

## Update on acute diarrhea in developing countries: oral rehydration, refeeding, probiotics, and beyond

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## Objectives

- To discuss acute diarrhea in developing countries
- To evaluate the efficacy of different oral rehydration solutions (ORS), zinc (Zn), probiotics for treatment of acute diarrhea
- To compare early and late reintroduction of feeding in children with acute diarrhea

## Introduction

- Diarrhea is the passage of loose or watery stools at least three times in a 24 hour period
- In developing countries episodes of diarrhea/year:
  - \* Infants experience a median of 6 episodes
  - \* Children experience a median of 3 episodes
- Acute diarrhea is the leading cause of child mortality, second only to pneumonia in developing regions

*Parashar UD et al. J Infect Dis 2009;200:s9-15*

## In the US

- Diarrhea caused by gastroenteritis remains the major cause of hospitalizations (>200,000/year) and outpatient visits (>1.5 million/year)
- Resulting in 300 deaths every year
- The annual direct medical costs are estimated to be more than 1 billion US dollars per year

*Santosham M et al. Pediatrics. 1997;100(5):E10*

## Etiology of Acute Diarrhea

- Acute watery diarrhea
  - **Rotavirus** worldwide 40% of hospitalized children < 5 years
  - Enterotoxigenic Escherichia coli (ETEC) in older children
  - Vibrio cholerae in endemic areas
  - Norovirus
- Invasive diarrhea
  - Shigella flexneri, dysenteriae, boydii, sonnei
  - Salmonella enterica
  - Campylobacter spp, Enterohemorrhagic E. coli (EHEC), Enteroinvasive E. Coli (EIEC)
  - Protozoan Entamoeba histolytica



## Implemented measures

- Thanks to World Health Organization (WHO), diarrhea mortality rates dropped by 75% from 1980 to 2008 worldwide

- Oral Rehydration Solution (ORS) first documented in 1945

*Harrison HE. Pediatr Clin North Am. 1954*

- 2006 two live oral, attenuated rotavirus vaccines were licensed
  - Pentavalent bovine-human reassortant vaccine (RotaTeq®)
  - Monovalent human rotavirus vaccine (Rotarix®)

## Oral Rehydration Solution

- 1960s an ORS that was isotonic with equimolar concentrations of glucose and Na was as effective as intravenous hydration

*Hirschhorn N et al. N Engl J Med. 1968;279(4):176*

- 1975 WHO standard ORS (90 mmol/liter Na<sup>+</sup>)
- Different sodium concentrations are routinely used in different countries
  - "Reduced osmolality" (75-45 mmol/liter Na<sup>+</sup>)

## Properties for ORS

Recommended by the WHO and UNICEF

- Total osmolality between 200 to 310 mmol/L
- Equimolar concentrations of glucose and sodium
- Glucose concentration not in excess of 20 g/L (111 mmol/L)
- Sodium concentration between 60 to 90 mEq/L
- Potassium concentration between 15 to 25 mEq/L
- Citrate concentration between 8 to 12 mmol/L
- Chloride concentration between 50 to 80 mEq/L

*World Health Organization. Reduced osmolality oral rehydration salts (ORS) formulation. UNICEF House, New York, NY 2001. Available at: [www.who.int/child-adolescent-health/New\\_Publications/NEWS/Expert\\_consultation.htm](http://www.who.int/child-adolescent-health/New_Publications/NEWS/Expert_consultation.htm)*

## "Reduced osmolality" ORS

- Fear of negative Na<sup>+</sup> balance and hyponatremia
  - \* Rotavirus stool losses of Na<sup>+</sup> range from 30 to 40 mEq/L, compared to cholera 90 to 120 mEq/L
- ESPGHAN ORS solution (60 mmol/liter Na<sup>+</sup>)
- Hypoosmolar solution (45 mmol/liter Na<sup>+</sup>) has been recommended for the management of acute diarrhea in the USA

*<http://www.cincinnatichildrens.org/service/janderson-center/evidence-based-care/gastroenteritis/>*

## Meta-analysis 2001

*Hahn S et al. BMJ. 2001;323(7304):81*

- 15 RCTs, N =2397, diarrhea < 5 days duration:
  - Reduced-osmolality ORS (osmolality ≤250 mosmol/kg)
    - ✓ decreased stool output, emesis, need for IV fluid compared to:
  - Standard WHO ORS (osmolality 311 mosmol/kg)

*\* Only 3 trials included cholera patients*

- Three trials measured serum sodium values:
  - ✓ same rate of hyponatremia with both formulations

## Original ORS replaced in May 2002

- WHO suggested a new ORS formulation with:
  - Lower osmolality (245 mosmol/kg); sodium (75 mEq/L)
  - Lower concentrations of glucose (13.5 g/L)
- To determine whether reduced-osmolality WHO ORS results in an increased rate of **symptomatic hyponatremia**
  - ✓ Observational study N=53,280 adults and children
  - ✓ Conducted at two hospitals in Bangladesh
    - \* Data were compared to retrospective data from one of the sites from the previous year when the higher-osmolality WHO ORS was used

*Alam NH et al. JAMA. 2006;296(5):567*

## Original ORS replaced in May 2002

### Conclusions

- Reduced-osmolality ORS is as safe as the previous formulation and can be used to treat most patients with acute diarrhea

*Alam NH et al. JAMA. 2006;296(5):567*

## Polymer-based ORS

- Replacement of glucose with complex carbohydrates (maltodextrin or rice) or other solutes (amino acids)
- CDC does not recommend polymer-based ORS as a first choice either in developing or developed countries as the standard WHO or commercial ORS
- Formulations that either used maltodextrins or added amino acids (glycine, alanine, and glutamine) to glucose are not more effective than standard ORS, and are more costly

## Zinc

- WHO and UNICEF recommended Zn for:
  - Children < 5 yr of age with diarrhea (10 mg/day) for 10 days
  - Infants < 6 months (20 mg/day)

*WHO/UNICEF. Joint statement: clinical management of acute diarrhea. The United Nations Children's Fund/WHO; New York/Geneva: 2004*

- Zinc may be of benefit in children aged 6 months or more in high prevalence areas of Zn deficiency or moderate malnutrition

*Lazzerini M et al. Cochrane Database of Systematic Reviews 2012, Issue 6*

## ORS Containing Zinc Does Not Reduce Duration or Stool Volume of Acute Diarrhea in Hospitalized Children

*\*Nitya Wadhwa, <sup>1</sup>Uma Chandra Mouli Natchu, <sup>1</sup>Halvor Sommerfelt, <sup>1</sup>Tor A. Strand, <sup>2</sup>Vishal Kapoor, <sup>3</sup>Savita Saini, <sup>4</sup>Udaypal S. Kainth, and <sup>5</sup>Shinjini Bhatnagar*

*(JPGN 2011;53: 161–167)*

TABLE 1. Composition of the 2 ORS used as interventions

|                          | Zinc-ORS | ORS |
|--------------------------|----------|-----|
| Osmolarity, mOsm/L       | 245      | 245 |
| Glucose, mmol/L          | 75       | 75  |
| Na <sup>+</sup> , mmol/L | 75       | 75  |
| K <sup>+</sup> , mmol/L  | 20       | 20  |
| Chloride, mmol/L         | 65       | 65  |
| Citrate, mmol/L          | 10       | 10  |
| *Zinc (elemental), mg/L  | 0        | 40  |

ORS = oral rehydration solution.

\* Does not contribute significantly to osmolality of the ORS.

## Pitfalls of Zinc supplementation

- Almost all available evidence is based on children living in developing countries
- Patro et al.* in a post hoc subgroup analysis enrolled children according to the nutrition status and showed greater effect of Zn supplementation in children severely malnourished
- Evidence in poor in nonmalnourished children

*Patro et al. Aliment Pharmacol Ther 2008;28:713-723*

## Efficacy of a New Hypotonic Oral Rehydration Solution Containing Zinc and Prebiotics in the Treatment of Childhood Acute Diarrhea: A Randomized Controlled Trial

*Annalisa Passariello, MD, PhD, Gianluca Terrin, MD, PhD, Giulio De Marco, MD, PhD, Gaetano Cecere, MD, Serena Ruotolo, MD, Antonio Marino, MD, Linda Cosenza, MD, Maria Tardi, MD, Rita Nocerino, NR, and Roberto Berni Canani, MD, PhD*

**Study design:** prospective, randomized, single blind controlled trial

- Age: children age 3-36 months
- Group 1: N=60; standard hypotonic ORS (225 mOsm/L) Na 60 mmol/L
- Group 2: N=59; hypotonic ORS with Zn and prebiotics (200 mOsm/L) Na 50 mmol/L

**Main outcome:** rate of resolution of diarrhea in 72 hours

**Conclusion...in Group 2:**

- \* Higher rate of diarrhea resolution ( $p = 0.10$ )
- \* Higher ORS intake in first 24hrs ( $p < .001$ )
- \* Lower number of missed working days by parents ( $p < .001$ )
- \* Fewer drugs needed for treatment of diarrhea ( $p = .004$ )

*J Pediatr 2011;158:288-92*

## Probiotics

- May be effective in adjunct to ORS
- Data limited to 2 strains
  - Lactobacillus rhamnosus GG (LGG)
  - Yeast Saccharomyces boulardii
- Mechanism of action yet to be defined
  - \* Acts by modifying the composition of the colonic microflora and by acting against enteric pathogen

Allen SJ et al. *Cochrane Database Syst Rev* 2010;11:CD003048  
Walker WA. *Clin Infect Dis* 2008;46:S87-91

## Lactobacillus rhamnosus GG and S. boulardii

- LGG strain showed significant reduction in the duration of diarrhea (weighted mean difference, WMD -1.1, 95% CI -1.9 to -0.3 days), especially in rotavirus-associated infection (WMD -2.1, 95% CI -3.6 to -0.6 days)
- S. boulardii showed moderately effective in reducing the duration of diarrhea in healthy children with acute diarrhea (WMD -1.1, 95% CI -1.3 to -0.8 days), although the evidence-base was smaller than for LGG

Allen SJ et al. *Cochrane Database Syst Rev* 2010;11:CD003048

Szajewska H et al. *Aliment Pharmacol Ther* 2009;29:800

## Pitfalls of Probiotics

- Studies on the efficacy of probiotics have been done almost exclusively in developed areas
  - \*Evidence of efficacy is limited to developing countries
- Recent guidelines produced in India do not recommend the use of probiotics
  - \*Lack of evidence
- Malnutrition and the high incidence of bacterial agents may explain the limited efficacy of probiotics

Bhatnagar S. *Indian Pediatr* 2007;44:380-9

## Racecadotril

- Nonopioid enkephalinase inhibitor exhibiting proabsorptive and antisecretory properties leading to a reduction transepithelial secretion
- First pediatric presentation authorized in France in 1999
- Study showed significant reduction in duration of diarrhea in hospitalized children in Peru

Tormo R et al. *Acta Paediatr* 2008;97:1008-15

Guarino A et al. *J Pediatr Gastroenterol Nutr* 2008;46:s81-184

Salazar-Lindo E et al. *N Engl J Med* 2000;343:463-7

## Evaluating the cost utility of racecadotril for the treatment of acute watery diarrhea in children: the RAWD model

**Table 2** Cost comparison results (deterministic)

| Cost results                | ORS     | Racecadotril + ORS |
|-----------------------------|---------|--------------------|
| Drug cost                   | £3.03   | £12.17             |
| Primary care                | £62.64  | £51.12             |
| Secondary care              | £416.82 | £40.20             |
| Adverse events              | £0.46   | £0.35              |
| Total mean cost per patient | £482.95 | £103.84            |

Rautenberg TA et al. *Clinical Economics and Outcomes Research* 2012;4:109-116

| Treatment          | Level of evidence   | Outstanding issues   |
|--------------------|---|--|
| Zn supplementation | Good; clinically relevant reduction in the duration and severity of diarrhea  | Uncertain efficacy in children without Zn deficiency   |
| Probiotic strains  | Good but strain-specific (LGG and SB); significant reduction of diarrhea duration in meta-analyses and controlled trials; no clear effect on stool output | Highly effective against viral diarrhea but not in bacterial diarrhea<br>Mechanism of action requires more investigation |
| Racecadotril       | Good; significant reduction of stool output (in 1 clinical trial) and diarrhea duration (in 3 controlled trials)  | Need for well-designed studies in the outpatient populations to evaluate efficacy and safety                             |
| Smectide           | Good; significant reduction of stool output (in 2 trials) and diarrhea duration (in meta-analyses and controlled trials)                                  | Need for well designed studies in the outpatient setting in developed countries  |
| Prebiotics         | None  | Lack of adequate trial data to support use   |

Guarino A et al. *Expert Opin. Pharmacother.* (2012) 13(1):17-26

## Goal of Nutritional Management

- Encourage sufficient feeding during and after diarrhea illness to prevent development of malnutrition and chronic enteropathy
- ✓ Infants breastfed should continue breastfeeding and ORS
- ✓ Infants that are not breast feeding should be encouraged to take undiluted formula in addition to ORS
- ✓ Children should be encouraged to take solids immediately after dehydration is corrected

## Early versus late feeding

- 12 trials, N=1226 children <5 yr of age
  - 724 given early refeeding (12 hours of start of rehydration)
  - 502 given late refeeding (>12 hours from start rehydration)

### Results

- There was no significant difference between the 2 refeeding groups

\* Number of participants who needed unscheduled intravenous fluids, who experienced episodes of vomiting and developed persistent diarrhoea

*Gregorio GV et al. Cochrane Database Syst Rev 2011;CD 007296*

## Multifaceted measures

- Fisher and Walker estimated reduce diarrhea deaths by 80% by end of 2015
  - Breastfeeding
  - Vitamin A supplementation
  - Handwashing with soap
  - Improved sanitation
  - Safe drinking water
  - Rotavirus vaccination
  - Treatment: ORS and Zn, and antibiotics for dysentery

*Fischer Walker CL et al. PLoS Med. 2011 Mar;8(3):e1000428. Epub 2011 Mar 22*

## In conclusion

- Acute diarrhea in developing regions still carrying substantial mortality and morbidity
- ORS is the first line therapy but need to develop composition for universal solution
- Worldwide immunization against rotavirus
- Inclusion of Zn in ORS is beneficial in malnourish children
- Limited efficacy of probiotics in acute diarrhea
- The goal of nutrition management in patient without malnutrition is to encourage sufficient feeding both during and after diarrheal illness