

## 9 | ENTEROVIRUSES (EXCLUDES HAV)

### 9.1 | Disease agent

- The enterovirus genus is in the family *Picornaviridae*; picornaviruses include four human enterovirus species A to D and three human rhinovirus species A to C. Within the enterovirus genus there are 81 non-polio and 3 polio enteroviruses that cause disease in humans. Of the 81 non-polio types, there are 28 Coxsackie viruses (22 A and 6 B), 28 echoviruses (enteric cytopathic human orphan) and 25 other enteroviruses.
- HAV was formerly classified as an enterovirus (enterovirus 72) but has been moved to a separate genus, *Hepatovirus*, and is not considered here.

### 9.2 | Disease agent characteristics

- Family: *Picornaviridae*; Genus: *Enterovirus* (poliovirus-1 is the prototype)
- Virion morphology and size: Nonenveloped, icosahedral nucleocapsid symmetry, spherical particles, 30 nm in size
- Nucleic acid: Linear, nonsegmented, positive-sense, single-stranded RNA, 7.4–7.5 kb in length
- Physicochemical properties: thermal stability at 42°C or up to 50°C in the presence of sulfhydryl reducing agents and magnesium cations or labile to heat at 60°C for 60 min or 100°C for 5 min; sensitive to guanidine and disoxaril (a phenol ether with known activity against human picornaviruses); relatively resistant to 70% ethanol, 5% Lysol, quaternary ammonium compounds; insensitive to ether, chloroform, and deoxycholate (a bile acid) at room temperature; retains infectivity at pH 3.0 but labile at pH 1.0; sensitive to 0.3% formaldehyde, glutaraldehyde, sodium hypochlorite, and UV light; drying on surfaces significantly reduces virus titers

### 9.3 | Disease name

- Many; see “Primary disease symptoms”

### 9.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical
- Public perception and/or regulatory concern regarding blood safety: Absent
- Public concern regarding disease agent: Absent

### 9.5 | Background

- Ubiquitous with a wide variety of clinical manifestations; sporadic epidemics; many show seasonal variation

### 9.6 | Common human exposure routes

- Predominantly fecal/oral transmission but also may spread via respiratory secretions and by direct contact (e.g., the common cold and conjunctivitis).
- Poliovirus RNA can be amplified from wastewater and is used as a surveillance tool for monitoring attenuated vaccine virus which very infrequently may revert to neurovirulence and result in symptomatic/paralytic disease in unvaccinated individuals.

### 9.7 | Likelihood of secondary transmission

- Moderate/high via gastrointestinal/respiratory shedding. This may not apply to parenterally acquired infection.

### 9.8 | At-risk populations

- Neonates, young children, patients with congenital and acquired B-cell deficiencies (including acquisition following treatment with rituximab)
- Possibly patients undergoing hematopoietic cell transplant

### 9.9 | Vector and reservoir involved

- None

### 9.10 | Blood phase

- Not well characterized for majority of these viruses.
- Based on a poliovirus model, primary infection occurs with viral replication in the GI tract and draining lymph nodes. A brief period of viremia with very low levels of virus occurs approximately 2–9 days following infection in about 25% of all infections. However, a major viremia occurs following amplification of the virus in the reticuloendothelial tissues with subsequent development of clinical manifestations in target organs.

### 9.11 | Survival/persistence in blood products

- Unknown

### 9.12 | Transmission by blood transfusion

- Theoretically possible; no enterovirus transfusion transmission related to infection or clinical disease has ever been demonstrated.
- Enterovirus RNA sequences were detected by RT-PCR in 19 minipools containing 95 component blood donor samples from 83,600 Scottish blood donors corresponding to a donor prevalence of at least 0.023%. Although infectivity was not evaluated, and transmission was not investigated, this study predicted that at least 1000-enterovirus contaminated blood components may be transfused annually in the United Kingdom. Sequences were not detected in clotting factor concentrates.

### 9.13 | Cases/frequency in population

- Ubiquitous with regional and seasonal epidemics.
- Young children are the most important transmitters of enteroviruses, especially within households, although the incidence is low in the first 4–6 months of life in developing countries as a result of maternal protective antibody. Children are more likely to develop significant symptomatology.
- Disease is more prevalent among lower socioeconomic populations and those living in urban areas. Disease is more common among males at a male-to-female ratio between 1.2 and 2.5:1.

### 9.14 | Incubation period

- Not well characterized; major viremia is thought to occur 6–9 days after exposure but may occur earlier and persist longer. Major symptoms occur after viremia, which disseminates infection to target organs.
- For poliovirus, the incubation period is estimated to be 9–12 days (range: 5–35 days) and 11–17 days (range: 8–36 days) until the onset of paralysis.

### 9.15 | Likelihood of clinical disease

- In adults, the majority of infections are asymptomatic.
- The incidence and severity of symptoms is higher in children, especially neonates.

- Among susceptible persons, only about 25% poliovirus infections are symptomatic with 1 in 100–200 resulting in paralytic disease.

### 9.16 | Primary disease symptoms

- Enteroviruses can cause many clinical syndromes:
  - Polioviruses can infect anterior horn cells in the spinal cord causing acute flaccid paralysis. An initiative to eradicate paralytic polio has been under way for decades with substantial success. Eradication in the developing world is being pursued, with few countries reporting wild-type infections. Major barriers persist, including the COVID pandemic and political instability. Vaccine-associated poliomyelitis from reversion of live vaccine strains (trivalent oral poliovirus vaccines, TOPV) to neurovirulence is rare (estimated at one per 3 million TOPV vaccinees) but well described and is leading to replacement of live attenuated vaccines with inactivated vaccine.
  - Nonpolio enteroviruses cause as many as 15,000,000 infections and thousands of hospitalizations annually in the United States alone; examples include: flaccid paralysis in Group A Coxsackievirus infections, whereas group B Coxsackieviruses are noted to cause a spastic paralysis due to focal muscle injury and degeneration of neuronal, pancreatic, and myocardial tissue.
  - Enterovirus D68 has caused limited outbreaks of acute flaccid paralysis among young children since 2014.
  - Pleurodynia, myositis, myocarditis, pericarditis, chronic heart disease.
  - Exanthems, herpangina (in children due to group A Coxsackie infections), hand, foot, and mouth disease.
  - Upper and lower respiratory illness.
  - Hemorrhagic conjunctivitis.
  - Severe neonatal infection with hepatitis (distinct from HAV infection).

### 9.17 | Severity of clinical disease

- Acute infection: Severity varies with age and immunocompetence of patient.
  - Adults: Usually asymptomatic or only mild symptoms.
  - Neonates: Usually mildly symptomatic but may be severely affected and infection may be fatal. Enteroviruses are a common cause of fever in neonates. The likelihood of severe sequelae varies.

- Implicated as a cause of insulin-dependent diabetes mellitus, possibly via an immune response mechanism, although it is unclear how often this occurs.
- Chronic infection: suspected to occur in some target organs; for example, polio, heart disease. Frequency and clinical significance are undetermined, except chronic enteroviral meningoencephalitis in B-cell immunodeficiency which can be lethal.

### 9.18 | Mortality

- It varies with age and agent but is uncommon where critical care medicine is available. Mortality occurs mainly in neonates; it may occur in immunodeficient patients.
- The case fatality ratio for paralytic polio is generally 2%–5% among children and up to 15%–30% among adolescents and adults.

### 9.19 | Chronic carriage

- Uncommon, but may occur in immunosuppressed patients.
- Shedding of live attenuated polio vaccine after immunization can be the source of neurovirulent revertant infections causing polio (reverts at an estimated frequency of one per 3 million vaccinees).

### 9.20 | Treatment available/efficacious

- None are available for routine use.
- Intravenous immunoglobulin has been used in B-cell deficiencies with mixed results reported.

### 9.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because transfusion transmission has not been demonstrated.
- No sensitive or specific question is feasible.

### 9.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- NAT is increasingly used for diagnosis (generic enterovirus and subtype-specific assays are available in research and public health labs).

- Serologic assays are available but not used for blood donation screening.
- Culture possible for some agents, but not useful as a screening tool; useful as a confirming method for surveillance.

### 9.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer donor until signs and symptoms are resolved.

### 9.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

### 9.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

### 9.26 | Leukoreduction efficacy

- Unlikely to be effective, as RNA has been detected in plasma.

### 9.27 | Pathogen reduction efficacy for plasma derivatives

- Nonenveloped viruses, so solvent/detergent would be ineffective.
- Probably susceptible to heat inactivation and ultraviolet light.

### 9.28 | Other prevention measures

- With the exception of poliovirus, no widely available vaccine.

### SUGGESTED READING

1. CDC. Enterovirus D68. <https://www.cdc.gov/non-polio-enterovirus/about/ev-d68.html>. Accessed 24 May 2021
2. Chakrabarti S, Osman H, Collingham KE, Fegan CD, Milligan DW. Enterovirus infections following T-cell depleted allogeneic transplants in adults. *Bone Marrow Transplant.* 2004;33:425–30.

3. Chang LY, Tsao KC, Hsia SH, Shih SR, Huang CG, Chan WK, et al. Transmission and clinical features of enterovirus 71 infections in household contacts in Taiwan. *JAMA*. 2004;291:222–7.
4. ICTV. Current ICTV taxonomy release. <https://ictv.global/taxonomy>. Accessed 11 May 2023
5. Larkin H. What all physicians need to know about the polio resurgence in New York State. *JAMA*. 2022;328(11):1020–2.
6. Modlin JF. Chapter 250—Enteroviruses: coxsackieviruses, echoviruses, and newer enteroviruses. In: Long SS, editor. *Principles and practice of pediatric infectious diseases*. 3rd ed. Philadelphia: Churchill Livingstone; 2008. p. 1149–57.
7. Padate BP, Keidan J. Enteroviral meningoencephalitis in a patient with non-Hodgkin's lymphoma treated previously with rituximab. *Clin Lab Haematol*. 2006;28:69–71.
8. Pallansch MA, Oberste MS, Whitton JL. Enteroviruses: polioviruses, coxsackieviruses, echoviruses, and newer enteroviruses. In: Knipe DM, Howley PM, editors. *Fields virology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. ch. 17. p. 490–530.
9. Racaniello VR. Picornaviridae: the viruses and their replication. In: Knipe DM, Howley PM, editors. *Fields virology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. ch. 16. p. 453–89.
10. Rittichier KR, Bryan PA, Bassett KE, Taggart EW, Enriquez FR, Hillyard DR, et al. Diagnosis and outcomes of enterovirus infections in young infants. *Pediatr Infect Dis J*. 2005;24:546–50.
11. Sandoni M, Ciardo L, Tamburini C, Boncompagni A, Rossi C, Guidotti I, et al. Enteroviral infections in the first three months of life. *Pathogens*. 2022;11(1):60.
12. Welch J, Maclaran K, Jordan T, Simmonds P. Frequency, viral loads, and serotype identification of enterovirus infections in Scottish blood donors. *Transfusion*. 2003;43:1060–6.
13. Welch JB, McGowan K, Searle B, Gillon J, Jarvis LM, Simmonds P. Detection of enterovirus viraemia in blood donors. *Vox Sang*. 2001;80:211–5.
14. Zeichhardt H, Grunert H-P. Enteroviruses: polioviruses, coxsackieviruses, echoviruses and enteroviruses 68-71. In: Cohen J, Powderly WG, Opal SM, editors. *Infectious diseases*. 2nd ed. London: Elsevier Health Sciences; 2003. p. 1993–2006.