**Definition:** Enteroviruses from *Black’s Medical Dictionary, 43rd Edition*

A family of viruses which include the Poliomyelitis, Coxsackie and ECHO (see ECHOVIRUSES) groups of viruses. Their importance lies in their tendency to invade the central nervous system. They receive their name from the fact that their mode of entry into the body is through the gut.

**Summary Article: Enteroviruses**

From *International Encyclopedia of Public Health*

The enteroviruses (polioviruses, group A and B coxsackieviruses, echoviruses, and numbered enteroviruses) are an ancient and important group of RNA viruses. Humans are the only hosts for the nonpolio enteroviruses (NPEVs). Enteroviral infections occur primarily in the summer and early fall. It is estimated that annually NPEVs cause 1 billion infections worldwide. The highest incidence of NPEV infection occurs in infants and children. This article will review the important clinical syndromes caused by the NPEV, the current technology for their detection, as well as the management and prevention of NPEV disease.

**Keywords**

- Acute flaccid paralysis
- Coxsackievirus
- Diagnosis
- Echovirus
- Encephalitis
- Enterovirus
- Hand
- foot
- mouth disease
- Herpangina
- Immunocompromised
- Meningitis
- Myocarditis
- Neonatal
- Picornaviridae

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Introduction

Enteroviruses (EVs) are important and ancient human pathogens. Evidence for the existence of polioviruses, the prototypic EVs, dates to Egypt in the fourteenth century BC. For most of the world, poliovirus is no longer a medical or public health issue because vaccination has led to its eradication. This article will focus on the nonpolio enteroviruses (NPEVs).

General Virology

Enteroviruses form a genus in the Picornaviridae family of viruses. The originally described EV serotypes were speciated into five groups: poliovirus, group A and B coxsackieviruses, echoviruses, and numbered EVs. Speciation was based on patterns of replication in cell cultures and disease manifestations in animal systems.

Today, EV taxonomy is based on phylogenetic analysis of the VPI coding sequence, the major capsid protein. Serotypes are now classified as the human enteroviruses A-D (Table 1). As a result of the advent of molecular methods for their detection, the original 64 EV serotypes have been expanded to more than 100 by the addition of new NPEV serotypes, and this number continues to grow.

Table 1 Species within the Enterovirus genus affecting humans based on revised criteria

<table>
<thead>
<tr>
<th>Species within the Enterovirus genus affecting humans based on revised criteria</th>
</tr>
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<tbody>
<tr>
<td>Human enterovirus A</td>
</tr>
<tr>
<td>• Coxsackievirus A2-8, 10, 12, 14, 16</td>
</tr>
<tr>
<td>• Enterovirus 71, 76, 89-90</td>
</tr>
<tr>
<td>Human enterovirus B</td>
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<tr>
<td>• Coxsackievirus A9</td>
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<tr>
<td>• Coxsackievirus bib1-B6</td>
</tr>
<tr>
<td>• Echovirus 1-7, 9, 11-21, 24-27, 29-33,</td>
</tr>
<tr>
<td>• Enterovirus 69, 73-75, 77, 78, 79-88, 100-101</td>
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<tr>
<td>Human enterovirus C</td>
</tr>
<tr>
<td>• Coxsackievirus A1, 11, 13, 17, 19-22, 24</td>
</tr>
<tr>
<td>Poliovirus</td>
</tr>
<tr>
<td>• Poliovirus 1-3</td>
</tr>
<tr>
<td>Human enterovirus D</td>
</tr>
<tr>
<td>• Enterovirus 68, 70</td>
</tr>
</tbody>
</table>

Serotypes in italics are not yet recognized by the International Committee on Taxonomy of Viruses.

The EVs are stable in liquid environments and remain viable in water and sewage for weeks. They are acid-chloroform-, and ether-stable and are not inactivated by nonionic detergents. Ultraviolet light, heat (>56 °C), chlorination, and formaldehyde are effective in inactivating the EV.

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Structurally, the EVs are nonenveloped icosahedral-shaped viruses containing a positive sense, single-stranded RNA genome. The genome is approximately 7.4 kilobases in length consisting of a long 5′ nontranslated region (NTR), a single open reading frame (ORF), and a short 3′ NTR followed by a polyadenylated tail. The 5′ and 3′ NTRs contain regulatory elements for translation, replication, and virulence. Conserved sequences within the 5′ NTR have permitted the design of oligonucleotide primers for detection of EVs in clinical specimens.

The ORF is divided into three regions: P1-3. The P1 region contains sequences that code for the four structural proteins (VP1-4) that make up the capsid, while the P2 and P3 regions contain the sequences for nonstructural proteins required for viral replication.

Epidemiology

The NPEV exist worldwide and cause an estimated 1 billion infections annually. In the United States, an estimated 30-50 million NPEV infections occur annually. The highest incidence of infection is in infants and children 5-10 years of age. While many NPEV serotypes exist, only a few are responsible for illness each year. Worldwide, the serotype and prevalence of NPEVs isolated from infected patients varies both geographically and annually.

Humans are the only known hosts for the NPEVs. In temperate climates, enteroviral infections occur primarily in the summer and early fall. However, NPEVs can be isolated from patients during the winter months, albeit, far less frequently. In tropical regions, the EVs are isolated year round with an increased incidence during the rainy season.

The most common mode of transmission for the NPEV is the fecal-oral route. Other documented modes are: Vertical, foodborne, waterborne, self-inoculation, and respiratory (rare). They can be shed in the stool for up to 18 weeks, thereby facilitating their transmission.

Clinically, NPEVs are the principal cause of viral meningitis where an etiologic agent can be identified. In this group of meningitides, they are responsible for more than 90% of cases. Group B coxsackieviruses and the echoviruses are the most frequently isolated NPEVs in this syndrome.

Among the causes of viral encephalitides, EVs are identified in 10-20% of cases. The serotypes most commonly identified belong to the group A coxsackieviruses. Infection with some strains of enterovirus 71 can result in severe life-threatening rhombencephalitis.

The paralytic potential of the polioviruses is well recognized. In regions of the world where they have been eradicated, the NPEVs and circulating vaccine-derived polioviruses are now the principal causes of EV-associated acute flaccid paralysis (AFP). Nonpolio EV serotypes known to cause AFP include coxsackieviruses A 4, 7, 21, 24, B 2, 3, 5; echovirus 3, 7, 9, 18, 19, 33; and EV 68 and 71.

The group B coxsackieviruses are among the most common etiologies of viral myocarditis. The echoviruses have also been identified as a cause of myocarditis, though far less frequently. Males, physically active adolescents, and young adults are at greatest risk.

Vertically transmitted NPEV infections in neonates can result in potentially life-threatening illnesses. The group B coxsackieviruses and echoviruses, in particular echovirus 11, are the most commonly associated. Significant morbidity and mortality occur in these infections; neonates who develop hepatitis and coagulopathy are at greatest risk for adverse outcomes.
The clearance of EV infection is dependent upon humoral (antibody-based) immunity, rather than cell-mediated immunity, as is the case in the majority of viral infections. Thus, individuals with B cell defects that result in certain humoral immunodeficiencies are susceptible to chronic NPEV infections of the central nervous system (CNS) that take the form of chronic meningoencephalitis. Echoviruses are most commonly isolated from these cases.

Pathogenesis
After the EVs are ingested, they infect the cells of the oropharynx and intestine. The EVs enter and replicate in the regional lymph nodes (e.g., tonsils, Peyer's patches), and are subsequently released into the bloodstream (primary or minor viremic stage). By way of the blood, the EVs may infect the CNS, liver, heart, pancreas, respiratory tract, skin, and/or mucous membranes. Vertical transmission to the fetus may occur at this stage of maternal infection. Replication occurs in these organs with subsequent virus release into the bloodstream, resulting in a secondary or major viremic phase. During this stage, the EV may invade the CNS if it was spared during the initial viremic phase of the illness. Viremia and viral replication in organs ceases once the host produces a type-specific antibody response.

Clinical Manifestations
The NPEVs cause a wide range of clinical syndromes ranging from asymptomatic infection to life-threatening diseases such as myocarditis and neonatal sepsis. Given the myriad of clinical syndromes resulting from NPEV infection, it is not possible to cover them in their entirety in this article. The most prominent NPEV syndromes will be discussed below.

No single NPEV serotype is associated with a unique clinical presentation. The overwhelming majority of NPEV infections do not result in clinical symptoms and cause only subclinical infection. Additionally, many of those infected experience only fever without additional signs and symptoms. Importantly, the majority of EV infections are self-limiting.

Meningitis
The illness is heralded by the acute onset of fever that may range from 38 to 40 °C. In some, the fever may be biphasic. Initially occurring in association with nonspecific constitutional symptoms followed by complete or near-complete resolution, and reappearance with the onset of signs and symptoms of CNS disease such as headache, photophobia, vomiting, and neck stiffness. Headache is the most common symptom in adults and children capable of reporting it. Other constitutional symptoms include abdominal pain, anorexia, cough, rhinorrhea, and myalgias. Physical examination reveals signs of meningeal irritation: Nuchal rigidity, Brudzinski’s sign, or Kernig’s sign. A rash may be present.

The definitive diagnostic procedure is the lumbar puncture. Examination of the cerebrospinal fluid (CSF) commonly reveals a predominantly lymphocytic pleocytosis with typically 100-500 white blood cells/mm³. A polymorphonuclear cell predominance may be present early in the course of the illness. The protein concentration is normal to mildly elevated and the glucose concentration is normal in most cases.

The typical clinical course is relatively benign. Most children and adults resolve their illness within 1 week. However, adults may experience headaches for several weeks. Neurological complications may occur and take the form of seizures, increased intracranial pressure, and coma. Additionally, some patients may release excessive quantities of antidiuretic hormone.

Encephalitis

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Most patients experiencing NPEV encephalitis present with mental status changes. Focal neurological findings such as partial motor seizures, hemichorea, and cerebellar ataxia may occur. These neurologic findings can mimic those seen in cases of herpes simplex virus encephalitis. In contrast to NPEV meningitis, evidence of meningeal irritation is often absent. The CSF cytochemical analysis is typically normal, although the protein concentration may be mildly elevated. Neuroimaging studies have demonstrated diffuse and focal lesions, but this is the exception rather than the rule. Most patients recover without neurological sequelae.

Rhombencephalitis, a brainstem encephalitis, has been observed as a result of infection with some strains of EV 71. Patients present with myoclonic jerks, tremors, and/or ataxia. Some progress rapidly to develop respiratory distress, shock, loss of doll's eye response, and apnea. Magnetic resonance imaging of the CNS may reveal lesions within the brainstem. A high mortality rate has been associated with this syndrome.

**Acute Flaccid Paralysis**

Acute flaccid paralysis may occur as a result of NPEV infections. As with the polioviruses, NPEV AFP may present as a biphasic illness. Initially, patients experience a nonspecific febrile illness that may be accompanied by upper respiratory or gastrointestinal complaints that resolve. Shortly thereafter, an acute onset of fever, muscle pain and hyporeflexia occurs. Rapid development of weakness and paralysis ensues, which typically involves proximal limb muscles. The paralysis is asymmetric, flaccid, and without involvement of the sensory branch of the CNS. The NPEV-associated AFP is typically less severe than seen with poliovirus and rarely affects the brainstem.

**Enteroviral Exanthems and Enanthems**

Many different exanthems have been described with NPEV infections. These rashes are generally nondescript and nonpathognomonic. They may resemble those seen with infections due to other viruses or bacteria such as measles or meningococcus or may even appear urticarial, suggesting an allergic reaction.

A commonly encountered NPEV-associated exanthem in children is hand, foot, and mouth disease (HFMD). HFMD is most frequently caused by coxsackievirus A16. Oral lesions (i.e., enanthema) are found on the tongue and buccal mucosa and typically ulcerate. The cutaneous lesions of HFMD are described as tender papules or vesicles on an erythematous base that can be found on the hands, feet, wrists, ankles, buttocks, and genitalia. Fever and sore throat appear coincident with the skin lesions. The disease is self-limited and generally lasts 7 days.

Herpangina, an enanthem, is characterized by the acute onset of fever and severe sore throat. It is most commonly associated with infections due to group A coxsackieviruses 1-6, 8, 10, and 22. The pharynx is hyperemic and in contrast to HFMD, the oral lesions (discrete vesicles) are located on the palate, uvula, posterior pharynx, anterior faucial pillars, and tonsils. The lesions evolve into painful ulcers. Typically, the fever resolves within 4 days, but the oral lesions may persist for a week.

**Myocarditis**

Myocarditis is a potentially life-threatening complication of NPEV infection. The onset of cardiovascular signs and symptoms may be preceded by an upper respiratory tract infection. Patients may present with fever, chest pain, shortness of breath, and exertional dyspnea. A gallop heart rhythm and/or pericardial friction rub may be present on auscultation of the heart. Echocardiographic findings may
include a decreased ejection fraction or ventricular dilatation.

Electrocardiographic findings vary and include low voltage QRS complexes, ST segment depression, and T wave inversion. Cardiac enzymes are commonly elevated.

In severe cases, acute congestive heart failure or life-threatening arrhythmias may occur and contribute to mortality. While the majority of patients survive, long-term sequelae in the form of chronic, dilated cardiomyopathy may occur.

**Severe Neonatal Enteroviral Infections**

Neonates are at risk of developing severe disease as a result of maternal NPEV infection at the time of delivery. In these cases, transplacental transfer of virus may occur. If the infant is delivered before maternal antibodies are transferred to the fetus, the newborn is at risk for overwhelming NPEV infection.

Typically, severe neonatal NPEV infections present during the first 1-2 weeks of life. Frequently, maternal symptoms such as severe abdominal pain or pleurodynia are present at time of delivery. The liver, heart, or brain may be involved individually or in combination. The most severe presentation, neonatal entero viral sepsis, is characterized by multisystem organ involvement. Clinically, the newborn may have a combination of the following conditions: Myocarditis, meningoencephalitis, hepatitis, and/or pneumonia. The presentation may be subtle, at first consisting of poor feeding, apnea, lethargy, hypotonia, and abdominal distention. Fever may be absent. As the illness progresses, obvious evidence of multiple organ involvement becomes apparent.

With neonatal NPEV, hepatitis, jaundice, and hepatomegaly occur. Extensive hepatic necrosis results in extreme elevations of liver transaminases along with prolonged prothrombin and partial thromboplastin times, leading to disseminated intravascular coagulopathy (DIC). Mortality is high in these patients.

Neonates with NPEV myocarditis have evidence of myocardial dysfunction: Tachycardia, respiratory distress, cyanosis, and decreased cardiac output.

Pneumonia and meningoencephalitis are frequent manifestations of neonatal infection. The meningoencephalitis may be manifested by generalized seizures, lethargy, or coma.

**Nonpolio Enterovirus Infections in Immunocompromised Hosts**

Individuals with B cell immunodeficiencies are at risk for chronic NPEV infections. Due to their lack of antibody production, the virus cannot be cleared by the host, resulting in chronic infection. In children with X-linked agammaglobulinemia, hyper-IgM syndrome, severe combined immunodeficiency syndrome, and common variable immunodeficiency, NPEV infection can result in chronic EV meningoencephalitis. Children with these forms of humoral immunodeficiency should receive life-long intravenous immunoglobulin (IVIG) replacement therapy in an attempt to prevent chronic infection. Reports exist of immunodeficient patients developing chronic EV meningoencephalitis despite immunoglobulin therapy.

Chronic NPEV meningoencephalitis has a subtle presentation. Patients initially complain of persistent headaches and lethargy. As the syndrome progresses, a constellation of neurologic symptoms develops, which includes ataxia, loss of cognitive skills, paresthesias, weakness, and seizures. Nonneurologic manifestations, including a dermatomyositis-like syndrome, edema, exanthems, and hepatitis, may occur. The CSF demonstrates a persistently elevated protein concentration and
pleocytosis. Viral culture and PCR from the CSF are repeatedly positive for EV.

Patients who have undergone bone marrow transplantation are also at risk for serious EV infections. Meningoencephalitis, pulmonary infections, and severe gastroenteritis have been reported. These infections can be severe and may result in poor outcomes.

**Diagnosis**

The current diagnostic method of choice for the NPEVs is detection using reverse transcription-polymerase chain reaction (RT-PCR). Prior to the advent of RT-PCR, NPEV detection using cell culture was the standard. Cell culture techniques have several limitations for the detection of the EVs. The time required to determine a positive result is too long to be of clinical utility in the acute management of the patient. Not all NPEV infections replicate in cell culture. Most importantly, cell culture lacks sensitivity.

The utilization of RT-PCR has been an important advancement in the diagnosis of EV infections. The use of RT-PCR provides the clinician with the ability to diagnose the overwhelming majority, if not all, NPEV serotypes using a single test. It provides a rapid detection method that is clinically useful and has excellent sensitivity and specificity. The sensitivity and specificity of RT-PCR for the detection of the EV from CSF is reported to be 86-100% and 92-100%, respectively. The result is generally available within 24 h. This results in decreased length of hospitalizations and allows for reduction in the use of antibiotics in individuals with NPEV meningitis. RT-PCR has been shown to reduce overall hospital cost associated with EV meningitis. The flexibility of this assay allows for the detection of NPEVs in different clinical specimens: serum, urine, stool, nasopharyngeal secretions, and tissues. Recent advances in RT-PCR methodologies permit both detection and determination of the infecting NPEV serotype.

Because RT-PCR detection of NPEV is not routinely available to all clinical laboratories, many continue to utilize cell culture for detection. When cell culture is employed, it is important that multiple cell lines be used in order to have the highest possible sensitivity. Shell vial techniques combined with the use of monoclonal antibodies shorten the detection time, but the technique has poorer sensitivity than traditional cell culture methods.

The interpretation of the results of cell culture and RT-PCR assay requires that the clinician take into account the specimen source from which the NPEV was detected. Because the NPEVs are shed from the oropharynx and gastrointestinal (GI) tract for weeks to months after infection, the significance of detection from these sites must be cautiously interpreted. The presence of NPEVs in specimens from these sites does not conclusively establish causality of the syndrome being evaluated. Stated more clearly, a NPEV isolated from a throat or GI specimen of a patient with meningitis, encephalitis, myocarditis, or febrile illness may represent viral shedding as a result of infection weeks earlier and may have no relationship with the current medical problem. In contrast, the identification of an NPEV from the CSF, blood, tissue, or urine is strongly supportive of an invasive infection and carries a high probability of being the causal agent of the illness being investigated. Samples from these sites represent the ideal sources from which to diagnose NPEV infections.

A final caveat relates to the diagnosis of neonatal NPEV infections occurring within the first 2 weeks of life. Because the incubation period for the NPEV is 3-6 days, their identification in the stool or oropharynx from patients in this age group with NPEV-compatible syndromes is highly supportive of

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their role in disease.

**Treatment**

No approved therapy exists for NPEV disease. An antiviral compound, pleconaril, is currently under investigation. Pleconaril inhibits binding and uncoating of EVs and rhinoviruses. The susceptibility of EVs to pleconaril varies by serotype and strain. Clinical trials have evaluated the utility of this drug for the therapy of NPEV meningitis and life-threatening enteroviral infections (immunodeficient patients with chronic meningoencephalitis, myocarditis, and severe neonatal infections). Data have not supported its use for therapy of infants with NPEV meningitis. Data from a clinical trial of the treatment of NPEV meningitis demonstrated a reduction in duration of headache in adult patients. In compassionate use, evaluation of pleconaril for immunodeficient patients with chronic EV meningoencephalitis, clinical and laboratory improvements were observed. Currently, a multicenter double-blind placebo-controlled trial is ongoing to evaluate its use in neonates with severe NPEV infections.

Intravenous immunoglobulin (IVIG) has been used in the therapy of patients with severe EV infections, since antibody is critical to immunity to EVs. This approach has been employed in neonates with severe disease, but it remains unclear whether it provides a clinical benefit. Similarly, its use in the treatment of children suspected of having EV myocarditis has gained widespread acceptance without strong evidence for its benefit.

Due to a lack of a proven therapeutic agent, supportive care is the cornerstone of management of individuals with NPEV infections. For patients with meningitis, analgesics for pain control of headaches and monitoring of fluid and electrolytes are essential. Respiratory and cardiovascular support and administration of blood products are essential in the neonate with severe disease and associated DIC. In cases of NPEV myocarditis, cardiovascular support in the form of inotropes, afterload reducers and, for those with life-threatening myocardial involvement, bridging with extracorporeal membrane oxygenation may be indicated.

**Prevention**

Enteroviruses are spread primarily by the lack of good hygiene. Handwashing is a key personal measure for the prevention of NPEV infection. Community-wide prevention of NPEV outbreaks requires adequate potable water, well-designed sewage systems, and waste treatment plants. During nursery outbreaks of NPEV infections, cohorting neonates is effective in limiting the outbreak. If a pregnant woman has an illness consistent with an NPEV disease and the fetus is doing well, attempts should be made to not deliver the baby. Waiting allows the fetus to acquire protective maternal antibodies.
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Further Reading

- H. A. Rotbart; A. Ahmed; S. Hickey et al. Diagnosis of enterovirus infection by polymerase chain

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