion on the back, where the large lesion border is composed of individual lesions; additionally, large healing lesions are seen on the neck and hands. (Source: CDC.)

A B FIGURE 201-2 Molluscum contagiosum lesions. Notice the classic pearly appearance of molluscum contagiosum in A and B. B also displays central umbilication. (Source: CDC.)
TREATMENT Poxvirus Treatment of poxvirus infection is largely supportive. Typical sup portive care goals include prevention of autoinoculation to sec ondary sites and bacterial superinfection, pain control, and scar minimization. Disease-specific therapies are generally reserved for severe illness. Recently, as part of smallpox preparedness efforts, two antiviral agents active against the orthopoxviruses have been approved by FDA for the treatment of smallpox. As these agents did not require comparative human trials, their role in human orthopoxvirus infections continues to be investigated. Both anti viral agents are virustatic; therefore an immune response is crucial to recovery for any orthopoxvirus infection. For mpox specifically, given the high proportion of individuals coinfected with HIV, a key aspect of management is initiation, continuation, or reinitiation of antiretroviral therapy. The degree of HIV control is directly corre lated with hospitalization, severe mpox manifestations, and mortal ity. As in other etiologies of immunosuppression, immune system optimization is critical for recovery. Immunosuppressive agents should be avoided or held if possible during illness. Tecovirimat is an inhibitor of a viral egress protein that prevents cell-to-cell dissemination of mature virions; it is virustatic, so concomitant optimized immune function is essential to favorable clinical outcomes. It was used as an investigational drug in isolated cases of vaccinia, cowpox, and borealpox, and used extensively dur ing the global mpox outbreak. It has a favorable safety profile and is the drug of choice for severe orthopoxviral infections; however, its effectiveness for treatment of human orthopoxvirus infections has not been systematically evaluated. Tecovirimat is dosed 600 mg orally or 200 mg intravenously every 12 h (with higher or more frequent dosing depending on patient weight) typically for 2 weeks. A fatty meal is necessary to optimize enteral bioavailability. For patients with severe immunocompromise and severe manifesta tions of mpox, the benefits of a prolonged treatment course (i.e., beyond the standard 14-day duration) may outweigh the harms (tecovirimat resistance). Importantly, a single-point amino acid change in the viral target of the drug can confer resistance to teco virimat; therefore it should be reserved for severe orthopoxvirus infections given its primary purpose as therapy during a smallpox incident. Additionally, genotypic tecovirimat resistance does not

consistently correlate with phenotypic resistance. To complicate tecovirimat resistance further, there have been different ranges of resistant virus observed, and it is unclear how these results should be interpreted for clinical treatment purposes. It is also unknown if resistance observed

within one lesion specimen correlates with viral populations throughout the infected individual, and it has been observed that resistance develops differently (with different viral mutations detected) in swabs from different parts of the body. Therefore, it is reasonable to continue therapy even when resistance is suspected or detected in a specimen.

The other FDA-approved therapy for smallpox is brincidofovir, a prodrug of cidofovir. Either cidofovir or brincidofovir can be given along with tecovirimat for severe poxviral infections. Brincidofovir is only available orally and dosed at 200 mg weekly for two doses. Cidofovir can be used if intravenous therapy is required at 5 mg/kg weekly with concurrent probenecid. Limited animal data suggest that brincidofovir may be synergistic with tecovirimat in orthopox virus disease. Therefore, combination therapy can be considered in severe infections. Cidofovir and brincidofovir have higher barriers to resistance, therefore, it is less likely to occur. Topical cidofovir has been used in orthopoxvirus and MCV infections with mixed results. Vaccinia immune globulin (VIG) is licensed for the treatment of adverse reactions to live, replicating smallpox (vaccinia virus) vac cine. The standard dose is 6000 U/kg intravenously; dosing can be repeated, and doses of up to 9000 U/kg can be used. Given antigenic similarities across the orthopoxvirus genus, VIG was used exten sively for severe mpox with unclear efficacy. It is used primarily for people who may not be able to mount a sufficiently robust immune response to clear virus in patients with severe immunocompromise. Monoclonal antibodies similar to VIG are currently being studied for variola virus. CHAPTER 201 Trifluridine is active against ocular orthopoxviral infections and can be administered for treatment or ocular prophylaxis for peri orbital lesions. Treatment dosing is instillation of one drop into the affected eye(s) every 2 h while awake for the first 2 weeks and then four times daily for an additional 2 weeks. Monkeypox, Molluscum Contagiosum, and Other Poxvirus Infections Treatment for MCV infection is on a case-by-case basis. Immu nomodulatory therapies such as imiquimod have been used. If quicker resolution is desired, curettage and topical liquid nitrogen is available along with the FDA-approved agent cantharidin, which is applied by a clinician to lesions every 21 days for up to four doses. ■ ■PROGNOSIS In immunocompetent hosts most poxvirus infections are self-limited, resolving in weeks or, in the case of molluscum contagiosum, months. The exceptions are the generalized orthopoxvirus infections caused by MPXV and variola virus, whose case–fatality rates are greater. In unvaccinated individuals smallpox carries a mortality of up to 30%, and MPXV clade I, IIa, and IIb mortality rates are 1.4–10%, 1%, and <1%, respectively. Immunocompromised hosts may have more severe orthopoxvirus and parapoxvirus infections (e.g., severe mpox, pro gressive vaccinia, eczema vaccinatum, severe borealpox) leading to higher mortality, or they may have atypical presentations (e.g., giant orf). In patients with advanced HIV, effective antiretroviral therapy is essential to favorable clinical outcomes. MCV infections can be diffuse in immunocompromised persons. Immune reconstitution inflamma tory syndrome (IRIS) has been associated with recrudescence of MCV infections. Poxvirus reinfections are seldom reported. ■ ■PREVENTION ACAM2000 is a live, replicating vaccinia virus vaccine administered as a single dose via a percutaneous needle. JYNNEOS is a live, nonrepli cating, modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine administered via two subcutaneous doses 28 days apart. Awareness of occupational risks and adherence to appropriate barrier precautions effectively prevent most poxvirus infections. Pre-exposure vaccination is recommended for specific persons at risk of occupational exposure

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