Enterovirus, Parechovirus, and Reovirus Infections

Chapter 210 | Part 5: Infectious Diseases

KEY CLINICAL POINTS

1. Enteroviruses are non-enveloped, single-stranded RNA viruses of the family Picornaviridae that multiply in the gastrointestinal tract.
2. Most enterovirus infections are subclinical; >90% of poliovirus infections and >50% of nonpoliovirus enterovirus infections are asymptomatic.
3. Poliovirus infection is limited to primates because host cells express the specific poliovirus receptor.
4. Enteroviruses are stable in acidic environments (stomach) but susceptible to chlorine-containing cleansers.
5. Vaccine-associated paralytic poliomyelitis (VAPP) risk is ~2000 times higher in immunodeficient persons, especially those with hypo- or agammaglobulinemia.
6. Hand-foot-and-mouth disease (HFMD) is caused by Coxsackievirus A16 or Enterovirus 71 and presents with fever, sore throat, and vesicular lesions on hands, feet, and mouth.
7. Acute flaccid myelitis (AFM) is associated with Enterovirus D68 and affects anterior horn cells in the spinal cord.
8. Vaccine-derived poliovirus (VDPV) outbreaks occur in areas with low vaccination coverage due to mutations restoring neurovirulence.
9. CSF in enteroviral meningitis shows lymphocytic pleocytosis, normal glucose, and normal or slightly elevated protein.
10. Enterovirus 70 and Coxsackievirus A24 cause acute hemorrhagic conjunctivitis, often with epidemics in Asia.

1. DEFINITION & OVERVIEW

- **Overview:** Enteroviruses, Parechoviruses, and Reoviruses are viral pathogens causing a spectrum of diseases ranging from mild febrile illness to severe neurologic and cardiac complications.
- **Classification:**
- **Enteroviruses:** Family Picornaviridae; encompass >115 human serotypes (3 poliovirus, 23 coxsackievirus A, 6 coxsackievirus B, 29 echovirus, and enteroviruses 68–71).
- **Parechoviruses:** Reclassified from Echoviruses; specifically, Echoviruses 22 and 23 are now classified as parechoviruses 1 and 2.
- **Other Viral Agents of Gastroenteritis:** Includes Rotavirus, Adenovirus, Astrovirus, Torovirus, and Picobirnavirus.

1.1 Enterovirus Classification & Characteristics

- **Serotype Distribution:**

- Coxsackievirus A: 23 serotypes
- Coxsackievirus B: 6 serotypes
- Echovirus: 29 serotypes
- Other Enteroviruses: 68–71
- **CDC Surveillance (2022):**
- Enterovirus D68: 41.1%
- Human parechovirus 2: 20.7%
- **Clinical Syndromes Associated with Serotypes:**
- **Acute hemorrhagic conjunctivitis:** Coxsackievirus A24, Echovirus 70; Coxsackievirus A2, 4, 7, 9, 10; Coxsackievirus B1–5
- **Encephalitis:** Coxsackievirus A9, B1–5; Echoviruses 3, 4, 6, 7, 9, 11, 18, 25, 30; Enterovirus 71; Coxsackievirus A4, 5, 6, 9, 10, 16; Coxsackievirus B1, 3–5
- **Generalized disease of the newborn:** Coxsackievirus B1–5; Echoviruses 4–7, 9, 11, 14, 16, 18, 19; Coxsackievirus A5–7, 9, 10, 16; Coxsackievirus B1, 2, 5
- **Herpangina:** Coxsackievirus A1–10, 16, 22; Coxsackievirus B1–5; Echoviruses 6, 9, 11, 16, 17, 25, 30; Enterovirus 71; Coxsackievirus A4, 9, 16; Coxsackievirus B1–5
- **Paralysis:** Coxsackievirus A4, 7, 9; Coxsackievirus B1–5; Echoviruses 2–4, 6, 7, 9, 11, 18, 30; Enterovirus D68, 70, 71; Coxsackievirus A1, 2, 4, 6, 9, 10, 16; Coxsackievirus B1–6
- **Pneumonia:** Coxsackievirus A9, 16; Coxsackievirus B1–5; Echoviruses 6, 7, 9, 11, 12, 19, 20, 30; Enterovirus D68, 71

TABLE 210-1

: Manifestations Commonly Associated with Enterovirus Serotypes

MANIFESTATION	SEROTYPE(S) OF INDICATED VIRUS
Acute hemorrhagic conjunctivitis	Coxsackievirus A24; Echovirus E70; Coxsackievirus A2, 4, 7, 9, 10; Coxsackievirus B1–5
Encephalitis	Coxsackievirus A9, B1–5; Echoviruses E3, 4, 6, 7, 9, 11, 18, 25, 30; Enterovirus 71; Coxsackievirus A4, 5, 6, 9, 10, 16; Coxsackievirus B1, 3–5
Generalized disease of the newborn	Coxsackievirus B1–5; Echoviruses E4–7, 9, 11, 14, 16, 18, 19; Coxsackievirus A5–7, 9, 10, 16; Coxsackievirus B1, 2, 5
Herpangina	Coxsackievirus A1–10, 16, 22; Coxsackievirus B1–5; Echoviruses E6, 9, 11, 16, 17, 25, 30; Enterovirus 71; Coxsackievirus A4, 9, 16; Coxsackievirus B1–5
Paralysis	Coxsackievirus A4, 7, 9; Coxsackievirus B1–5; Echoviruses E2–4, 6, 7, 9, 11, 18, 30; Enterovirus D68, 70, 71; Coxsackievirus A1, 2, 4, 6, 9, 10, 16; Coxsackievirus B1–6
Pneumonia	Coxsackievirus A9, 16; Coxsackievirus B1–5; Echoviruses E6, 7, 9, 11, 12, 19, 20, 30; Enterovirus D68, 71

TABLE 210-2

: Laboratory-Confirmed Cases of Poliomyelitis in 2023

COUNTRY	WILD-TYPE POLIO	VACCINE-DERIVED POLIO
Pakistan	6	0
Democratic Republic of the Congo	0	223
Chad	0	55
Madagascar	0	24
Central African Republic	0	14
Others	0	0
Total	12	526

1.2 Other Viral Agents of Gastroenteritis

- **Enteric adenoviruses (serotypes 40/41):**
- 70–80 nm double-strand DNA viruses.
- Cause ~2–12% of childhood diarrhea.
- **Astroviruses:**
- 28–30 nm positive-sense RNA viruses.
- Serotype 1 is the most common in pediatric gastroenteritis (~2–10% cases).
- **Toroviruses:**
- 100–140 nm enveloped RNA viruses.
- Linked to neonatal necrotizing enterocolitis.
- **Picobirnaviruses:**
- Bisegmented double-strand RNA viruses.
- Associated with HIV-related gastroenteritis.

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2. EPIDEMIOLOGY

- **Prevalence:**
- >50% of nonpoliovirus infections are subclinical.
- >90% of poliovirus infections are subclinical.
- **Incubation Period:**
- 2–14 days (typically <1 week).
- **Risk Factors:**
- Higher prevalence in socioeconomically disadvantaged, crowded, or tropical regions.
- **Seasonality:**
- Summer/fall in temperate climates; no seasonal pattern in tropics.

2.1 Transmission Dynamics

- **Primary Routes:** Fecal–oral and oral–oral.
- **Secondary Routes:**
- Contaminated food/water.

- Direct inoculation to eye (e.g., enterovirus 70).
- Airborne spread (coxsackievirus A21).
- **Vertical Transmission:** Placental passage → severe neonatal disease.
- **Nosocomial Spread:** Hospital nurseries for coxsackievirus/echovirus.
- **Outbreak Factors:** Correlate with immunity levels and birth rates.

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3. ETIOLOGY & PATHOPHYSIOLOGY

- **Structure:** Single-stranded RNA genome; icosahedral capsid; no lipid envelope.
- **Stability:** Stable in acidic environments (stomach); susceptible to chlorine-containing cleansers.

3.1 Pathogenesis of Poliovirus

- **Pathway:** Gastrointestinal tract → lymphoid tissue → viremia → CNS via neural pathways (muscle → spinal cord).
- **Viremic Phase:**
- 3–5 days post-infection; virus replicates in reticuloendothelial system.
- **Neurotropism:** Poliovirus receptor (immunoglobulin superfamily) expressed at neuromuscular junctions.
- **Long-term Shedding:** Hypogammaglobulinemic patients may shed virus >20 years post-infection.

3.2 Immunity

- **Humoral Immunity:**
- IgM (6 months).
- IgG (lifelong).
- Target: VP1 capsid protein.
- **Secretory Immunity:** IgA critical for reducing gastrointestinal replication/shedding.
- **Cellular Immunity:** Role uncertain; severe disease more common in agammaglobulinemia.

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4. CLINICAL FEATURES

- **Poliovirus Infection Statistics:**
- 95% asymptomatic.
- 5% abortive poliomyelitis (fever, myalgias; resolves in 3 days).
- 1% aseptic meningitis.
- <0.1% paralytic disease.
- **Neonatal Enterovirus Infection:**
- Presents like bacterial sepsis: fever, lethargy, thrombocytopenia, elevated liver enzymes.
- **Complications:** Myocarditis, fulminant hepatitis, meningitis, pneumonia.

4.1 Poliovirus Infection Syndromes

- **Abortive poliomyelitis:** Fever, malaise, sore throat (resolves in 3 days).
- **Aseptic meningitis:** Lymphocytic pleocytosis, normal glucose/protein.
- **Paralytic disease:** Asymmetric proximal weakness; biphasic presentation more common in children.

- **Postpolio syndrome:** Late-onset weakness (20–40 years post-infection) due to motor neuron degeneration.

4.3 Aseptic Meningitis and Encephalitis

- **Prevalence:** 90% of identified aseptic meningitis cases in children/young adults are enteroviral.
- **CSF Findings:** Lymphocytic pleocytosis (<1000/μL), normal glucose, slightly elevated protein.
- **Enteroviral encephalitis:** 10–35% of viral encephalitis cases; more severe in immunocompromised patients.

4.4 Other Enterovirus Syndromes

- **Acute flaccid myelitis (AFM):** Linked to enterovirus D68; presents with rapid flaccid paralysis.
- **Pleurodynia:** Coxsackievirus B-induced chest/abdominal pain; resolves in days.
- **Myocarditis/pericarditis:** Coxsackievirus B causes 1/3 of cases; ST-segment changes on ECG.

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5. DIFFERENTIAL DIAGNOSIS

- **Aseptic meningitis:** Distinguish from bacterial meningitis (normal glucose), mumps (low glucose), and other viral causes.
- **Acute flaccid myelitis:** Differentiate from Guillain-Barré syndrome, transverse myelitis, and spinal cord tumors.

5.1 Distinguishing Features

- **Enteroviral meningitis:** Lymphocytic pleocytosis with normal glucose; no focal neurologic signs.
- **AFM:** MRI shows spinal cord gray matter changes; CSF lymphocytosis but rare viral detection in CSF.

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6. INVESTIGATIONS & DIAGNOSIS

1. **Initial Testing:**
   - Perform PCR for enterovirus RNA in CSF, stool, or respiratory samples.
2. **Serology:**
   - Detect IgM/IgG to identify recent or previous infection.
3. **Viral Culture:**
   - Limited use due to rapid mutation rates.
4. **CSF Analysis (Key Diagnostic Step):**
   - Identify lymphocytic pleocytosis (<1000/μL) and normal glucose to differentiate from bacterial meningitis.

6.2 CSF Findings

- **Lymphocytic pleocytosis:** <1000/μL.
- **Glucose:** Normal.
- **Protein:** Slightly elevated.
- **Acute Phase:** Early polymorphonuclear leukocytes may be present.

7. MANAGEMENT & TREATMENT

1. **Supportive Care:** Mainstay of treatment for all enterovirus infections.
2. **Immunoglobulin Therapy:**
   - IV immunoglobulin for chronic meningitis in hypogammaglobulinemia.
3. **Pharmacologic Treatment:**
   - No FDA-approved antivirals available.
   - Ribavirin: Investigational use in severe cases (e.g., neonatal myocarditis).
4. **Vaccination Strategies:**
   - **Inactivated polio vaccine (IPV):** Prevents paralytic disease.
   - **Oral polio vaccine (OPV):** Associated with VAPP; phased out in most countries.
   - **VDPV Control:** Managed through mass immunization campaigns.

7.1 Pharmacologic Treatment

- **Antiviral Agents:** No FDA-approved antivirals for enterovirus infections.
- **Ribavirin:** Investigational use in severe cases (e.g., neonatal myocarditis).

8. PROGNOSIS & COMPLICATIONS

- **General:** Most enterovirus infections resolve without sequelae.
- **Paralytic disease:** 2/3 of patients have residual neurologic deficits.
- **Postpolio syndrome:** Progressive weakness decades after acute infection.
- **Myocarditis:** Dilated cardiomyopathy in 10% of cases.

8.1 Long-term Sequelae

- **Chronic meningitis/encephalitis:** In immunodeficient patients (dermatomyositis-like syndrome).

9. SPECIAL CONSIDERATIONS

- **Immunocompromised hosts:** Higher risk of chronic infection and severe disease.
- **Hypogammaglobulinemia:** Prolonged viral shedding, chronic meningitis/encephalitis.
- **Hematopoietic cell transplant recipients:** Disseminated enterovirus infections.
- **Travelers:**
- **Risk:** VDPV exposure in areas with <80% OPV coverage.
- **Action:** Pre-travel counseling for high-risk regions.

10. KEY PEARLS & CLINICAL TRAPS

- **AFM:** More common in children; Enterovirus D68 detected in respiratory samples but rarely in CSF.
- **Postpolio syndrome:** Mimics progressive MS; history of prior poliomyelitis is key differentiator.
- **Myocarditis:** May present with chest pain and ST-segment changes on ECG.

REFERENCE TABLES

TABLE 210-1

Manifestations Commonly Associated with Enterovirus Serotypes

MANIFESTATION	SEROTYPE(S) OF INDICATED VIRUS	
	COXSACKIEVIRUS	ECHOVIRUS (E) AND ENTEROVIRUS (Ent)
Acute hemorrhagic conjunctivitis	A24	E70
	A2, 4, 7, 9, 10; B1–5	
Encephalitis	A9; B1–5	E3, 4, 6, 7, 9, 11, 18, 25, 30; Ent71
	A4, 5, 6, 9, 10, 16; B1, 3–5	
Generalized disease of the newborn	B1–5	E4–7, 9, 11, 14, 16, 18, 19
	A5–7, 9, 10, 16; B1, 2, 5	
Herpangina	A1–10, 16, 22; B1–5	E6, 9, 11, 16, 17, 25, 30; Ent71
	A4, 9, 16; B1–5	
Paralysis	A4, 7, 9; B1–5	E2–4, 6, 7, 9, 11, 18, 30; EntD68, 70, 71
	A1, 2, 4, 6, 9, 10, 16; B1–6	
Pneumonia	A9, 16; B1–5	E6, 7, 9, 11, 12, 19, 20, 30; EntD68, 71

TABLE 210-2

Laboratory-Confirmed Cases of Poliomyelitis in 2023 COUNTRY Pakistan Afghanistan Democratic Republic of the Congo...

COUNTRY	WILD-TYPE POLIO	VACCINE-DERIVED POLIO
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	6	
Democratic Republic of the Congo	0	223
	0	
Chad	0	55
	0	
Madagascar	0	24
	0	

COUNTRY	WILD-TYPE POLIO	VACCINE-DERIVED POLIO
Central African Republic	0	14
	0	
Total	12	526