Module on Childhood Diarrhea

Introduction to Global Health
April 2010

Global Aspects of Childhood Diarrhea

- Diarrhea is the second leading cause of death in children under five years of age (*)
  - Pneumonia: 2.0 million/year
  - Diarrheal disease: 1.9 million/year
  - Malaria: 853 thousand/year
  - Measles: 395 thousand/year
  - HIV/AIDS: 321 thousand/year
- (*) Excluding neonatal causes


Cause-specific childhood deaths* in Developing Nations

(*) Under 5 years of age

Global Aspects of Childhood Diarrhea

- “Why is diarrhea, an easily preventable and treatable disease, one that in the developed world is considered little more than an inconvenience, causing an estimated 1.5 million under-five deaths every year?”

Time Magazine – Oct. 16, 2006

Module on Childhood Diarrhea

- Biomedical perspectives
- Epidemiological perspectives
- History of a global health initiative

Module on Childhood Diarrhea
Part 1 - Biomedical perspectives of diarrhea

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Biomedical Perspectives

- Intestinal structure and function
- Diarrhea
  - General causes
  - Types of diarrhea
  - Prevention & treatment
- Rotaviruses
  - Virus characteristics & replication
  - Pathogenesis of rotaviral diarrhea

Gastro-Intestinal System

- The gastro-intestinal system has two main purposes:
  - Nutrition:
    - Process, digest, and absorb nutrients
    - Maintenance of water & electrolyte balance
    - Eliminate waste and harmful substances
  - Defense:
    - Protect the body from external physical and biological agents

Intestinal Track

- The intestinal track is composed of:
  - Small Intestine:
    - Duodenum (25 cm)
    - Jejunum (2.5 m)
    - Ileum (3.5 m)
  - Large intestine
    - 1.5 m

Small Intestine Structure

- Mesentery
  - Attachment & support
  - Holds blood vessels, & nerves

Small Intestine Structure

- Muscularis
  - Two smooth muscle layers
    - Outer is longitudinal
    - Inner is concentric

Small Intestine Structure

- Sub-Mucosa
  - Connective tissue
  - Nerve endings, blood & lymph capillaries
  - Lymphoreticular tissue
**Small Intestine Structure**

- Mucosa
  - Crypts
  - Villous (only in small intestine)

**Intestinal Crypts & Villi**

- Small Intestine
- Large Intestine

**Intestinal Cell Dynamics**

- Stem cells are located at the bottom of crypts
  - Stem cells replicate and differentiate into several specialized enterocytes
  - Enterocytes are pushed up changing function as they migrate up the villous
  - Old enterocytes are slough off at the tips of the villous and proteins are digested

**Regeneration of Intestinal Mucosa**

- As long as the crypt stem cells are not affected, the intestinal mucosa continuously regenerate even after injury
- The entire small intestinal epithelium is replaced every 3-5 days

**Intestinal Cells**

- Enterocytes
- Goblet Cells

**Intestinal Cells**

- Microvilli & Glycocalyx
- Goblet cells
Intestinal Surface Area

- The entire intestinal surface is amplified by:
  - Intestinal folds (~3x)
  - Intestinal villi (~10x)
  - Enterocyte microvilli (~20x)
- Total surface area is amplified ~1,000 fold

Intestinal Surface Area

- In a typical adult, the entire active intestinal surface is approximate 2,000 sq feet
  - The size of a tennis court!
- This is the surface available for intestinal digestion of nutrients and the maintenance of water and electrolyte balance

Intestinal Fluid Dynamics (Adult)

- Total intestinal fluids:
  - Ingested fluids (diet): 1.5 liters (51 oz)
  - Secreted fluids: 7.0 liters (237 oz)
    - Gastric, salivary, pancreatic, biliary, & intestinal secretions
- Intestinal absorption:
  - Small intestine: 6.5 liters (220 oz)
  - Large intestine: 1.9 liters (64 oz)
- Fecal fluids:
  - 0.1 liters (3.4 oz)

Intestinal Electrolyte Dynamics (Adult)

- Total sodium absorbed/day: 25-35g/day
  - Ingested: 5-8 g of sodium/day
  - Secreted: 20 – 30g of sodium/day
- Absorption of sodium helps in absorbing sugars from the intestinal tract
- Normally less than 0.5 g of sodium is lost in the feces per day
  - 1 to 5 miliequivalents of sodium and chloride ions in fecal output

Intestinal Electrolyte Dynamics (Adult)

- Small intestine:
  - Absorbs net amounts of water, Na⁺, Cl⁻, and K⁺
  - Secretes HCO₃⁻
- Large intestine:
  - Absorbs net amounts of water, Na⁺ and Cl⁻
  - Secretes both K⁺ and HCO₃⁻

Sodium & Water Transport

- Active transport of sodium through the microvilli into the enterocyte
- Followed by active transport of sodium through basolateral membranes
- Osmosis of water into the paracellular spaces
Small Intestine Nutrient Absorption

- Absorbed water, electrolytes and water soluble nutrients reach the general circulation through the villous venous capillaries
- Absorbed fats and fat soluble nutrients reach the blood through the villous lacteals & lymphatic duct

Fecal Composition

- 75% water (~100ml)
- 25% solids
  - 30% dead bacteria
  - 10-20% fat
  - 10-20% inorganic matter
  - 3% protein
  - 30% undigested roughage

Intestinal Immune System

- Gut-associated lymphoid tissue (GALT)
  - Peyer’s patches
  - Other lymphoid aggregates
  - Plasma cells in intestinal sub mucosa

Intestinal Immunity

- Active secretory immunity
  - Uptake of intestinal antigens (“M” cells)
  - Antigen presentation in lymph nodes
  - Production of antibodies in intestinal plasma cells
  - Secretion of antibodies into intestinal lumen
- Passive secretory immunity
  - Ingestion of breast milk antibodies
    - Colostrum
    - Milk

Secretory IgA Antibodies (sIgA)

- Secretory immunoglobulin A (sIgA) is the main antibody protecting mucosal surfaces
  - Respiratory
  - Gastrointestinal
  - Genitourinary
  - Colostrum and breast milk are very rich in sIgA antibodies
- Between 3 and 5g of sIgA are actively secreted into the intestinal lumen each day

Secretory IgA Antibodies (sIgA)

- The sIgA molecule is a dimer antibody joined together by the “J” piece with an associated “secretory” component
- The secretory component of sIgA protects the immunoglobulin from digestion by proteolytic enzymes, thus sIgA can survive in the gastrointestinal tract environment providing protection against intestinal microbes
Secretory IgA Antibodies (sIgA)

- Ingested sIgA from breast colostrum and milk coat the intestinal tract providing passive protection against intestinal microbes
- A portion of the ingested sIgA can be absorbed from the intestinal tract and transported to other mucosal sites like the respiratory tract

Definition of Diarrhea

- “Diarrhea is the passage of unusually loose or watery stools, usually at least three times in a 24 hour period”
- However, it is the consistency of the stools rather than the frequency that is most important
- Diarrhea is due to an imbalance between digestion, secretion and absorption at the intestinal level

Normal Homeostasis

<table>
<thead>
<tr>
<th>IN</th>
<th>OUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Intake</td>
<td>GI secretion</td>
</tr>
<tr>
<td>Water Reabsorption</td>
<td>Fecal water</td>
</tr>
</tbody>
</table>

Malabsorption Diarrhea

<table>
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Secretory Diarrhea

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General Causes of Diarrhea

- Bacterial infections
- Viral infections
- Food intolerances
- Parasites
- Reaction to medicines
- Intestinal diseases
- Functional bowel disorders
Clinical Types of Diarrhea

- Acute watery diarrhea
  - Too much secretion (V. cholera, E. coli), or
  - Lack of absorption (Rotaviruses)
- Acute bloody diarrhea (Dysentery)
  - Intestinal damage (Shigella)
- Persistent diarrhea (> 14 days duration)
  - Severe undernourishment
  - AIDS
- Diarrhea with severe malnutrition
  - Marasmus or kwashiorkor

Prevention of Diarrhea

- Sanitation to prevent fecal-oral transmission of intestinal pathogens
  - Sanitary disposition of human excreta
  - Adequate source of clean water
  - Washing of hands
  - Washing or peeling of fresh fruits and fresh vegetables
  - Proper cooking of foods

Global Water Resources

- TOTAL WATER
  - Salt Water (97.5%)
  - Fresh Water (2.5%)

- FRESH WATER
  - Polar Caps (70.0%)
  - Soil Moisture (29.0%)
  - Surface Water (1.0%)

Prevention of Diarrhea

- Maintenance of adequate level of nutrition
- Adequate provision of breast colostrum and milk for infants
- State of general good health
  - Prevention of intestinal parasites
- Hygienic handling of diarrheal patients

Treatment of Diarrhea

- Provision of water and electrolytes to prevent dehydration and electrolyte imbalances
  - Oral therapy
  - IV therapy in severe cases
- Maintenance of adequate nutrition
  - Soft easily digestible diets
  - Maintenance of breast feeding of infants
- No need for routine use of antibiotics!

Causes of Childhood Diarrhea

- Childhood diarrhea is a common symptom of gastrointestinal infections caused by a large variety of pathogens, Rotaviruses being one of the most common causes around the globe
Rotaviruses ("Rota" = wheel)

- **Genus: Reoviridae**
  - Non-enveloped
  - Double-stranded RNA viruses
  - Segmented genome
- **Family: Rotavirus**
  - 3 layered capsid
  - 11 ds RNA Segments
  - 7 Groups:
    - A, B, C, D, E, F and G.
    - Type A, most common in humans

Rotaviruses – Virus Structure

- 6 Structural proteins (VP)
  - VP1, VP2, VP3, VP4, VP6 and VP7
- 6 Non-structural proteins (NSP)
  - NSP1, NSP2, NSP3, NSP4, NSP5 and NSP6

Rotavirus Serotype Determinants

- Grouped by neutralizing antibody responses to each of the two outer capsid proteins
  - VP7 (G serotype): 10 "G" serotypes
    - 80% comprise G1, G2, G3, and G4 human rotavirus strains
    - G9 emerging as an important strain
  - VP4 (P serotype): 7 "P" serotypes

Rotavirus Shedding

- During acute infection, one gram of feces can contain up to $10^{12}$ infectious particles
  - Only 10-100 particles are required to transmit infection to another person

1 gram = 100 billion infective doses

Rotavirus Environmental Stability

- Resistant to lipid solvent disinfectants
- Can remain infectious in fecal matter for 7 months at room temperature

Rotavirus Replication

- Rotavirus targets the mature enterocyte cells located in the upper areas of the intestinal villi
Rotavirus infection of enterocytes results in cell death and villous atrophy

Other Effects of Rotavirus Infection

- Enterotoxic NSP4 protein:
  - Induces age- and calcium ion-dependent chloride secretion
  - Disrupts SGLT1 transporter-mediated reabsorption of water
  - Apparently reduces activity of microvilli membrane disaccharidases
  - Possibly activates the calcium ion-dependent secretory reflexes of the enteric nervous system

Rotavirus Transmission

- Rotaviruses are mainly transmitted thru the fecal-oral route
  - Some indications of probable respiratory route infection
- Common infections in children and adults
  - No clinical effects on adults
  - Severe clinical diarrhea in children
    - High case fatality rate in untreated children
- Children with Rotavirus diarrhea can shed virus for 4 to 56 days (average 10 days)

Other Effects of Rotavirus Infection

- Post-rotavirus infection, immature enterocytes are deficient in secretion of lactase leading to milk intolerance which can persist for weeks
- A recurrence of mild diarrhea often follows the reintroduction of milk into the child’s diet, due to bacterial fermentation of the lactose in the intestinal lumen
- Normal digestive function returns when only when the villous epithelium has fully recovered
  - At least 5 to 7 days in the absence of additional injury

Rotavirus Transmission

- Nosocomial Rotavirus infections occur frequently in contaminated nurseries
  - 32% of rotaviral diarrhea diagnosed in children in developing countries was acquired while in the hospital
Rotavirus Immunity

► Levels of serum (IgG type) antibodies are not associated with rotavirus protection
  • Acquired through passive maternal antibodies or acquired through infection
► However, levels of mucosal antibodies, particularly of sIgA antibodies has been demonstrated to provide good immunity against rotavirus infection
  • Acquired through passive ingestion of maternal colostrum & milk or acquired through active intestinal infection
  • Protective antibodies are induced by rotavirus VP4 and VP7 surface proteins

Discussion Time ...

► Size of countries in relation to prevalence of childhood diarrhea found in children aged 0-4