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Gastrointestinal Viruses

The gastrointestinal tract is the portal of entry for a wide variety of viral pathogens of humans. Some of these act locally, causing diarrhea and other gastrointestinal symptoms. Others may enter and replicate in the GI tract but then disseminate, causing pathology at distant sites. In this lecture, we will discuss rotavirus, a major viral cause of diarrhea, especially in children, and the enteroviruses, which are important causes of disease throughout the body -- but rarely in the GI tract.

Rotavirus

Epidemiology

Diarrheal disease is the cause of tremendous morbidity and mortality worldwide, and rotavirus is the most common and most important agent of this disease. Essentially all children have been infected with rotavirus by age 5. In the United States, the illness is treated with hydration, and despite the vast numbers of pediatric hospitalizations from rotavirus diarrhea (just wait until your peds rotation -- you'll see!), mortality from rotavirus is exceedingly rare. In contrast, in the developing world, where access to medical care and IV hydration are lacking, more than 600,000 pediatric rotavirus deaths occur annually. This accounts for nearly 5% of all-cause childhood mortality and ranks rotavirus disease as a top global public health priority.

In the U.S., rotavirus is a seasonal disease, starting in the Southwest in November and December, and moving eastward across the country, with late winter peaks in the Northeast.

Clinical Manifestations

Rotavirus is highly infectious and is spread through the fecal-oral route. It enters and replicates in the mature villus cells of the duodenum and jejunum. Following a 1-3 day incubation period, fever and vomiting are the initial symptoms. These are followed within 2-4 days by voluminous non-bloody diarrhea. Loss of fluids and electrolytes during vomiting and diarrhea leads to dehydration. Extraintestinal complications occur rarely, if ever. Initial episodes of rotavirus diarrhea are generally the most severe, with asymptomatic or mild infection being common in adulthood.

Molecular Biology/Pathogenesis/Evolution

Rotaviruses are large, non-enveloped dsRNA viruses of the family *Reoviridae*. They have segmented genomes, allowing for reassortment in a manner analogous to influenza viruses. The virus carries its own RNA-dependent RNA polymerase to aid in replication and mRNA synthesis. Rotaviruses are classified into groups (A-F, based on the VP6 protein), but only groups A, B, and C cause disease in humans. Group A is further subdivided into serotypes based on the VP7 (G type) and VP4 (P type) proteins. This grouping is important in vaccine design, as different serotype epidemiology may exist in different regions. Attachment of rotaviruses to host cells is via the VP4 protein spikes. Once inside the cell, in addition to production of viral proteins needed for replication, a potent enterotoxin (NSP4) is produced, leading to epithelial cell death and to the clinical syndrome of diarrhea.

Diagnosis
Diagnosis of rotavirus diarrhea is generally based on the clinical presentation and the time of year. A febrile child with vomiting and diarrhea in the winter is likely to have rotavirus. In clinical practice, detection of rotavirus antigens in stool by ELISA is clinically useful and has high sensitivity and specificity. Other techniques (stool electron microscopy, PCR, serology) are not frequently used in clinical settings.

Treatment
Treatment of rotavirus disease is based on correction of dehydration. Oral or IV rehydration and electrolyte repletion may be lifesaving. Early reintroduction of feeding (normal diet, not simple sugars) can decrease the duration of symptoms. Antidiarrheal medications are not beneficial and may be harmful.

Prevention
Careful handwashing and cleaning of potential fomites is crucial to preventing the spread of rotavirus within homes and daycare settings. In the hospital, contact isolation and improved attention to hand hygiene can slow or stop outbreaks.

Rotavirus is a vaccine-preventable illness. There are two licensed oral, live-attenuated rotavirus vaccines in the U.S. Rotarix is a monovalent human vaccine, and Rotateq is a pentavalent human-bovine reassortant vaccine. Both are given at 2, 4, and 6 months of age and are effective at decreasing the burden of rotavirus disease. A prior vaccine formulation, RotaShield, was removed from the market after fears of an increase in the rate of intussusception in children following vaccine. This vaccine was effective, and it is unclear whether the increased risk was ever truly substantiated. None of these vaccine formulations is currently available in the developing world, where the burden of disease and death due to rotavirus are highest.

Enteroviruses

The enteroviruses cause a wide spectrum of disease in humans. In this section, we will discuss some of the common themes in enteroviral pathogenesis and then discuss poliomyelitis as well as some other significant enteroviral infections.

Molecular Biology/Pathogenesis/Evolution
Enteroviruses are members of the *Picornaviridae* (small RNA viruses). They are non-enveloped viruses with positive-sense ssRNA genomes and have protein coats (capsids) with icosahedral symmetry. The viruses bind cell surface receptors (CD155 in the case of poliovirus) and enter the cell via endocytosis. In the cytoplasm, the viral genome, because it is a positive-sense RNA, can function essentially as a large RNA, leading to the production of a long polyprotein. This polyprotein is processed by viral enzymes to release functional viral proteins. In addition, new viral genomes are synthesized and packaged into new virions, which are released upon cell lysis.

The enteroviruses are acid-stable and enter the body through the GI tract. They replicate in cells of the gastrointestinal tract and regional lymph nodes. From there, they enter the bloodstream and seed distant sites (viremia). Different enteroviral types have tropism for different anatomic sites. This tropism determines the clinical syndromes associated with a particular enterovirus.

Polio

Clinical Manifestations

The range of clinical syndromes associated with poliovirus is striking. The incubation period for polio is between 6 and 20 days, during which the virus replicates in the oropharynx and regional lymph nodes. The vast majority of infections (90%) are clinically inapparent and cease at this point. In the remainder, the minor viremia is followed by a mild clinical syndrome, including fever, headache, and sore throat. This is called abortive poliomyelitis. Some patients have this syndrome plus signs of meningeal irritation (headache with stiff neck and/or photophobia). This is nonparalytic poliomyelitis and, despite the presence of virus in the cerebrospinal fluid, resolves completely within 10 days.

Fewer than 1% of patients have the more severe paralytic poliomyelitis syndromes. In these, an illness consistent with abortive polio is followed by seeding of the central nervous system with virus during the major viremia and replication within anterior horn cells. Headache, fever, and vomiting are followed by neurologic signs resulting from neuronal necrosis. Weakness and asymmetric paralysis, often involving the proximal muscles of the lower extremities, can lead to lifelong disability. Involvement of the respiratory muscles can lead to death due to respiratory failure. Spinal paralytic polio has a 10% fatality rate. Bulbar paralytic poliomyelitis involves the cranial nerves (especially CN 9 and 10), leads to dysphagia and alterations of speech, and can affect the vasomotor and respiratory centers in the CNS. Fatality rates approach 50%.

Treatment of poliomyelitis is supportive, including mechanical ventilation when needed.

Diagnosis

Poliovirus can be isolated from the oropharynx by culture early in disease and may be shed in the feces for several weeks. Serology may be useful in some settings.\

Epidemiology

The epidemiology of polio is a triumphant story for public health, but until eradication is achieved it is also cause for constant vigilance. Polio used to be a worldwide disease with yearly peaks in the summer months. Following the introduction of the inactivated polio vaccine (see below) in 1955, there was a rapid and sustained decline in polio in the U.S. The last indigenous case in the U.S. was in 1979, and the disease was eradicated from the Western hemisphere in 1991. Residual cases in the U.S. since 1980 have either been imported cases (rare) or, prior to discontinuation of the use of oral polio vaccine in 1999, vaccine-associated (VAPP). In 2008, there were 1,655 cases of polio worldwide, and sustained transmission occurs in only 4 countries. A concerted public health effort is dedicated to making sure that eradication is achieved.

Prevention

As mentioned above, vaccination is key to the control of poliovirus infections. There are two vaccine formulations currently in use (only one in the U.S.). Inactivated polio vaccine (IPV) contains all three poliovirus serotypes in a chemically inactivated form. The three-dose primary series leads to immunity in about 95% of recipients, and a booster is given at 4-6 years. The duration of immunity is unknown. This is the primary method of immunization in the United States.

Oral polio vaccine (OPV) has several advantages over IPV. It also contains all three serotypes and provides high levels of protection. Immunity is lifelong, and because virus is excreted in the stool, there can be spread of attenuated vaccine virus to unvaccinated people, leading to improved population-level immunity. OPV is associated with a very small risk of vaccine-associated paralytic polio, due to reversion of vaccine virus to a virulent form within the host. In areas with endemic polio, the greater efficacy far outweighs this small risk. However, OPV use was discontinued in the U.S. in 2000, as it was felt that the absence of wild-type polio in the hemisphere for more than a decade made the transition to IPV safe and allowed for the elimination of the risk of VAPP.

Other Enteroviral Infections

In addition to poliomyelitis, enteroviruses cause a wide variety of clinical syndromes, some of which are mentioned briefly here.

Non-specific febrile or rash illnesses are the most common outcome of enteroviral infections. These are self-limited and are not associated with long-term sequelae.

Aseptic meningitis caused by coxsackieviruses (often type B) or echoviruses is common in summer months. Children are commonly affected, but adults may have more complicated courses. Most cases are self-limited. Diagnosis is by PCR of spinal fluid, and treatment is supportive. Recurrent enteroviral meningitis may occur in patients with B lymphocyte immunodeficiencies, and these individuals may benefit from intravenous immunoglobulin (IVIG) therapy.

Myocarditis/pericarditis, mainly due to coxsackievirus type B, occurs most often in childhood and adolescence, with a striking (2:1) male predominance. Following an upper respiratory illness, viral invasion of cardiomyocytes leads to local necrosis and inflammatory infiltrates. IVIG may be of some benefit. The outcome ranges from full resolution to progressive cardiac failure requiring transplant.

Acute hemorrhagic conjunctivitis caused by enterovirus 70 or coxsackievirus A24 is highly contagious and is spread by fingers or other fomites. Eye involvement can be striking and occurs rapidly, but complete recovery is the norm.

Hand/foot/mouth disease and herpangina are commonly caused by coxsackievirus A16 or enterovirus 71. These self-limited diseases, sometimes associated with fever, are commonly seen in pediatric offices. Oral lesions may be so painful that children refuse to drink and become dehydrated.

Enteroviral infections of newborns may be associated with overwhelming disease. The virus is often transmitted perinatally from the mother (who may have mild or asymptomatic disease). Hepatic necrosis, sepsis-like syndromes, and high fatality rates are associated. Treatment consists of IVIG to help control viral replication.

Other GI Viruses

Norovirus (calicivirus)

For the boards: I say cruise ship and gastroenteritis, you say norovirus.

Adenovirus

Small, non-enveloped DNA viruses. Many serotypes, many distinct disease states.