

Enterovirus Infections

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Education Gap

Clinicians must learn to recognize the spectrum of clinical syndromes associated with enteroviruses. Examples include the association of asthma exacerbation with enterovirus D68 and the association of acute eczema flare-up with coxsackievirus A16.

Objectives After completing this article, readers should be able to:

1. Understand the epidemiology of enterovirus infections.
2. Recognize the wide spectrum of clinical presentations with enterovirus infection.
3. Plan appropriate laboratory evaluation for enterovirus infection.

CASE SCENARIO

During Monday morning clinic in mid-July, you refer 2 cases to the emergency department (ED). The first is a 2-week-old neonate who has had 1 day of decreased oral intake and a temperature of 102°F (38.9°C) at your clinic. The baby appears alert with normal findings on physical examination. Later in the morning you receive an update call from the ED attending physician. Examination of the cerebrospinal fluid (CSF) shows pleocytosis with 55 white blood cells/ μ L but normal glucose (68 mg/dL) and protein (90 mg/dL) measurements. The Gram stain is negative. The CSF is positive for enterovirus (EV) by polymerase chain reaction (PCR) assay.

The second case is a 5-year-old boy with a history of asthma who has had a cough for 3 days and difficulty breathing for 1 day. He does not respond to 2 back-to-back treatments with inhaled albuterol, so you refer him to the ED. He is subsequently admitted to the pediatric intensive care unit for management of status asthmaticus. A nasopharyngeal multiplex film array assay is positive for EV/rhinovirus.

INTRODUCTION

EV infections peak in the summer months; the pathogen remains one of the most common causes of community outbreaks encountered by pediatricians. The prevalence is determined by weather, with most EV infections seen in summer and fall in the temperate northern hemisphere and the virus circulating

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throughout the year in the tropics. EVs are highly contagious, spreading through fecal-oral and respiratory secretions. The organs affected and the severity of the illnesses are largely determined by virulence of the virus and immunity of the host. Molecular technology has helped in isolation of many newer serotypes. For example, EV D68 was responsible for a large outbreak of severe respiratory illness in children with asthma across the United States (initial reports from Missouri and Illinois) in 2014. (1) The testing strategy for EVs has evolved over the years, and widespread availability of PCR assays has provided clinicians with the ability to diagnose such infections rapidly.

HISTORY

Poliovirus is the most famous EV of the 20th century. President Franklin Roosevelt, who himself was affected by the virus, founded the National Foundation for Infantile Paralysis in 1938 to combat polio. As a result of the successful worldwide campaign for polio vaccination, the last case of confirmed wild-type paralytic poliomyelitis in the western hemisphere was reported in 1991.

Poliovirus has a long history. (2) The earliest descriptions of infection are found on an Egyptian stone (1580 BC) showing a man with a shrunken short leg, depicting characteristic effects of the infection. In 1908, Landsteiner and Popper isolated poliovirus in monkeys. It was not until 1949 that Enders and colleagues described virus growth in tissue culture. Ultimately their techniques led to recovery of many other EVs and enabled the development of polio vaccines over subsequent decades.

VIRUS CHARACTERISTICS

EVs belong to the family Picornaviridae (pico = small). Parechoviruses (PVs) and Saffold viruses (SVs) are now grouped with EVs because they share certain morphologic and functional properties.

The virion is nonenveloped, spherical, and about 30 nm in diameter. The genome is a positive sense RNA, with an approximate length of 7.4 kb. Infections occur with adsorption of the virus to cellular receptors, primarily integrins and immunoglobulin-like proteins. (3) After penetration, there is rapid replication (5-10 hours) inside the cytoplasm of the cell.

EVs are relatively stable viruses that can retain activity for several days at room temperature and can be stored indefinitely at freezer temperatures (-4°F [-20°C]). They are also stable at the low pH of stomach acid. EVs grow rapidly when adapted to susceptible host systems and can cause cytopathologic features within 2 to 7 days.

CLASSIFICATION

Original Classification

The original classification of EVs was based on differences in their effects in tissue culture and pattern of disease in experimentally infected animals. Human EVs were grouped as polioviruses and nonpolio EVs (echo-, coxsackie-, and other numbered EVs). At first, researchers believed that the human alimentary tract was a natural habitat for these viruses, hence, the name enterovirus. As more viruses were identified, the association of some of these viruses with human diseases was not known and they were grouped as enteric cytopathogenic human orphan or ECHO viruses. The coxsackie groups of viruses were named after a small town, Coxsackie, near the Hudson River in New York, where Dalldorf and Sickles isolated the virus in mice in 1948 from fecal specimens.

Reclassification

Many EV strains have been isolated that do not fit into these categories, leading to the presently used revised classification. (4) This newer classification is based on molecular serotyping, which includes determination of the nucleotide (RNA) sequence encoding the viral polypeptide capsid (Table 1).

Recently, 2 echoviruses (E22 and E23) were reclassified as the initial members of the new genus *Parechovirus* as PV types 1 and 2 because they differ in terms of their genomics and proteomics from other EVs. Similarly, hepatitis A virus initially was assigned the designation EV72, but it was reclassified as the sole member of the *Hepatovirus* genus within the Picornavirus family (Table 2).

Recently, the Cardiovirus genus of the Picornaviridae family has been expanded by identification of the Saffold viruses (SVs). Beginning with a strain isolated in 2007, 8 genetically distinct SVs have been identified. SVs have been recognized as a cause of mild human disease in children.

Recombination between circulating picornaviruses is a frequent event and is likely to increase genetic diversity and pose future challenges in classification.

EPIDEMIOLOGY

Transmission

EVs are spread from person to person via fecal-oral and respiratory routes. Most of the EVs are shed in the respiratory secretions for 1 to 3 weeks and in the feces for 2 to 8 weeks after primary infection. EV 71, the cause of hemorrhagic conjunctivitis, is spread via fingers, fomites, and tears. Infants, particularly those in diapers, are effective

TABLE 1. **Traditional Versus Newer Enterovirus Classification**

	TRADITIONAL CLASSIFICATION Host disease pattern and tissue culture effects in infected animal models	NEWER CLASSIFICATION Molecular serotyping (RNA sequence)
Groups & Serotype	<p>Coxsackieviruses A 1–22, 24*</p> <p>Coxsackieviruses B 1–6</p> <p>Echoviruses 1–9, 11–27, 29–33</p> <p>Polioviruses 1–3</p> <p>Enterovirus 68–72</p>	<p>Group A Coxsackievirus A serotypes 2–8, 10, 12, 14, 16; Enterovirus serotypes 71, 76, 89–92</p> <p>Group B Coxsackievirus A serotype 9; B serotypes 1–6</p> <p>Echovirus serotypes 1–7, 9, 11–21, 24–27, 29–33; Enterovirus serotypes 69, 73–75, 77–88, 93, 97, 98, 100, 101, 106, 107</p> <p>Group C Poliovirus serotypes 1–3; Coxsackievirus A serotypes 1, 11, 13, 17, 19–22, 24</p> <p>Group D Enterovirus D68, D70, D94, D111</p>

*Coxsackievirus A23 was reclassified as echovirus 9.
Adapted from <http://www.picornastudygroup.com/taxa/taxa.htm>.

vehicles of transmission. Virus shedding by symptomatic and asymptomatic persons may contribute to transmission of these agents.

The incubation period for brief febrile illness due to EVs is 1 to 3 days and for poliovirus is 9 to 12 days.

Distribution and Season

EVs have worldwide distribution. Neutralizing antibodies for specific viral types have been noted in serologic surveys throughout the world (71 serotypes to date). In any given area, frequent fluctuations occur in the predominant types. Epidemics may be localized and sporadic, and they may vary in origin from place to place in the same year. (5) The prevalence of unrecognized infection far exceeds that of clinical disease.

Surveillance of Outbreaks

Data collected by the National Enterovirus Surveillance System (NESS) of the Centers for Disease Control and

Prevention (CDC) has increased understanding of the epidemiology and nature of outbreaks. Between 1970 and 2005, 15 serotypes represented 83.5% of all EV isolates submitted from state and local public health laboratories. (6) EV detections were found to have remarkable seasonality, with the number of cases increasing sharply during summer and fall months and peaking in August. This summer-fall seasonality was more prominent for EV detections from CSF specimens (81.3%) in contrast to fecal (77.6%) or respiratory specimens (69.8%).

PATHOGENESIS

Human EVs are acquired directly or indirectly by ingestion of a virus shed in the feces or upper respiratory tract of infected contacts. Initial viral replication occurs in the upper respiratory tract and distal small bowel. Infectious virus is detectable in the ileal lymphoid tissue 1 to 3 days after ingestion of the virus, and fecal shedding can be detectable for 6 or more weeks (Fig 1).

Viral replication in the submucosal lymphoid tissue results in brief primary viremia that distributes virus to reticuloendothelial tissue in distant lymph nodes, liver, spleen, and bone marrow. Further replication in these organs leads to continued secondary viremia and dissemination of virus to target organs such as the central nervous system (CNS), heart, and skin. Organ-specific disease (ie, poliomyelitis, myocarditis) results from virus-induced cell necrosis and the accompanying inflammatory response. Many infected persons clear the infection before the secondary viremia and experience only transient symptoms or have an asymptomatic infection.

TABLE 2. **Classification of Human Picornavirus Family**

GENUS	SPECIES
Enterovirus	Human enterovirus A-D, Human rhinovirus A-C
Parechovirus	Parechovirus
Hepatovirus	Hepatitis A virus
Cardiovirus	Saffold virus

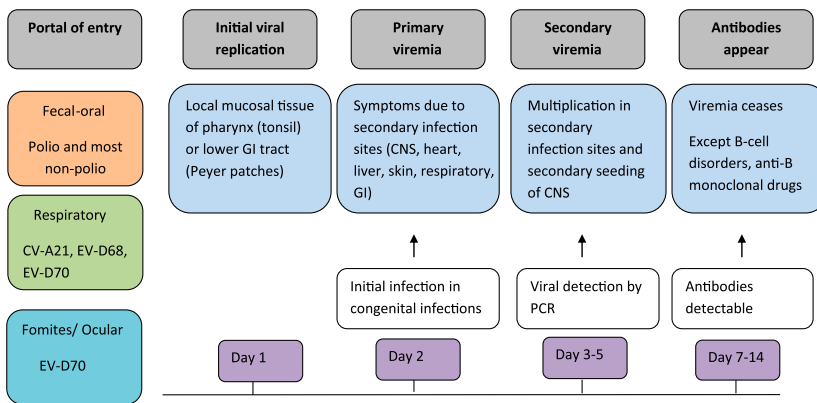


Figure 1. Timeline of events in enterovirus infection: pathogenesis. CNS=central nervous system, GI=gastrointestinal, PCR=polymerase chain reaction.

CLINICAL PRESENTATION

EVs other than poliovirus are not reportable; therefore, the actual burden of symptomatic infection is not available. EVs are believed to account for an estimated 10 to 15 million symptomatic infections in the United States every year.

Symptomatic infections range from a minor illness such as a common cold to fulminant sepsis and meningitis. The variation in presentation represents the wide variety of serotypes and the host's immunity. NESS has provided valuable data since 1961 on the clinical association with specific serotypes and nature of community outbreaks (Table 3).

Asymptomatic Infection

An estimated 50% of EV infections are asymptomatic. Young age is associated with higher frequency of symptomatic infection. Asymptomatic infection from CV A16 occurs in only approximately 10% of children younger than age 5 years, whereas rates are reported to be higher in older children and adults. (7)

Nonspecific Febrile Illness

Most of the EVs cause a brief febrile illness with no other symptom or sign. Usually, there is a sudden-onset fever that can last up to 3 days. However, biphasic illness, characterized by an initial day of fever and a recurrence 2 to 3 days later for 2 to 4 days, can also be seen. Younger children can have malaise and older children can experience headache or a sore throat without pharyngeal injection. The physical examination and the white blood cell count usually yield unremarkable findings.

CNS Infections

Aseptic Meningitis. EVs are the most common cause of aseptic meningitis. Epidemic disease has occurred most

commonly with CV B5 as well as echoviruses 4, 6, 9, 13, and 30 through 33. In general, aseptic meningitis is seen in young children, but adolescents and adults can also be affected during outbreaks.

The clinical course typically involves an initial episode of nonspecific fevers and follows a biphasic pattern, with fever recurrence in conjunction with CNS symptoms. Initial symptoms may also include headache, malaise, nausea, and vomiting. The headache usually is frontal or generalized and can be accompanied by photophobia. Physical examination typically demonstrates generalized muscle stiffness or spasm. The Kernig and Brudzinski signs are positive in fewer than 50% of cases. Pharyngitis occurs frequently, as does a maculopapular skin rash. The rash can have a petechial component, as seen in infections due to echovirus 9. Aseptic meningitis caused by EV 71 can have associated hand-foot-and-mouth (HFM) disease.

Examination of CSF reveals considerable variation among patients and even in the same patient on repeated examination. CSF leukocyte counts vary from a few cells to a few thousand per cubic millimeter; the median is in the range of 100 to 500 cells/mm³. The percentage of neutrophils also varies greatly. Initial examinations frequently reveal a predominance of neutrophils. Repeated evaluations of CSF demonstrate an increasing percentage of mononuclear cells. (8) CSF protein values are mildly elevated, and glucose concentrations usually are within normal ranges. Most patients have normal neurologic and cognitive outcomes.

Encephalitis. EVs are an uncommon (2%) cause of encephalitis in the United States. Echovirus 9 is most often the cause. Since the mid-1970s, epidemics of HFM disease associated with encephalitis have been reported in Asian-Pacific countries.

Nonpolio Paralysis. In contrast to polioviruses, which led to epidemic paralytic disease, the nonpolio EVs cause

TABLE 3. **Clinical Syndromes Associated With Enteroviruses**

SYNDROME	VIRAL TYPE	CLINICAL FEATURES
Nonspecific febrile illness	All viral types	Fevers for 3-4 days; can be biphasic. Minimal respiratory or GI symptoms.
Aseptic meningitis	CV B5; echoviruses 4, 6, 9, 13, and 30-33	Fever with meningeal signs. Mild CSF pleocytosis; normal protein and glucose.
Acute hemorrhagic conjunctivitis	EV 70; CV A24 (rare)	Sudden onset of eye pain with subconjunctival hemorrhage.
Herpangina	CV A & B; PV 1 & 6; EV 71; SV 2 & 3	Fevers with painful vesicles or ulcers over posterior palate and/or tonsils.
Hand-foot-mouth	CV A (6, 16) & B; EV 71; echovirus	Fever with enanthem (vesicles in the mouth) and exanthem (vesicles on hands and feet).
Carditis	CV B1-5	Myopericarditis presenting with heart failure or arrhythmias.
Nonspecific exanthem	CV A16 (most common), A6, A9; echovirus 9	Variable rash (vesicular, maculopapular, urticarial, petechial, purpuric) after fevers (+/-) for 1-2 days.
Newly Described Syndromes		
Eczema coxsackium	CV A6	Acute onset of vesicles or erosions in children with atopic dermatitis. Milder and shorter course of illness.
Acute flaccid paralysis	EV 71; CV A7	Paralysis, but less severe illness and less bulbar involvement than poliovirus.
Acute respiratory illness	EV D68	Acute onset of cough, dyspnea, wheezing, and hypoxemia in children with history of asthma or wheezing.

CSF=cerebrospinal fluid, CV=Coxsackievirus, EV=enterovirus, GI=gastrointestinal, PV=Parachovirus, SV=Saffold virus.

sporadic paralytic disease. Paralytic disease has been reported in outbreaks due to CV A7 and EV 71. In 2014, a cluster of pediatric cases of acute flaccid myelitis was identified in the midst of an outbreak of EV D68 causing severe respiratory distress, although no direct link between EV D68 and paralytic disease was confirmed. (9)

Guillain-Barré syndrome, transverse myelitis, and cerebral ataxia have also been associated with EVs and echoviruses.

Ocular Infections

Outbreaks of acute hemorrhagic conjunctivitis are typically due to EV 70 or CV A24. Presentation is characterized by a sudden onset of severe eye pain and associated photophobia. Subconjunctival hemorrhages are frequently present. Systemic symptoms, including fever, are rare.

Skin and Mucous Membrane Infections

Herpangina. This is an enanthematous (mucous membrane) disease that presents with painful vesicles of the oral mucosa along with fever and sore throat. All age groups are affected, but it is most common in children ages 3 to 10 years. CVs A and B, PVs 1 and 6, EV 71, and SVs 2 and 3 are known causes of herpangina. The onset is sudden, with high

temperatures (103°-104°F [39.4-40°C]). Higher temperatures (106°F [41.1°C]) and seizures may occur at disease onset. Young children may be irritable, occasionally listless, and anorexic for a few hours before the fevers appear. Older children frequently complain of headache and backache.

The oropharyngeal lesions usually erupt around the time of first fever. The characteristic lesions are small (1 to 2 mm) vesicles and ulcers (Fig 2). These lesions start as papules, become vesicular, and ulcerate in a short period of time. The lesions are discrete and surrounded by an erythematous ring, with an average of 5 to 6 lesions (range, 1-14). The most common site of the lesions is the anterior tonsillar pillars. The duration of illness is 3 to 6 days.

Acute Lymphonodular Pharyngitis. This variant of herpangina has a similar distribution of mouth lesions. However, the lesions are white to yellow and may persist for 6 to 10 days.

Hand-foot-and-mouth Disease. This common clinical syndrome manifests as a vesicular skin rash on the hands and feet along with vesicles in the oral cavity. It most commonly affects toddlers and school-age children. The frequent etiologic agents are CVs A6 and A16, CV B, EV 71, and echovirus. The presentation includes fevers, rash, and the characteristic exanthema and enanthem. Temperatures

range from 100.4° to 102.2°F (38°-39°C) and last for 1 to 2 days. The oral vesicles usually are located on the buccal mucosa and tongue and are only mildly painful. The exanthem involves vesicles on the palms, soles, and the interdigital surfaces of the hands and feet. Onychomadesis (separation of the fingernail from the nail bed) has been reported 2 to 3 weeks after HFM disease (Fig 3).

The differential diagnosis for HFM disease includes varicella-zoster virus infection, herpes simplex virus infection, or aphthous ulcers. Unlike HFM, varicella lesions are more extensive, located more centrally, and in different stages simultaneously, and they usually spare the palms and soles. In herpetic gingivostomatitis, the lesions are primarily anterior in the mouth, and the child has a higher temperature, prominent cervical lymphadenopathy, and no rash. Aphthous ulcers are large, ulcerative lesions of the lips, tongue, and buccal mucosa that are extremely painful. In comparison to HFM disease, such ulcers are seen most commonly in older children and adults, involve multiple recurrences, have no rash, and typically are not associated with constitutional symptoms.

Skeletal Muscle Infection

Pleurodynia (Bornholm disease) is characterized by an acute onset of severe muscular pain in the chest and abdomen accompanied by fever. It is more common in older children and adolescents. CV B₃ and B₅ are the major causes of epidemic presentations. The muscular pain is sharp and spasmodic, with episodes typically lasting 15 to 30 minutes. During spasms, patients can have signs of respiratory distress or appear in shock, with diaphoresis and pallor. The illness usually lasts 1 to 2 days, but frequently a biphasic pattern is seen, with recurrences possible several weeks after the initial episode.

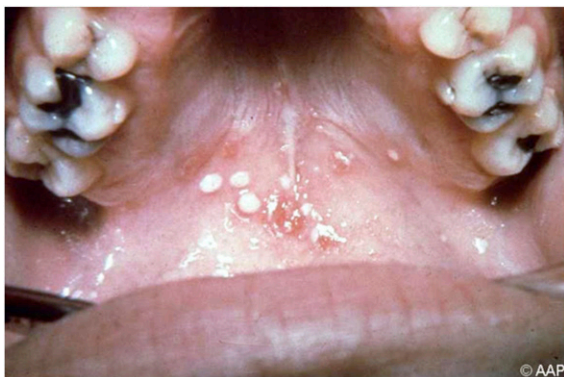


Figure 2. Herpangina (Coxsackievirus) lesions on the posterior palate of a young adult male. Coxsackievirus lesions typically are found in the posterior aspect of the oropharynx and may progress rapidly to painful ulceration. Source: *AAP Red Book*, 2015.

Heart Infections

Pathologic studies have shown that both the myocardium and the pericardium are involved in myopericarditis, which is why that term is preferred. CV B₅ has been implicated as the most common causative agent, but types 2, 3, and 4 as well as echovirus type 6 can also cause myopericarditis.

Myopericarditis affects all ages, but physically active adolescents and adults are at higher risk. The usual presentation is fever, fatigue, and dyspnea on exertion, but more fulminant symptoms, including heart failure or dysrhythmia, can occur. Echocardiography may confirm diminished cardiac ejection fraction or show acute ventricular dilation. Serum concentrations of troponins are frequently elevated. The mortality rate for acute CV and echoviral heart disease is less than 5%. Children who survive acute CV myocarditis usually recover completely without any residual disability. An association between idiopathic dilated cardiomyopathy and group B CV has been suggested.

NEWLY RECOGNIZED CLINICAL SYNDROMES

Asthma Exacerbation and EV D68

EV D68 was first identified in 1962 during sporadic outbreaks of respiratory infections, but it emerged as a significant pathogen in 2014 when the United States experienced a nationwide outbreak. It was associated with severe respiratory illness in children with asthma or a history of wheezing. From mid-August 2014 to January 15, 2015, the CDC confirmed a total of 1,153 people in 49 states and the District of Columbia with respiratory illness caused by EV D68. (1)

Eczema Coxsackium

An atypical skin rash was reported in children with atopic dermatitis during the 2011 to 2012 outbreak of HFM disease associated with CV A6. This rash was characterized by accentuation of vesicles and erosions within areas of eczema and was termed “eczema coxsackium.” (10) This morphology was strikingly similar to eczema herpeticum caused by herpes simplex virus 1. However, eczema coxsackium is generally less painful and the child remains reasonably well.

EV infections, particularly CV A6, should be considered in the differential diagnosis of patients presenting with new-onset vesicles and extensive erosions in preexisting areas of eczema (Fig 4). EV PCR on the vesicle fluid allows for early diagnosis, thus potentially avoiding antibiotics or acyclovir.

Figure 3. Vesicular eruptions in hand (A), foot (B), and mouth (C) of a 6-year-old boy with coxsackievirus A6 infection. Several of his fingernails shed (D) 2 months after the pictures were taken. Courtesy of Centers for Disease Control and Prevention/Emerging Infectious Diseases. Source: *AAP Red Book*, 2015.



SPECIAL HOST INFECTIONS

Neonatal Infection

Neonates are at high risk of disseminated disease resulting from EV infections acquired during the perinatal period. Most of the infections are due to echoviruses (serotypes 6, 9, and 11), group B CVs (serotypes 1 to 5), and PVs (serotype 3).

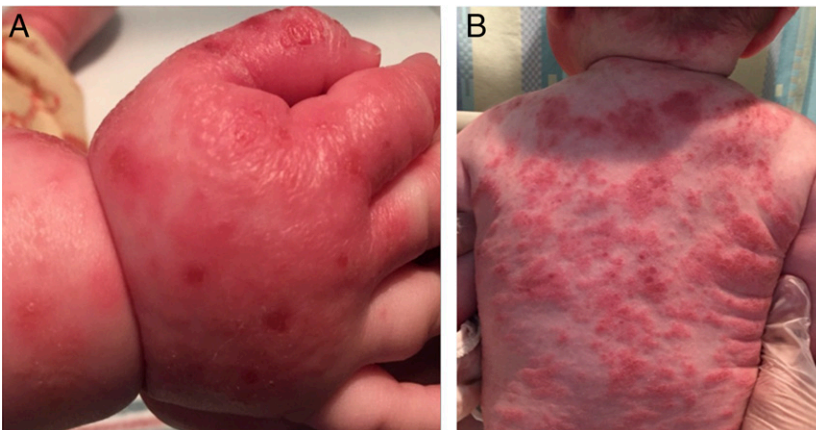
EV infections acquired perinatally present within the first postnatal week. Onset of serious EV infection beyond 10 days of age is uncommon. A wide range of clinical disease has been reported in neonates, including non-specific febrile illnesses, exanths, and aseptic meningitis. The most severe manifestations are myocarditis with or without encephalitis, hepatitis, and pneumonia. The

outcome of neonatal infection is strongly influenced by the presence or absence of passively acquired maternal antibody specific for the infecting EV serotype. EV infection should be considered in cases of neonatal sepsis when neither bacteria nor herpes simplex virus is isolated.

Infection in Immunocompromised Hosts

EVs are known to cause serious as well as persistent infections in patients with congenital or acquired defects in B-lymphocyte function. Persistent infections are seen in children with X-linked agammaglobulinemia or severe combined immunodeficiency syndrome or in adolescents with common variable immunodeficiency. Chronic infections also occur in bone marrow transplant recipients.

Figure 4. Eczema coxsackium on the hands (A) and back (B) of a 6-month-old infant with underlying atopic dermatitis and acute onset of vesicles and erosive rash.



Echoviruses (particularly serotype 11) are responsible for most of these infections, but individual cases caused by group A and group B CVs have been reported.

Chronic meningoencephalitis, the most common clinical syndrome in these immunodeficient patients, typically presents with insidious headache, fatigue, mild meningismus, or seizures. The symptoms fluctuate in severity, disappear, or slowly progress. Persistent CSF pleocytosis and a high CSF protein concentration are characteristic of chronic EV meningoencephalitis. The prognosis for immunodeficient children who are persistently infected is poor.

INFECTION WITH POLIOVIRUS

Poliovirus infection occurs only in humans. Transmission is primary through the fecal-oral and respiratory routes. The virus is present in the throat for 1 to 2 days before the onset of illness and is shed in feces for 3 to 6 weeks, rendering it contagious for this duration. Most poliovirus infections are asymptomatic (74%) or mild (4%). Acute paralytic disease may be caused by naturally occurring wild polioviruses or by mutated vaccine-derived polioviruses. In addition, rare cases of vaccine-associated paralytic poliomyelitis occur in recipients of oral poliovirus vaccine (OPV) or their close contacts.

In classic paralytic polio, the rapid onset of paralysis occurs 1 to 3 days after a minor febrile illness with sore throat, headache, and myalgias. The paralysis is asymmetric and affects the proximal muscles more than the distal muscles. Lower limbs are more frequently affected and sensation is usually intact except in severe cases. CSF analysis suggests aseptic meningitis, and the virus can be readily isolated from the throat or stool of an affected child. Postpolio syndrome is characterized by new onset of muscle weakness and atrophy occurring about 14 to 25 years after the initial infection. The affected muscle groups are usually the same as in the original illness.

In the United States, 4 doses of inactivated polio vaccine are recommended for routine immunization of all infants and children. In most countries, OPV remains the vaccine of choice. The original trivalent OPV induces humoral immunity to all types of poliovirus (1–3) in addition to local gastrointestinal mucosal immunity, which prevents spread of infection. In April and May 2016, a global switch from trivalent to bivalent OPV(1,3) was made because the only cases of type 2 paralytic polio were due to vaccine-related strains. To maintain immunity levels to type 2 polio, high-risk countries introduced inactivated polio vaccine (1–3) into routine immunization programs before the switch.

Polio was virtually eradicated from the western hemisphere by 1991. Four of the 6 regions of the World Health Organization have been certified polio-free: the Americas (1994), Western Pacific (2000), Europe (2002), and South East Asia (2014). Pakistan and Afghanistan continue to have ongoing polio transmission. In 2015, 74 cases of wild poliovirus were reported: 54 from Pakistan and 20 from Afghanistan.

LABORATORY DIAGNOSIS

The 3 common methods used to aid in the diagnosis of an EV infection are PCR, viral culture, and serology (Table 4).

Polymerase Chain Reaction

PCR is more sensitive (86%) than culture (30%) for identification of EVs in CSF and respiratory tract secretions. PCR has been most useful in detecting EV in CSF. (11) Four commercially available multiplex PCR panels are available in the United States that detect EVs in a swab from a nasopharyngeal specimen. Some of these assays report enterovirus together with rhinovirus (both are picornaviruses). PCR testing of fecal specimens has been less successful because of the presence of substances that inhibit the polymerization step.

TABLE 4. Laboratory Diagnosis of Enteroviruses

TEST	METHOD	SENSITIVITY	SPECIFICITY
Viral culture (3-8 days)	Cell culture	0% to 80%	100%
PCR assay (1-2 hours)	-CSF PCR -Respiratory multiplex PCR (picornavirus: EVs/rhinovirus)	100% Variable	97% Variable
Serology (weeks)	Microneutralization	Limited use	

CSF=cerebrospinal fluid, EV=enterovirus, PCR=polymerase chain reaction.

Virus Isolation

EVs can be isolated in cell culture from CSF, pericardial fluid, tissue, blood, or stool, with cytopathic effects usually seen between 2 and 5 days after inoculation in cell culture. Once isolated, the virus serotype can be identified for most of the common EVs with use of RNA sequencing. The chances of recovering a virus in cell culture are optimized by sampling multiple sites. Isolation of virus from stool is less definitive because unrelated intercurrent asymptomatic infections can occur.

Serology

Serology is of limited use in acute infections due to the need for acute and convalescent titers, cross-reactivity among different serotypes, and lack of sensitivity of immunoglobulin M assays.

The microneutralization test is the method used most widely for determining EV antibodies. This serotype-specific assay has limited usefulness in the routine diagnosis of EV infections because it is not feasible to incorporate all relevant live viral antigens into the assay. The methods based on neutralization are relatively insensitive, poorly standardized, and labor-intensive.

TREATMENT

No specific treatment for EV infections exists to date. The mainstay of management is supportive care whether the presentation is a mild cold or a life-threatening viremia.

Intravenous Immunoglobulin (IVIG)

Some evidence suggests that administering IVIG in neonatal EV infections can result in faster cessation of viremia. (12) IVIG treatment has been used in cases of chronic EV meningoencephalitis in immunodeficient patients. In addition, in cases of life-threatening EV infection, IVIG can be considered for older immunocompetent children, specifically for myocarditis and EV 71 neurologic disease, although supportive data comprise only anecdotal reports. A specific recommended dose is not known, but 400 mg/kg per day for 4 days or 2 g/kg in 1 dose has been used.

Pleconaril

Pleconaril is an antiviral agent with demonstrated activity against EVs. In a study comparing enteroviral meningitis treatment with pleconaril and control, the duration of disease was shortened from 9.5 days in controls to 4.0 days in drug recipients. (12) However, the drug is not licensed or available in United States at this time.

INFECTION CONTROL AND PREVENTION

Transmission can be reduced with simple measures such as handwashing and careful disposal of soiled diapers. When a child becomes ill with an EV infection, he or she should be kept out of school, swimming pools, and child care settings for the first few days until the fevers defervesce. In the health care setting, contact precautions are indicated for the duration of EV illness, particularly conjunctivitis. Immunocompromised children and pregnant women should be advised to avoid contact with a patient who has suspected EV infection.

Summary

- On the basis of strong research evidence, (6) enteroviruses (EVs) cause a wide range of clinical diseases with peak prevalence in the summer months. They are the most common cause of aseptic meningitis in children and are responsible for community outbreaks of hand-foot-and-mouth disease.
- On the basis of strong research, (4) the nomenclature of these EVs has changed with the discovery of new serotypes and is based on RNA sequencing.
- On the basis of some evidence, (11) polymerase chain reaction has a higher sensitivity for detecting EVs with a much shorter turnaround time than culture.
- On the basis of some evidence, (12) treatment is symptomatic, with no presently available antiviral therapy. Intravenous immunoglobulin can be considered in neonatal infections, cases of meningoencephalitis in immunocompromised patients, or life-threatening infections in immunocompetent children.

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1. A previously healthy 15-year-old boy is admitted to the pediatric intensive care unit in July with a 4-day history of fever, nasal congestion, and increasing fatigue. Over the 2 days, he has had increasing shortness of breath. There are bilateral crackles on lung examination. His heart rate is 108 beats per minute, respiratory rate is 28 breaths per minute, and oxygen saturation on room air is 95%. Electrocardiography shows decreased QRS voltages. Viral respiratory polymerase chain reaction (PCR) panel is negative for adenovirus and positive for human rhinovirus/enterovirus. A serum level of which of the following is most likely to be elevated?
 - A. Albumin.
 - B. Bicarbonate.
 - C. Calcium.
 - D. Prealbumin.
 - E. Troponin.
2. For the same 15-year-old boy in the previous question, which is the most likely outcome of his illness?
 - A. Chronic congestive heart failure.
 - B. Complete heart block.
 - C. Complete recovery.
 - D. Death.
 - E. Persistent mitral regurgitation.
3. A previously healthy 11-year-old boy is admitted to the hospital in August with a 3-day history of headache, neck stiffness, and fever. Kernig and Brudzinski signs are negative, although he has mild pain with neck flexion. After lumbar puncture, cerebrospinal fluid (CSF) reveals 428 white blood cells per cubic millimeter with 21% neutrophils, 62% lymphocytes, and 17% monocytes. CSF glucose is 72 mg/dL and protein is 58 mg/dL. CSF Gram stain shows no organisms, and results of CSF culture, blood culture, and herpes simplex virus PCR are pending. Which of the following is the most appropriate next step in diagnosis?
 - A. Blood Coxsackievirus immunoglobulin M.
 - B. CSF enterovirus PCR.
 - C. CSF viral culture.
 - D. Stool enterovirus PCR.
 - E. Stool viral culture.
4. A 16-year-old girl is admitted to the hospital with an 11-day history of headache and fatigue. Her maximum temperature at home was 101.1°F (38.4°C). Her past medical history includes recurrent acute bacterial sinusitis and acute otitis media. She has had 2 episodes of pneumonia. After lumbar puncture, the CSF PCR for enterovirus is positive. Her immunoglobulin (Ig)G measures 228 mg/dL (2.28 g/L), IgA is 25 mg/dL (250 mg/L), and IgM is 40 mg/dL (400 mg/L). Her tetanus and diphtheria antibody levels are low. T- and B-cell lymphocyte numbers are normal by flow cytometry. Management with which of the following should be considered if she continues to be symptomatic?
 - A. Acyclovir.
 - B. Bone marrow transplant.
 - C. Ganciclovir.
 - D. Interferon- γ .
 - E. Intravenous immunoglobulin.

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5. A 2-month-old girl is admitted to the hospital for decreased feeding and temperature to 104°F (40°C) for 2 days. She is fussy but consolable and not lethargic. There are no focal findings on physical examination. A complete blood cell count and urinalysis yield unremarkable results. Urine and blood cultures are pending. A nasopharyngeal swab submitted for multiplex PCR panel is positive for enterovirus. Which of the following is indicated for infection control?
- A. Airborne precautions.
 - B. Airborne and droplet precautions.
 - C. Contact precautions.
 - D. Droplet precautions.
 - E. Only standard precautions.

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