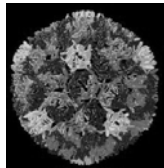
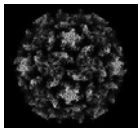
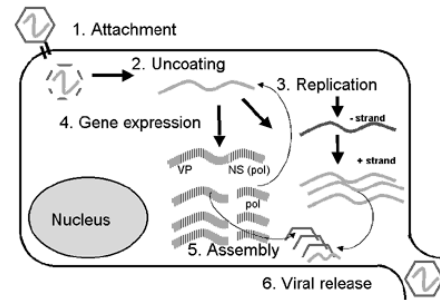


## The GI Viruses

Enteroviruses, rotavirus and caliciviruses

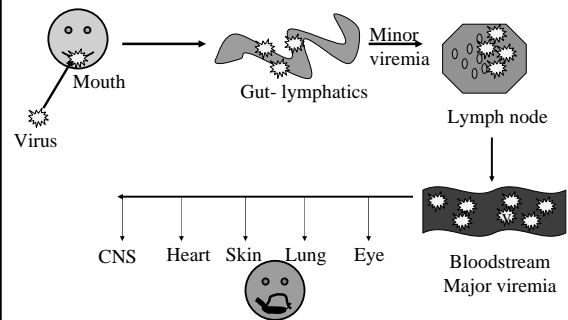
### Replication of Picornaviruses



### ENTEROVIRUSES



### Pathogenesis

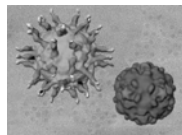


### Molecular Biology

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



### POLIO



## 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

### • *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



## 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

### • *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



## Clinical Features

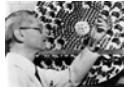
- Range from inapparent illness to severe paralysis and death
- 95% of infections are asymptomatic
- *Abortive poliomyelitis*
  - Mild viral syndrome
  - Fever, headache, sore throat, listlessness
  - Normal neurologic exam
  - Lasts a few days
- *Nonparalytic poliomyelitis*
  - Like abortive polio but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

## Diagnosis

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

## Prevention

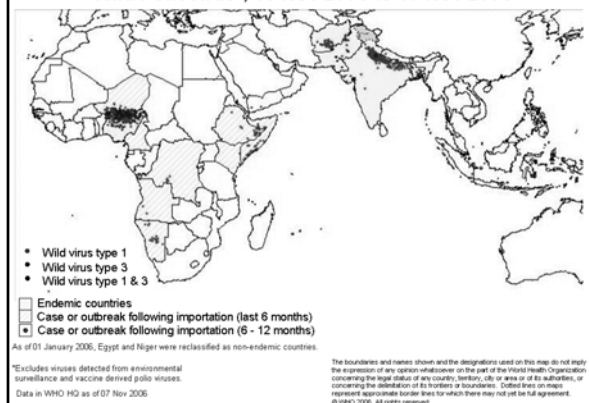
- Two vaccine formulations
- Oral Polio vaccine (OPV)
  - Live attenuated vaccine
  - Given orally
  - Excreted in feces- allows spread of vaccine to unimmunized individuals- herd immunity
  - Very rare- paralytic disease
- Inactivated Polio vaccine (IPV)
  - Modified from original Salk vaccine
  - At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



## 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

Wild Poliovirus\*, 08 Nov 2005 to 07 Nov 2006



## 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

## 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

- *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

- *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

## Exanthems

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



**Hand, foot and mouth disease**

- *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

## Herpangina

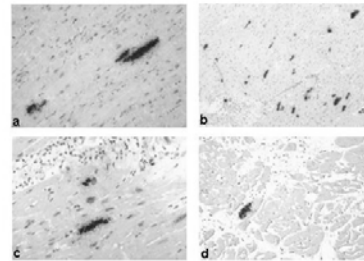


- Special predilection for physically active adolescents and young adults
- Males outnumber females 2:1
- Symptoms
  - URI in 70% followed by
  - Dyspnea
  - Chest pain- precordial, dull
  - Fever
  - Malaise
- EKGs usually abnormal, cardiac enzymes elevated
- Can lead to chronic congestive heart failure

## 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 (Bornholm disease, Sylvest's disease, devil's grip, and epidemic benign dry pleurisy)*
  - Acute disease with fever and sharp, spasmodic pain in chest/upper abdomen muscles
  - Fever peaks one day after onset of pain spasm
  - Lasts 4-6 days usually but can persist for months

## 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).

## 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

- 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

- 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
- Antigenic groups G1-G4 cause 80% of group G infections worldwide
- Antigenic group P1 causes >75% of P group infections worldwide

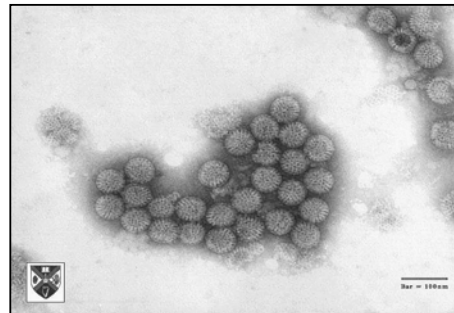


## Acute hemorrhagic conjunctivitis

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

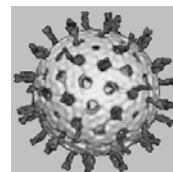


Electron micrograph of rotavirus particles

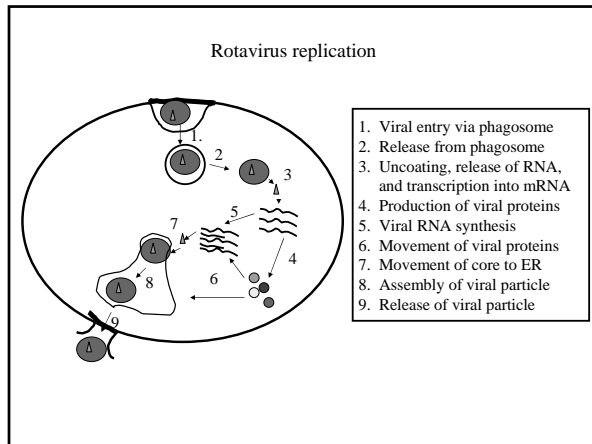


## Rotaviruses

### 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



- **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

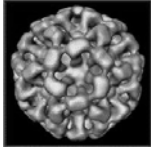
- **Pathogenesis**
  - Spread by fecal-oral route
  - Virus enters and replicates in mature villus cells of the small intestine
  - Infection kills cells and loss of absorptive area ensues
    - Lactose intolerance common following infection
    - Enterotoxin may also contribute to diarrhea
  - Highly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

- **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

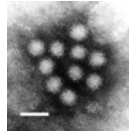
- **Epidemiology**
  - Worldwide distribution
  - Most common cause of diarrhea requiring hospitalization in the world
    - Account for 10-20% of diarrhea-related deaths in children
    - Up to 120,000 hospitalizations in US/year
  - Seasonal in temperate climates
    - Occur in winter months in North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

- **Prevention**
  - Wash your hands
  - Chlorine containing disinfectants
  - Vaccine
    - Rotashield®
      - 15 cases of intussusception in first 10 months after licensure led to withdrawal
    - RotaTeq®
      - Approved 2006
      - Human-bovine reassortment
      - Pentavalent
        - Strains G1-4 and P1





## Noroviruses



- 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

In 2002, there were 25 reported outbreaks, with 2,648 passengers becoming ill from the virus.



## Epidemiology

- Widespread and common throughout the world
- Highly contagious
- Spread through oral-fecal route
  - Person to person (aerosolized vomit)
  - Fecally contaminated food or water
  - Environmental and fomite contamination
- Contaminated water is usual source of outbreaks
  - Seafood a problem (contact with contaminated water)
  - Swimming pools and lakes
  - Can survive heat inactivation (cooking)

## 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

## Clinical manifestations

- Important causes of outbreaks
- Short lived illness (2-3 days duration)
- Vomiting a predominant symptom
- Incubation period 24-48 hours
- High secondary attack rates
- Both vomiting and diarrhea occur
- Myalgia, malaise and fever common

## Immunity

- Likely strain specific
- Lasts only a few months
- People with blood group O most susceptible
- B and AB partially protective

## Treatment

- Supportive only
- May require IV hydration in severe cases
- All resolve without sequelae

## Diagnosis

- Realtime RT-PCR available at most state health departments
- Can test stool or vomitus and environmental swabs
- Electron microscopy
- ELISA



## Gastroenteritis Is it viral or bacterial?

- Mean illness duration of 12-60 hours
- Median incubation period of 24-48 hours
- More than 50% of people vomiting
- No bacterial agents found