**Diarrhea**

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**Diarrhea is both a sign and symptom**

A. As a symptom:
1. ↑ Frequency
2. ↑ Volume
3. ↑ Consistency

B. As a sign:
Stool weight > 150 to 200 g per 24 hr.
(stool water > 150 to 200 ml per 24 hr.)

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**The frequency of bowel movements varies considerably in the general population**

- Mean Number of Bowel Movements/Day

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**Daily intake and endogenous secretions are efficiently absorbed by the gastrointestinal tract**

- Oral Intake: 2000
- Salivary Glands: 1500
- Stomach: 2500
- Bile: 500
- Pancreas: 1500
- Intestines: 1000

Net Balance: 2000 - 200 = 1800

Endogenous Secretions: 7000

% Absorbed: 8800/9000 = 98%

Total presented to intestine: 8800

Absorbed: 200

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**Diarrhea is a major cause of worldwide morbidity and mortality**

- 3-5 Billion Episodes per Year
- 5 Million Deaths per Year, 80% under One Year of Age
- A Major Cause of Work Absenteeism
- A Major Economic Burden, Particularly in Developing Nations

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**The amount of fluid absorbed differs throughout the intestine**

- Duodenum/
  Jejunum: -5.5 L
- Ileum: -2 L
- Colon - Rectum: -1.3 L

Intake: -2 L

Endogenous secretions: Enteric, pancreatic, salivary, biliary, gastric

Maximum Absorptive Capacity:

- Duodenum/
  Jejunum: -12 L
- Ileum: -4.4 L
- Colon - Rectum: -8 L
Intestinal mucosa

- Large surface area
- Stable ionic microenvironment
- Epithelial cell turnover
- Epithelial cell maturation
- Structural and functional adaptations
- Epithelial cell polarity

The intestine has a very large surface area for absorption

<table>
<thead>
<tr>
<th>Type of Surface</th>
<th>Amplification Factor</th>
<th>Surface Area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal cylinder</td>
<td>1</td>
<td>3,300</td>
</tr>
<tr>
<td>Fold of Kerkring</td>
<td>3</td>
<td>10,000</td>
</tr>
<tr>
<td>Villi</td>
<td>10</td>
<td>100,000</td>
</tr>
<tr>
<td>Microvilli</td>
<td>20</td>
<td>2,000,000</td>
</tr>
</tbody>
</table>

Total surface area = 200 m²
Double Tennis Court = 175 m²

Intestinal epithelial cells are continually renewed

Villus Region
- Cell death and sloughing
- Turnover time ~ 48-72 hr
- Dividing Cells
- Paneth Cells

Crypt Region
- Normally: # Cells entering villus = # Cells dying

The intestinal mucosa changes with nutrient availability and disease

Normal Mucosa | Villus Atrophy | Villus Hypertrophy

Examples:
- Starvation
- Diabetes, Short-bowel

Nutrient and Electrolyte Absorptive Capacity per Unit Area
Pathophysiology of diarrhea

- Osmotic
  - decreased surface area
  - unabsorbable solute
- Secretory
  - nutrient
  - toxin
  - other mediator
- Mixed mechanisms
Pathogenic mechanisms

- Decreased mucosal surface area
- Ileal dysfunction
- Exudative enteropathy
- Inflammatory or tumor-associated secretagogues
- Altered motility
  - Slow transit/bacterial overgrowth
  - Rapid transit

Consequences of intestinal resection

<table>
<thead>
<tr>
<th></th>
<th>Jejunal resection</th>
<th>Ileal resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total nutrient absorption</td>
<td>Normal (if &lt;75%)</td>
<td>Normal</td>
</tr>
<tr>
<td>B12, bile salt absorption</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Adaptation</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Transit</td>
<td>Normal</td>
<td>Rapid</td>
</tr>
</tbody>
</table>

Viruses associated with gastroenteritis

- Rotaviruses
- Adenoviruses
- Caliciviruses
- Norwalk like viruses or SRSV (Small Round Structured Viruses)
- Astroviruses
- SRV (Small Round Viruses)
- Coronaviruses
- Toroviruses
Hydroxy fatty acids (OHFA) are produced from dietary lipids by enzymes of enteric bacteria.

\[
\text{Oleic Acid} \quad \text{CH}_3 \cdot (\text{CH}_2)_7 \cdot \text{CH} \cdot (\text{CH}_2)_7 \cdot \text{COOH} \\
\text{Hydroxy Stearic Acid} \quad \text{CH}_3 \cdot (\text{CH}_2)_7 \cdot \text{CH} \cdot (\text{CH}_2)_7 \cdot \text{COOH}
\]

Ricinoleic acid, the active ingredient of castor oil, is an OHFA.

**Mycobacterium avium**

**Laxatives are exogenous compounds that act similar to endogenous secretagogues**

- **Endogenous**
  - Bile Acids
  - Fatty Acids
  - Hydroxy Stearate
- **Exogenous**
  - Phenolphthalein
  - Bisacodyl
  - Diocetyl Sodium Sulfonate
  - Ricinoleate (in castor oil)

**Inflammation-induced diarrhea results from several mechanisms**

1. Stimulated secretion and inhibited absorption
2. Stimulation of enteric nerves causing propulsive contractions and stimulated secretion
3. Mucosal destruction and increased permeability
4. Nutrient malabsorption and malabsorption

**Mycobacterium avium**

- Ulcerative colitis
- Cytomegalovirus colitis
Guidelines - why?

- Response to need for cost effective approach to diagnosis and management
- Evidence-based approach
  - Identify uncertainties
  - Grades the quality of the evidence as much as the evidence itself
- Work in progress: needs periodic revision

Guidelines

<table>
<thead>
<tr>
<th>Strength</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - Good evidence to recommend</td>
<td>I - At least 1 RCT</td>
</tr>
<tr>
<td>B - Fair evidence to recommend</td>
<td>II - At least 1 well-designed trial</td>
</tr>
<tr>
<td>C - Poor evidence to recommend for or against</td>
<td>- not RCT</td>
</tr>
<tr>
<td>D - Fair evidence to recommend against</td>
<td>- cohort, case control, dramatic uncontrolled studies</td>
</tr>
<tr>
<td>E - Good evidence to recommend against</td>
<td>III - Expert opinion</td>
</tr>
</tbody>
</table>

Diarrhea: magnitude of the problem

- Second leading cause of morbidity and mortality worldwide
- >200 million cases of diarrhea per year in the US
- 73 million physician consultations, 1.8 million hospitalizations, 3,100 deaths (mostly in the elderly)
- Other morbidities: HUS, Guillain-Barre, malnutrition
- Etiology hardly ever determined
- Etiologic diagnosis usually is too late to be of clinical use in outpatients
- Often untreated, even if diagnosis is made
- The large majority of cases are self-limited in otherwise healthy children and adults

Practice guidelines for the management of infectious diarrhea

C. difficile toxin A stimulates net intestinal secretion and causes diarrhea through several mechanisms

Diarrhea associated with Zollinger-Ellison Syndrome is caused by multiple mechanisms

Diabetes mellitus is characterized by hyperglycemia due to insulin deficiency or resistance, resulting in hyperosmolar dehydration, low serum ionized calcium, and elevated serum phosphorus levels.
The conflict

Widening array of enteric pathogens: enterohemorrhagic E. coli, Salmonella, Shigella, Cyclospora, Cryptosporidium, Giardia, Campylobacter jejuni, Clostridium difficile, microsporidia, caliciviruses, other enteric viruses

Cost containment

Guidelines

- Oral rehydration
- Clinical and epidemiological evaluation
- Stool tests
- Antimicrobial therapy
- Antidiarrheals
- Available immunizations

Etiologic diagnosis: who cares?

- Public health: passive surveillance for common source outbreaks or serious pathogens
- Bioterrorism
- Vulnerable populations
  - Extremes of life
  - Malnourished
  - Immune deficient

Other considerations

- Regional and seasonal variation in the US
- Globalization
- Infections promoted by crowding and uncertain hygiene
  - Child care
  - Schools
  - Cruise ships
- Decreased recovery with immune deficiency: HIV, immune suppressed, post-transplant, aging

Clinical recommendations

- Initial rehydration: ORS A-I
  - available commercially
  - 3.5 gm NaCl, 2.5 gm NaHCO₃, 1.5 gm KCl, and 20 gm glucose or glucose polymer per liter of water
  - glucose can be supplied as sucrose or cooked cereal flour
  - Na 90 mM, K 20 mM, Cl 80 mM, HCO₃ 30 mM, glucose 111 mM
Jugoal Fluid Movement

280 mOsm 280 mOsm 280 mOsm
Glu Glu NaCl NaCl H2O
Net absorption Na+ Net secretion

Composition of oral solutions

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>Glucose</th>
<th>osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-ORS</td>
<td>90</td>
<td>111</td>
<td>310</td>
</tr>
<tr>
<td>Chicken soup</td>
<td>250</td>
<td>0</td>
<td>450</td>
</tr>
<tr>
<td>Sports drink</td>
<td>20</td>
<td>111</td>
<td>145</td>
</tr>
<tr>
<td>Ginger ale</td>
<td>3</td>
<td>500</td>
<td>540</td>
</tr>
<tr>
<td>Apple juice</td>
<td>3</td>
<td>690</td>
<td>730</td>
</tr>
</tbody>
</table>

*Na and glucose as mM, osmolality in mosm*