Gastrointestinal Viruses:
Rotavirus and the Enteroviruses

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Gastrointestinal Viruses

- Viral diarrheal illness
  - tremendous cause of morbidity/mortality worldwide
  - rotavirus, calicivirus (norovirus), astrovirus, adenovirus 40/41

- Viruses that replicate in the gastrointestinal tract but generally don’t cause diarrhea

- One from each category:
  - Rotavirus – most important cause of childhood diarrhea worldwide
  - Enteroviruses – replicate in GI tract, cause a wide spectrum of disease
Childhood diarrheal disease
Poverty

• Ubiquitous viral diarrheal illness – essentially all children infected by age 5

• Most common cause of viral gastroenteritis in childhood

• High mortality rates in developing world (>600,000 global deaths/yr)
  ~5% of all-cause mortality in under 5 year-olds
  death is due to dehydration – not overwhelming viral replication

• In U.S., tremendous numbers of hospital admissions, doctor visits
  1 in 72 children hospitalized, 1 in 19 seen by physician

• Seasonality – peak in winter – later as you move East in U.S.
Rotavirus: pathogenesis

- Member of Reoviridae
  - Large, non-enveloped dsRNA virus (rota = wheel)
  - 11 segments of dsRNA
    - Structural proteins (VP1-VP4, VP6, VP7)
    - Non-structural (NS) proteins
    - Reassortment can occur
    - RNA-dependent RNA polymerase used in replication

- Classified by group (A-F, based on VP6 protein)
  - Only A, B, C cause disease in humans
  - Group A also classified by serotype (based on VP7 (G) and VP4 (P) proteins)
    - Specific groups/serotypes important for vaccine design
    - G1-G4, P1 most common
Rotavirus: pathogenesis

Rotavirus: clinical syndrome

- Fecal-oral spread – highly infectious (1 pfu = disease), survives on fomites
- Enters and replicates in mature villus cells of duodenum/jejunum
- Fever, nausea/vomiting following 1-3 day incubation period lasts 2-4 days
- Diarrhea – watery, generally not bloody; lasts 5-8 days
  - loss of brush-border enzymes
  - enterotoxin-mediated epithelial cell lysis
  - activation of enteric nervous system
- Dehydration, electrolyte abnormalities, transient hepatitis
- Extraintestinal complications occur exceedingly rarely, if ever
- Asymptomatic cases may occur, especially in adults
Rotavirus: treatment

- Rehydration (oral or IV) may be life-saving
- Early reintroduction of feeding promotes enterocyte renewal
  avoid foods/drinks high in simple sugars due to osmotic load
- Probiotic therapies – unproven
- No benefit of antimotility agents

Rotavirus: diagnosis

- Clinical diagnosis
- ELISA detection of rotavirus antigen in whole stool
  widely used in hospital, office settings (>90% sensitive, specific)
- PCR – gold standard for sensitivity, specificity but not widely available
- Stool electron microscopy – not used clinically
- Serology – epidemiological tool
- Pyrosequencing – pathogen discovery
Rotavirus: prevention

- Breastfeeding infants provides some IgA-mediated protection
- Handwashing, cleaning of fomites, keep symptomatic kids home
- Contact isolation in hospital
- Vaccination (oral, live attenuated vaccines)
  - 2 currently licensed vaccines for children at 2, 4, 6 months of age
    RotaTeq, pentavalent bovine reassortant
    RotaRix, monovalent human
  - Prior U.S. vaccine (RotaShield) removed from market based on possible increase in cases of intussusception – was effective, unclear if risk was real.

Enteroviruses

- Members of Picornaviridae
- 4 subgroups (polioviruses, coxsackieviruses, echoviruses, enteroviruses)
- More than 70 subtypes
- Non-enveloped viruses with positive-sense ssRNA genomes
  - capsids: icosahedral symmetry, 60 copies of each of 4 proteins (VP1-4)
- Acid-stable, enter through GI tract, fecal-oral transmission
- Replication in oropharynx, intestine, submucosal lymphoid tissues, regional lymph nodes
- Viremic stage
- Cause a wide variety of clinical syndromes
Enteroviruses

- Non-enveloped viruses with positive-sense ssRNA genomes
capsids: icosahedral symmetry, 60 copies of each of 4 proteins (VP1-4)
Poliovirus

- Cause of poliomyelitis, three serotypes
- Human-specific
- Fecal-oral spread, environmental reservoir
- Predilection for spread to CNS following viremia
  - replicates within neurons: especially anterior horn cells of spinal cord
  - necrosis of neurons
  - both motor and autonomic

<table>
<thead>
<tr>
<th>Site of Virus Replication</th>
<th>Time (Days)</th>
<th>Clinical Illness</th>
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</thead>
<tbody>
<tr>
<td>Pharynx and intestine</td>
<td>0–1</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Regional lymph nodes</td>
<td>1–3</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Blood (minor viremia), muscle, fat, liver, spleen, bone marrow</td>
<td>3–7</td>
<td>Minor illness</td>
</tr>
<tr>
<td>Blood (major viremia), central nervous system</td>
<td>7–21</td>
<td>Major illness</td>
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</tbody>
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Polio: clinical features

• Incubation period = 6-20 days

• Diagnosis: viral isolation from throat (early) or stool (3-6 weeks); serology

• May range from clinically inapparent illness (~90% of infections) to paralytic polio

• Abortive poliomyelitis (~8% of cases)
  • Mild viral syndrome
  • Fever, headache, sore throat
  • No neurological sequelae

• Nonparalytic poliomyelitis (1-2% of cases)
  • As above but with signs of meningeal infection
  • Severe headache, neck stiffness (“aseptic meningitis”)
  • Full recovery after 2-10 days

Polio: clinical features

• Spinal paralytic poliomyelitis (<1% of cases)
  • biphasic illness
    • first phase mimics abortive polio
    • followed 2-5 days later by headache, fever, vomiting, myalgia
  • weakness and flaccid paralysis
  • asymmetric paralysis: generally lower limbs, proximal muscles
  • can involve respiratory muscles
  • recover from paralysis (often incomplete) can occur
  • ~10% fatality rate

• Bulbar paralytic poliomyelitis (<0.1% of cases)
  • Cranial nerve paralysis (mostly CN 9, 10)
  • Vasomotor and respiratory centers involved
  • May be fatal due to respiratory muscle paralysis
  • ~50% fatality rate
Polio: Epidemiology

- Used to be world-wide disease, yearly peaks in summer months

- U.S. outbreak in 1950s
  - Improved sanitation had increased age at first exposure
  - More paralytic cases (>13,000/yr in U.S.)

- Polio vaccine introduced 1955

- Transmission interrupted in U.S. in 1979
- Last case in Western hemisphere 1991

- 2008: 1655 cases world wide
  - India, Nigeria, Afghanistan, Pakistan are the only countries in which transmission has never been interrupted.

  Almost there.

Polio vaccines

- Inactivated polio vaccine (IPV, Salk vaccine)
  - Contains all three serotypes
  - Formalin-inactivated
  - Injected subcutaneously or intramuscular
  - >95% immune after primary 3-dose series (2, 4, 6 months) booster dose given at 4-6 yrs
  - Duration of immunity unknown

- Oral polio vaccine (OPV, Sabin)
  - Contains all three serotypes (10:1:3 ratio)
  - Vaccine virus excreted in stool (herd immunity)
  - Immunity probably life-long
  - Very rare cases of vaccine-associated paralytic polio (VAPP)
  - Still used in most of the world
  - Not currently recommended in U.S. because risk of VAPP greatly exceeds risk of wild-type polio
Polio in the U.S. (1950-2008)

- Inactivated vaccine
- Live oral vaccine
- Last indigenous case


- VAPP
- Imported

*Vaccine-acquired paralytic polio (VAPP) in a U.S. resident acquired outside the U.S.
Wild Poliovirus 1988

Wild Poliovirus 2008
Other enteroviral infections

• Generally not associated with symptomatic gastrointestinal disease

• World-wide distribution, summer peaks

• Common causative agents of disease in children

• Diagnosis either clinical or by viral culture or PCR

• Serology less reliable (many distinct serotypes)

Other enteroviral infections

• Non-specific febrile illnesses (often with rash)

• Aseptic meningitis, encephalitis
  o recurrent enteroviral meningitis seen in patients lacking functional B lymphocytes
  o rarely, polio-like syndromes may occur

• Myocarditis
  o mainly coxsackie A, B and echovirus 16

• Acute hemorrhagic conjunctivitis (enterovirus 70, highly contagious)

• Hand/foot/mouth disease (coxsackie A16, enterovirus 71)

• Enterovirus infections of newborn
  can be overwhelming disease, sepsis-like syndrome, hepatic necrosis
  perinatal acquisition
Enteroviral meningitis

- Most common cause of aseptic meningitis
- Common in infants under 3 months, especially in summer
  - Can also occur in older kids, adults
- 90% caused by coxsackie B or echoviruses
- Febrile prodrome
- Most cases uncomplicated, recover in less than 1 week
- Adults may have more prolonged course
  - higher rate of complications (seizures, obtundation)
- CSF profile with 10-500 WBC, lymphocyte predominance
- Diagnosis by PCR or viral culture of CSF

Myopericarditis

- Group B coxsackieviruses account for majority of cases
- Viral replication in myocardium
- Preceeding upper respiratory illness
- Male predominance (2:1)
- Local necrosis and inflammatory infiltrate
- Detectable by PCR or immunofluorescence of cardiac biopsy
- Some benefit to intravenous immune globulin
### Acute hemorrhagic conjunctivitis

- highly contagious
- person-to-person transmission via fingers, fomites
- enterovirus 70, coxsackie A24

- symptoms peak on first day of illness
- generally no long-term ophthalmic complications

### Hand, foot, and mouth disease