
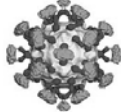


The GI Viruses

Enteroviruses, rotavirus and
caliciviruses



ENTEROVIRUSES

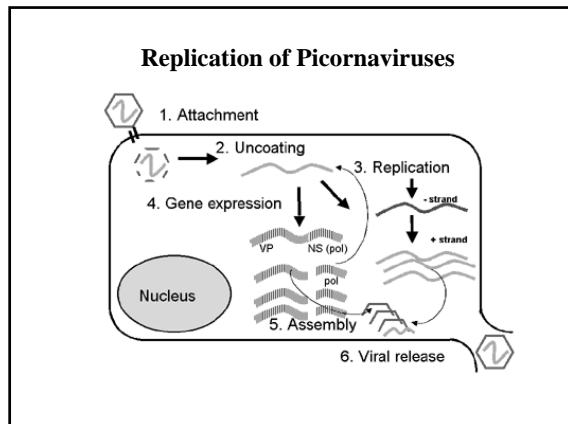


**Viruses that enter the body
through the GI tract**

- Molecular Biology**
- Belong to picornaviridae family
 - Aphthoviruses, enteroviruses, cardioviruses, rhinoviruses
 - 4 subgroups
 - Polioviruses, coxsackieviruses, echoviruses, newer enteroviruses
 - Non-enveloped, single-stranded, positive sense RNA viruses
 - Enter through the gastrointestinal tract

Case number 1

AK is a 22 year old bartender who presents to the ER in August with complaints of fever, chills, headache, and neck stiffness. He reports being well until a few days before admission when he noted the onset of fever, chills and general malaise. Over the past day his headache has become more prominent and his neck is now stiff. In the ER he is noted to have a temperature of 102°F, some pharyngeal erythema, and some mild neck stiffness. An LP is performed and shows a WBC count of 80 with 95% lymphocytes, normal protein and normal glucose. What's going on?



Epidemiology

- World-wide in distribution
- Non-polio enteroviruses have marked summer and fall seasonality in temperate zones
 - Spread person-person, by houseflies, wastewater and sewage
 - Fecal-oral spread facilitated by minimal clothing
- Humans only significant natural reservoir
- Physical exercise may impact manifestations of infection
 - Provocation polio
 - Myocarditis

Polioviruses

- Cause of poliomyelitis
- Humans only natural reservoir
- Predilection for the central nervous system
 - Extensive necrosis of neurons in gray matter
 - Affects primarily motor and autonomic neurons
 - Anterior horn of spinal cord
 - Motor nuclei of pons and medulla

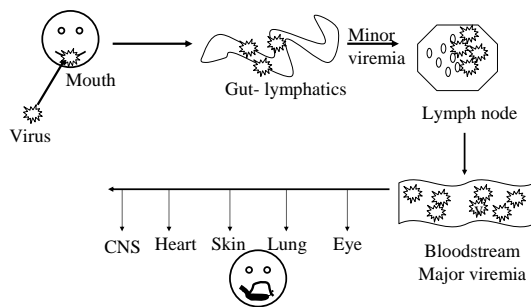
Fecal Oral Spread



Epidemiology

- In US prior to 1900 a usually subclinical disease of young infants
 - Milder disease than older children
 - Partial protection from maternal antibody
- Improved hygiene- older kids affected
 - Increased paralytic disease
 - Epidemic 1950s
- Vaccine 1955
 - 2002- Polio eradicated in western hemisphere and Europe

Pathogenesis



Clinical Features

- Range from inapparent illness to severe paralysis and death
- 95% of infections are asymptomatic
- *Abortive poliomyelitis*
 - Mild viral syndrome
 - Fever, headache, sore throat, listlessness
 - Normal neurologic exam
 - Lasts a few days
- *Nonparalytic poliomyelitis*
 - Like abortive polio but signs of meningeal irritation
 - Full recovery

- *Spinal paralytic poliomyelitis*

- 0.1% of cases
- Biphasic course
 - Minor illness- like abortive polio
 - Major illness- follows 2-5 days after recovery from minor illness
 - Abrupt illness- headache, fever, vomiting, neck stiffness, muscle pain for 1-2 days
 - Weakness and flaccid paralysis
 - Variable severity
 - Sensory loss rare



Diagnosis

- Viral isolation from throat- first week of illness
- Isolation from stool for several weeks
- Rarely isolated from CSF
- Paired serology

- *Bulbar Paralytic Poliomyelitis*

- Paralysis of muscles innervated by cranial nerves
- Dysphagia, nasal speech, dyspnea
- Cranial nerves 9 and 10 most commonly affected
- Can involve vasomotor and respiratory centers
 - Rapid pulse
 - Hypoxia
 - Circulatory collapse



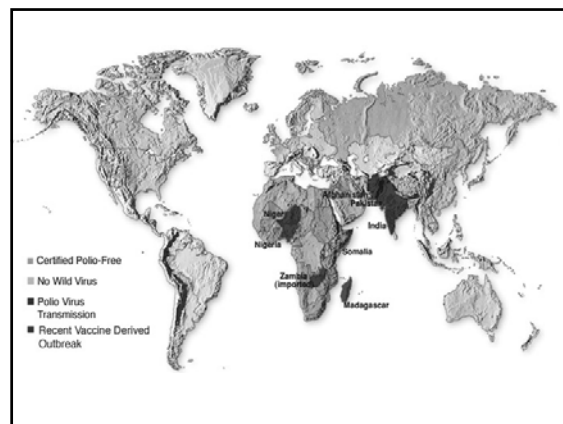
Prevention

- Two vaccine formulations
- Oral Polio vaccine (OPV)
 - Live attenuated vaccine
 - Given orally
 - Excreted in feces- allows spread of vaccine to unimmunized individuals- herd immunity
 - Very rare- paralytic disease
- Inactivated Polio vaccine (IPV)
 - Modified from original Salk vaccine
 - At least as immunogenic as OPV
 - Only vaccine used in US currently



- *Polioencephalitis*

- Uncommon
- Confusion and change in mental status
- Most common in infants
- Paralysis is spastic



Other Enteroviruses

Coxsackieviruses, echoviruses, and newer enteroviruses

- *Encephalitis*
 - Unusual manifestation of echovirus and coxsackievirus CNS infection
 - Accounts for 11-22% of viral encephalitis when you include polioviruses
 - Prognosis, except in infants, is excellent
- *Chronic meningoencephalitis*
 - Seen in patients with acquired or congenital defects in B cell function
 - Echoviruses can be recovered from CSF for months-years
 - Try to prevent with monthly IG

Clinical Manifestations

- Do not usually cause symptomatic infections of the gastrointestinal system
- Distributed worldwide
- More prevalent in summer and autumn in temperate climates (June-October)
- Most infections occur in children < 1 year

- *Paralytic Infections*
 - Occasionally associated with coxsackie and echovirus infections
 - Outbreaks of flaccid paralysis associated with coxsackievirus A7 and enterovirus 71
 - Usually less severe than poliomyelitis
 - Paresis not permanent

Central Nervous System

- *Aseptic meningitis*
 - Prodrome- fever, chills, malaise, URI
 - Headache, fever, stiff neck, photophobia
 - 90% of viral aseptic meningitis in the community due to group B coxsackieviruses and echoviruses
 - CSF: 10-500 WBC, lymphocytes, nl to slightly elevated protein, nl glucose
 - PCR of spinal fluid usually reveals cause
 - Therapy is supportive

Exanthems

- *Morbilliform rashes*
 - Fine, erythematous, maculopapular rashes
 - Common in summer months
 - Rash appears simultaneously with fever and starts on face
 - Associated with echovirus 9



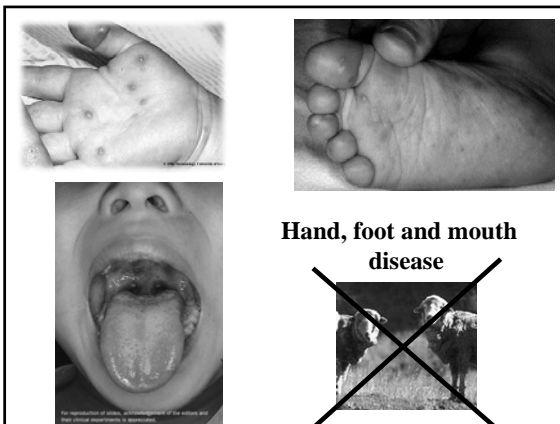
- *Roseoliform rashes*

- Discrete, nonpruritic, salmon-pink macules and papules on the face and upper chest
- Prodrome of fever and pharyngitis
- Rash appears after defervescence and lasts 1-5 days
- Contagious especially amongst young children
- Echovirus 16 most commonly associated



- *Generalized vesicular eruptions*

- Most frequently caused by coxsackievirus A9 and echovirus 11
- Lesions look like those of hand-foot-and-mouth but occur in crops on the head, trunk and extremities
- Do not evolve into pustules or scabs (unlike chickenpox)



- *Herpangina*

- Vesicular rash involving pharynx and soft palate
- Summer outbreaks of group A coxsackievirus
- Fever, vomiting, myalgia and headache associated with prodrome



- *Hand-foot-and-mouth disease*

- Distinctive vesicular eruption usually caused by coxsackie A16 or enterovirus 71
- Most common in children under age 10
- Fever and vesicles in the mouth and on the hands and feet
- Can look like chickenpox but illness is generally milder

Respiratory Disease

- *Upper respiratory infections*

- Fever with sore throat, cough and coryza
- Cause majority of summer colds in children
- Coxsackieviruses A21 and A24; echovirus 11

- *Epidemic pleurodynia*

- Acute disease with fever and sharp, spasmodic pain in chest/upper abdomen muscles
- Fever peaks one after onset of pain spasm
- Lasts 4-6 days usually but can persist for months

Myopericarditis

- Inflammation of the myocardium and pericardium
- Enteroviruses, especially group B coxsackieviruses, group A types 4 and 16 and echoviruses 9 and 22 account for 50% of all cases of acute myopericarditis
- Virus appears to replicate in the myofibers leading to myofiber necrosis and focal inflammation

Enterovirus infection of the newborn

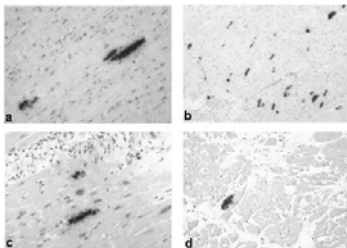
- Neonates are especially susceptible to severe enterovirus infection
- Most serious infections appear to occur perinatally and probably are acquired from the mother
- Lack of macrophage activity in the neonate is probably responsible for seriousness of infections

- Special predilection for physically active adolescents and young adults
- Males outnumber females 2:1
- Symptoms
 - URI in 70% followed by
 - Dyspnea
 - Chest pain- precordial, dull
 - Fever
 - Malaise
- EKGs usually abnormal, cardiac enzymes elevated
- Can lead to chronic congestive heart failure

• Clinical Manifestations

- Biphasic illness
- Mild non-specific symptoms between 3 and 7 days of life followed by 1-7 days of well-being
- Generalized disease follows
 - Myocarditis with encephalitis- group B coxsackieviruses
 - Fulminant hepatitis- hypotension, bleeding, multiple organ failure- echovirus 11
- Diagnosis by PCR of urine, feces, blood, CSF
- Treatment is supportive; pleconaril disappointing

Patterns of enterovirus infection in human heart disease



In situ detection of enteroviral RNA in the human heart muscle of patients with acute myocarditis (a,b), chronic myocarditis (c), and dilated cardiomyopathy (d).

Acute hemorrhagic conjunctivitis

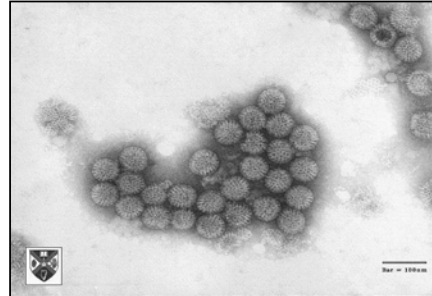
- Enterovirus 70 associated
- Epidemic outbreaks of eye pain, swelling and subconjunctival hemorrhage
- Highly contagious
- Usually bilateral
- Most cases resolve spontaneously



Case Number 1

- 22yo man with aseptic meningitis in August
- Differential diagnosis
 - Enteroviruses
 - Other viruses
 - Rickettsiae
 - Lyme disease
 - Non-infectious- especially NSAIDs
- PCR of spinal fluid positive for enterovirus

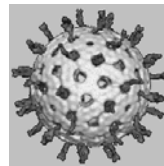
Electron micrograph of rotavirus particles



Case Number 2

- EM is an 8 month old girl who is brought into her pediatrician's office in early March because of fever, vomiting, and diarrhea. Her mother reported that she had begun to have fever and vomiting 2 days previously and started having profuse watery diarrhea that day. She was enrolled in a daycare program and her mother reported that several other children in her class were sick with similar symptoms. On exam the baby was lethargic and had a temperature of 103°F, an elevated pulse, and normal blood pressure. Her mucous membranes appeared dry and her skin turgor was reduced. In passing Mom notes that Dad's got a mild case of "the runs".

Viral Proteins



- Yellow- outer capsid
 - vp7
- Red spikes- hemagglutinin
 - vp4
- Blue and green- inner capsid and core
 - vp1, vp2, vp3, vp6
- Nonstructural proteins- NS53, NS34, NS35, NS28, NS26, NS12
 - NS26 acts as enterotoxin

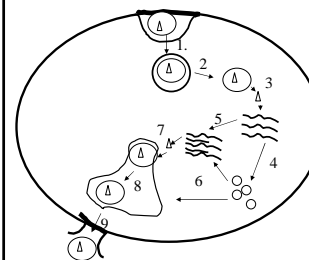
• Rotavirus

– Microbiology

- Reovirus family
 - Wheel-like appearance
 - Large, non-enveloped RNA viruses
 - Eleven segments of double stranded RNA
 - » Reassortment occurs
 - » Require RNA polymerase to make mRNA
- Seven antigenic groups named A-G
 - groups A-C cause disease in humans
 - group A viruses account for most human disease worldwide.



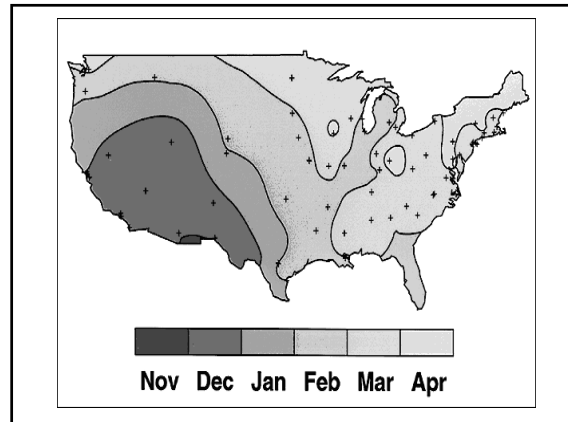
Rotavirus replication



1. Viral entry via phagosome
2. Release from phagosome
3. Uncoating, release of RNA, and transcription into mRNA
4. Production of viral proteins
5. Viral RNA synthesis
6. Movement of viral proteins
7. Movement of core to ER
8. Assembly of viral particle
9. Release of viral particle

- Pathogenesis

- Spread by fecal-oral route
- Virus enters and replicates in mature villus cells of the small intestine
- Infection kills cells and loss of absorptive area ensues
 - Lactose intolerance common following infection
 - Enterotoxin may also contribute to diarrhea
- Highly infectious and hardy
 - 1 pfu can cause disease
 - Not killed by many disinfectants



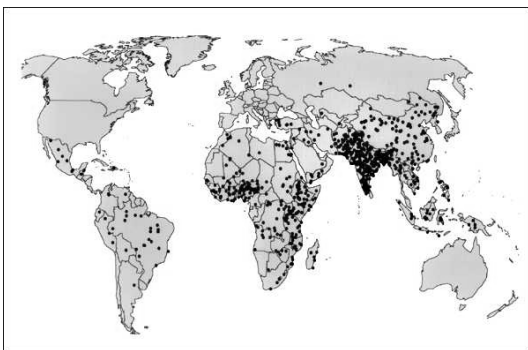
- Epidemiology

- Worldwide distribution
- Most common cause of diarrhea requiring hospitalization in the world
 - Account for 10-20% of diarrhea-related deaths in children
 - Up to 120,000 hospitalizations in US/year
- Seasonal in temperate climates
 - Occur in winter months in North America
 - Outbreaks start in the south west and move up to the north east by spring
- Everyone infected by age 3

- Clinical Features

- Range from asymptomatic to severe diarrhea
 - First infection more severe than subsequent
 - Maximal disease incidence in infants 6-24 mos
 - Up to 30% of adult cases are symptomatic
- Symptoms include
 - Fever
 - Nausea/vomiting
 - Watery diarrhea without blood/mucous
- Dehydration/electrolyte imbalance lead to hospitalization and death

Estimated global distribution of the 800,000 annual deaths caused by rotavirus diarrhea



- Diagnosis

- Clinical- febrile infant with diarrhea in the winter
- ELISA- detect rotavirus antigen in stool sample
- PCR
- Electron microscopy
- Serology- epidemiological tool

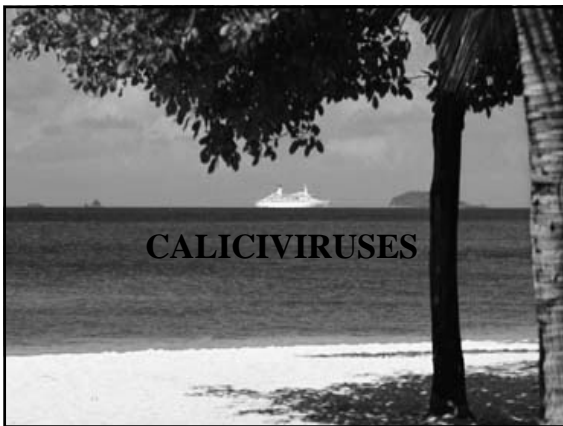
- Treatment

- Replace fluids and electrolytes (oral or IV)
- Early feeding- promote enterocyte regeneration
- Do NOT give antidiarrheal agents

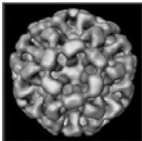
- Prevention
 - Wash your hands
 - Chlorine containing disinfectants
 - Vaccine
 - Rotashield®
 - Live, oral vaccine
 - Rhesus-human recombinant
 - 15 cases of intussusception in first 10 months after licensure led to withdrawal

Molecular Biology and Pathogenesis

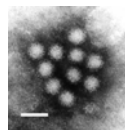
- Non-enveloped, single stranded, positive sense RNA viruses
- RNA encodes 4 proteins
 - Helicase- unwinds double helical regions in RNA during replication
 - Protease- cleaves single polypeptide into proteins
 - RNA polymerase- replicates RNA
 - Capsid- covers RNA genome



- Spread through oral-fecal route
- Survive stomach acid and move to jejunum
- Blunting of villi in jejunum seen on pathologic specimens
- Diarrhea associated with transient malabsorption and decreased enzyme activity
- Viral shedding highest in first 24-48 hours of illness



Caliciviruses



Epidemiology

- Widespread and common throughout the world
- Fecal-oral spread
- Incredibly hardy
 - Survives routine chlorination
 - Difficult to eradicate
 - Can persist for weeks

- Secondary and tertiary cases common
- No seasonal variation
- Affects all age groups
- Important causes of outbreaks of gastroenteritis
- Incubation period 24-48 hours followed by abrupt onset of vomiting and diarrhea with fever
- Lasts 24-72 hours

“The happiest place on earth...”



- Diagnosis clinical and epidemiologic
- Can't grow in tissue culture
- EM of stool
- Treatment is supportive- may require IV hydration

Case Number 2

- 8 month old baby with vomiting, diarrhea, fever
- Epidemiology clues
 - Winter
 - Daycare
 - Dad with mild illness
- Differential diagnosis
 - Rotavirus
 - Caliciviruses
 - Salmonella
 - Giardia
 - Shigella
 - Campylobacter
 - C. diff