

# VIRUS CAUSING DIARRHEA (Viral Gastroenteritis)

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## GENERALITIES:

Virus – smallest infectious particle agent and not a cell

## STRUCTURE OF A VIRUS

### 1. Core / Nucleoid

- Chemically made up of nucleic acid either RNA or DNA depending upon the specie (never both)
- found at the center of the virus maybe single stranded (RNA) or double stranded (DNA) virus

Functions:

- Infectious unit of virus particle
- Bearers of hereditary characteristics of the virus
- Responsible for the metabolic activity of the virus
- Contains information necessary for virus multiplication

### 2. Capsid (cell wall of bacteria)

- Rigid layer and is made up of structural protein unit called CAPSOMERES
- Surrounds the nucleoid which are chemically protein in nature – *nucleocapsid, virion, virus particle or naked virus*

Functions:

- Protects nucleoid from both physical and enzymatic digestion and hazards of environment like heat and drying
- Contains the antigenic characteristics of the virus which distinguishes them
- Contains the complimentary receptor sites for the host cell binding

### 3. Nucleocapsid

- capsid together with enclosed nucleic acid

### 4. Capsomeres

- Structural or morphologic unit of proteins

### 5. Envelope (chemically lipids, fats, triglyceride)

- Lipid-bilayer enclosing the nucleocapsid
- derived from host cell membrane and acquired during virus maturation by budding
- contains virus encoded glycoproteins or enzymes which are seen as SPIKES exposed on the surface of the envelope. These are the neuraminidase enzyme and hemagglutinin enzyme
- Virus is divided into two divisions:
  - a. envelope virus – sensitive to ether
  - b. naked virus – resistant to ether

Functions:

- Contains an antigen that would help in identifying the virus

Functions of SPIKE or POLYMER:

- Virus attachment to host cell surface
- Maybe used for identification

NEURAMINIDASE – aids in penetrating the mucous layer of the respiratory epithelium to reach the host cell. Ex. Influenza

HEMAGGLUTININS – can bind virions to red cell membrane

VIRION – complete virus particle which serves to transfer viral nucleic acid from one cell to another

- Mature virus particle; which denotes both intactness of structure and the property of infectiousness

DEFECTIVE VIRUS – a virus particle that is functionally deficient in aspects of replication. It may interfere with replication of normal viruses.

## VIRUS MULTIPLICATION CYCLE

(One-step growth cycle)

### 1. Stage of Adsorption or Attachment

- Virus invades the host cell, interaction of a virion with specific receptor sites on the surface of the cell
  - a. ionic attraction between virus and host cell counterion  $Mg^{++}$  or  $Ca^{++}$  - enhance absorption
  - b. physical alignment of virus with appropriate cell surface receptor

### 2. Entry or Penetration (viropexis)

- After adsorption → cell membrane invaginate around the absorbed virus particle
- Virus is engulfed by cell membrane → transported to cytoplasm → phagocytized → formation of phagocytic vesicle

### 3. Uncoating

- Stage of protein hydrolysis
- Physical separation or removal of protein coat (CAPSID) from outer structural unit of the virion
  - A. lysozomal enzyme
  - B. special uncoating protein

### 4. Eclipse

- Attachment of virus to host nucleic acid → takes control host cell
- Release of viral nucleic acid and loss of viral infectivity

### 5. Synthesis

- Viral nucleic acid becomes template for production of mRNA which code for synthesis of viral proteins
- Union of viral nucleic acid with host cell DNA

### 6. Maturation (assembly)

- capsid encloses nucleic acid unite to form virion

### 7. Stage of Release

- a. Lysis (naked virus)
  - Rupture of infected cell → disintegrate rapidly
- b. Budding
  - Envelope protein incorporated host cell membrane

## VIRAL PATHOGENESIS

Viruses are transmitted from persons to persons by:

1. Respiratory route
2. Fecal-oral route
3. Trauma
4. Injection with contaminated needles and or objects
5. By tissue transplant (including blood transfusion)
6. By arthropod or animal bites

Once introduced into the host → virus infects susceptible cells → local infection → viremia → inoculation of secondary target tissues distant from primary sites → symptomatic disease ensues → disease resolves when specific-antibody cell mediated immune mechanism halts continued viral replications → tissue reaction varies → 1. lysis virus-infected cell or 2. immunopathologic mechanism directed against the virus but also destructive to neighboring tissues

## GENERAL CHARACTERISTIC OF VIRUS CAUSING DIARRHEA

- It produces Noninflammatory Diarrhea which is characterized by watery stools that may exceed 1 Liter in volume, without associated symptoms suggestive of inflammation.
- Interfere with the absorptive or secretory mechanism of the intestine, resulting in diarrhea.
- Major cause of Acute Diarrhea
- Viral gastroenteritis ranges from a self-limited watery diarrheal illness (usually <1 wk) associated with symptoms of nausea, vomiting, anorexia, malaise, or fever to severe dehydration resulting in hospitalization or even death.
- The clinician encounters acute viral gastroenteritis in 3 settings.
  - The first is sporadic gastroenteritis in infants, which most frequently is caused by rotavirus.
  - The second is epidemic gastroenteritis, which occurs either in semiclosed communities (eg, families, institutions, ships, vacation spots) or as a result of classic food-borne or water-borne pathogens. Most of these infections are caused by caliciviruses.
  - The third is sporadic acute gastroenteritis of adults, which most likely is caused by caliciviruses, rotaviruses, astroviruses, or adenoviruses.

### Frequency:

- **In the US:** Each year, more than 3.5 million infants develop acute viral gastroenteritis, resulting in more than 500,000 office visits, 55,000 hospitalizations, and 30 deaths. Statistics on sporadic cases of adult viral gastroenteritis are not known; food- and water-borne epidemics of viral gastroenteritis are monitored by the US Centers for Disease Control and Prevention (CDC) surveillance programs. The CDC estimates that viruses cause 9.2 million (out of a total of 13.8 million from all causes) cases of food-related illness each year.

- **Internationally:** Acute viral gastroenteritis is a leading cause of infant mortality throughout the world. By age 3 years, virtually all children become infected with the most common agents.

**Mortality/Morbidity:** Severe cases are seen in the elderly, infant, and immunosuppressed population, including transplant patients.

- Rotavirus infantile gastroenteritis is an important cause of infant mortality in the developing world.
- In the United States, elderly persons have the highest risk for death from gastroenteritis.
- Caliciviruses may kill more people in the United States than do rotavirus disease.

#### **Age:**

- Acute viral gastroenteritis occurs throughout life. Severe cases are seen in very young and elderly. Etiology also varies with age.
- In infants, most cases are due to rotavirus.
- In adults, the most common cause is norovirus

#### **Clinical:**

**History:** The clinical spectrum of acute viral gastroenteritis ranges from asymptomatic infection to severe dehydration and death. Viral gastroenteritis typically presents with short prodrome with mild fever and vomiting, followed by 1-4 days of nonbloody, watery diarrhea. Viral gastroenteritis is usually self-limited.

- The history should *focus on severity and dehydration*. The onset, frequency, quantity, and duration of diarrhea and vomiting are important factors in assessing the status. Oral intake, urination, and weight loss are important considerations. Viruses are the suspected cause of acute gastroenteritis when vomiting is prominent, when the incubation period is longer than 14 hours, and when the entire illness is over in less than 3 days. Travel history (including cruise ships), eating history, and daycare history are important epidemiology factors.
- A viral cause should be suspected when the warning signs of bacterial infection (ie, high fever, bloody diarrhea, severe abdominal pain, **>6 stools/24 h**) are absent and an alternative diagnosis is not suggested by epidemiologic clues from the history (eg, travel, sexual practices, antibiotic use).
- Factors associated with severe and prolonged disease are immunodeficiency and immune suppression, comorbid disease, and malnutrition.
- Death results from dehydration and acidosis.
- Ruling out other diagnoses is important.

**Physical:** The physical examination can be helpful in determining the etiology of gastroenteritis and in assessing the presence and degree of dehydration.

- Temperature, blood pressure and pulse, and body weight can provide evidence of severity of the condition.
- Temperature may be slightly elevated. High fever suggests bacterial infection. Tachycardia, thready pulse, and hypotension suggest severe dehydration.
- The degree of weight loss may be related to dehydration and the duration of the diarrhea.
- The mucous membranes and the skin should be examined carefully. Dry mouth, no tears, skin tenting, dry skin, and capillary refill are all signs of dehydration.
- The mental status in elderly patients and infants may be abnormal, especially when blood pressure and circulation are compromised.
- The abdominal examination may demonstrate mild tenderness. Severe abdominal pain and tenderness suggest bacterial infection or an abdominal emergency.

### Causes:

#### Sporadic infantile viral gastroenteritis

- Group A rotavirus *causes 25-65%* of severe infantile gastroenteritis worldwide.
- Acute infections with group C are quite frequent in the United States and worldwide.
- After rotavirus, the most important cause of acute infantile gastroenteritis probably is calicivirus infection. Seroepidemiologic studies have shown that antibodies to **caliciviruses** are present in *50-90%* of children younger than 2 years in Kuwait, Italy, Kenya, China, London, and South Africa. Using broadly reactive reverse-transcription polymerase chain reaction for calicivirus to study stool specimens from children with acute gastroenteritis, recent studies have found these viruses in *7-22%* of cases.
- **Astrovirus** infection is associated with *2-9%* of cases of infantile gastroenteritis worldwide, making it the third most frequent cause after rotavirus and calicivirus. The burden of astrovirus disease in developing countries might be especially high.
- Researchers have recognized for a long time that certain enteric **adenoviruses** are an important cause of infantile gastroenteritis. Recent studies confirm that they cause *2-6% of cases*.

#### Epidemic viral gastroenteritis

- Most cases of epidemic viral gastroenteritis in adults and children are caused by the caliciviruses or small, round-structured viruses. Some examples include **Norovirus** (formerly called Norwalk-like viruses), **genogroup I** (eg, Norwalk, Southampton, Desert Shield, Cruise Ship); **genogroup II** (eg, Snow Mountain, Mexico, White River, Lordsdale, Bristol, Camberwell, Toronto, Hawaii, Melksham); and **Sapovirus** (formerly Sapporo-like viruses), which *sometimes are referred to as*

*genogroup III*, although they are not like Norwalk (eg, Sapporo, Parkville, Manchester, Houston, London).

- Modern molecular diagnostic techniques, such as **broadly reactive reverse-transcription polymerase chain reaction**, have linked these viruses to epidemics associated with oysters, contaminated community water supplies, restaurant food, hospital patients and staff, day-care facilities, nursing homes, college dormitories, military ships, cruise ships, and vacation spots.
- *Rotavirus and astrovirus also may cause epidemics of viral gastroenteritis.*

#### Sporadic adult viral gastroenteritis

- Few studies have examined the causes of sporadic cases of adult viral gastroenteritis.
- Seroepidemiologic evidence suggests that the etiologies are (in descending order of frequency) **caliciviruses, non-group A rotavirus, astrovirus, and adenovirus.**

#### Work Up:

#### Lab Studies:

#### General laboratory evaluation

- In most cases that fit the clinical features of viral gastroenteritis, lab tests are not indicated.
- If bacterial or protozoal infection is suspected, stool studies for occult blood, WBC count, microscopy for protozoa, *Clostridium difficile* toxin, *Giardia lamblia* by enzyme immunoassay (EIA), or bacterial culture may be indicated.
- Consider investigating high fever, abdominal pain, and extreme dehydration by evaluating serum electrolytes, urea, creatinine, amylase, CBC count, and abdominal imaging studies.

#### Diagnosis of **rotavirus infection**

- **Rapid antigen testing of the stool**, either by EIA (>98% sensitivity and specificity) or latex agglutination tests (less sensitive and specific as compared to EIA) is used to aid in the diagnosis of rotavirus infection.
- **Expect antirotavirus antibodies** (immunoglobulin M and immunoglobulin A) to be excreted in the stool after the first day of illness. Antibody tests can remain positive for 10 days after primary infection and longer after reinfection; therefore, they can be used as an adjunct to diagnosis.

## Diagnosis of **calicivirus infection**

- In epidemics, save stool and emesis specimens for evaluation by public health officials. PCR is valuable in both the outbreak setting and the sporadic case setting.
- Researchers have cloned several of the caliciviruses and placed the genome in a baculovirus that produces unlimited amounts of recombinant calicivirus capsid protein. Enzyme immunoassays for serum antibody and stool antigen have been developed using this antigen source.
- A modification to the polymerase chain reaction has allowed many of the different strains of caliciviruses to be recognized with just a few primers (broadly reactive reverse-transcription polymerase chain reaction). These primers are directed at a region of the genome that is common to many of the strains of calicivirus. This has been an important tool for identifying caliciviruses as the most common cause of epidemic viral gastroenteritis

## **Treatment:**

**Medical Care:** In 1996, the American Academy of Pediatrics formulated and published practice guidelines for the management of acute gastroenteritis in children. Use the following parameters to assess the degree of dehydration: blood pressure, pulse, heart rate, skin turgor, fontanelle, mucous membranes, eyes, extremities, mental status, urine output, and thirst.

- The treatment of rotavirus diarrhea is based primarily on replacing fluids and electrolytes, as directed by the estimated degree of dehydration.
- Oral rehydration therapy is recommended for preventing and treating early dehydration and continued replacement therapy for ongoing losses.
- Shock, severe dehydration, and decreased consciousness require intravenous therapy.
- Age-appropriate diets should be continued in children with diarrhea who are not dehydrated. When mild-to-moderately dehydrated children are rehydrated, resume age-appropriate diet.
- Administering antiemetics and antidiarrheal agents to small children is not recommended.
- Several studies have shown that antirotavirus immunoglobulin, as pooled gamma globulin, bovine colostrum, or human milk, may decrease frequency and duration of diarrhea.
- Research has consistently shown that probiotics, such as *Lactobacillus casei* GG and *Saccharomyces boulardii*, reduce the frequency and/or duration of diarrhea in acute infantile gastroenteritis by 30-70%. Their role in the treatment and prevention of acute infantile gastroenteritis is still undefined.
- Small studies have suggested that zinc supplements may reduce the severity and duration of illness.

## Follow Up:

### Deterrence/Prevention:

- Natural infection with rotavirus does not afford complete immunity, and multiple infections in the first few years of life probably are common; however, immune response to these infections reduces the frequency and severity of subsequent rotavirus infection.
- On February 21, 2006, the CDC Advisory Committee on Immunization Practices (ACIP) recommended **RotaTeq, an oral attenuated pentavalent live vaccine**, for the vaccination of infants. **Three doses should be given at 2, 4, and 6 months.** *The third dose should be given no later than 32 weeks.*
- In the REST trial, a double-blind placebo-controlled trial of over 60,000 infants, RotaTeq demonstrated a 74% reduction in all rotavirus cases. There was a 98% reduction in severe cases and a 96% reduction in hospitalized cases.
- Of note, there was a 59% reduction in all-cause gastroenteritis admissions, highlighting rotavirus as a larger contributor to the cause of acute gastroenteritis than originally expected.
- The oral live attenuated vaccine was not tested in immunocompromised patients and not approved for this use
- There was no association of RotaTeq with intussusception in this trial.
- The former RotaShield virus was pulled from the market for increased intussusception. However, this risk was only seen in older infants. The RotaTeq trial did not test older infants. For these reasons, the RotaTeq virus is not approved for infants older than 32 weeks, and a "catch-up" vaccination is not recommended.
- There are some questions as to the efficacy in less developed countries where the vaccine was not tested and nonvaccine serotypes (VP4, VP6, and VP7) are more prevalent.
- Rotarix is a monovalent vaccine that has produced slightly less efficacious results than RotaTeq in clinical trials. This vaccine was tested in less developed countries. It is not yet approved for clinical use.
- RotaShield is also not approved for use, but it is being considered for reintroduction into the marketplace in limited use for early infant vaccination only.
- Research on a vaccine for calicivirus infection is proceeding rapidly. Baculovirus-produced antigens spontaneously form viruslike particles without RNA that are immunogenic and possibly protective. Genomes also can be inserted into edible foodstuffs such as potatoes or bananas.
- Proper hygiene is still the first preventative step in viral gastroenteritis. Hand washing to prevent fecal oral transmission is very important. It also includes properly handling food and using clean water supplies.
- On a community level, proper sanitation, clean water supplies, and surveillance programs for outbreaks are important steps in prevention.

# Pathophysiology of Diarrhea

## Inflammatory and Infectious Diarrhea

- The epithelium of the digestive tube is protected from insult by a number of mechanisms constituting the **gastrointestinal barrier**, but like many barriers, it can be breached.
- Disruption of the epithelium of the intestine due to microbial or viral pathogens is a very common cause of diarrhea in all species.
- Destruction of the epithelium results not only in exudation of serum and blood into the lumen but often is associated with widespread destruction of absorptive epithelium. In such cases, absorption of water occurs very inefficiently and diarrhea results.
- The immune response to inflammatory conditions in the bowel contributes substantively to development of diarrhea.
- Activation of white blood cells leads them to secrete inflammatory mediators and cytokines which can stimulate secretion, in effect imposing a secretory component on top of an inflammatory diarrhea.
- **Reactive oxygen** species from leukocytes can damage or kill intestinal epithelial cells, which are replaced with immature cells that typically are deficient in the brush border enzymes and transporters necessary for absorption of nutrients and water. In this way, components of an osmotic (malabsorption) diarrhea are added to the problem.

## The Gastrointestinal Barrier

The gastrointestinal mucosa forms a barrier between the body and a luminal environment which not only contains nutrients, but is laden with potentially hostile microorganisms and toxins. The challenge is to allow efficient transport of nutrients across the epithelium while rigorously excluding passage of harmful molecules and organisms into the animal. The exclusionary properties of the gastric and intestinal mucosa are referred to as the "gastrointestinal barrier".



It is clear that a number of primary gastrointestinal diseases lead to disruption of the mucosal barrier, allowing escalation to systemic disease. It is equally clear that many systemic disease processes result in damage to the gastrointestinal barrier, thereby adding further insult to an already compromised system.

Two components of the Gastrointestinal Barrier:

- The **intrinsic barrier** is composed of the epithelial cells lining the digestive tube and the tight junctions that tie them together.
- The **extrinsic barrier** consists of secretions and other influences that are not physically part of the epithelium, but which affect the epithelial cells and maintain their barrier function.

### The Intrinsic Gastrointestinal Barrier

- Is lined by sheets of epithelial cells that are circumferentially tied to one another by tight junctions, which seal the paracellular spaces and thereby establish the basic gastrointestinal barrier which forms the defining structure of the mucosa.
- Throughout the digestive tube, maintenance of an intact epithelium is thus critical to the integrity of the barrier. **In general, toxins and microorganisms that are able to breach the single layer of epithelial cells have unimpeded access to the systemic circulation.**
- There is diversity among different types of epithelial cells in specific barrier functions.
  - **Apical plasma membranes** of gastric parietal and chief cells have atypically low permeability to protons, which aids in preventing damage due to back diffusion of acid into the cells.
  - **Small intestinal epithelial cells** lack this specialized ability and thus are much more susceptible to acid-induced damage.
- **Tight junctions** encircling gastrointestinal epithelial cells are a critical component of the intrinsic barrier, their permeability may be regulated by a number of factors that affect the epithelial cells.
- **Functionally-mature cells** derived from proliferation of stem cell, show rapid turnover rates, and die within only a few days after their formation. Maintenance of epithelial integrity thus requires a precise balance between cell proliferation and cell death, these includes:
  - **Mucous cells** in the stomach
  - **Absorptive cells** in the small intestine,
- **Stem cells**
  - support continual replenishment of gastrointestinal epithelium reside in the middle of the gastric pits and within the crypts of the small and large intestine.
  - proliferate continually to supply cells that then differentiate into *absorptive enterocytes, mucus-secreting goblet cells, enteroendocrine cells and Paneth cells*. Except for Paneth cells, which remain in the crypts, the other cells differentiate into their mature forms as they migrate up from the crypts to replace cells extruded from the tips of the villi. This migration takes approximately 3 to 6 days.

## The Extrinsic Gastrointestinal Barrier

### Mucus and Bicarbonate



### Mucus

- coat the entire gastrointestinal epithelium, which is synthesized by cells that form part of the epithelium.
- Serves an important role in mitigating shear stresses on the epithelium and contributes to barrier function in several ways. The abundant carbohydrates on mucin molecules bind to bacteria, which aids in preventing epithelial colonization and, by causing aggregation, accelerates clearance.
- Diffusion of hydrophilic molecules is considerably lower in mucus than in aqueous solution, which is thought to retard diffusion of a variety of damaging chemicals, including gastric acid, to the epithelial surface.

### Bicarbonate ion

- secreted by the gastric and duodenal epithelial cells on their apical faces which serves to maintain a neutral pH along the epithelial plasma membrane, even though highly acidic conditions exist in the lumen.

Other Substances Includes:

- **Hormones and Cytokines** - are known to rent forms of injury to the epithelium can lead to either enhanced or suppressed rates of cell proliferation.
- **Prostaglandins**, particularly prostaglandin E2 and prostacyclin, have long been known to have "cytoprotective" effects on the gastrointestinal epithelium. Their cytoprotective effect appears to result from a complex ability to stimulate mucosal mucus and bicarbonate secretion, to increase mucosal blood flow and, particularly in the stomach, to limit back diffusion of acid into the epithelium. Considerable effort is underway to develop NSAIDs that fail to inhibit mucosal prostaglandin synthesis.
- **Epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha (barrier maintenance))**
  - EGF is secreted in saliva and from duodenal glands, while TGF-alpha is

produced by gastric epithelial cells.

- Both peptides bind to a common receptor and stimulate epithelial cell proliferation. In the stomach, they also enhance mucus secretion and inhibit acid production.

- Other cytokines such as **fibroblast growth factor and hepatocyte growth factor** have been shown to enhance healing of gastrointestinal ulcers in experimental models.
- **Trefoil proteins** are a family of small peptides that are secreted abundantly by goblet cells in the gastric and intestinal mucosa, and coat the apical face of the epithelial cells.
- **Nitric oxide** (NO - plays a crucial role in mucosal integrity and barrier function is). Paradoxically, NO also contributes to mucosal injury in a number of digestive diseases. This molecule is synthesized from arginine through the action of one of three isoforms of nitric oxide synthase (NOS).
- **Antibiotic Peptides and Antibodies**

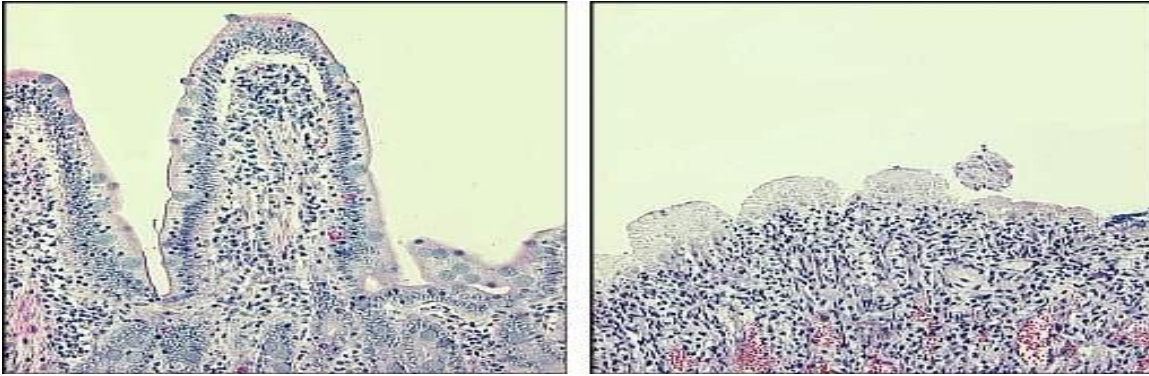
**Paneth cells** are epithelial granulocytes located in small intestinal crypts of many mammals. They synthesize and secrete several antimicrobial peptides, chief among them isoforms of alpha-defensins known also as cryptidins ("crypt defensin").

**Gastrointestinal immune system.** One facet of this defense systems is that **much of the epithelium is bathed in secretory immunoglobulin A**. This class of antibody is secreted from subepithelial plasma cells and transcytosed across the epithelium into the lumen. Luminal IgA provides an antigenic barrier by binding bacteria and other antigens. This barrier function is specific for particular antigens and requires previous exposure for development of the response.

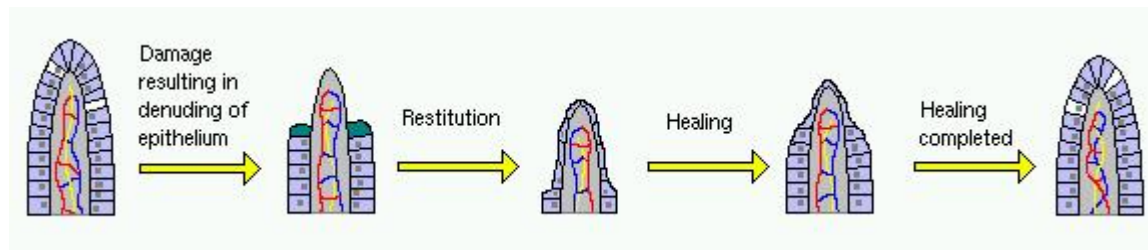
### **Disruption of Barrier Function**

Despite its robust and multi-faceted nature, the gastrointestinal barrier can be breached. Local infections by bacteria and virus, exposure to toxins or physical insults, and a variety of systemic diseases lead to its disruption. Such problems can be mild and readily repaired, or massive and fatal.

The micrographs below depict severe disruption of the barrier. On the left is mucosa from a normal canine small intestine, with large villi covered by intact epithelium extended into the lumen. The image on the right (same magnification) shows small intestinal mucosa from a dog that died of Salmonella enteritis - note the totally denuded epithelium and destruction of villi.



## Restitution and Healing After Injury



- This rapid restoration of epithelium is accomplished by a process called restitution - epithelial cells adjacent to the defect flatten and migrate over the exposed basement membrane. In the small intestine, this process is aided by a rapid contraction and shortening of the affected villi, which reduces the area of basement membrane that must be covered.
- Restitution provides a rapid mechanism for covering a defect in the barrier and does not involve proliferation of epithelial cells. It results in an area that, while protected, is not physiologically functional. Healing requires that the epithelial cells on the margins of the defect proliferate, differentiate and migrate into the damaged area to restore the normal cellular architecture and function.
- Restitution has been shown to be stimulated by a number of *mostly paracrine regulators*. Local prostaglandins and trefoil proteins are clearly involved in this process, and suppression of their production significantly delays restitution.
- Another group of molecules involved in restitution is the polyamines such as spermine, spermidine and putrescine. These molecules are present in many diets and also synthesized by the gastrointestinal mucosa. Enteral administration of polyamines has been shown in experimental models to accelerate restitution and healing of mucosal lesions.

COMMON VIRUS CAUSING DIARRHEA:

## Norwalk Virus

- Is most likely a member of the Caliciviridae family

- Naked virus with an icosahedral nucleocapsid containing single-stranded positive-sense RNA
- Replicates in the cytoplasm
- Cause epidemic gastroenteritis
- Has never been grown in tissue culture
- Maybe demonstrated by Radioimmunoassay blocking test or immunoadherence
- Norwalk and Norwalk-like viruses cause an estimated 181,000 cases of "stomach flu" each year. *Norwalk, Ohio*, where the first such virus was identified.
- Most commonly associated with **oysters** that are harvested from sewage-contaminated waters and eaten raw. Recently, the viruses have ruined cruise vacations by ravaging popular ships, and have been named as the culprits in several community outbreaks.

### How it's spread

The only known way the Norwalk virus is spread is through the fecal matter of those who are infected. These viruses only affect people, and can't be spread by animals. They can be spread through:

- Shellfish from waters contaminated with sewage
- Infected people who don't wash their hands properly after using the bathroom, and then prepare food or touch food that another person might eat.
- Water or ice that is contaminated with sewage

### Symptoms

The Norwalk and Norwalk-like viruses cause brief, but intense gastrointestinal distress. Symptoms usually last two to three days and may include:

- Watery diarrhea
- Abdominal cramps
- Nausea
- Headache
- Low-grade fever

These symptoms are not life-threatening and usually go away on their own. In certain cases, particularly in young children, symptoms can cause dehydration that may require hospital treatment.

### Treatment

As with other gastrointestinal viruses, the biggest health threat is dehydration. The best treatment for Norwalk virus is to drink plenty of fluids. **Antibiotics have no effect on this illness.**

### Reduce your risk

- Your best protection against contracting Norwalk virus is to practice *proper handwashing techniques* and to only eat thoroughly cooked shellfish.
- Avoid any food or water that you suspect might be prepared in an unsanitary way.

The U.S. Centers for Disease Control predicts that the viruses will continue to turn up until laws regarding the proper disposal of sewage, from sewage plants and by fishermen and recreational boaters, are enforced.

## Rotavirus

- Have 11 segments of double-stranded RNA
- Exist in at least 9 serotypes with type A being involved in most human infection
- Cause infantile diarrhea or most common cause of gastroenteritis in Children
- Frequent cause of nosocomial infection
- Diagnosis is by serologic test particularly ELISA

### Clinical features

- Most common cause of severe diarrhea among children, resulting in the hospitalization of approximately 55,000 children each year in the United States and the death of over 600,000 children annually worldwide.
- **Incubation period** for rotavirus disease is **approximately 2 days**. The disease is characterized by vomiting and watery diarrhea for 3 - 8 days, and fever and abdominal pain occur frequently. *Immunity after infection is incomplete, but repeat infections tend to be less severe than the original infection.*

### The virus

- Has a characteristic **wheel-like appearance** when viewed by electron microscopy (the name rotavirus is derived from the Latin *rota*, meaning "wheel").
- Nonenveloped, double-shelled viruses. The genome is composed of 11 segments of double-stranded RNA, which *code for six structural and five nonstructural proteins*. The virus is stable in the environment.

### Pathophysiology

The most extensive studies have been done with rotavirus. Rotaviruses attach and enter mature enterocytes at the tips of small intestinal villi. They cause structural changes to the small bowel mucosa, including villus shortening and mononuclear inflammatory infiltrate in the lamina propria.

Morphologic abnormalities can be minimal, and recent studies demonstrate that rotavirus can be released from infected epithelial cells without destroying them. Viral attachment and entry into the epithelial cell without cell death may be enough to initiate diarrhea. **The epithelial cell** synthesizes and secretes numerous *cytokines and chemokines*, which can direct the host immune response and potentially regulate cell morphology and function. Recent studies also suggest that one of the nonstructural viral proteins may act as an *enterotoxin*, promoting active chloride secretion mediated through increases in intracellular calcium concentration. Toxin-mediated diarrhea would explain the observation that villus injury is not necessarily linked to diarrhea.

## Epidemiologic features

The primary mode of transmission is **fecal-oral**, although some have reported low titers of virus in respiratory tract secretions and other body fluids. Because the virus is stable in the environment, transmission can occur through ingestion of contaminated water or food and contact with contaminated surfaces. In the United States and other countries with a temperate climate, the disease has a winter seasonal pattern, with annual epidemics occurring from November to April. The highest rates of illness occur among infants and young children, and most children in the United States are infected by **2 years of age**. Adults can also be infected, though disease tends to be mild.

Frequency is seasonal. The highest incidence of rotavirus cases occurs during the months from November to April.

## Diagnosis

- **Rapid antigen detection** of rotavirus in stool specimens.
- Strains may be further characterized by *enzyme immunoassay or reverse transcriptase polymerase chain reaction*, but such testing is not commonly done.

## Treatment

For persons with healthy immune systems, rotavirus gastroenteritis is a self-limited illness, lasting for only a few days. Treatment is nonspecific and consists of oral **rehydration therapy** to prevent dehydration. About one in 40 children with rotavirus gastroenteritis will require hospitalization for intravenous fluids.

## Prevention

FDA News - In a report issued February 3rd, 2006, the U.S. Food and Drug Administration approved a **live, oral vaccine (RotaTeq™)** for use in children. The Advisory Committee on Immunization Practices (ACIP) voted to recommend a newly licensed vaccine to protect against rotavirus.

## Global Rotavirus Surveillance

- Globally, rotavirus is the cause of about 600,000 diarrheal deaths every year, 80% of which occur in poorer countries. In addition, many more children will get dehydrated and require medical intervention and hospitalization. Several vaccines against rotavirus have been or are being developed to reduce this burden.
- The Rotavirus Vaccine Program (RVP), collaboration between the World Health Organization (WHO), the Program for Appropriate Technology in Health (PATH), and the U.S. Centers for Disease Control and Prevention (CDC), is funded by the Global Alliance for Vaccines and Immunizations (GAVI).

**Oral rehydration solution (ORS)** – rehydration can be accomplished by an composed of 3.5 gm sodium chloride, 2.5 gm sodium bicarbonate (or 2.9 gm sodium citrate), 1.5 gm potassium chloride, and 20 gm glucose or 40 gm sucrose per liter of water, as recommended by the World Health Organization. Any pharmacist can prepare this. In many parts of the world, an ORS is readily available as premixed packets, and only water needs to be added. Many home remedies and commercially available rehydration

products are also useful in the management of mild acute diarrhea. Some patients may require intravenous rehydration.

#### LESS COMMON VIRUS CAUSING DIARRHEA

### Noroviruses

- Cause approximately 23 million cases of acute gastroenteritis each year and are the leading cause of outbreaks of gastroenteritis. They are responsible for 68-80% of all outbreaks in industrialized countries.
- The genus *Norovirus* was formerly called the Norwalk-like virus. The genus is in the family Caliciviridae. Noroviruses were attributed to 9 out of the 21 outbreaks of acute gastroenteritis on cruise ships reported to the CDC's Vessel Sanitation Program from January 1, 2002, to December 2, 2002.
- Cruise ship outbreaks of noroviruses are more common during summer months.

### Adenoviruses

- double-stranded non-envelope virus
- only virus with fiber protruding from each of the 12 vertices of the capsid
- **FIBER** – organ of attachment and is a hemagglutinin
  - Toxic to human cells when purified free of virions
- There 41 antigenic types and it is the **type 40 and 41** that causes infantile gastroenteritis

Transmission:

- Aerosol droplet
- Fecal-oral route (most commonly children)
- Direct inoculation of conjunctiva by fingers and tonometers (used by physician in treating the eyes)

### Astroviruses