ENTEROVIRUSES & OTHER ENTERIC VIRUSES

DISEASES CAUSED BY ENTEROVIRUSES

At least 72 serotypes of human enteroviruses exist, including: coxsackie, echo and Hepatitis A virus. These viruses are transmitted predominantly by fecal-oral contamination or respiratory transmission (EV-D68 and echoviruses) and cause a variety of clinical syndromes.

The clinical syndrome manifested by the enterovirus infection depends on the target tissue that is infected during the primary viremia (see Figure 57-4, next page)

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

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Occurrence</th>
<th>Polioviruses</th>
<th>Coxsackie A</th>
<th>Coxsackie B</th>
<th>Echoviruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralytic disease</td>
<td>Sporadic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Encephalitis, meningitis</td>
<td>Outbreaks</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Carditis</td>
<td>Sporadic</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neonatal disease</td>
<td>Outbreaks</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pleurodynia</td>
<td>Outbreaks</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Herpangina</td>
<td>Common</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hand-foot-mouth disease</td>
<td>Common</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rash disease</td>
<td>Common</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute hemorrhagic conjunctivitis</td>
<td>Epidemic</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Undifferentiated fever</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diarrhea, gastrointestinal disease</td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Diabetes, pancreatitis</td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Disease in immunodeficient patients</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
LABORATORY DIAGNOSIS OF ENTEROVIRUSES

In acute enterovirus-caused syndromes, diagnosis is most readily established by detection of the virus (either by cell culture or RT-PCR of genetic information) from throat swabs, stool or rectal swabs, body fluids and occasionally tissues. Viremia is usually undetectable by the time symptoms appear. When there is CNS involvement, cerebrospinal fluid culture taken during the acute phase of the disease may be positive in 10 to 85% of cases, depending on the stage of illness and the viral serotype involved. Direct isolation of virus from affected tissues or body fluids in enclosed spaces (e.g. spinal fluid) usually confirms diagnosis. Isolation of an enterovirus from the throat is highly suggestive of an etiologic association, as the virus is usually detectable at this site for only 2 days to 2 weeks after infection; isolation of virus from fecal specimens only must be interpreted more cautiously, as asymptomatic shedding from the bowel may persist for as long as 4 months.

ANTI-VIRAL THERAPY

A drug that exhibits anti-viral activity against multiple members of the picornavirus family is currently under development. The drug, termed Pleconaril, is an orally active, low molecular weight compound that binds to a hydrophobic pocket of the virion coat protein while virus particles are being assembled. Once pleconaril is bound and incorporated into the virion, the shape of the receptor binding canyon on the virion is altered, and the virion is unable to attach to the receptor and uncoat. Therefore, pleconaril blocks the production of infectious progeny virus particles. Pleconaril has undergone extensive in vitro sensitivity testing against over 215 clinical isolates of enterovirus strains known to cause human disease; over 90% of the strains are inhibited by the drug. Greater than 90% of rhinovirus serotypes are inhibited at concentrations of
Studies suggest only limited efficacy of Pleconaril against enterovirus meningitis or myocarditis in children. Perhaps the biggest challenge is getting the antiviral to the patient at a very early stage when there is a chance to reduce the viremia.

HEPATITIS A VIRUS

Hepatitis A virus is responsible for 20-50% of hepatitis cases. It is an Enterovirus which is transmitted via the fecal-oral route and the most common sources of contamination are shell fish, food handlers and day care centers.

PATHOGENESIS

- Incubation period is 15-45 days
- Acute onset of fever, malaise, anorexia, headache, nausea and vomiting
- Clinical jaundice, hepatomegaly, dark urine
- Liver transaminases (ALT) is elevated for 5 to 10 days prior to onset of jaundice and may persist for 2 to 6 weeks
- The infection is usually self-limiting and non-fatal
- Subclinical cases are common in younger age groups

DIAGNOSIS

- Many viruses present the same symptoms - especially hepatitis viruses! Clinical presentation alone is not a reliable diagnosis.
- During acute infection, anti-HAV IgM is detected in the serum
- HAV particles and/or HAV antigens are detectable by immunoassay of the feces
VACCINE

HAV vaccine has been licensed by the FDA. This vaccine is inactivated HAV and is very effective in preventing disease.
The recommended dosing for adults is an initial intramuscular injection, followed by a booster dose in 6 to 12 months

It should be administered to travelers to countries with high or intermediate endemicity of infection (Africa, Asia excluding Japan, eastern Europe, Middle East, Mexico, Central and South America and parts of the Caribbean), children who live in high risk communities (Alaskan Native villages, American Indian reservations, selected other communities), sexually active homosexual men and others with high risk sexual behavior, persons with chronic liver disease (particularly hepatitis C infection), and persons who have occupational risk for infection.

VIRUSES OF DIARRHEA

A variety of infectious agents can be responsible for acute diarrheal disease. Approximately 75-80% of cases are of viral origin (in 20-25% of cases, bacteria or protozoa are detected). The most common viruses of diarrhea are:

1. Rotaviruses – segmented double stranded RNA virus, no envelope
   The segmented genome can undergo re-assortment

2. Noroviruses – small, ssRNA virus, no envelope
3. Astroviruses – ssRNA virus, no envelope
4. Adenoviruses – double strand DNA virus, no envelope
5. Coronaviruses – enveloped, positive strand RNA virus

Unfortunately, most of these viruses are difficult to grow in the laboratory, even though a patient may be producing $10^8$ virus particles per gram of diarrheal stool. The best diagnostic test, visualization of virus particles by electron microscopy, is impractical and not cost effective. There is a very good enzyme immunoassay (EIA) for detection of rotavirus particles. Similar EIAs’s for all viruses should be developed.

**ROTAVIRUS**

The annual impact of rotavirus infection is enormous. Over 3 million people (mostly children < 2yrs of age) are infected, 65,000 – 75,000 are hospitalized at an annual cost of > $1 billion.

**PATHOGENESIS**

**Previous dogma** - malabsorption secondary to destruction of enterocytes results in osmotic diarrhea.

**New idea** - Rotavirus encodes a viral enterotoxin, NSP4. The viral enterotoxin (NSP4) causes the diarrhea (Ball et al, Science 272: 101-104, 1996)
DETECTION OF ROTAVIRUS INFECTION

Large numbers of virus particles are excreted. These virus particles can be readily detected in a stool sample using the EIA, which is inexpensive. Some clinical labs are now using film array PCR for detection of multiple pathogens. Children hospitalized with rotavirus infection should be isolated due to high incidence of nosocomial transmission.

IMMUNITY

Type-specific humoral and secretory IgA antibodies are protective, probably inducing life-long immunity, however, at least (4) serotypes of rotavirus exist.

VACCINES

Rotavirus vaccines:

RotaTeq received FDA approval on February 3, 2006. RotaTeq is a live, attenuated virus vaccine. This vaccine was developed by placing the genes encoding the human rotavirus capsid proteins of different serotypes into a bovine rotavirus. Five rotavirus serotypes are included, hence the pentavalent vaccine. In clinical trials, the vaccine provided 98% protection against severe diarrhea caused by rotavirus, and reduced clinic visits by 86% (Vesikari et al., 2006, NEJM 354: 23-33). The researchers and FDA concluded that the pentavalent bovine rotavirus-based vaccine induced a high level of protection against severe diarrheal illness caused by human rotavirus. Furthermore, this study showed that the risk of intussusception was similar in vaccine and placebo recipients.

This vaccine should be given in 3 doses, spaced approximately 2 months apart. The vaccine is given by mouth. The first dose is given when the child is 6 to 12 weeks of age, and the last dose should be given by 32 weeks of age.

RotaRix is a human, live-attenuated rotavirus vaccine based on the predominant G1 genogroup of rotaviruses. This vaccine is also FDA approved and both RotaTeq and RotaRix are used in the USA. The use of these vaccines has reduced the incidence and severity of rotavirus disease!

Noroviruses

Noroviruses are the most common cause of non-bacterial, acute epidemic diarrhea. Outbreaks commonly occur on college campuses and on cruise ships. There is rapid onset and relatively rapid resolution (~48 hrs) of the symptoms. Transmission is via fecal-oral contamination. Noroviruses are non-enveloped viruses (positive strand RNA viruses in the family Calicivirus, genus Norovirus, species MANY) that are excreted in large quantities and stable for hours on surfaces. There are many serotypes of Noroviruses so multiple episodes are possible.
Pathogenesis: Norovirus causes disease by compromising the function of the intestinal brush borders, preventing proper absorption of water and nutrients.

Detection: generally not done due to the acute nature of the illness – people get better before they have a chance to call the doctor and get an appointment. Adults generally do not get dehydrated enough to show up in the emergency room. Newest film array RT-PCR assays can detect noroviruses in fecal samples.

Protection: The use of virus-like particles (VLPs) is being tested as vaccines for noroviruses. Initial testing using a Norovirus VLP showed protection from severe disease in the majority of vaccines. What for future developments.

SEVEN QUESTION APPROACH
It is easy to be overwhelmed with all the information currently available about viruses. My aim is to help you categorize what is already known about viruses in such a way that new information can be added and updated. Therefore, I developed a list of the major questions critical to Medical Virology. If you can answer these questions for any given virus or viral disease, you will be well prepared for your future in medicine. Please refer to the Tables in the study aids section to help address these questions.

1. What virus is associated with the disease?

Virus ↔ Disease
Common name and classification ↔ Major disease and/or most medically important disease
Example: Varicella Zoster Virus (Herpesviridae) ↔ chickenpox and zoster

2. How is the virus transmitted?

Respiratory
Fecal-oral
Transcutaneous
Sexual
Mother-to-child
Zoonoses
Also – is a particular group (age, risk factors) most likely to be infected? Is there a peak season for infection?

3. How is the viral infection detected?

Virus isolation look for CPE
Serology (acute IgM, convalescent IgG)
Detection of viral antigens (ELISA)
Detection of viral sequences (PCR)
Other methods?

4. What is the mechanism/pathogenesis of disease?
Viremia?
Target organ?
Lytic virus?
Immunopathology?

5. Are there any anti-viral therapies?
   Acyclovir
   Ganciclovir
   Amantadine
   RT-inhibitors, protease inhibitors
   Neuraminidase inhibitors

6. Are there any vaccines?
   Live-attenuated
   Killed virus
   Subunit vaccine

7. Are there any long-term consequences?
   Immunity
   Persistent infection
   Latent infection/recurrence
   No long-term immunity therefore re-infection is possible

STUDY QUESTIONS
1. How do serum IgG antibodies protect us from disease caused by enteroviruses?
2. How do you detect infection with Hepatitis A virus?
3. Why is it important to determine if babies hospitalized for diarrhea are infected with rotavirus?

EXAMPLE OF TEST QUESTION
Major characteristics of the enterovirus group of viruses include all of the following EXCEPT:

A. Fecal-oral route of transmission.
B. Acid stable virion.
C. Proteolytic processing of the viral polyprotein to yield capsid and nonstructural proteins.
D. Primary viremia leading to spread of the virus to target tissues.
E. Majority of infections result in frank cases of disease.

CORRECT ANSWER TO ABOVE QUESTION: E