

Polio, Common Cold, and Norwalk Virus (Enteroviruses, Rhinoviruses, and Caliciviruses)

Reading: Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapter 32 and Chapter 37 (pp. 374-375).

I. **Overview/Classification.** This first group of positive-strand RNA viruses includes etiologic agents of poliomyelitis, meningitis, hepatitis, myocarditis and the common cold.

A. *Picornaviridae* family of viruses encompasses a large group (>200 viruses) of human pathogens. This family's name is derived from *pico* (small) and *RNA* highlighting the fact that these are among the smallest viruses. Subdivided into five genera (three of which include human pathogens):

1. *Enterovirus*

- a) Polioviruses 1-3
- b) Coxsackieviruses A1-A24 (no A23), B1-B6
- c) Echoviruses 1-34 (no 10 or 28)
- d) Enteroviruses 68-71

2. *Rhinovirus*

- a) Rhinoviruses 1>110

3. *Hepatovirus*

- a) Hepatitis A virus (will be covered in the *RNA virus III: Hepatitis* Lecture)

B. *Caliciviridae* family includes several viruses that cause gastroenteritis, and one that causes hepatitis. The name of this family is derived from *calix* (cup) to describe the 32 cup-shaped depressions on the surface of the virion.

1. Norwalk virus

C. Hepevirus- Hepatitis E virus (will be covered in the *RNA virus III: Hepatitis* Lecture)

II. **Biologic properties/virion structure/genome**

A. Biologic properties- common themes

- 1. Heat and detergent stable
- 2. Acid stability (ability to survive gastric acids following ingestion)
 - a. *Enterovirus*, *Hepatovirus*, and *Calicivirus* are acid-stable (pH >3)
 - b. *Rhinovirus* is acid-labile (pH <5)

B. Virion structure

- 1. *Picornaviridae*: nonenveloped icosahedral capsid, 30 nm in diameter, 60 protomers
- 2. *Caliciviridae*: nonenveloped icosahedral capsid, 30 – 38 nm, 90 capsomers; named for the 32 characteristic cup-shaped depressions on the virion surface

C. Genome structure

- 1. Linear, plus sense ssRNA, 7 – 8 kb
- 2. Protein primer at 5' end, polyadenylated at 3' end
- 3. Genome RNA is infectious

D. Replication

1. Attachment to receptor – canyon hypothesis
2. Virion RNA acts as mRNA and is translated into a polyprotein which auto-cleaves to yield non-structural (RNA dependent RNA polymerase) and structural proteins
3. Cytoplasmic site of replication
4. Virus inhibits cellular transcription, DNA replication & protein synthesis, cytotoxic.
5. Assembly of genome into capsids

III. Diseases Mechanism

- A. Viruses ingested and enter via the oropharynx, intestinal mucosa or upper respiratory tract and infect the underlying lymphatic tissue; rhinoviruses are restricted to the upper respiratory tract.
- B. In the absence of serum antibody, enteroviruses spread by viremia to cells of a receptor-bearing target tissue.
- C. Different viruses bind to different receptors, many of which belong to the immunoglobulin superfamily (ie, ICAM-1).
- D. The infected target tissue determines the subsequent disease.
- E. Viral, rather than immune, pathologic effects are usually responsible for causing disease symptoms- cytopathic viruses.
- F. Serum antibody blocks viremic spread to target tissue, preventing symptoms.
- G. Enterovirus is shed in feces for long periods.
- H. Infection is often asymptomatic or causes mild flu-like or upper respiratory disease.
- I. Disease is often more severe in adults and asymptomatic in young children. (Except for coxsackievirus (newborns)).

IV. Clinical Syndromes – Summary slide

- A. Neurologic
 1. Meningitis (“aseptic meningitis”)- acute illness, headache, fever, neck and back stiffness. May be a rash; recovery usually uneventful.
 - a) many enteroviruses (are most common cause of meningitis)
 - b) differential diagnosis with bacterial meningitis is very important
 2. Paralysis
 - a) Polioviruses 1, 2, 3
 - b) Enteroviruses
 - c) Coxsackievirus A and B
 3. Chronic meningoencephalitis/dermatomyositis
 - a) Echoviruses
 4. Outline of poliovirus infection
 5. Types of poliomyelitis: spinal and bulbar, predisposing factors- age, pregnancy, wound
- B. Cardiac and Muscular

1. Myocarditis - Coxsackievirus B
 - a) most severe in neonates, fever and sudden heart failure, high mortality. Brain, liver and pancreas also involved. Acute benign pericarditis in young adults.
 - b) some Coxsackievirus A and echoviruses
 2. Pleurodynia – (Bornhold's disease). Coxsackievirus B
 - a) Acute illness with sudden onset of fever and unilateral low thoracic, severe pleuritic chest pain. Lasts ~ 4 days, but may relapse.
- C. Skin and Mucosae
1. Herpangina - Coxsackievirus A
 - a) Fever, sore throat, pain on swallowing, anorexia and vomiting. Classic finding is vesicular ulcerated lesions on soft palate. Self limiting.
 2. Hand-foot-and-mouth disease - Coxsackieviruses A16
 - a) vesicular lesions on the hands, feet, mouth and tongue, mild fever, last 2-3 days.
- D. Respiratory
1. Colds- pH and temperature sensitivity restrict replication to upper respiratory tract; fever, runny nose, malaise, nasal obstruction; peaks at 3-4 days.
 2. 50% asymptomatic infection, transmitted by aerosols and fomites (hands)
 3. Immunity transient and many serotypes
 4. Drugs which bind canyon limit duration
 - a) Rhinoviruses – 50% of colds, >100 serotypes
 - b) Coxsackieviruses A
 - c) Echoviruses
 - d) Coxsackievirus B
- E. Ocular
1. Acute hemorrhagic conjunctivitis – extremely contagious, 24 hr incubation period, resolves within 1-2 weeks.
 - a) Enterovirus 70
 - b) Coxsackievirus A24
- F. Hepatitis
1. Hepatitis A virus
 2. Hepatitis E virus
- G. Gastroenteritis
1. Caliciviruses
 2. various enteroviruses
- H. Treatment/Vaccines. The polio vaccine represents an important milestone in vaccine technology
1. Salk vaccine – killed, inactivated (IPV and EIPV)
 2. Sabin vaccine – live attenuated (oral)
 3. Advantages and disadvantages of vaccines
 4. World-wide eradication effort

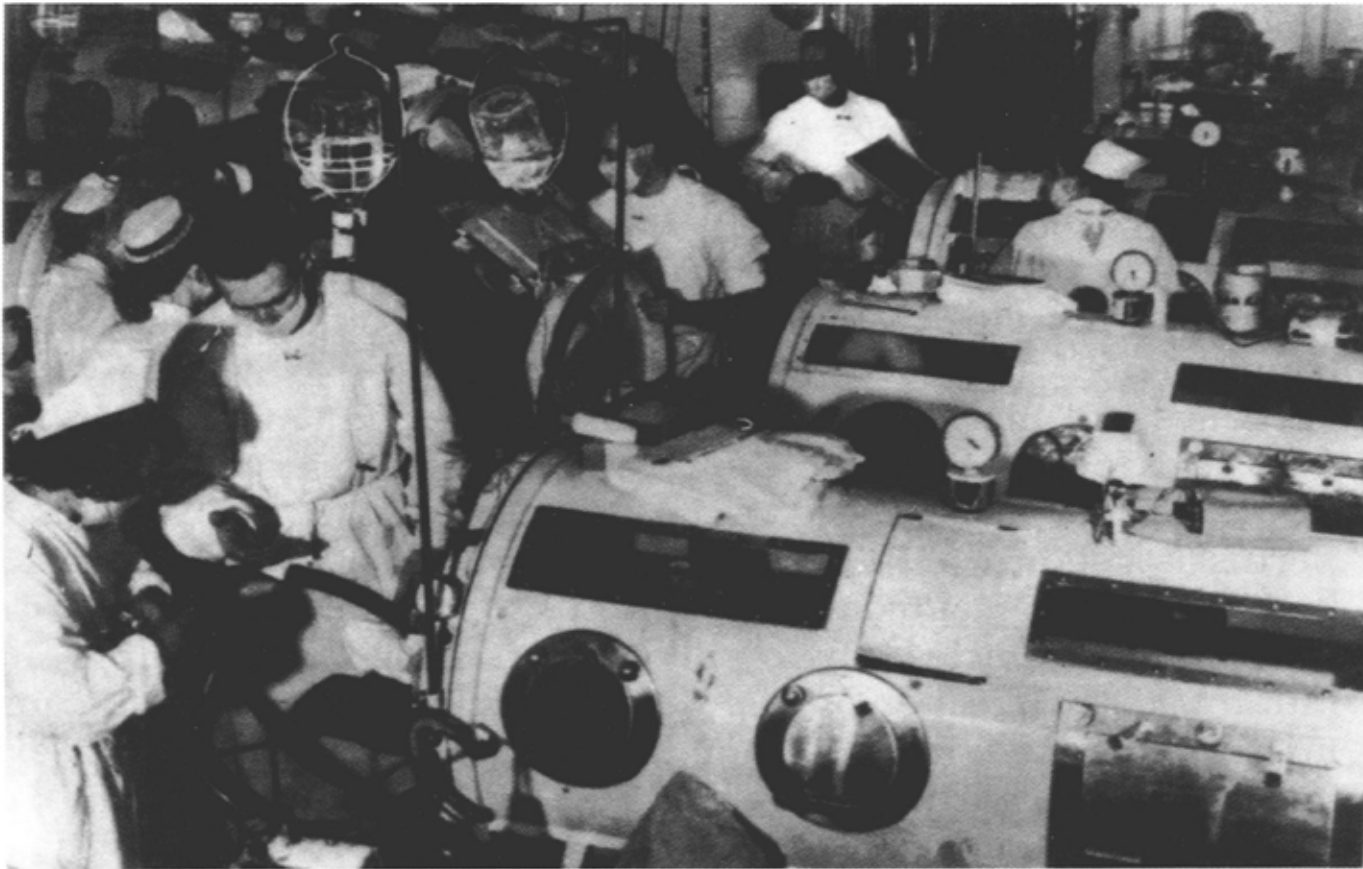
V. Caliciviruses - Caliciviruses (Norwalk agent- Cruise ship virus). Transmitted by fecal oral route. Incubation period 1-2 days; diarrhea, vomiting, abdominal cramps, nausea, fever; resolves in 1-3 days.

(+) Stranded RNA Viruses I

- Polio**
- The Common Cold**
 - Norwalk Virus**

Totally Paralyzed Poliomyelitis Patients in Mechanical Respirators

- Last US epidemic before universal immunization (1955).



Picornaviridae family

1. *Enterovirus*

- a) Polioviruses types 1, 2 and 3
- b) Coxsackieviruses A1-A24 (no A23), B1-B6
- c) Echoviruses 1-34 (no 10 or 28)
- d) Enteroviruses 68 -71

2. *Rhinovirus*

- a) Rhinoviruses 1 -100+

3. *Hepatovirus*

- a) Hepatitis A virus

4. *Cardiovirus*

Caliciviridae family

- 1. Norwalk virus
- 2. Hepatitis E virus

Biologic properties

Heat and detergent stable

Acid stability (ability to survive gastric acids following ingestion)

- a. *Enterovirus, Hepatovirus* , and *Calicivirus* are acid-stable (pH >3)
- b. *Rhinovirus* is acid-labile (pH <5)

Virion structure

1. *Picornaviridae*: non-enveloped icosahedral capsid, 30 nm in diameter, 60 protomers

2. *Caliciviridae*: nonenveloped icosahedral capsid, 30 – 38 nm, 90 capsomers; named for the 32 characteristic cup-shaped depressions on the virion surface

Genome structure

1. Linear, plus sense ssRNA, 7 – 8 kb
2. Protein primer at 5' end, polyadenylated at 3' end
3. Genome RNA is infectious

Virus Structure and Adsorption

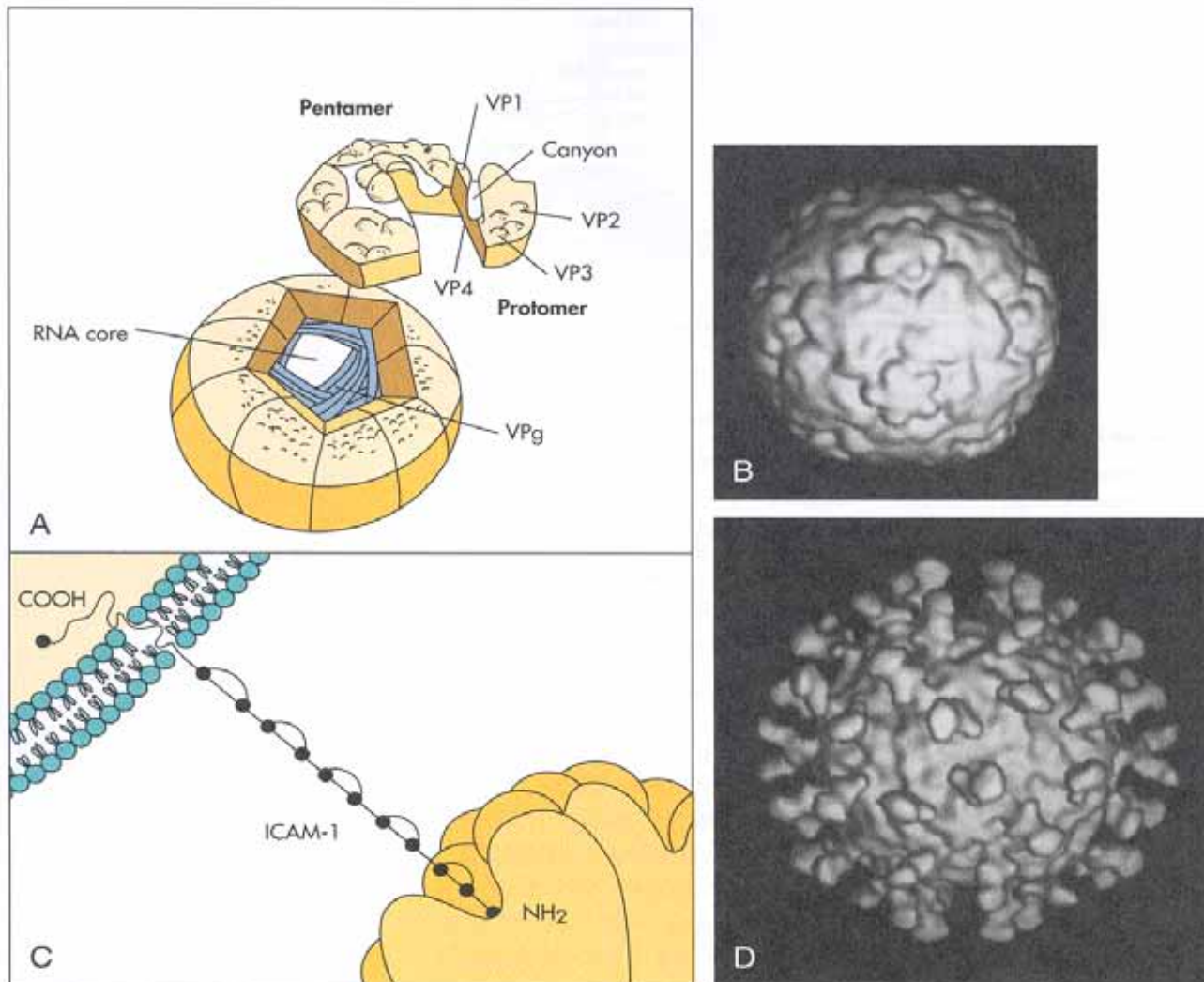


Fig. 57-2 From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 57, published by Mosby Philadelphia

Replication

1. Attachment to receptor- canyon
2. Virion RNA acts as mRNA and is translated into a polyprotein which auto-cleaves to yield non-structural and structural proteins- RNA dependent RNA polymerase
3. Cytoplasmic site of replication
4. Virus inhibits cellular transcription, DNA replication & protein synthesis. Cytocidal.
5. Assembly of genome into capsids

Poliovirus RNA and Posttranslational Processing of the Poliovirus Polyprotein

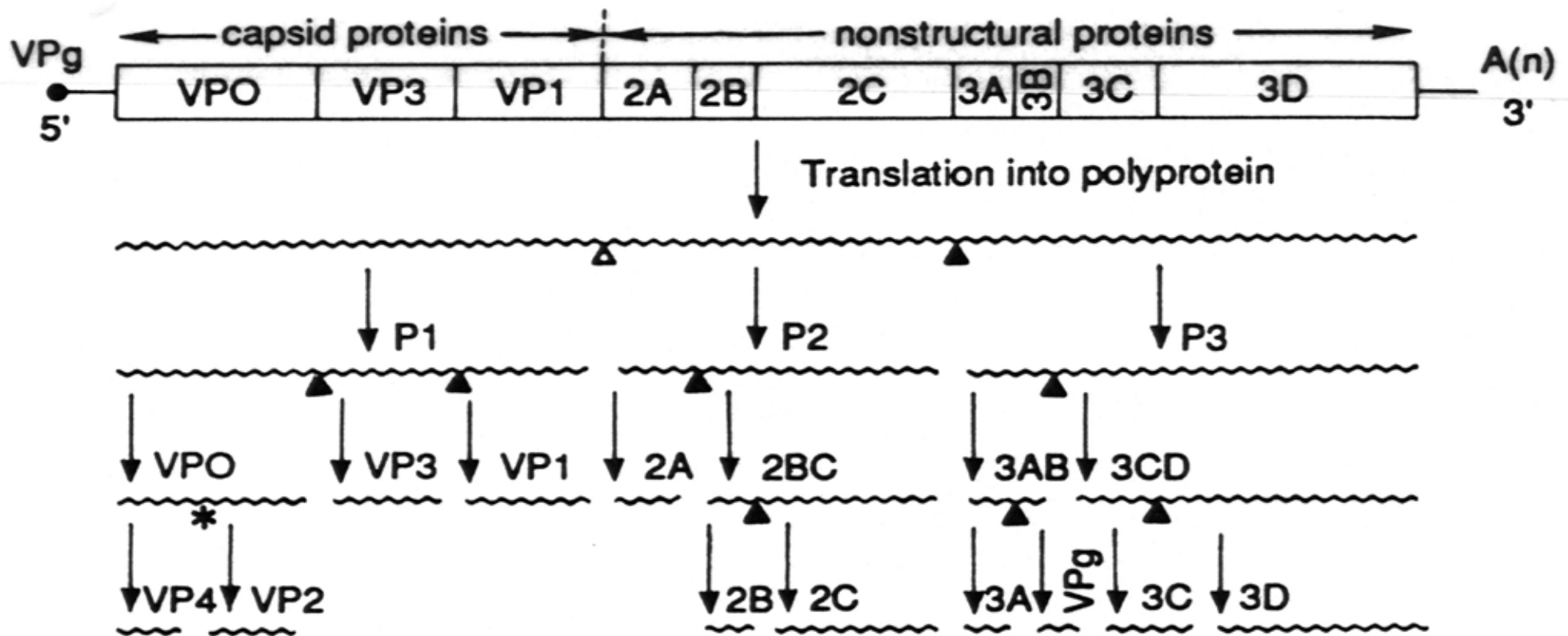
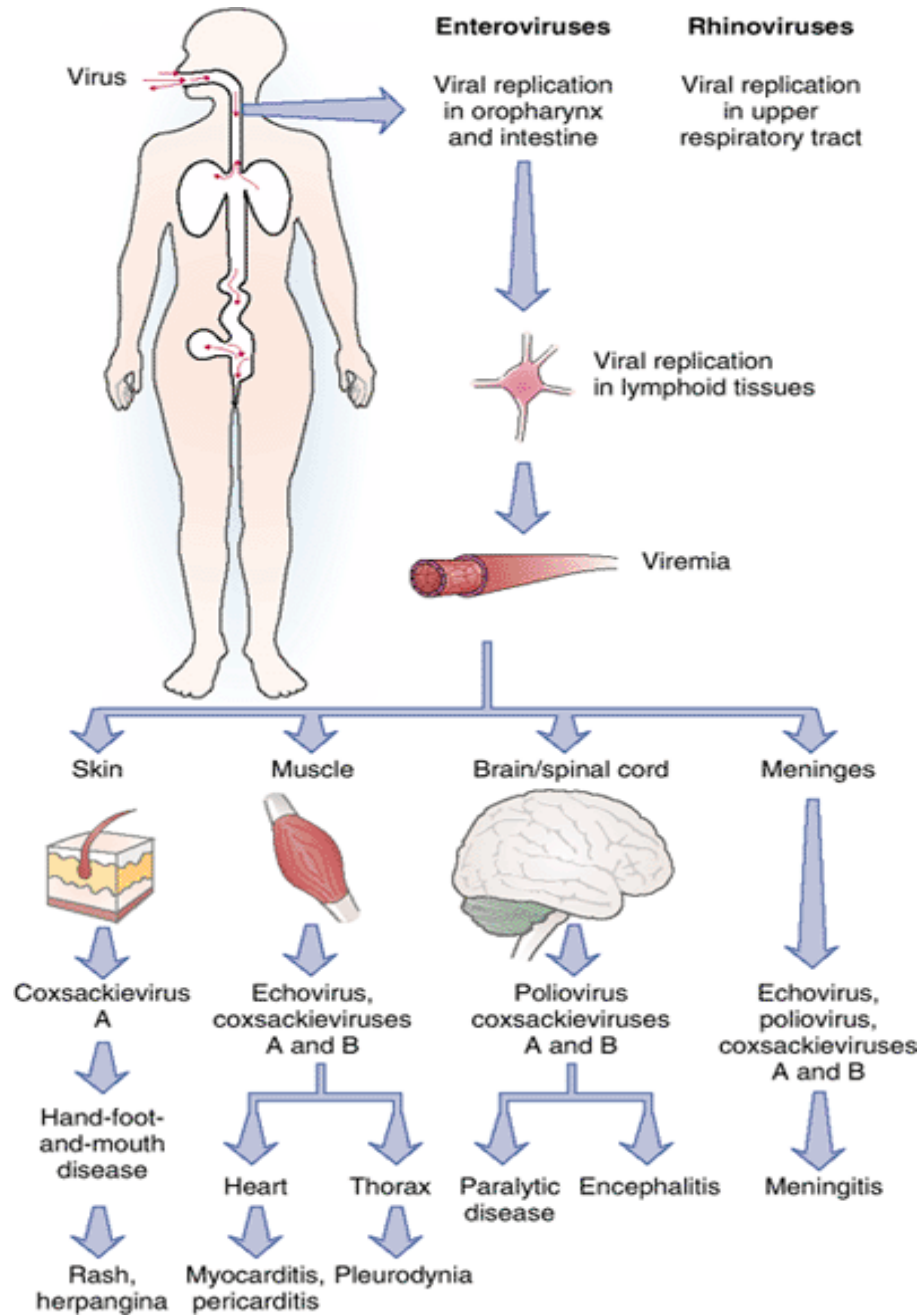


Fig. 32-2 Pathogenesis of Enterovirus Infection



From Engleberg, et. al., Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapter 43, published by Lippincott Williams & Wilkins, Philadelphia.

Table 32-1 Enterovirus Disease

Disease	Coxsackievirus						
	Poliovirus	Type A	Type B	Echovirus	Enterovirus 70	Enterovirus 71	Parechovirus
Asymptomatic infection	+	+	+	+	+	+	+
Paralytic disease	+	+	+	+	+	+	+
Encephalitis, meningitis	+	+	+	+	-	+	+
Myocarditis	-	+	+	+	-	-	-
Pleurodynia	-	-	+	-	-	-	-
Herpangina	-	+	-	-	-	-	-
Hand-foot-and-mouth disease	-	+	-	-	-	+	-
Acute hemorrhagic conjunctivitis	-	+	-	-	+	-	-
Respiratory tract disease	+	+	-	+	-	-	+
Gastrointestinal disease	-	-	-	+	-	-	+
Diabetes, pancreatitis	-	-	+	-	-	-	-
Orchitis	-	-	+	-	-	-	-

From Engleberg, et. al., Schaechter's
 Mechanisms of Microbial Disease, Fourth Edition,
 Chapter 43, published by Lippincott Williams &
 Wilkins, Philadelphia.

Neurologic

1. Meningitis (“aseptic meningitis”)

- a) many enteroviruses (are most common cause of meningitis)
- b) differential diagnosis with bacterial meningitis is very important

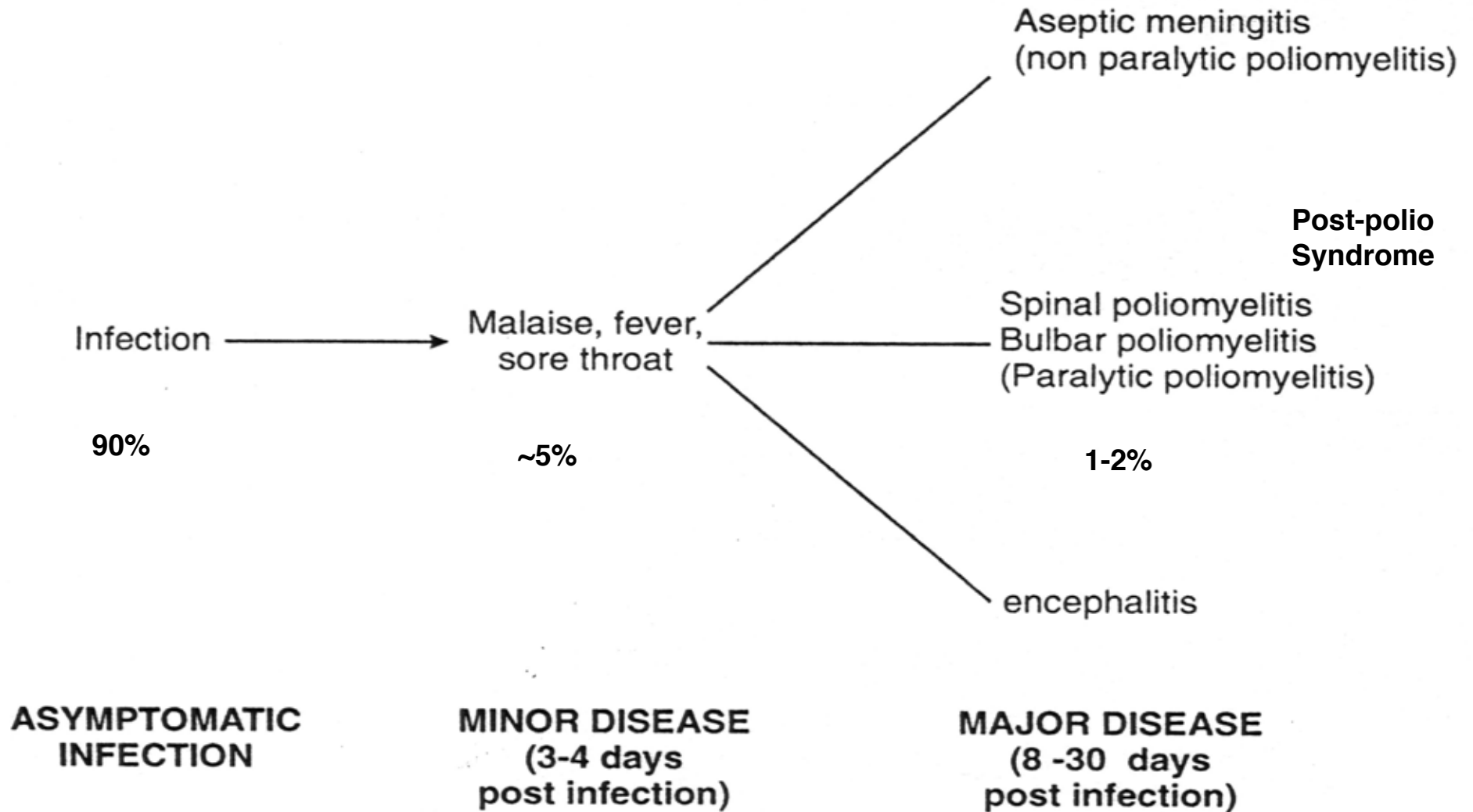
2. Paralysis

- a) Polioviruses 1, 2, 3
- b) Echoviruses
- c) Coxsackieviruses A and B

3. Chronic meningoencephalitis/ dermatomyositis

- a) Echoviruses

Idealized Scheme of the Course of Infection with Poliovirus



1. Paralytic poliomyelitis - 85%

- a. Infection anterior horn cells of spinal cord
- b. Asymmetric flaccid paralysis of one or more limbs, no sensory loss
- c. Outcome
 - i. 6 months - 2 yrs complete recovery
 - ii. residual paralysis
 - iii. death

2. Bulbar poliomyelitis - 15%

- a. medulla oblongata of brain affecting the muscles of the pharynx and respiration, need respirator
- b. 75% fatal

Cardiac and Muscular

1. **Myocarditis**

- a) Coxsackievirus B
- b) some coxsackievirus A and echoviruses

2. **Pleurodynia**

- a) Coxsackievirus B

Skin and Mucosae

1. Herpangina

a) Coxsackievirus A

2. Hand-foot-and-mouth disease

a) Coxsackievirus A16

Respiratory

1. **Colds**

- a) Rhinoviruses
- b) Coxsackieviruses A
- c) Echoviruses
- d) Coxsackievirus B

Ocular

1. **Acute hemorrhagic conjunctivitis**
 - a) Enterovirus 70
 - b) Coxsackievirus A24

Hepatitis

1. Hepatitis A virus
2. Hepatitis E virus

Gastroenteritis

1. Caliciviruses (Norwalk agent)
2. various enteroviruses

Treatment/Vaccines

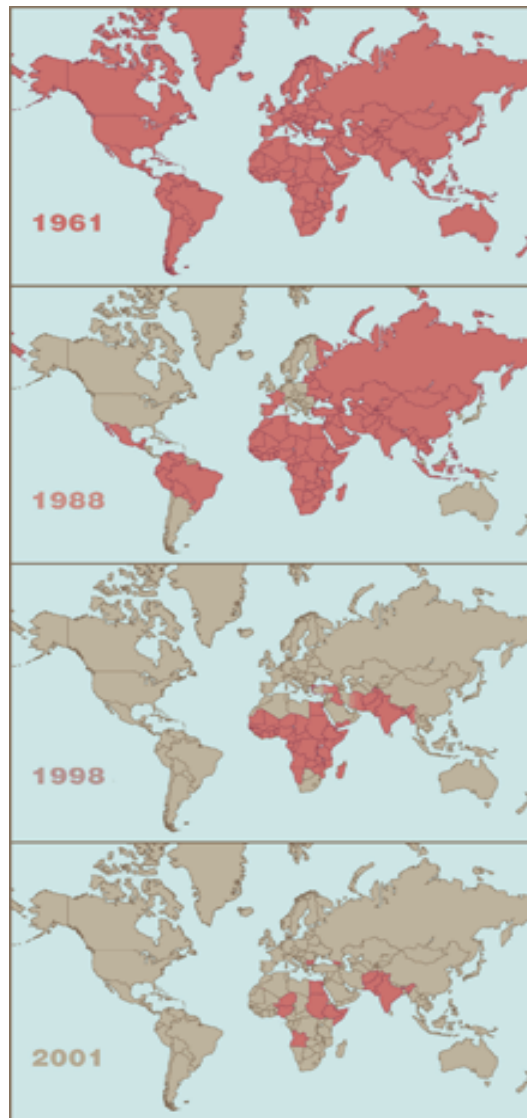
The polio vaccine represents an important milestone in vaccine technology

1. **Salk vaccine** – killed, inactivated (IPV and EIPV)
Since 2000 used exclusively in US
2. **Sabin vaccine** – live attenuated (oral -OPV)
No longer used in US
3. **World-wide eradication effort- OPV**

TABLE 57-2 Advantages and Disadvantages of Polio Vaccines

Vaccine	Advantages	Disadvantages
Live (oral polio vaccine)	Effective Lifelong immunity Induction of secretory antibody response similar to that of natural infection Spread of attenuated virus circulating to contacts promotes indirect immunization (herd immunity) Ease of administration No need for repeated booster vaccine	Risk of vaccine-associated poliomyelitis in vaccine recipients or contacts Spread of vaccine to contacts without their consent Not safe for administration to immunodeficient patients
Inactivated polio vaccine	Effective Good stability during transport and in storage Safe administration in immunodeficient patients No risk of vaccine-related disease	Lack of induction of secretory antibody Booster vaccine needed for lifelong immunity Injection more painful than oral administration Higher community immunization levels needed than with live vaccine

From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 57, published by Mosby Philadelphia,,



Worldwide elimination of wild poliovirus (1961–2001). Shown in red are countries with indigenous wild poliovirus in 1961, 1988, 1998, and 2001. Maps produced by the CDC after data from the World Health Organization.

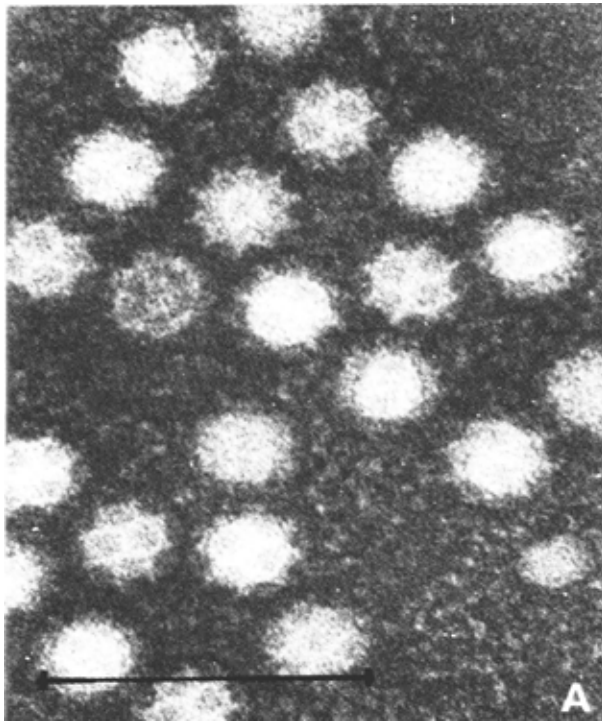
Caliciviridae

family includes several viruses that cause gastroenteritis

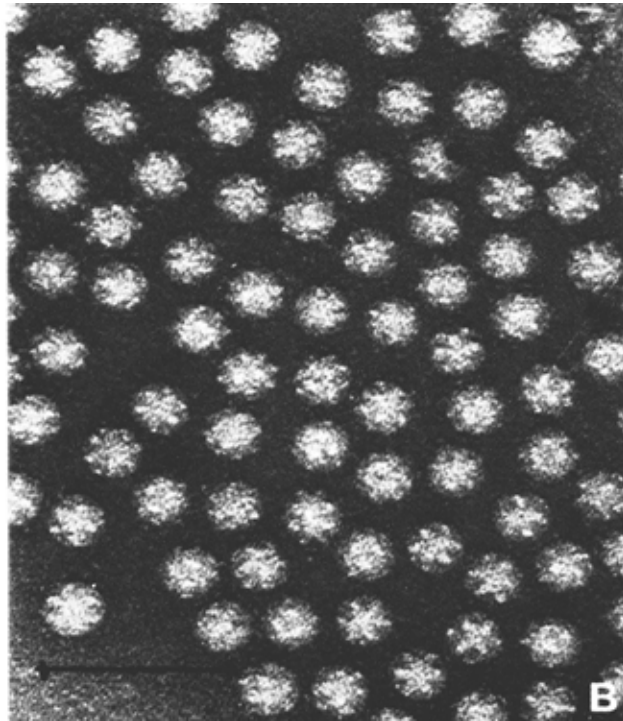
Norwalk virus

Negatively Stained Electron Micrographs of Noroviruses

Caliciviridae



Astroviridae



Enteroviruses

Structure

- Positive sense ssRNA genome, protein coat

Pathogenesis

- Fecal oral transmission
- replication in cytoplasm
- Viremia to diverse target tissues, viruses very cytopathic killing cells they infect
- Infections often asymptomatic; polio causes paralytic poliomyelitis; rhinoviruses restricted to upper respiratory tract, common cold; caliciviruses diarrhea

Diagnosis

- Serology and nucleic acid

Treatment/prevention

- Only polio vaccines, Salk and Sabin

TABLE 57-1. Summary of Clinical Syndromes Associated with Major Enterovirus Groups

Syndrome	Occurrence	Polioviruses	Coxsackie A Viruses	Coxsackie B Viruses	Echoviruses
Paralytic disease	Sporadic	+	+	+	+
Encephalitis, meningitis	Outbreaks	+	+	+	+
Carditis	Sporadic		+	+	+
Neonatal disease	Outbreaks			+	+
Pleurodynia	Outbreaks			+	
Herpangina	Common		+		
Hand-foot-and-mouth disease	Common		+		
Rash disease	Common		+	+	+
Acute hemorrhagic conjunctivitis	Epidemics		+		
Respiratory tract infections	Common	+	+	+	+
Undifferentiated fever	Common	+	+	+	+
Diarrhea, gastrointestinal disease	Uncommon				+
Diabetes, pancreatitis	Uncommon			+	
Orchitis	Uncommon			+	
Disease in immunodeficient patients	—	+	+		+
Congenital anomalies	Uncommon		+	+	