# 102 - 210 Enterovirus, Parechovirus, and Reovirus Infections

## 210 Enterovirus, Parechovirus, and Reovirus Infections

RV Vaccine Introduction Current Vaccine Intro Status Current Vaccine Intro Status Introduced Not Introduced Planning Introduced Subnationally Program Suspended January 8, 2024 © The International Vaccine Access Center (IVAC) FIGURE 209-3 Countries that have implemented national rotavirus vaccination programs, January 8, 2024. (Source: View-Hub, http://www.view-hub.org/viz/. © The International Vaccine Access Center [IVAC].) PART 5 Infectious Diseases ■ ■OTHER VIRAL AGENTS OF GASTROENTERITIS Enteric adenoviruses of serotypes 40 and 41 belonging to subgroup F are 70- to 80-nm viruses with double-strand DNA that cause ~2–12% of all diarrhea episodes in young children. Unlike adenoviruses that cause respiratory illness, enteric adenoviruses are difficult to cultivate in cell lines, but they can be detected with commercially available EIAs. Adenovirus types 31 and 42–49 have been linked to diarrhea in HIVinfected and other immunocompromised persons. Astroviruses are 28- to 30-nm viruses with a characteristic icosahe dral structure and a positive-sense, single-strand RNA. At least seven serotypes have been identified, of which serotype 1 is most common. Astroviruses are primarily pediatric pathogens, causing ~2–10% of cases of mild to moderate gastroenteritis in children. The availability of simple immunoassays to detect virus in fecal specimens and of molecular methods to confirm and characterize strains will permit more comprehensive assessment of the etiologic role of these agents. Toroviruses are 100- to 140-nm, enveloped, positive-strand RNA viruses that are recognized as causes of gastroenteritis in horses (Berne virus) and cattle (Breda virus). Their role as a cause of diarrhea in humans is still unclear, but studies from Canada have demonstrated associations between torovirus excretion and both nosocomial gastroenteritis and necrotizing enterocolitis in neonates. These associations require further evaluation. Picobirnaviruses are small, bisegmented, double-strand RNA viruses that cause gastroenteritis in a variety of animals. Their role as primary causes of gastroenteritis in humans remains unclear, but several studies have found an association between picobirnaviruses and gastroenteritis in HIV-infected adults. Several other viruses (e.g., enteroviruses, reoviruses, pestiviruses, Aichivirus, and parvovirus B) have been identified in the feces of patients with diarrhea, but their etiologic role in gastroenteritis has not been proven. Diarrhea has also been noted as a manifestation of infection with recently recognized

viruses that primarily cause severe respiratory illness: the SARS-CoV viruses, the influenza A/H5N1 virus, and the current pandemic strain of influenza A/H1N1 virus. ■ ■FURTHER READING Armah G et al: Vaccine value profile for norovirus. Vaccine 41 Suppl 2:S134, 2023. Clark A et al: Estimating the global impact of rotavirus vaccines on child mortality. Int J Infect Dis 137:90, 2023.

Cohen A et al: Aetiology and incidence of diarrhoea requiring hos pitalisation in children under 5 years of age in 28 low-income and middle-income countries: findings from the Global Pediatric Diar rhea Surveillance. BMJ Global Health 7:e009548, 2022. Flynn T et al: Viral gastroenteritis. Lancet 403:862, 2024. Tate J et al: Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000–2013. Clin Infect Dis 62:S96, 2016. Jeffrey I. Cohen

Enterovirus, Parechovirus,

and Reovirus Infections ENTEROVIRUSES ■ ■CLASSIFICATION AND CHARACTERIZATION Enteroviruses, members of the family Picornaviridae, are so designated because of their ability to multiply in the gastrointestinal tract. Despite their name, these viruses are not a prominent cause of gastroenteritis. Enteroviruses encompass more than 115 human serotypes: 3 sero types of poliovirus, 23 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 29 serotypes of echovirus, enteroviruses 68–71, and multiple new enteroviruses (beginning with enterovirus 73) that have been identified by molecular techniques. Human enteroviruses have been reclassified into four species designated A–D. Echoviruses 22 and 23 have been reclassified as parechoviruses 1 and 2 on the basis of low nucleotide homology and differences in viral proteins. Enterovirus and parechovirus surveillance conducted in the United States by the Cen ters for Disease Control and Prevention (CDC) in 2022 showed that the most common enteroviruses and parechoviruses were enterovirus D68 (41.1% of cases) and human parechovirus 2 (20.7%), followed by

coxsackievirus A6, A9, B3, and B5, each of which accounted for 4–5% of all isolates. Human enteroviruses contain a single-stranded RNA genome sur rounded by an icosahedral capsid comprising four viral proteins. These viruses have no lipid envelope and are stable in acidic environments, including the stomach. They are susceptible to chlorine-containing cleansers but resistant to inactivation by standard disinfectants (e.g., alcohol, detergents) and can persist for days at room temperature. ■ ■PATHOGENESIS AND IMMUNITY Much of what is known about the pathogenesis of enteroviruses has been derived from studies of poliovirus infection. After ingestion, poliovirus is thought to infect epithelial cells in the mucosa of the gastrointestinal tract and then to spread to and replicate in the submu cosal lymphoid tissue of the tonsils and Peyer’s patches. The virus next spreads to the regional lymph nodes, a viremic phase ensues, and the virus replicates in organs of the reticuloendothelial system. In some cases, a second episode of viremia occurs and the virus replicates fur ther in various tissues, sometimes causing symptomatic disease. It is uncertain whether poliovirus reaches the central nervous system (CNS) during viremia or whether it also spreads via peripheral nerves. Since viremia precedes the onset of neurologic disease in humans, it has been assumed that the virus enters the CNS via the bloodstream. The poliovirus receptor is a member of the immunoglobulin super family. Poliovirus infection is limited to primates, largely because their cells express the viral receptor. Studies demonstrating the poliovirus receptor in the end-plate region of muscle at the neuromuscular junc tion suggest that, if the virus enters the muscle during viremia, it could travel across the neuromuscular junction up the axon to the anterior horn cells. Studies of monkeys and of transgenic mice expressing the

poliovirus receptor show that, after IM injection, poliovirus does not reach the spinal cord if the sciatic nerve is cut. Taken together, these findings suggest that poliovirus can spread directly from muscle to the CNS by neural pathways. Poliovirus can usually be cultured from the blood 3–5 days after infection, before the development of neutralizing antibodies. While viral replication at secondary sites begins to slow 1 week after infection, it continues in the gastrointestinal tract. Poliovirus is shed from the oropharynx for up to 3 weeks after infection and from the gastrointesti nal tract for as long as 12 weeks; hypogammaglobulinemic patients can shed poliovirus for >20 years. During replication in the gastrointestinal tract, attenuated oral poliovirus can mutate, reverting to a more neu rovirulent phenotype within a few days; however, additional mutations are probably required for full neurovirulence. One patient with hypo gammaglobulinemia who had been infected 12 years earlier and was receiving IV immune globulin suddenly developed quadriplegia and respiratory muscle paralysis and died; analysis showed that the virus had reverted to a more wild-type sequence. Humoral and secretory immunity in the gastrointestinal tract is important for the control of enterovirus infections. Enteroviruses induce specific IgM, which usually persists for <6 months, and specific IgG, which persists for life. Capsid protein VP1 is the predominant target of neutralizing antibody, which generally confers lifelong protection against subsequent disease caused by the same serotype but does not prevent infection or virus shedding. Enteroviruses also induce cellular immu nity of uncertain significance. Patients with impaired cellular immunity are not known to develop unusually severe disease when infected with enteroviruses. In contrast, the severe infections in patients with agam maglobulinemia emphasize the importance of humoral immunity in controlling enterovirus infections. Disseminated enterovirus infections have occurred in hematopoietic cell transplant recipients. IgA antibodies are instrumental in reducing poliovirus replication in and shedding from the gastrointestinal tract. Breast milk contains IgA specific for enterovi ruses and can protect humans from infection. ■ ■EPIDEMIOLOGY Enteroviruses have a worldwide distribution. More than 50% of nonpoliovirus enterovirus infections and >90% of poliovirus infec tions are subclinical. When symptoms do develop, they are usually

nonspecific and occur in conjunction with fever; only a minority of infections are associated with specific clinical syndromes. The incu bation period for most enterovirus infections ranges from 2 to 14 days but usually is <1 week.

Enterovirus infection is more common in socioeconomically dis advantaged areas, especially in those where conditions are crowded and in tropical areas where hygiene is poor. Infection is most com mon among infants and young children; serious illness develops most often during the first few days of life and in older children and adults. In developing countries, where children are infected at an early age, poliovirus infection has less often been associated with paralysis; in countries with better hygiene, older children and adults are more likely to be seronegative, become infected, and develop paralysis. Passively acquired maternal antibody reduces the risk of symptomatic infection in neonates. Young children are the most frequent shedders of entero viruses and are usually the index cases in family outbreaks. In temper ate climates, enterovirus infections occur most often in the summer and fall; no seasonal pattern is apparent in the tropics. Most enteroviruses are transmitted primarily by the fecal–oral or oral–oral route. Patients are most infectious shortly before and after the onset of symptomatic disease, when virus is present in the stool and throat. The ingestion of virus-contaminated food or water also can cause disease. Certain enteroviruses (such as enterovirus 70, which causes acute hemorrhagic conjunctivitis) can be transmitted by direct inoculation from the fingers to the eye. Airborne transmission is important for

some viruses that cause respiratory tract disease, such as coxsackievirus A21. Enteroviruses can be transmitted across the placenta from mother to fetus, causing severe disease in the newborn. The transmission of enteroviruses through blood transfusions or insect bites has not been documented. Nosocomial spread of coxsackievirus and echovirus has taken place in hospital nurseries. Outbreaks of enteroviruses correlate with levels of preexisting immunity to specific serotypes and birth rates. CHAPTER 210 Enterovirus, Parechovirus,and Reovirus Infections ■ ■CLINICAL FEATURES Poliovirus Infection Most infections with poliovirus are asymp tomatic. After an incubation period of 3–6 days, ~5% of patients pres ent with a minor illness (abortive poliomyelitis) manifested by fever, malaise, sore throat, anorexia, myalgias, and headache. This condition usually resolves in 3 days. About 1% of patients present with aseptic meningitis (nonparalytic poliomyelitis). Examination of cerebrospinal fluid (CSF) reveals lymphocytic pleocytosis, a normal glucose level, and a normal or slightly elevated protein level; CSF polymorphonuclear leukocytes may be present early. In some patients, especially children, malaise and fever precede the onset of aseptic meningitis. PARALYTIC POLIOMYELITIS The least common presentation is that of paralytic disease. After one or several days, signs of aseptic meningitis are followed by severe back, neck, and muscle pain and by the rapid or gradual development of motor weakness. In some cases, the disease appears to be biphasic, with aseptic meningitis followed first by appar ent recovery but then (1–2 days later) by the return of fever and the development of paralysis; this form is more common among children than among adults. Weakness is generally asymmetric, is proximal more than distal, and may involve the legs (most commonly); the arms; or the abdominal, thoracic, or bulbar muscles. Paralysis develops dur ing the febrile phase of the illness and usually does not progress after defervescence. Urinary retention also may occur. Examination reveals weakness, fasciculations, decreased muscle tone, and reduced or absent reflexes in affected areas. Transient hyperreflexia sometimes precedes the loss of reflexes. Patients frequently report sensory symptoms, but objective sensory testing usually yields normal results. Bulbar paralysis may lead to dysphagia, difficulty in handling secretions, or dysphonia. Respiratory insufficiency due to aspiration, involvement of the respira tory center in the medulla, or paralysis of the phrenic or intercostal nerves may develop, and severe medullary involvement may lead to circulatory collapse. Most patients with paralysis recover some func tion weeks to months after infection. About two-thirds of patients have residual neurologic sequelae.

Paralytic disease is more common among older individuals, preg nant women, and persons exercising strenuously or undergoing trauma at the time of CNS symptoms. Tonsillectomy predisposes to bulbar poliomyelitis, and IM injections increase the risk of paralysis in the involved limb(s).

VACCINE-ASSOCIATED POLIOMYELITIS The risk of developing polio myelitis after oral vaccination is estimated at 1 case per 2.5 million doses. The risk is ~2000 times higher among immunodeficient per sons, especially persons with hypo- or agammaglobulinemia. Before 1997, an average of eight cases of vaccine-associated poliomyelitis occurred—in both vaccinees and their contacts—in the United States each year. With the change in recommendations first to a sequential regimen of inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV) in 1997 and then to an all-IPV regimen in 2000, the number of cases of vaccine-associated polio declined. From 1997 to 1999, six such cases were reported in the United States followed by one case in 2022. POSTPOLIO SYNDROME The postpolio syndrome presents as new onset of weakness, fatigue, fasciculations, and pain with additional atrophy of the muscle group involved during the initial paralytic disease

20–40 years earlier. The syndrome is more common among women and with increasing time after acute disease. The onset is usually insidious, and weakness occasionally extends to muscles that were not involved dur ing the initial illness. The prognosis is generally good; progression to further weakness is usually slow, with plateau periods of 1–10 years. The postpolio syndrome is thought to be due to progressive dysfunc tion and loss of motor neurons that compensated for the neurons lost during the original infection and not to persistent or reactivated poliovirus infection. PART 5 Infectious Diseases Other Enteroviruses An estimated 5–10 million cases of symp tomatic disease due to enteroviruses other than poliovirus occur in the United States each year. Among neonates, enteroviruses are the most common cause of aseptic meningitis and nonspecific febrile illnesses. Certain clinical syndromes are more likely to be caused by certain serotypes (Table 210-1). NONSPECIFIC FEBRILE ILLNESS (SUMMER GRIPPE) The most com mon clinical manifestation of enterovirus infection is a nonspecific febrile illness. After an incubation period of 3–6 days, patients present TABLE 210-1 Manifestations Commonly Associated with Enterovirus Serotypes SEROTYPE(S) OF INDICATED VIRUS ECHOVIRUS (E) AND ENTEROVIRUS (Ent) MANIFESTATION COXSACKIEVIRUS Acute hemorrhagic conjunctivitis A24 E70 Aseptic meningitis A2, 4, 7, 9, 10; B1–5 E4, 6, 7, 9, 11, 13, 16, 18, 19, 30, 33; Ent70, 71 Encephalitis A9; B1–5 E3, 4, 6, 7, 9, 11, 18, 25, 30; Ent71 Exanthem A4, 5, 6, 9, 10, 16; B1, 3–5 E4–7, 9, 11, 16–19, 25, 30; Ent71 Generalized disease of the newborn B1–5 E4–7, 9, 11, 14, 16, 18, 19 Hand-foot-and-mouth disease A5–7, 9, 10, 16; B1, 2, 5 Ent71 Herpangina A1–10, 16, 22; B1–5 E6, 9, 11, 16, 17, 25, 30; Ent71 Myocarditis, pericarditis A4, 9, 16; B1–5 E6, 9, 11, 22 Paralysis A4, 7, 9; B1–5 E2–4, 6, 7, 9, 11, 18, 30; EntD68, 70, 71 Pleurodynia A1, 2, 4, 6, 9, 10, 16; B1–6 E1–3, 6, 7, 9, 11, 12, 14, 16, 19, 24, 25, 30 Pneumonia A9, 16; B1–5 E6, 7, 9, 11, 12, 19, 20, 30; EntD68, 71

with an acute onset of fever, malaise, and headache. Occasional cases are associated with upper respiratory symptoms, and some cases include nausea and vomiting. Symptoms often last for 3–4 days, and most cases resolve in a week. While infections with other respiratory viruses occur more often from late fall to early spring, febrile illness due to enteroviruses frequently occurs in the summer and early fall. GENERALIZED DISEASE OF THE NEWBORN Most serious enterovirus infections in infants develop during the first week of life, although severe disease can occur up to 3 months of age. Neonates often pres ent with an illness resembling bacterial sepsis, with fever, irritability, and lethargy. Laboratory abnormalities include leukocytosis with a left shift, thrombocytopenia, elevated values in liver function tests, and CSF pleocytosis. The illness can be complicated by myocarditis and hypotension, fulminant hepatitis and disseminated intravascular coagulation, meningitis or meningoencephalitis, or pneumonia. It may be difficult to distinguish neonatal enterovirus infection from bacterial sepsis, although a history of a recent virus-like illness in the mother provides a clue. ASEPTIC MENINGITIS AND ENCEPHALITIS In children and young adults, enteroviruses are the cause of up to 90% of cases of aseptic meningitis in which an etiologic agent can be identified. Patients with aseptic meningitis typically present with an acute onset of fever, chills, headache, photophobia, and pain on eye movement. Nausea and vomiting also are common. Examination reveals meningismus without localizing neurologic signs; drowsiness or irritability also may be apparent. In some cases, a febrile illness may remit and return sev eral days later in conjunction with signs of meningitis. Other systemic manifestations may provide clues to an enteroviral cause, including diarrhea, myalgias, rash, pleurodynia, myocarditis, and herpangina. Examination of the CSF invariably reveals pleocytosis; the CSF cell count shows a shift from neutrophil to lymphocyte predominance within 1 day of presentation, and the total cell count does not exceed 1000/μL. The CSF glucose level is usually normal (in contrast to

the low CSF glucose level in mumps), with a normal or slightly elevated protein concentration. Partially treated bacterial meningitis may be particu larly difficult to exclude in some instances. Enteroviral meningitis is more common in summer and fall in temperate climates, while viral meningitis of other etiologies is more common in winter and spring. Symptoms ordinarily resolve within a week, although CSF abnormali ties can persist for several weeks. Enteroviral meningitis is often more severe in adults than in children. Neurologic sequelae are rare, and most patients have an excellent prognosis. Enteroviral encephalitis is much less common than enteroviral aseptic meningitis. Occasional highly inflammatory cases of enteroviral men ingitis may be complicated by a mild form of encephalitis that is recog nized on the basis of progressive lethargy, disorientation, and sometimes seizures. Less commonly, severe primary encephalitis may develop. An estimated 10–35% of cases of viral encephalitis are due to enteroviruses. Immunocompetent patients generally have a good prognosis. Patients with hypogammaglobulinemia, agammaglobulinemia, or severe combined immunodeficiency may develop chronic meningitis or encephalitis; about half of these patients have a dermatomyositis-like syndrome, with peripheral edema, rash, and myositis. They may also have chronic hepatitis. Patients may develop neurologic disease while receiving immunoglobulin replacement therapy. Echoviruses (espe cially echovirus 11) are the most common pathogens in this situation. Paralytic disease due to enteroviruses other than poliovirus occurs sporadically and is usually less severe than poliomyelitis. Most cases are due to enterovirus 70 or 71 or to coxsackievirus A7 or A9. GuillainBarré syndrome is also associated with enterovirus infection. While earlier studies suggested a link between enteroviruses and chronic fatigue syndrome, most recent studies have not demonstrated such an association. ACUTE FLACCID MYELITIS Patients with acute flaccid myelitis pres ent with fever or respiratory symptoms and progress within hours to a few days to flaccid paralysis in one or more limbs. The disease is much more frequent in children. Less commonly, the disease can affect

cranial nerves and respiratory or bulbar muscles. Like polio and some other enteroviruses, the disease affects the anterior horn cells in the spinal cord; gray matter changes can be seen on MRI of the spinal cord. The CSF shows a lymphocytic pleocytosis and often a mildly elevated protein. Cases of acute flaccid myelitis have occurred in late summer or early fall since 2012. Several studies have shown antibodies to entero viruses in the CSF; antibodies to enterovirus D68 are most frequently detected. While enterovirus D68 has been detected in respiratory, stool, and nasopharyngeal samples from patients with acute flaccid myelitis, the virus has been rarely detected in the CSF. Treatment is supportive, and most patients have persistent neurologic deficits. PLEURODYNIA (BORNHOLM DISEASE) Patients with pleurodynia present with an acute onset of fever and spasms of pleuritic chest or upper abdominal pain. Chest pain is more common in adults, and abdominal pain is more common in children. Paroxysms of severe, knifelike pain usually last 15–30 min and are associated with diaphore sis and tachypnea. Fever peaks within an hour after the onset of parox ysms and subsides when pain resolves. The involved muscles are tender to palpation, and a pleural rub may be detected. The white blood cell count and chest x-ray results are usually normal. Most cases are due to coxsackievirus B and occur during epidemics. Symptoms resolve in a few days, and recurrences are rare. Treatment includes the administra tion of nonsteroidal anti-inflammatory agents or the application of heat to the affected muscles. MYOCARDITIS AND PERICARDITIS Enteroviruses are estimated to cause up to one-third of cases of acute myocarditis. Coxsackievirus B and its RNA have been detected in pericardial fluid and myocardial tissue in some cases of acute myocarditis and pericarditis. Most cases of enteroviral myocarditis or pericarditis occur in newborns, ado lescents, or young adults. More than two-thirds

of patients are male. Patients often present with an upper respiratory tract infection that is followed by fever, chest pain, dyspnea, arrhythmias, and occasionally heart failure. A pericardial friction rub is documented in half of cases, and the electrocardiogram shows ST-segment elevations or ST- and T-wave abnormalities. Serum levels of myocardial enzymes are often elevated. Neonates commonly have severe disease, while older children and adults recover completely. Up to 10% of cases progress to chronic dilated cardiomyopathy. Chronic constrictive pericarditis also may be a sequela. EXANTHEMS Enterovirus infection is the leading cause of exanthems in chil dren in the summer and fall. While exanthems are associated with many enteroviruses, certain types have been linked to specific syndromes. Echovi ruses 9 and 16 have frequently been associated with exanthem and fever. Rashes may be discrete or confluent, beginning on the face and spreading to the trunk and extremities. Echovirus 9 is the most common cause of a rubel liform (discrete) rash. Unlike the rash of rubella, the enteroviral rash occurs in the summer and is not associated with lymphadenopathy. Roseola-like rashes develop after defervescence, with mac ules and papules on the face and trunk. The Boston exanthem, caused by echo virus 16, is a roseola-like rash. A variety of other rashes have been associated with enteroviruses, including erythema multiforme (see Fig. A1-24A) and vesicular, urticarial, petechial, bullous, or purpuric lesions. Enanthems also occur, including lesions that resemble the Koplik's spots seen with measles (see Fig. A1-2). A B C D FIGURE 210-1 Vesicular eruptions of the hand (A), knee (B), and mouth (C) of a 6-year-old boy with coxsackievirus A6 infection. Several of his fingernails were shed 2 months later (D). (Images reprinted courtesy of Centers for Disease Control and Prevention/Emerging Infectious Diseases.)

HAND-FOOT-AND-MOUTH DISEASE (FIG. 210-1) After an incubation period of 4–6 days, patients with hand-foot-and-mouth disease pres ent with fever, anorexia, and malaise; these manifestations are followed by the development of sore throat and vesicles (see Fig. A1-22) on the buccal mucosa and often on the tongue and then by the appearance of tender vesicular lesions on the dorsum of the hands, sometimes with involvement of the palms. The vesicles may form bullae and quickly ulcerate. About one-third of patients also have lesions on the palate, uvula, or tonsillar pillars, and one-third have a rash on the feet (includ ing the soles) or on the buttocks. Generalized rashes also have been reported. The disease is highly infectious, with attack rates of close to 100% among young children. The lesions usually resolve in 1 week. Most cases are due to coxsackievirus A16 or enterovirus 71.

An epidemic of enterovirus 71 infection in Taiwan in 1998 resulted in thousands of cases of hand-foot-and-mouth disease or herpangina (see below). Severe complications included CNS disease, myocarditis, and pulmonary hemorrhage. About 90% of those who died were children ≤5 years old, and death was associated with pulmonary edema or pulmonary hemorrhage. CNS disease included aseptic meningitis, flaccid paralysis (similar to that seen in poliomyelitis), and rhomb encephalitis with myoclonus and tremor or ataxia. The mean age of patients with CNS complications was 2.5 years, and MRI in cases with encephalitis usually showed brainstem lesions. Follow-up of children at 6 months showed persistent dysphagia, cranial nerve palsies, hypoven tilation, limb weakness, and atrophy; at 3 years, persistent neurologic sequelae were documented, with delayed development and impaired cognitive function. Yearly epidemics of enterovirus 71 infection have occurred in China since 2008, with thousands of cases and hundreds of deaths each year. Infections have been associated with fever, rash, brainstem encephalitis with myoclonic jerks, and limb trembling; some cases have progressed to seizures and coma. Lung findings include pulmonary edema and

hemorrhage. While the level of creatine kinase MB is sometimes elevated, myocardial necrosis generally is not found. CHAPTER 210 Enterovirus, Parechovirus,and Reovirus Infections Cyclic epidemics occur every 2–3 years in other Asian countries. However, the virus circulates at lower rates in the United States, Europe, and Africa. In the United States, hand-foot-and-mouth disease is most commonly associated with coxsackievirus A16. Between November 2011 and February 2012, outbreaks of hand-foot-and-mouth disease

due to coxsackievirus A6 occurred in several U.S. states, and 19% of the affected persons were hospitalized.

HERPANGINA Herpangina is usually caused by coxsackievirus A and presents as acute-onset fever, sore throat, odynophagia, and grayishwhite papulovesicular lesions on an erythematous base that ulcerate. The lesions can persist for weeks; are present on the soft palate, anterior pillars of the tonsils, and uvula; and are concentrated in the posterior portion of the mouth. In contrast to herpes stomatitis, enteroviral herpangina is not associated with gingivitis. Acute lymphonodular pharyngitis associated with coxsackievirus A10 presents as white or yellow nodules surrounded by erythema in the posterior oropharynx. The lesions do not ulcerate. ACUTE HEMORRHAGIC CONJUNCTIVITIS Patients with acute hemor rhagic conjunctivitis present with an acute onset of severe eye pain, blurred vision, photophobia, and watery discharge from the eye. Examination reveals edema, chemosis, and subconjunctival hemor rhage and often shows punctate keratitis and conjunctival follicles as well (Fig. 210-2). Preauricular adenopathy is often found. Epidemics and nosocomial spread have been associated with enterovirus 70 and coxsackievirus A24. Outbreaks have been due to coxsackievirus A24 in China and India (2010), Japan (2011), and Thailand (2014). Systemic symptoms, including headache and fever, develop in 20% of cases, and recovery is usually complete in 10 days. The sudden onset and short duration of the illness help to distinguish acute hemorrhagic conjunc tivitis from other ocular infections, such as those due to adenovirus and Chlamydia trachomatis. Paralysis has been associated with some cases of acute hemorrhagic conjunctivitis due to enterovirus 70 during epidemics. PART 5 Infectious Diseases OTHER MANIFESTATIONS Enteroviruses are an infrequent cause of childhood pneumonia and the common cold. From mid-August 2014 to January 2015, enterovirus D68 infection was confirmed in more than 1000 persons with mild to severe respiratory illnesses in 49 U.S. states. Nearly all reported cases were in children, many of whom had asthma. Severe respiratory illness due to enterovirus D68 continues to occur; case numbers were lower in 2020, likely due to mitigation efforts for COVID-19, but rose in 2022. A prospective study of >300 children showed that prolonged shedding of enteroviruses in the stool was asso ciated with development of islet cell autoantibodies and type 1 diabetes. Coxsackievirus B has been isolated at autopsy from the pancreas of a few children presenting with type 1 diabetes mellitus; however, most attempts to isolate the virus have been unsuccessful. Other diseases that have been associated with enterovirus infection include parotitis, bronchitis, bronchiolitis, croup, infectious lymphocytosis, polymyosi tis, acute arthritis, and acute nephritis. ■ ■DIAGNOSIS Isolation of enterovirus in cell culture had been the traditional diag nostic procedure; PCR is used now more often. Cultures of stool, FIGURE 210-2 Acute hemorrhagic conjunctivitis due to enterovirus 70. (Image reprinted courtesy of Jerri Ann Jenista, MD.)

nasopharyngeal, or throat samples from patients with enterovirus diseases do not prove that the virus is directly associated with disease because these sites are frequently colonized for weeks in patients with subclinical infections. Isolation of virus from the throat is more likely to be associated

with disease than is isolation from the stool since virus is shed for shorter periods from the throat. Cultures of CSF, serum, fluid from body cavities, or tissues are positive less frequently, but a positive result is indicative of disease caused by enterovirus. Cultures are more likely to be positive earlier than later in the course of infec tion. Cultures may be negative because of the presence of neutralizing antibody, lack of susceptibility of the cells used, or inappropriate han dling of the specimen. Coxsackievirus A may require inoculation into special cell-culture lines or into suckling mice. Identification of the enterovirus serotype is useful primarily for epi demiologic studies and, with a few exceptions, has little clinical utility. It is important to identify serious infections with enterovirus during epidemics and to distinguish the vaccine strain of poliovirus from the other enteroviruses in the throat or in the feces. Stool and throat samples for culture as well as acute- and convalescent-phase serum specimens should be obtained from all patients with suspected polio myelitis. In the absence of a positive CSF culture, a positive culture of stool obtained within the first 2 weeks after the onset of symptoms is most often used to confirm the diagnosis of poliomyelitis. If poliovi rus infection is suspected, two or more fecal and throat swab samples should be obtained at least 1 day apart and cultured for enterovirus as soon as possible. If poliovirus is isolated, it should be sent to the CDC for identification as either wild-type or vaccine virus. Reverse-transcription polymerase chain reaction (PCR) has been used to amplify viral nucleic acid from CSF, serum, urine, stool, conjunctiva, throat swabs, and tissues. A pan-enterovirus PCR assay can detect all human enteroviruses. With the proper controls, PCR of the CSF is highly sensitive (70–100%) and specific (>80%) and is more rapid than culture. PCR of the CSF is less likely to be positive when patients present ≥3 days after the onset of meningitis or with enterovirus 71 infection; in these cases, PCR of throat or rectal swabs— although less specific than PCR of CSF—should be considered. PCR of serum is also highly sensitive and specific in the diagnosis of disseminated disease. PCR may be particularly helpful for the diag nosis and follow-up of enterovirus disease in immunodeficient patients receiving immunoglobulin therapy, whose viral cultures may be nega tive. Antigen detection is less sensitive than PCR. Serologic diagnosis of enterovirus infection is limited by the large number of serotypes and the lack of a common antigen. Demonstra tion of seroconversion may be useful in rare cases for confirmation of culture results, but serologic testing is usually limited to epidemiologic studies. Serum should be collected and frozen soon after the onset of disease and again ~4 weeks later. Measurement of neutralizing titers is the most accurate method for antibody determination; measurement of complement-fixation titers is usually less sensitive. Titers of virusspecific IgM are elevated in both acute and chronic infection. TREATMENT Enterovirus Infections Most enterovirus infections are mild and resolve spontaneously; however, intensive supportive care may be needed for cardiac, hepatic, or CNS disease. IV, intrathecal, or intraventricular immu noglobulin has been used with apparent success in some cases for the treatment of chronic enterovirus meningoencephalitis and dermatomyositis in patients with hypogammaglobulinemia or agammaglobulinemia. The disease may stabilize or resolve during therapy; however, some patients decline inexorably despite therapy. IV immunoglobulin often prevents severe enterovirus disease in these patients. IV administration of immunoglobulin with high titers of antibody to the infecting virus has been used in some cases of life-threatening infection in neonates, who may not have maternally acquired antibody. In one trial involving neonates with enterovirus infections, immunoglobulin containing very high titers

of antibody to the infecting virus reduced rates of viremia; how ever, the study was too small to show a substantial clinical benefit. The level of enteroviral antibodies varies with the immunoglobu lin preparation. While a phase 2 trial of pleconaril for neonatal enterovirus sepsis showed that the

time to serum PCR negativity was reduced and the survival rate increased in newborns who had confirmed enterovirus infections and were treated with the drug, the differences did not reach significance and the drug is not avail able on a compassionate-use basis. Pocapavir and vapendavir also are being tested for enterovirus infections; resistance developed rapidly to OPV in a clinical trial of pocapavir. Glucocorticoids are contraindicated. Good hand-washing practices and the use of gowns and gloves are important in limiting nosocomial transmission of enteroviruses during epidemics. Enteric precautions are indicated for 7 days after the onset of enterovirus infections. Inactivated enterovirus 71 vac cines have been licensed in China. ■ ■PREVENTION AND ERADICATION OF POLIOVIRUS (See also Chap. 129) After a peak of 57,879 cases of poliomyelitis in the United States in 1952, the introduction of IPV in 1955 and of OPV in 1961 ultimately eradicated disease due to wild-type poliovirus in the Western Hemisphere. Such disease has not been documented in the United States since 1979, when cases occurred among religious groups who had declined immunization. In the Western Hemisphere, paralysis due to wild-type poliovirus was last documented in 1991. Paralysis due to vaccine-derived poliovirus (VDPV) was reported in 2022 in New York (see below). In 1988, when ~350,000 cases of polio occurred in 125 countries, the World Health Organization adopted a resolution to eradicate poliomyelitis by the year 2000. Wild-type poliovirus type 2 and wildtype poliovirus type 3 were declared eradicated in 2015 and 2019, respectively. The Americas were certified free of indigenous wild-type poliovirus transmission in 1994, the Western Pacific Region in 2000, the European Region in 2002, and Southeast Asia in 2014. After a nadir of 496 cases in 2001, 21 countries that had previously been free of polio reported cases imported from 6 polio-endemic countries in 2002–2005. By 2006, polio transmission had been reduced in most of these 21 countries. In 2017, there were 22 cases of wild-type polio, the lowest ever reported for 1 year—all of these cases were from Pakistan and Afghanistan. In 2021 wild-type polio remerged in Africa. After another peak of 176 cases in 2019, the number of cases of wild-type polio had fallen to 12 in 2023, all from 2 countries and all due to polio type 1 (Table 210-2). Polio is a source of concern for unimmunized or partially immunized travelers. Clearly, global eradication of polio is necessary to eliminate the risk of importation of wild-type virus. TABLE 210-2 Laboratory-Confirmed Cases of Poliomyelitis in 2023 COUNTRY WILD-TYPE POLIO VACCINE-DERIVED POLIO Pakistan

Afghanistan

Democratic Republic of the Congo

Nigeria

Chad

Guinea

Madagascar

Mali

Central African Republic

Others

61a Total

aOthers with <10 cases; Kenya, Somalia, Yemen 8 cases; Cote d’Ivoire, Indonesia 6 cases; Mozambique 5 cases; Benin, Burkina Fossa, Niger, South Sudan 3 cases; United Republic of Tanzania 2 cases; Burundi, Ethiopia, Israel, Mauritania, Zambia, Zimbabwe 1 case each.

Outbreaks are thought to have been facilitated by suboptimal rates of vaccination, isolated pockets of unvaccinated children, poor sanitation and crowding, improper vaccine-storage conditions, and a reduced level of response to one of the serotypes in the vaccine. While the global eradication campaign has markedly reduced the number of cases of endemic polio, doubts have been raised as to whether eradication is a realistic goal, given the large number of asymptomatic infections and the political instability in developing countries.

Use of OPV, especially in areas with low vaccination rates, has been associated with vaccine-derived polio due to mutations that result in restoration of viral fitness and neurovirulence during prolonged replication in individuals or person-to-person transmission. Vaccinederived polio was recognized in Egypt in 1983–1993, and hundreds of cases have been reported in many countries, including 385 cases in Nigeria in 2005–2012. Epidemics have been rapidly terminated after intensive vaccination with OPV. In 2005, a case of vaccine-derived polio occurred in an unvaccinated U.S. woman returning from a visit to Central and South America. In the same year, an unvaccinated immunocompromised infant in Minnesota was found to be shedding VDPV; further investigation identified 4 of 22 infants in the same com munity who were shedding the virus. All 5 infants were asymptomatic. These outbreaks emphasize the need for maintaining high levels of vaccine coverage and continued surveillance for circulating virus. In 2016, only 5 cases were reported; however, this number increased with a peak of 1113 cases in 2020 and subsequently declined to 526 cases of vaccine-derived polio in 2023 from 24 countries; 96% of these cases were from Africa and 3% were from the Eastern Mediterranean Region (Table 210-2). This decline in VDPV type 2 is associated with the use of a safer, novel type 2 OPV (see below). A case of vaccine-derived polio type 2 occurred in an unvaccinated adult in New York in 2022 and was genetically linked to wastewater collected in the area about 1 month before and after the case; the patient had not traveled internationally during the incubation period. VDPV due to OPV2 has been detected in wastewater from other countries in 2022, including Canada, Israel, and the United Kingdom, where virus transmission has been elimi nated. From 2018 to March 2020, 92% of cases of vaccine-derived polio were due to type 2 virus. Cessation of vaccination with type 2 OPV is believed to be responsible for this increase in polio type 2. IPV is used in most industrialized countries and OPV in most developing coun tries, including those in which polio still is or recently was endemic. While IM injections of other vaccines (live or attenuated) can be given concurrently with OPV, unnecessary IM injections should be avoided during the first month after OPV vaccination because they increase the risk of vaccine-associated paralysis. Since 1988, an enhanced-potency inactivated poliovirus vaccine has been available in the United States. CHAPTER 210 Enterovirus, Parechovirus,and Reovirus Infections After several doses of OPV alone, the seropositivity rate for indi vidual poliovirus serotypes may still be suboptimal for children in developing countries; one or more supplemental doses of IPV can increase the rate of seropositivity for these serotypes. Against a given serotype, monovalent OPV containing only that serotype is more immunogenic than trivalent vaccine because of a lack of interference from other serotypes. Given the eradication of wild-type poliovirus type 2 and the establishment of OPV type 2 as the primary cause of vaccine-derived polio, bivalent OPV (types 1 and 3), which had been shown to be superior to trivalent OPV in

inducing antibodies to types 1 and 3, replaced trivalent OPV vaccine in April 2016. However, outbreaks of vaccine-derived polio due to polio type 2 have required vaccination with monovalent OPV type 2. A novel type 2 oral polio virus vaccine (nOPV2) was engineered to be impaired in reversion to neurovirulence. After ~700 million doses of nOPV2 were administered in response to circulating VDPV type 2, from 2021 to 2023, 61 cases of paralysis were associated with nOPV2, with all the cases in Africa. The rate of emergence of paralysis with nOPV2 is about 10-fold lower than with monovalent OPV2. Another approach to reduce VDPV is to vac cinate with IPV followed by OPV. Addition of at least one dose of tri valent IPV after immunization with bivalent OPV will also reduce the risk of vaccine-derived polio associated with type 2 virus and enhance immunity to poliovirus types 1 and 3. Accordingly, in 2016, ~90% of countries included trivalent IPV in their immunization schedules.

---

Revision #1
Created 2026-01-06 16:32:34 UTC by Omar Ayman
Updated 2026-01-06 16:32:34 UTC by Omar Ayman