Module on Childhood Diarrhea

Introduction to Global Health
April 2010

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 number that is most important. Frequent passing of formed stools is not diarrhea.
► Babies fed only breastmilk often pass loose, “pasty” stools; this also is not diarrhea.

Epidemiological Perspective

► Epidemiology of rotaviral childhood diarrheas
► Clinical manifestations of rotaviral diarrhea
► Management of rotaviral diarrhea
► Rotaviral diarrhea vaccines

Global Distribution of Childhood Diarrheas

► Size of countries in relation to prevalence of childhood diarrhea found in children aged 0-4
**Cause-specific childhood deaths in Developing Nations**

- Under 5 years of age

**Distribution of Childhood Diarrhea Mortality**

- Size of countries in proportion to the absolute number of people who died from diarrheal in 2002

**Causes of Childhood Diarrhea**

- Childhood diarrhea is a common symptom of gastrointestinal infections caused by a large variety of pathogens:
  - Bacteria
    - *E. coli*, *Shigella*, *Campylobacter*, *Salmonella*, *V. cholerae*
  - Viruses
    - Mainly Rotaviruses
  - Protozoa
    - *Cryptosporidium*


- Estimated deaths due to rotavirus in children <5yr old

One dot = 1,000 deaths (2004)

Number of deaths due to rotavirus in children <5yrs old (% of the global total - 2004)


Childhood Rotaviral Diarrhea
Clinical Manifestations

- Fever: >37.9°C
- Vomiting: 1 – 2 days
- Diarrhea: average 4 days (1-16 days)
  - >5ml to >200ml/kg body weight/day
- Duration of hospitalization: 4 days (2-14 days)
- Dehydration
- Malnutrition
- In some cases rotavirus infection has been associated with intussusception

Childhood Intussuception: Rotavirus related?

Folding-over of the small intestine leading to occlusion of blood flow and intestinal gangrene

Dehydration

- Increased loss of water and electrolytes (Na+, Cl-, K+ and HCO3-) in the liquid stool during diarrhea.
- Water and electrolytes are also lost through vomit, sweat, urine and breathing.
- Dehydration occurs when these losses are not replaced adequately and a deficit of water and electrolytes develops.
Dehydration

► The volume of fluid lost through the stools in 24 hours can vary from 5 ml/kg (near normal) to 200 ml/kg, or more.
► The concentrations and amounts of electrolytes lost also vary. The total body sodium deficit in young children with severe dehydration due to diarrhea is usually about 70-110 millimoles per liter of water deficit. Potassium and chloride losses are in a similar range.

Dehydration Clinical Signs

► Early stages:
  • No clinical signs or symptoms
► Late stages:
  • Severe thirst and lack of skin turgor
  • Severe sunken eyes, and sunken fontanelle (in infants)
  • Evidence of hypovolemic shock:
    • Diminished consciousness, lack of urine output, cool moist extremities, a rapid and feeble pulse (the radial pulse may be undetectable), low or undetectable blood pressure, and peripheral cyanosis.
  • Death follows soon if rehydration is not started quickly.

Dehydration Clinical Signs

► Mid stages:
  • Thirst, restless or irritable behavior
  • Decreased skin turgor
  • Sunken eyes, and sunken fontanelle (in infants)

Vesikari’s Clinical Diarrhea Score System

<table>
<thead>
<tr>
<th>Point Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diarrhea (days)</td>
<td>1 - 4</td>
<td>5</td>
<td>≥ 6</td>
</tr>
<tr>
<td>Maximum number of diarrheal stools (24 hours)</td>
<td>1 - 3</td>
<td>4 - 5</td>
<td>≥ 6</td>
</tr>
<tr>
<td>Duration of vomiting (days)</td>
<td>1</td>
<td>2</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Maximum number of vomiting episodes (24 hours)</td>
<td>1</td>
<td>2 - 4</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.1 – 38.4</td>
<td>38.5 – 38.9</td>
<td>≥ 39.0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>-</td>
<td>Mild</td>
<td>Moderate to Severe</td>
</tr>
<tr>
<td>Treatment</td>
<td>Rehydration</td>
<td>Hospitalisation</td>
<td>-</td>
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</tbody>
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Diarrhea & Malnutrition

► Diarrhea is as much a nutritional disease as one of fluid and electrolyte loss
► Children who die from diarrhea, despite good management of dehydration, are usually malnourished and often severely so
► In turn, malnutrition contributes to diarrhea which is more severe, prolonged, and possibly more frequent in malnourished children.
Diarrhea & Malnutrition
► This vicious circle can be broken by:
  • Continuing to give nutrient rich foods during and after diarrhea
  • Giving a nutritious diet, appropriate for the child’s age, when the child is well
► When these steps are followed, malnutrition can be prevented and the risk of death from a future episode of diarrhea is much reduced.

Prevention of Dehydration
► Adequate supply of salted drinks, such as:
  • ORS solution
  • salted drinks (e.g. salted rice water or a salted yoghurt drink)
  • vegetable or chicken soup with salt.
► With a balance with fluids that do not contain salt, such as:
  • plain water
  • water in which a cereal has been cooked (e.g. unsalted rice water)
  • unsalted soup
  • yoghurt drinks without salt
  • green coconut water
  • weak tea (unsweetened)
  • unsweetened fresh fruit juice.

Prevention of Dehydration
► Some fluids are potentially dangerous and should be avoided during diarrhea as they may cause osmotic diarrhea and hypernatremia:
  • commercial carbonated beverages
  • commercial fruit juices
  • sweetened tea.
► Other fluids to avoid are those with stimulant, diuretic or purgative effects, for example:
  • Coffee
  • some medicinal teas or infusions.

Diarrhea Treatment Options
► Oral rehydration therapy
► Zinc supplementation
► Antimicrobial therapy
► Antidiarrheal drugs

Oral Rehydration Salts (ORS)
► An important development has been the discovery that dehydration from acute diarrhea of any etiology and at any age, except when it is severe, can be safely and effectively treated in over 90% of cases by the simple method of oral rehydration using a single fluid containing glucose and several salts in a mixture that are dissolved in water to form the ORS solution.

Oral Rehydration Salts (ORS)
► ORS solution is absorbed in the small intestine even during copious diarrhea, thus replacing the water and electrolytes lost in the feces.
► ORS solution and other fluids may also be used as home treatment to prevent dehydration.
Oral Rehydration Therapy (ORT)

After 20 years of research, an improved ORS solution has been developed. Called reduced (low) osmolarity ORS solution:
- Reduces by 33% the need for supplemental IV fluid therapy after initial rehydration
- Reduces the incidence of vomiting by 30% and stool volume by 20%.

This new reduced (low) osmolarity ORS solution, containing 75 mEq/l of sodium and 75 mmol/l of glucose, is now the ORS formulation officially recommended by WHO and UNICEF.

Guidelines for ORS Treatment for Infants

<table>
<thead>
<tr>
<th>APPROXIMATE AMOUNT OF ORS SOLUTION TO GIVE IN THE FIRST 4 HOURS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>1 ml</td>
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- Give with spoon, dropper or syringe (without needle)
  - (not with an infant feeding bottle)
- One teaspoonful every 1-2 minutes
  - If vomiting a spoonful every 2-3 minutes

Zinc Supplementation

- Zinc has been shown to play critical roles in metallo-enzymes, polyribosomes, the cell membrane, cellular function, cellular growth and in the function of the immune system.
- Zinc supplementation (10-20 mg/day until cessation of diarrhea) significantly reduces the severity and duration of diarrhea in children <5 yrs old
- Additional studies have shown that short course supplementation with zinc (10-20 mg/day for 10 to 14 days) reduces the incidence of diarrhea for 2 to 3 months.

Antimicrobial Therapy

- Antimicrobials should not be used routinely:
  - Non-bacterial diarrheas are not susceptible to antimicrobial therapy (such those caused by Rotavirus or Cryptosporidium)
  - If antibiotics were to be used for bacterial diarrheas, it would be important to know their sensitivity to the drug available, information that is usually unavailable.
  - In addition, the use of antimicrobials adds to the cost of treatment, risks adverse reactions and enhances the development of resistant bacteria.

Antimicrobial Therapy

- Antimicrobials are helpful only for:
  - Children with bloody diarrhea (probable shigellosis)
  - Suspected cholera with severe dehydration, and
  - Serious non-intestinal concurrent infections such as pneumonia
- Anti-protozoal drugs are rarely indicated.
Antidiarrheal Drugs

- "Antidiarrheal" drugs and antiemetics have no practical benefits for children with acute or persistent diarrhea.
- They do not prevent dehydration or improve nutritional status, which should be the main objectives of childhood diarrhea treatment.
- Some have dangerous, and sometimes fatal, side-effects. These drugs should never be given to children <5 yrs old.

Rotavirus Vaccines

- In 1998 a rhesus monkey rotavirus vaccine (RotaShield™ - Wyeth) was licensed for use in the United States.
- RotaShield™ was withdrawn from the market in 1999 by the after it was discovered that the vaccine may have contributed to an increased risk for intussusceptions in one of every 12,000 vaccinated infants.
  - Recalculated after the fact to be 1:32,000 vaccinees.
- This event sparked a debate about the relative risks and benefits of child rotavirus vaccination.

Rotavirus Vaccines

- After a decade of research and discussion, a new generation of animal-human rotavirus reassortant vaccine candidates were developed.
- A meeting in 2001 of the GAVI Alliance (Global Alliance for Viral Immunization) and the WHO concluded that "the lack of quality scientific data from developing countries needed to be addressed before widespread, routine global use of rotaviral vaccines could become a reality."

Rotavirus Vaccines

- In 2003 the Rotavirus Vaccine Program (RVP) was launched by a consortium led by PATH (Program for Appropriate Technology in Health), the CDC and the WHO with funding from GAVI.
- This program stimulated the epidemiological studies of rotaviral diarrhea and the development and commercialization of oral rotaviral vaccines.
- In 2006, two live attenuated oral vaccines against Rotavirus A infection were shown to be safe and effective in children.

Current Rotavirus Vaccines

- RotaTeq™ - Merck
  - Pentavalent vaccine with 5 bovine – human reassortant strains (G1, G2, G3, G4 and P)
  - 3 doses (2, 4, & 6 months of age)
  - First dose at >6 weeks and <12 weeks
  - Licensed by the FDA in 2006
**Current Rotavirus Vaccines**

- **Rotarix™ - GlaxoSmithKline**
  - Monovalent human rotavirus G1 strain
  - 2 doses (2 & 4 months of age)
  - First dose at >6 weeks and < 20 weeks
  - Licensed by the FDA in 2008
  - Approved for use in 114 countries
  - About 68 million doses of Rotarix have been sold worldwide, including approximately 2.5 million doses in the United States.

**Rotarix™ & RotaTeq™ Vaccines**

- Very large trials of both vaccines in Europe, North America and Latin America shown an efficacy of 85% - 95% against severe rotaviral diarrhea and hospitalizations
- No findings of increased or any other statistical association with intussusception among vaccine recipients

**WHO Recommendation**

- Additional trials of rotavirus vaccination in Africa and other developing countries further demonstrated the efficacy of these vaccines in saving lives of children with rotaviral diarrheas
- In June 5, 2009 the WHO recommended that rotavirus vaccination be included in all national immunization programs

**Latest Developments re: Rotarix™**

- March 15, 2010: FDA warning regarding the detection of DNA from porcine circovirus type 1 (PCV1) in Rotarix™.
- While there is no current evidence that this finding poses a safety risk, the FDA recommended a US temporary suspension on the use of Rotarix™.
- FDA has tested lots of RotaTeq™ for evidence of PCV1. Preliminary studies have not found DNA from PCV1 in RotaTeq™.

**Latest Developments re: Rotarix™**

- “Both FDA and GlaxoSmithKline are reviewing all available evidence and conducting additional tests to obtain more information about the presence of PCV1 DNA in Rotarix™, including whether intact virus (as opposed to DNA fragments) is present.”

  FDA posted information on March 30, 2010

**Discussion Time ...**