Gastroenteritis and Bacterial Pathogenicity

Jay Reuben, DrPH
Director, Research and Development
Becton Dickinson Diagnostics

10/16/2009
October 16, 2009
Reuben @Lehigh U
Gastroenteritis

- Gastroenteritis
  - Generally refers to a variety of symptoms such as diarrhea and vomiting associated with irritation and inflammation of the stomach, large and small intestines (the gastrointestinal tract).
  - (Usually...bacteria or parasites in spoiled food or unclean water. , there may be other causes (irritants and agents that cause intolerance)
Gastroenteritis Worldwide

• In 1980 gastroenteritis from all causes caused 4.6 million deaths in children with most of these occurring in the third world.
• Current death rates have come down significantly to approximately 1.5 million deaths annually in the year 2000, largely due to the global introduction of oral rehydration therapy.
• The incidence in the developed world is as high as 1-2.5 cases per child per year and is a major cause of hospitalization in this age group.
Gastroenteritis

• About 1 billion episodes occur worldwide each year, most commonly in developing countries among children under 5 years of age. Severe gastroenteritis results in dehydration and in an imbalance of blood chemicals (electrolytes) because of a loss of body fluids in the vomit and stool.

• Source Merck Manual
Diarrheal Diseases

• Leading cause of childhood death worldwide
• 1.8 million children die every year
• More than 6000 deaths everyday
• More than 10000 deaths in the US every year

Ref: Principles and Practice of Inf Dis Mendell, Douglas and Bennett
7th Ed Elsevier 2010
Diarrheal Diseases

• Diarrheal disease is the second leading cause of infectious disease morbidity and mortality worldwide, resulting in an estimated 2.2 million deaths in 2004

Bacterial Gastroenteritis

• *Bacterial* gastroenteritis is an inflammation of the stomach and intestines caused by bacteria or bacterial toxins.

• *Viral* gastroenteritis is caused by viruses and is usually associated with watery diarrhea and vomiting.

• Less frequently, non-bacterial, non-viral gastroenteritis could also be caused by parasites.
Viral Gastroenteritis
Not associated with bacteria or parasites

- Most frequently associated with **Rotavirus** on a worldwide basis
- Every year worldwide rotavirus in children under 5 causes 111 million cases of gastroenteritis and nearly half a million deaths. 82% of these deaths occur in the world's poorest nations.

Other viruses associated with viral gastroenteritis include

- **Noravirus** (previously known as Norwalk virus)
- **Sapovirus**
- **Adenovirus**
- **Astroviruses**

www.cdc.gov/ncidod/dvrd/revb/gastro/faq.htm
Infectious diarrhea and parasites

- Giardia lamblia
- Cryptosporidium
- Isospora belli
- Cyclospora
- Entamoeba histolytica

Gastroenteritis may also be caused by protozoans and parasites. Risk increases after travel to tropical countries.
Food-borne Gastroenteritis

• Estimates in the United States suggest that 76 million episodes of food borne illness occur annually, resulting in 325,000 hospitalizations and 5000 fatalities, and that endemic waterborne disease results in 4.3 to 32.8 million cases of acute gastrointestinal illnesses annually.
Foods associated with GE

• Some sources of the infection are improperly prepared food, reheated meat dishes, seafood, dairy, and bakery products.
Risk Factors (for Gastroenteritis)

• Consumption of contaminated foods or water
• Living in or Travel to areas of poor sanitary conditions
• Risk for Gastroenteritis is estimated to be 1 in 1000
Clinical Symptoms
(that may be associated with Gastroenteritis)

- Nausea and Vomiting
- Diarrhea
- Loss of appetite
- Abdominal pain
- Abdominal cramps
- Bloody stools
Infectious Diarrhea
(adapted from IDSA guidelines)

Community Acquired (or Traveler’s) Diarrhea
(fever, bloody stools)
• Salmonella
• Shigella, E coli O157, Campylobacter, C.difficile

Nosocomial Diarrhea
• (onset after 3 days in hospital)
• C.difficile

Persistent Diarrhea
(consider parasites. Giardia, Cryptosporidium, Isospora etc)
(If HIV positive consider Mycobacterium (MAI complex)
Causative Bacteria
(most frequently associate with bacterial gastroenteritis)

- *Campylobacter jejuni*
- Clostridium
- *E. coli*
- Salmonella
- Shigella
- Staphylococcus
- Yersinia
Bacterial Pathogenicity

**Pathogen**: is a biological infectious agent that causes disease or illness to its host

**Pathogenesis**: is the ability of a pathogen to produce an infectious disease in the host
Pathogens and Commensals

- Principal Pathogens
- Opportunistic Pathogens
- Commensals
Virulence and Pathogenicity

Virulence

– a quantitative measure of Pathogenicity or the likelihood of causing disease.
– *Virulence factors* refer to the properties that enable a microorganism to establish itself, replicate on or within a specific host species, and enhance the microbe's potential to cause disease.
Types of Microbial Adhesins for adherence to host cells

• **Lectins**
  • Sialic acid binding among viruses, E coli fimbriae, haemagglutinins

• **Fimbriae**
  • E coli type k-88, k-99 CFA-1, Vibrio (Tcp)

• **Non-fimbrial adhesins**
  • Yersinia (Inv)

• **Glycosaminoglycans**
  • Chlamydia

• **Lipids**
  • lipoteichoic acid in strep pyogenes
Pathogenicity Islands (PAI)

• Many virulence determinants are encoded or associated with mobile genetic elements such as phages, plasmids, insertion elements, or transposons.
• Many such determinants are located in certain “gene clusters” which were later termed Pathogenicity Islands (PAI)
Common features of PAI

- Presence of virulence genes
- Specific presence in pathogens, absence in benign relatives
- Large distinct chromosomal regions (10 to 200 kb)
- Characteristic base composition different from core genome
- Insertion of PAI adjacent to tRNA genes
- Frequent association with mobile genetic elements, i.e., presence of: Direct Repeat ((DR) sequences
- Cryptic or functional integrase or transposase
- IS elements
- Chromosomally integrated conjugative transposons, plasmids, and phages
- Genetic instability (if functional mobility elements are present)
PAIs observed among gastrointestinal pathogens

- Helicobacter pylori
- Pseudomonas aeruginosa
- Shigella sp.,
- Yersinia
- Vibrio cholera
- Salmonella sp.,
- E coli (EHEC, EPEC)
- Staph aureus
- C difficile
Diarrheagenic Escherichia coli

- STEC (EHEC)
  - Shiga Like Toxin producing aka Enterohaemorrhagic E coli
- ETEC
  - Enterotoxigenic E coli
- EPEC
  - Enteropathogenic E coli
- EAEC
  - Enteroaggregative E coli
- EIEC
  - Enteroinvasive E coli
Stages of Pathogenesis associated with diarrheagenic *E coli*

- Colonization of host surfaces
- Evasion of host defenses
- Multiplication
- Host damage

*Nataro, James P., Kaper, James B. Diarrheagenic Escherichia coli*  
Pathogenesis
(associated with diarrheagenic *E coli*)

Attachment and Colonization of host surfaces

- Special adherence fimbriae / pili that enables colonization of small bowel mucosa

- Adhesion components (fibronectin and collagen binding proteins)

- Many GN bacteria possess adhesive organelles called fimbriae or pili that facilitate attachment to host cells
- There are also tissue specific (tissue tropism) fimbriae (Uropathogenic *E coli* or UPEC) in Urinary tract infections, cystitis, pyelonephritis
Pathogenesis

Evasion of host defenses

• Mucosal defenses, phagocytes, cell-mediated immunity
• OMP in non enteric GN bacteria, Peptidoglycans of cell walls in GP,
• LipoTeichoic acids (Gr A Strep), Protein A in Staph
• Encapsulated bacteria K pneumo, S pneumo (Polysaccharide capsule prevents opsonization and phagocytosis)
• Yersinia secrets proteins to deter phagocytosis
Adherence to host cells

Courtesy: ASM Microbe Library
Bacterial Biofilms or “slime”

- Bacterial communities enclosed in a matrix of extracellular polymeric substances
- Enable bacteria to adhere to host surfaces
- Bacterial biofilms or slime contribute to the pathogens' ability to avoid host defenses including exposure to optimum concentrations of antibacterial agents
- These present challenges to eradication or killing of bacteria in the medical arena (medical implants, catheters, contact lenses etc)
Multiplication

• Microbial invasion into sub mucosal sub-surface
• Virulence factors activated
• May involve destructive enzymes targeted against host cells and tissue
  • (hyaluronidases, collagenases, nucleases)
• May Invade deeper into host cells (Shigella, EIEC) or cause disease from site of attachment (diphtheria)
Toxins

In the context of Infectious Diseases,
Molecules produced by microbes (including bacteria, parasites, fungi, and viruses) that target cells and tissues within the infected host

The word toxin is derived from the Greek toxikon, or “bow poison,” referring to poisonous material placed on arrows by Greek warriors.
Infectious Doses of Enteric Pathogens

• Post exposure, Development and progression of an enteric infection depends on the number of bacteria ingested.

• Usually, in bacterial infections a very large dose is required for disease progression (\(10^5\) to \(10^8\))

• But there are exceptions:
  • Shigella 10 – 100 cells
  • Enterohaemorrhagic E coli 10 – 100
  • Campylobacter jejuni 100 – 1000000
  • Giardia, Entamoeba – 10 -100 cysts
  • Cryptosporidium 1 – 1000 Oocysts
Pathogenic mechanisms among Diarrheagenic E coli

- **ETEC**
  - Adherence (via CFA I-IV), LT-1 and STa, STb toxins encoded in plasmids (LT-II in chromosome)

- **EHEC**
  - Attachment similar to EPEC, produce Shiga-Like (Vero) toxin 1 or 2 that inhibit protein synthesis-chromosomally encoded (PAI)

- **EIEC**
  - Mucosal invasion, EIET (secretory toxin) Plasmid, Chromosomally encoded, pINV plasmid encoding*

- **EAEC**
  - Local adherence with pili, plasmid encoded, AggR plasmid*

- LT and ST = heat labile and stable Enterotoxins
- CFA = Colonization Factor antigen

* J.Antikainin et al., *Ref Eur J Microbiol Inf Dis 2009*
Virulence tests (Sereny Test) for cell invasion properties in animal models Keratoconjunctivitis in rabbits
Endo and Exo Toxins

- **ENDOTOXINS**
  - Mostly in Gram negative bacteria
  - Lipo-polysaccharide of cell envelope
  - Released upon cell lysis
  - May Cause
    - disruption of clotting
    - Hypotension
    - Shock and Death
Toxins contd.,

• **EXOTOXINS**
  - Mostly in Gram Positive bacteria
  - Diffuses into the environment
  - Does not require cell lysis or death
  - Target specific to host cells
  - May kill host cells
  - May interfere with specific intracellular functions (protein synthesis, neuromuscular damage)
Types of Toxins

- **Chemical composition**
  - Proteins, Lipids, Lipopolysaccharides

- **Host Target (cells, Tissue)**
  - Enterotoxins (*Vibrio cholera* cAMP, *E. coli* LT, *St. cGMP*)
  - Neurotoxins (*C. botulinum*)
  - Cytotoxin (cell effacing, *Shigella*)

- **Mechanism of action**
  - ADP ribosylating, Proteolytic

- **Molecular Target**
  - Low molecular wt proteins,

- **Biological effect**
  - Hemolytic, edema causing, exfoliating

- **Origin**
  - Diphtheria, Pertussis, Cholera, Anthrax
Pathogenesis and Disease progression

- Host factors
  - Exposure
  - Surface defenses
  - Degree of Immunity
  - Medical intervention
- Pathogen
  - Infectious dose
  - Degree of virulence
  - State of host defense
  - Inadequate medical intervention
Outcomes

- Full recovery
- Residual effects
- Health severely compromised
- Death
Prevention Strategies

- Personal Hygiene
- Health Education
- Minimizing risk of exposure
- Preventing Transmission
- Containment of microbial reservoirs
- Minimizing risk before and after
  - Immunization
  - Prophylaxis
Thank you

Jay-reuben@bd.com