VIRAL AGENTS CAUSING GASTROENTERITIS

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Pathogens discussed in our lectures

1. **Rotavirus**
2. **Enteric adenoviruses**
3. **Caliciviruses**
4. **Astroviruses**
5. **Toroviruses**

Viruses as a causative organism of diarrheal disease

Detection of a specific virus in the stool of symptomatic pts is not sufficient to establish the role of the virus in causing disease. These criteria need to be fulfilled:

1. Virus is detected in ill pts significantly more than asymptomatic controls and virus shedding correlate with symptoms
2. Significant humoral or secretory antibody response or both in pts shedding the disease.
3. Reproduce the disease by experimental inoculation of nonimmune human or animal hosts
4. Exclude other causes of diarrhea such as bacteria, bacterial toxins and protozoa.

Feature	Rotavirus	Calicivirus	Astrovirus	Adenovirus	Torovirus
Nucleic acid	DS RNA	SS RNA	SS RNA	DS DNA	SS RNA
Shape	Naked, Double shelled capsid	Naked, round	Naked, star shaped	Naked, icosahedral	Enveloped, donut shaped
Replication in CC	Usually incomplete	None	None	None or incomplete	None
Serotypes	5	>4	8	unknown	unknown
Site of infection	Duodenum, jejunum	Jejunum	Small intestine	Small intestine	Small intestine
Immunity	Local IgA	unknown	unknown	unknown	unknown
Seasonality	winter	Not known	Not known	Not known	Not known
Ages primarily affected	Infants, < 2 yrs	Older children, adults	Infants, children	Infants, children	Infants, children
Transmission	Fecal-oral	Fecal-oral	Fecal-oral	Fecal-oral	Fecal-oral
IP (days)	1-3	0.5-2	1-2	8-10	----------
Dx	EIA, EM	IEM, PCR	EM, PCR	EIA, EM	EM, ELISA

ROTAVIRUS

Family *Reoviridae*

Genus *Rotavirus*

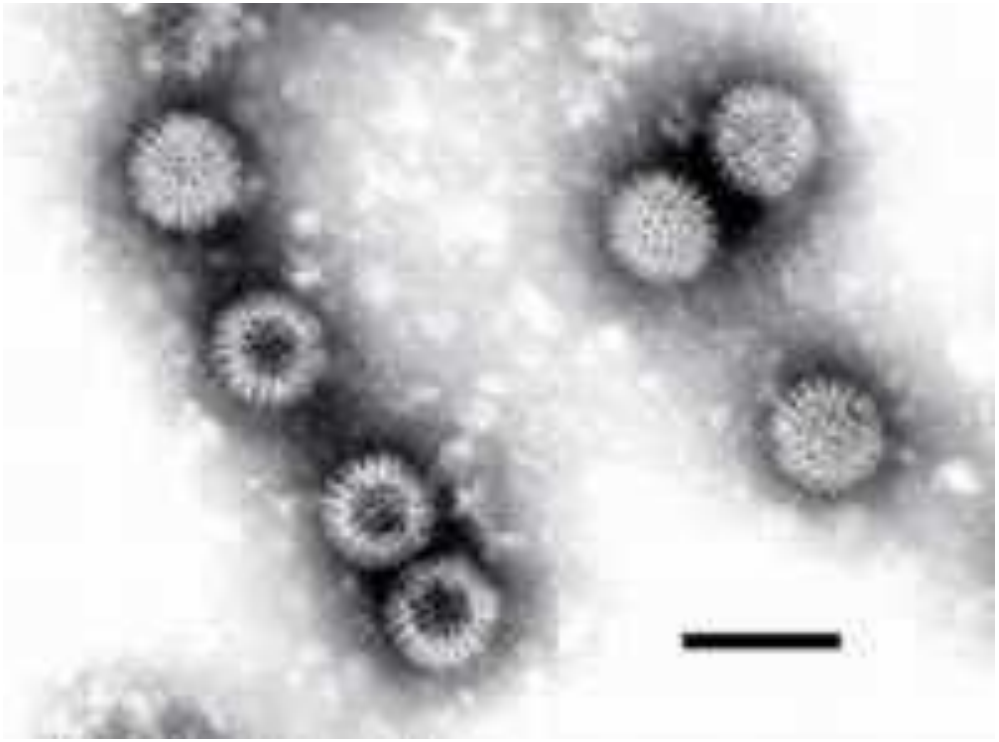
Other genera *Orthreovirus,*

Coltivirus, orbivirus (sheep)

ROTAVIRUS- discovery

- First isolated in 1973 in Australia by Ruth Bishop at the Royal Children's Hospital in Melbourne.
- EM identification from duodenal biopsies from children with diarrhea.
- "Virus particles in epithelial cells of duodenal mucosa from children with acute non-bacterial gastroenteritis," *Lancet*, 1:1281-3, 1973.
- Described in stool samples from children by Albert Z. Kapikian, in the US
- Human and animal strains are recognized

ROTAVIRUS EM STRUCTURE

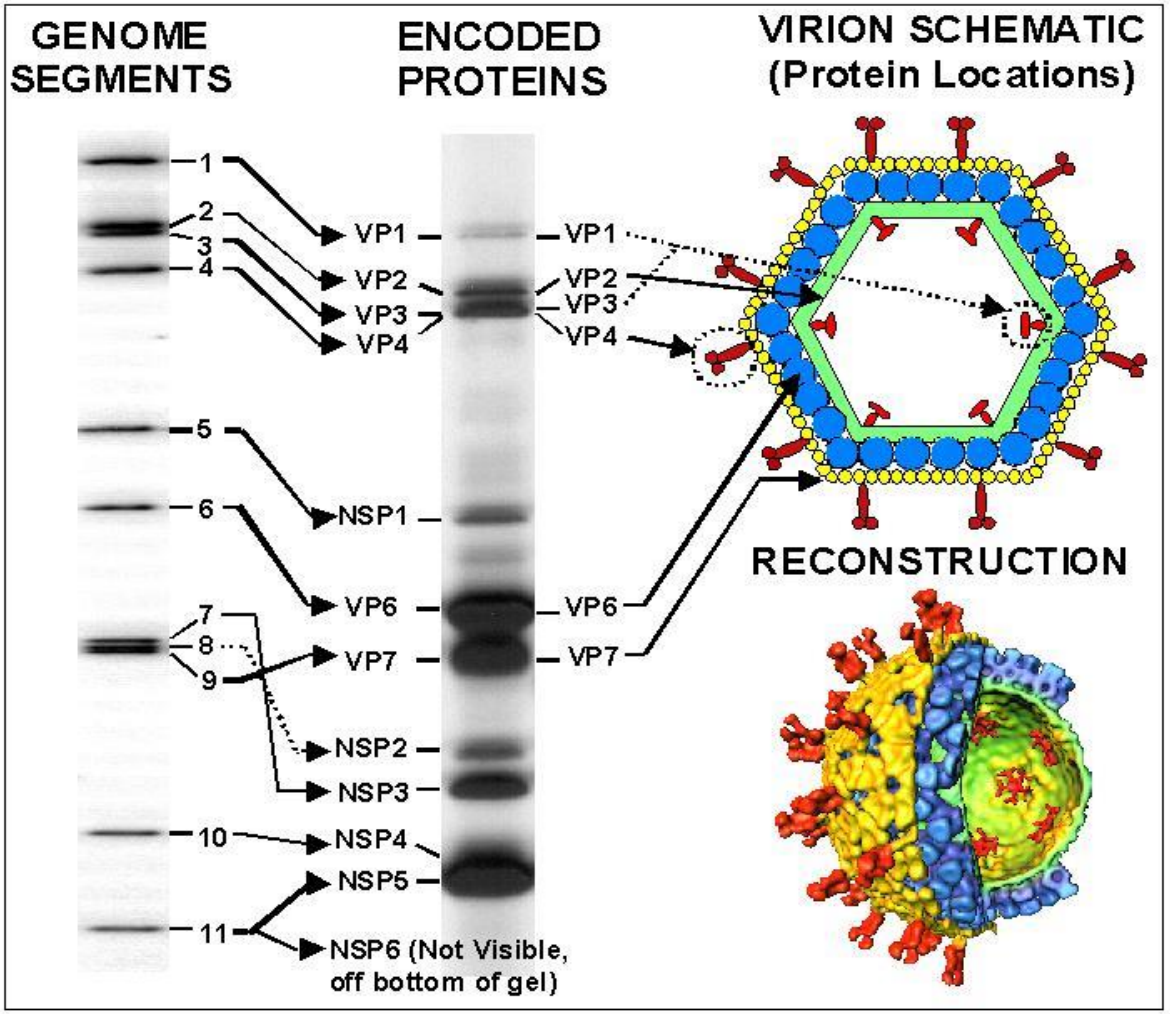


STRUCTURAL FEATURES OF ROTAVIRUS

- 65-75nm in size
- Non-enveloped virus (naked)
- EM appearance of a wheel with radiating spikes
- Icosahedral symmetry
- Double capsid (outer and inner capsid)
- Double stranded (*ds*) RNA in 11 segments
- Core with genome
- Capsid is cleaved by trypsin to form ***ISVP***

  [intermediate/infective sub-viral particle]

Rotavirus structure



VIRAL STRUCTURAL PROTEINS (VP)

- Outer structural proteins - VP7 and VP4

  VP7 - Glycoprotein

  VP4 - protease-cleaved, P protein, viral hemagglutinin; forms spikes from the surface

- Inner core structural proteins VP 1, 2, 3, 6
- VP6 is an important antigenic determinant

CLASSIFICATION- Groups

- 7 Groups (A through G) and 2 subgroups (I and II) based on VP6 differences
- Group A is the most common
- Group B (outbreaks in China)
- Group C (worldwide)

CLASSIFICATION - Serotypes

- Serotypes based on viral capsid proteins inducing neutralizing Ab
- 14 G serotypes based on G protein (VP 7) differences
  - 5 predominant strains in U.S. (G1-G4, G9) account for 90% of isolates
  - Strain G1 accounts for 73% of infections
- 20 P serotypes based on P protein (VP4) with P4/P8 predominance
- Common PG combinations are: P8G1, P8G2, P4G2, P8G4

ROTAVIRUS- PROPERTIES

- Virus is stable in the environment (months)
- Relatively resistant to handwashing agents
- Susceptible to disinfection with 95% ethanol, Lysol, formalin

PATHOGENESIS

- Targeted host cells - mature enterocytes lining the tips of intestinal villi
- Intermediate/infective sub-viral particle (ISVP) produced through proteolysis
- Enter host cell by endocytosis
- Virus replicates in the host cell cytoplasm

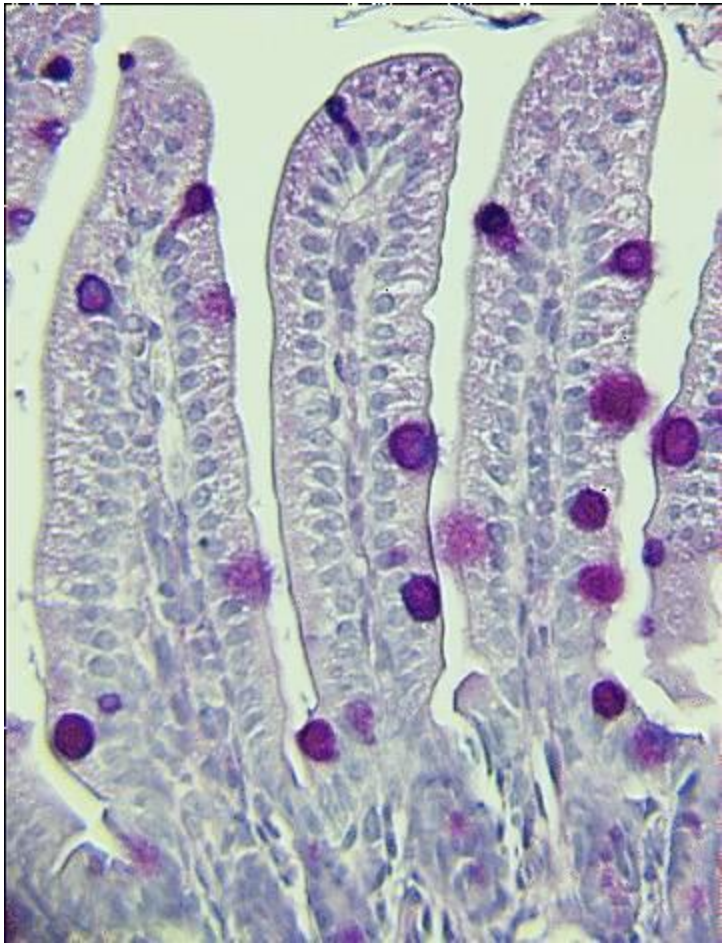
REPLICATION

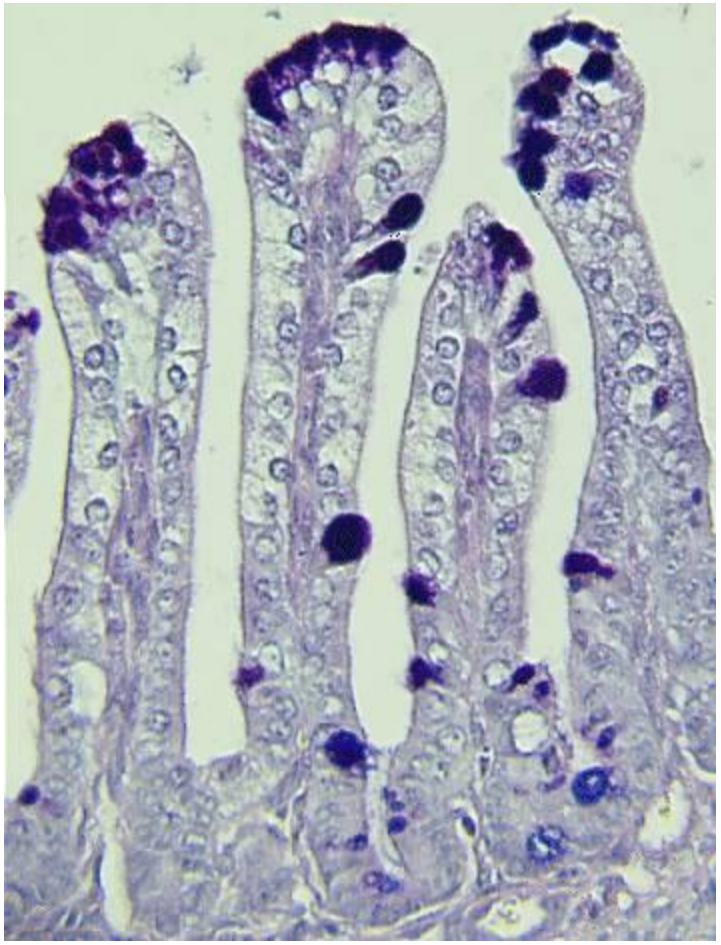
- mRNA transcription with viral RNA polymerase
- Capsid proteins formed, assembled into immature capsid
- RNA replicated to form double stranded RNA genome

HISTOPATHOLOGY

- Mature enterocytes lining the tips of intestinal villi are affected
- Villous atrophy and blunting
- Death of the mature enterocytes
- Infiltration of lamina propria with mononuclear cells
- Repopulation of the villous tips with immature secretory cells [*crypt hyperplasia*]

HISTOPATHOLOGY



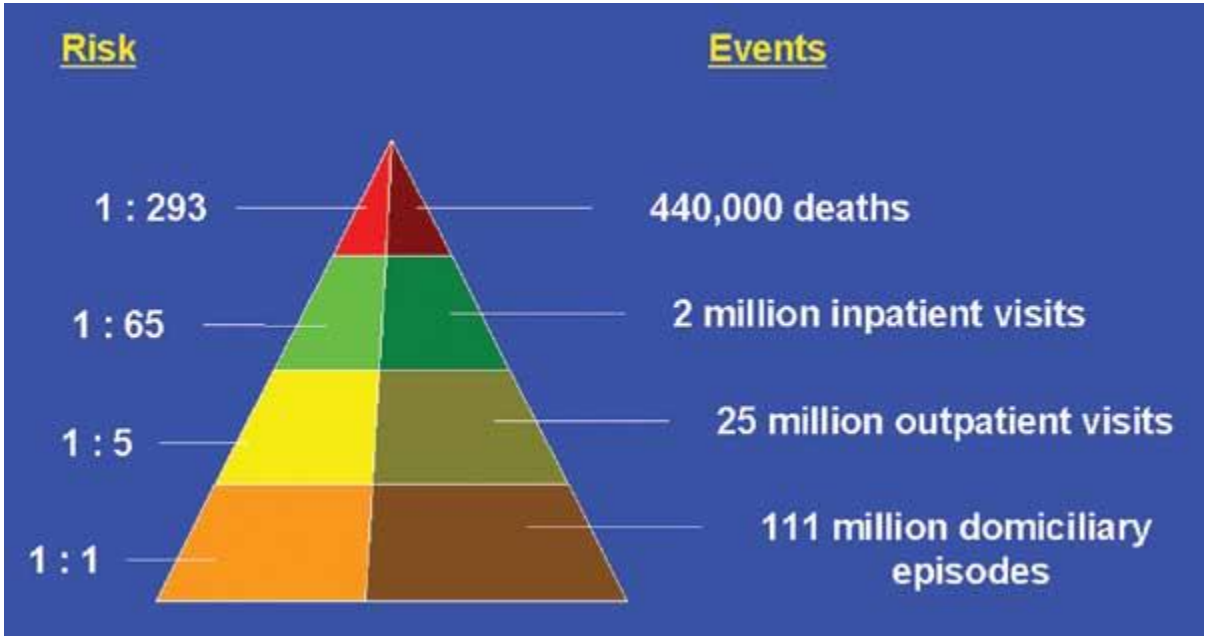


EPIDEMIOLOGY

- A major cause of diarrhea-associated hospitalizations and deaths
- Sero-prevalence studies show that antibody is present in most (90%) by age 4y

ROTAVIRAL DISEASE BURDEN

Worldwide



EPIDEMIOLOGY

- Age- children 4mo - 2 years are most affected
  Protection of younger infants through through transplacental antibody transfer
- Asymptomatic infections are common, especially in adults
- Nosocomial infections
- Outbreaks
- Severe Disease young, immunocompromised
- Seasonality Winter months
- Incubation period - thought to be <4 days

TRANSMISSION

- Mainly person to person via fecal-oral route
- Food and water-borne spread is possible
- Fomites
- Spread via respiratory route is speculated

EPIDEMIOLOGY - spread

- Contagious from before onset of diarrhea to a few days after end of diarrhea
- Large amounts of viral particles are shed in diarrheal stools
- Infective dose 10-100 pfu

Rotavirus Immunity

- Type specific humoral antibody (VP7 and VP4) are partially protective (last for years)
- Type specific secretory (IgA) antibodies are produced in the GIT
- First infection usually does not lead to permanent immunity
- Reinfection can occur at any age
- Subsequent infections generally less severe
- Breast feeding protect against rotavirus disease:
  - Colostrum and breast milk IgA antibodies
  - Breast milk mucin glycoproteins: bind rotavirus and inhibit their replication

CLINICAL FEATURES

- Incubation period - thought to be <4 days
- Fever- can be high grade (>39°C in 30%)
- Vomiting (1-3 days), nausea precede diarrhea
- Diarrhea
  - usually watery (no blood or leukocytes)
  - lasts 3-9 days
  - longer in malnourished and immune deficient individuals.
  - NEC and hemorrhagic GE seen in neonates
- *Dehydration* is the main contributor to mortality
- *Secondary malabsorption* of lactose and fat, and chronic diarrhea are possible

MECHANISM OF DIARRHEA

- Rotavirus localize to duodenum and proximal jejunum leading to:
  - destruction of villous epithelial cells
  - blunting of the villi
  - Infiltration of the villi with inflammatory cells
- Watery diarrhea due to net secretion of intestinal fluid and loss of absorptive surface (recover in 3-8 weeks)
- Activation of the enteric nervous system
- Role of NSP4 peptide regions as an enterotoxin

DIAGNOSIS

- Antigen detection in stool

  ELISA
- EM- non-Group A viruses also
- Culture- Group A rotaviruses can be cultured in monkey kidney cells
- Serology for epidemiologic studies

TREATMENT AND PREVENTION

- Treatment

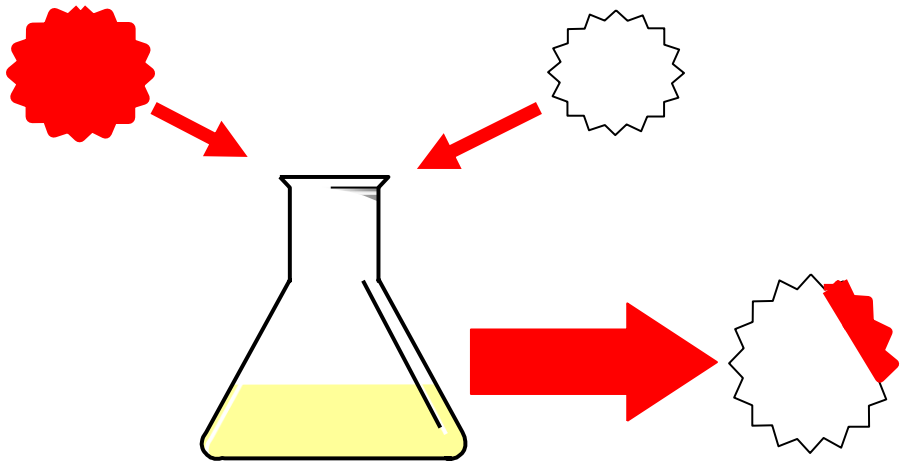
  Supportive- oral, IV rehydration

- Prevention

  Hand hygiene and disinfection of surfaces

- **Vaccine**

Rotavirus Vaccine (Rota)



- **Created by genetic reassortment**
  - **Causes nonhuman rotavirus strains to express human rotavirus antigens on their surface**
  - **Nonhuman rotaviruses have low pathogenicity for humans**
  - **Replicate but do not cause disease**

RotaTeq® (Merck)

- Live oral vaccine licensed 2006 in US
- Contains 5 reassortants (WC3 bovine strain with viral surface proteins of human serotypes G1-4 and P1A)
- Contains no preservatives or thimerosal
- 3-dose schedule – age 2,4,6 month
- Minimum age of first doses is 6 weeks
- First dose should be administered between 6 and 12 weeks of age (until age 13 weeks)
- Do not initiate series after 12 weeks of age