

**CURRENT APPROACH IN THE MANAGEMENT OF DIARRHEA IN CHILDREN:  
From theory and research to practice and pragmatism.**

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**ABSTRACT**

Diarrhea is the second leading cause of deaths in children under five - after pneumonia- with 1.5 million deaths per year. Several studies and meta-analysis, show that low osmolarity oral rehydration salts and zinc, significantly reduce morbidity and mortality in children with diarrhea. Since 2004, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommended their routine use in children with diarrhea alongside existing preventive measures. Since then, these recommendations are still not yet put into practice in many countries. This article highlights current available evidence of the efficacy of low osmolarity oral rehydration salts and zinc in the management of diarrhea in children. It is hoped this will raise awareness in policy makers and health personnel to adopt these recommendations so that morbidity and mortality from diarrhea in children could be curbed.

**KEY WORDS:** Low osmolarity oral rehydration salts – Zinc – Diarrhea – Children.

**PRISE EN CHARGE ACTUELLE DE LA DIARRHEE CHEZ L'ENFANT: De la  
théorie et la recherche à la pratique et au pragmatisme.****RESUME**

La diarrhée est la deuxième cause de décès chez les enfants de moins de 5 ans - après la pneumonie- avec 1,5 million de décès par an. Plusieurs études et meta-analyses ont démontré l'efficacité des sels de réhydratation orale et du zinc dans la réduction de la morbidité et la mortalité des enfants avec la diarrhée. Depuis 2004, l'Organisation Mondiale de la Santé (OMS) et le Fonds des Nations Unies pour l'Enfance (UNICEF) ont recommandé leur utilisation dans la prise en charge de la diarrhée chez l'enfant en plus des mesures préventives existantes. Depuis lors, ces recommandations ne sont toujours pas mises en œuvre dans plusieurs pays. Cet article fait la mise au point des recherches récentes sur l'efficacité des sels de réhydratation orale et le zinc dans la prise en charge de la diarrhée chez l'enfant. Le but est de sensibiliser les décideurs et le personnel de santé à adopter ces recommandations afin de réduire la morbidité et la mortalité chez des enfants avec la diarrhée.

**MOTS CLES:** Sels de réhydratation orale a faible osmolarité – Zinc – diarrhée – Enfants.

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**1-INTRODUCTION**

According to the World Health Organization (WHO), an estimated 2.5 billion cases of diarrhea occur among children under 5 years of age each year, and estimates suggest that the overall incidence has become stable over the past two decades. More than half of the cases occur in Africa and South-East Asia, where bouts of diarrhea are likely to result in death or other severe outcomes. The incidence varies with the season and the child's age: incidence varies in the first two years and declines thereafter [1].

Diarrhea is the second leading cause of death among children under five. Nearly one in five child deaths (about 1.5 billion each year) is due to diarrhea [1].

Mortality from diarrhea has declined over the past two decades from an estimated 5 million deaths among children under 5 to 1.5 million deaths in 2004, which parallels downward trends in overall under-five mortality during this period. Despite these declines, diarrhea remains the second most common cause of death among children under 5 globally, following closely behind pneumonia, the leading killer of young children, and before malaria [1-2].

Why should diarrhea, an easily preventable and treatable disease still be causing an estimated 2.5 billion under five deaths every year? Reducing these deaths depends not only on preventive measures and the rotavirus vaccine, but largely on delivering life saving treatment of low osmolarity oral rehydration salts (ORS) and zinc tablets to all children with diarrhea. Today, only 39% of children with diarrhea in developing countries receive the recommended treatment, and limited trend data suggest that there has been little progress since 2000 [1].

In this paper we highlight the potential benefits from current available evidence, of low osmolarity ORS and zinc in the treatment of diarrhea in children, to incite health professionals to adopt and implement WHO recommendations which have proven their worth.

## II- FROM RESEARCH TO ADVOCACY

Diarrhea with severe zinc deficiency had been observed in children in developing countries. Studies linking diarrheal diseases with zinc deficiency were first described in reports of low plasma zinc levels in children with diarrhea [3].

Researchers at the John Hopkin's School of Public Health conducted pooled analyses including all available published and unpublished randomized controlled trials of the effects of supplementary oral zinc in children aged less than 5 years with acute or persistent diarrhea, and found that zinc supplements significantly reduced the duration of acute and persistent diarrhea in children [4]. Meta-analysis of randomized, controlled studies that had assessed the therapeutic benefit of zinc supplement in conjunction with ORS in children under 5 was done. Acute diarrhea was defined as 3 or 4 loose stools or more per day and persistent diarrhea as that which has lasted for 14 days or more. The results showed that zinc supplementation gave a 15% reduction in the duration of acute diarrhea and a 24% reduction in those with persistent diarrhea [4-5].

In the early 1980s, the introduction of ORS led to significant and continuing decrease in the rate of diarrhea mortality. Until recently, ORS, increased fluids, and

continuing feeding have been the only recommended treatments for episodes of non complicated diarrhea. Although ORS had proven efficacy, researchers continued to work on developing a new formula that would allow for more hydration while decreasing the amount of stool output. As a result, an ORS formula with lower glucose and sodium (lower osmolarity ORS) was developed, and has proven to be more effective by decreasing the need for intravenous therapy, decreasing stool output and decreasing the rate of vomiting [6-9]. In 2004, WHO and UNICEF issued a joint declaration on new recommendations for the treatment of diarrhea as follows [10]:

### 1. To mothers and other care givers

- Give low osmolarity ORS and home-based fluids to prevent dehydration.
- Continue feeding (or increase breastfeeding during, and increase all feeding after the period of diarrhea).
- Recognize signs of dehydration and take the child to a health provider for ORS or intravenous electrolyte solution as indicated as well as familiarizing with other symptoms refining medical treatment (bloody diarrhea).
- Provide children with 20 mg per day of zinc supplementation for 10–14 days (10 mg per day for infants under six months old).

### 2. To health-care workers

- Counsel mothers to begin administering suitable available home fluids immediately upon onset of diarrhoea in a child.
- Treat dehydration with ORS solution (or with an intravenous electrolyte solution in cases of severe dehydration).
- Emphasize continued feeding or increased breast-feeding during, and increased feeding after the diarrhoeal episode.
- Use antibiotics only when appropriate, i.e. in the presence of bloody diarrhoea or shigellosis, and abstain from administering anti-diarrhoeal drugs.
- Provide children with 20 mg per day of zinc supplementation for 10–14 days (10 mg per day for infants under six months old).
- Advise mothers of the need to increase fluids and continue feeding during future episodes.

Health-care workers treating children for diarrhoea are encouraged to provide caretakers with two 1-litre packets of the new ORS, for home-use until the diarrhoea stops. Caretakers should also be provided with enough zinc supplements to continue home treatment for 10–14 days.

### 3. To countries

- Develop a 3–5 year plan to reduce mortality rates from diarrhoeal diseases.
- Assess progress in controlling diarrhoeal diseases by monitoring usage rates of ORT/ORS, home-based treatment and zinc supplementation.
- Using the media and face-to-face communication, promote and refine messages on diarrhea prevention, home management of diarrhoea and appropriate care-seeking.
- Prioritize improving the availability of the new ORS solution and zinc supplements through private and public channels.
- Craft suitable strategies to educate health-care workers at all levels about using the new ORS and zinc supplements in treating diarrhea.
- Promote the availability of a zinc formulation that is cost-effective and easily administered to both infants and children.
- Identify obstacles to the use of ORS, zinc supplements and home-based treatments in managing acute diarrhoea.

### III. IMPLEMENTING RECOMMENDATIONS

Since 2004, WHO and UNICEF have incorporated the above recommendations in guidelines for field practice [10-13].

Presently many comities are stalled in technicalities of

**Table 1-** Compared composition of the standard ORS used since 1985 and the new reduced formulation recommended by WHO and UNICEF since 2004 [7,10,15-17].

	Standard ORS tandard (g/l)	Reduced osmolarity ORS (g/l)		Standard SRO mmo/l	Reduced osmolarity ORS mmol/l
Sodium chloride	3.5	2.6	Sodium	90	75
			Chloride	80	65
Glucose, anhydrous	20.0	13.5	Glucose, anhydrous	111	75
Potassium chloride	1.5	1.5	Potassium	20	20
Trisodium citrate, dihydrate	2.9	2.9	Citrate	10	10
<b>Total</b>	<b>27.9</b>	<b>20.5</b>	<b>Total osmolarity</b>	<b>311</b>	<b>245</b>

adapting national policy, while others are struggling to find funds for start up activities. For nearly all countries, zinc supplements for children are not available locally; thus zinc procurement continues to be a major obstacle [14]. Presently, only 39% of children with diarrhea in the developing world receive the recommended treatment and limited trend data suggest that there has been little progress since 2000 [1].

In 2005, zinc was integrated in the Integrated Management of Childhood Illness (IMCI) guidelines, and included in the WHO list of essential drugs. In 2006, zinc was included in the UNICEF/WHO emergency kit for the treatment of diarrhea. In 2008, Cameroon adopted it in the framework of IMCI, although it is not still available in the National Centre for Essential Drug Supply (CENAME).

#### III.1. Reduced low osmolarity ORS

Before 1985, WHO and UNICEF recommended ORS formulation with 30mmol/l of citrate. Replacement of citrate in the new formation improves stability and increases duration of conservation. Although this single ORS formulation is recommended, WHO and UNICEF have previously published criteria, which remain unchanged, for acceptable ORS formulations. These criteria are listed below; they specify the desired characteristics of the solution after it has been prepared according to the instructions on the packet [7]:

The total substance concentration	(including that contributed by glucose) should be within the range of 200-310 mmol/l
<b>The individual substance concentration</b>	
Glucose	should at least equal that of sodium but should not exceed 111 mmol/l
Sodium	should be within the range of 60-90 mEq/l
Potassium	should be within the range of 15-25 mEq/l
Citrate	should be within the range of 8-12 mmol/l
Chloride	should be within the range of 50-80 mEq/l

### III.2. Zinc

Zinc is the most ubiquitous of all trace elements involved in human metabolism and facilitates in catalytic, structural and cellular regulatory functions, of several enzymes.

In its structural role, it facilitates folding of proteins into three-dimensional configurations stimulating growth in-utero, childhood and adolescence. Zinc also plays a major role in the perpetuation of genetic material, including Deoxyribonucleic acid (DNA), translation of Ribonucleic acid (RNA) and ultimately cellular division and a critical role of zinc in the normal functioning of the gastrointestinal and immune system [18].

The most common causes of zinc deficiency include: Inadequate intake of zinc in the daily diet, increase in the losses of zinc from the body, such as when copper exposure is high, and when body requirement for zinc increases for one reason or another (such as when lactating or pregnant). These conditions tend to occur more in the elderly, in mothers, and in young children. Gastrointestinal malabsorption and losses can also lead to zinc deficiency symptoms [19].

Zinc occurs naturally in many foods in varying amounts. Good sources of zinc include shellfish (especially oysters), fish, red meat, poultry, beans, peas, whole grains, nuts, seeds, eggs and dairy products. Some foods are also fortified with zinc, such as breakfast cereals. It is not just the amount of zinc in particular foods that is important to consider, but also the bioavailability of this important mineral. That is, the extent to which zinc is absorbed by the body. For example, although zinc is present in large amounts in legumes and grains, these foods also contain phytates (phytates are a stored form of phosphorous) which bind to zinc and hinder its absorption in the intestines. Zinc is absorbed more easily from animal sources. Preparing foods in certain ways may help to increase the bioavailability of zinc. For example, soaking grains and beans before cooking, and the leavening process used to make breads helps to break down phytates [20].

### IV. CURRENT AVAILABLE EVIDENCE OF EFFICACY OF LOW OSMOLARITY ORS AND ZINC IN DIARRHEA TREATMENT.

Several meta-analyses of randomized clinical trials have been done ever since low osmolarity ORS and zinc were found to be beneficial in the treatment of diarrhea. In this review, only a summary of the most recent will be cited.

### IV. 1. Low osmolarity ORS and diarrhea

HAHN *et al.*, in 2009 [21], following a Cochrane meta-analysis of 8 randomized trials reduced osmolarity ORS was associated with fewer unscheduled intravenous fluid infusions compared with the WHO standard ORS.

In a multicenter randomized double blind trial in 125 children of 1- 17 years with diarrhea, the recovery of systemic symptoms, dehydration signs and diarrhea occurred in 96%, 97% and 78% of patients in the low osmolarity group [22]. In a joint UNICEF/WHO statement in 2001, following a meta-analysis of 19 trials comparing reduced with standard ORS in children with acute non- cholera diarrhea, it was noted that reduced osmolarity ORS reduced by 35% the need for IV fluids, reduced stool output and by 20% in pooled analysis, significant reduction (30%) in the incidence of vomiting in children, and a non statistically significant incidence of hyponatremia in those who received reduced osmolarity ORS [9].

The same findings were noted by the Choice Study Group in 2001 [23] following a multicenter double blind, randomized controlled clinical trial conducted in 675 children of 1 to 24 months with acute diarrhea in 5 developing countries (Bangladesh, Brazil, India, Peru and Vietnam).

However there have been some reserves with the use of low osmolarity salts in cholera. In the jointly organized UNICEF/WHO meeting of experts in India in 2001, it was recognized and unanimously agreed that low osmolarity ORS were affective in the treatment of cholera in children and adults, and that treatment is associated with and increased risk of transient hyponatremia [9].

In 2004, in a Cochrane review by MURPHY *et al.*, randomized controlled trials comparing reduced osmolarity ORS with standard ORS for treating adults and children with acute diarrhea due to cholera indicated that, reduced osmolarity ORS is associated with biochemical hyponatremia when compared with standard ORS, although there are similar benefits in terms of other outcomes. Although this risk does not appear to be accompanied by serious consequences, the total patient experience in existing trials is small. Under wider practice conditions, especially where patient monitoring is difficult, caution is warranted [24].

The same concerns have been raised by NALIN *et al.*, in an extensive review comparing the two formulations [25].

## IV.2. Zinc and diarrhea

### - Acute diarrhea

In a community - based double- blind, randomized trial in urban India in 1997, it was noted that zinc supplementation resulted in a 17% lower diarrhea incidence in children with plasma zinc concentrations <9.18 μmol/l at enrollment and a 33% lower incidence in children with concentrations < 50 μmol/l [26].

In 2000, the Zinc Investigators' Collaborative Group conducted a pooled analysis of randomized trials of the effects of supplementary oral zinc in children with acute or persistent diarrhea. Zinc supplemented children had a 15% lower probability of continuing diarrhea on a given day in the acute diarrhea trials [5].

These results were also confirmed by other 2 surveys in India and Haryana in 2008 [27].

In 2004, BHATNAGAH et al did a double blind, randomized, controlled trial in 2 urban hospitals in New Dehli. Zinc treatment with ORS reduced total stool output (ratio of geometric means, 0.69% confidence interval [CI]: 0.48, 0.99), and stool output per day of diarrhea (ratio of geometric means, 0.76; 95%, C I: 0.59, 0.98) [28].

The risk of continued diarrhea was lower (relative hazards, 0.76; 95% CI: 0.59, 0.97) and the proportions of diarrhea episodes lasting ≥ 5 days (odds ratio, 0.49; 95% CI: 0.25, 0.97) or 7days was less (odds ratio, 0.09; 95% CI: 0.01, 0.73) in the zinc group. This study demonstrated the beneficial effect of zinc administered during acute diarrhea on stool output, diarrhea duration, and proportion of episodes lasting more than 7days.

In 2001, a group of experts met in New Dehli to review trials of the therapeutic effect of zinc supplementation on acute diarrhea, and from hospital and community studies it was concluded that zinc supplementation for

10-14 days was efficacious in reducing the severity of diarrhea and the duration of the episode significantly [29]. In a recent Cochrane meta-analysis in 2008, zinc supplementation resulted in a shorter duration of acute diarrhea duration, and less diarrhea at day 3, 5 and 7 [30].

These studies and many more other meta-analyses, demonstrate that zinc supplementation on acute diarrhea reduces by 20-25% the duration acute diarrhea, 25% reduction in the proportion of diarrhea more than 7days and 30% in the reduction of the volume of stools.

### - Persistent diarrhea ( 14 days)

In 2000, a pooled analysis of randomized controlled trials of the effects of supplementary oral zinc in children with acute or persistent diarrhea, there was a 24% lower probability of continuing diarrhea (95% C I: 9%, 37%) and a 42% lower rate of treatment failure and death (95% CI: 10%, 63%) in the persistent diarrhea trials group [5,18].

In another meta-analysis of randomized controlled trials of zinc supplementation with placebo, in children with acute or persistent diarrhea by LUKACIK et al in 2008, those who received zinc reported an 18.8% and 12.5% reduction in average stool frequency, 15% and 15.5% shortening of diarrhea duration, and a 17.9% and 18%, probability of reducing diarrhea over placebo in acute and persistent diarrhea trials respectively [31].

Similarly, beneficial effects were demonstrated by LAZZERINI et al in Cochrane meta-analysis review in 2008 [30].

As a whole, these meta analysis of zinc supplementation in persistent diarrhea shows that there is a lower risk of continuing diarrhea (-24%; CI 95%: - 9%, -37%) and less risk of treatment failure (- 42%; CI 95%: -10%, - 63%) than in the control group [32].

**Figure 1-** Comparison of the efficacy of zinc treatment in acute and persistent diarrhea. (Available from: <http://rehydrate.org/zinc/index.html> (accessed 24/03/2010))



**- Cholera:** Zinc supplementation significantly reduces the duration of diarrhea and stool output in children with cholera. Children with cholera should be supplemented with zinc to reduce its duration and severity [33].

**- Shigellosis:** zinc supplementation significantly shortens the duration of acute shigellosis, promotes better weight gain during recovery and reduces diarrheal morbidity during the subsequent 6 months [34-35]. Intestinal permeability improves significantly with resolution of small mucosal damage [36].

#### **IV-3. Cost effectiveness of zinc supplementation and oral rehydration salts**

The availability of zinc supplements, along with oral rehydration therapy (ORT) with appropriate education programs was associated with significant higher use of ORT and lower use of antibiotics which can have an impact on the emergence of resistant strains of germs [27,37]. In 2004, ROBBERSTAD *et al.*, also demonstrated cost-effectiveness of zinc as adjunct therapy to standard treatment of acute childhood diarrhea including dysentery in Tanzania [34]. The direct effect of the reduction in duration and severity of diarrhea is the decreased need for expensive and prolonged hospitalizations.

#### **IV-4. Zinc and preventive effects**

Supplementation of zinc for 10-14 days has a beneficial effect in the 2-3 months following treatment with a 34% reduction in the prevalence of diarrhea [6, 11, 18, 38, 39, 40]. Preventive effects have also been demonstrated in acute lower respiratory infections with a reduction to as much as 45% (95% CI: 10%, 67%) in zinc supplemented children [39, 41]. Beneficial preventive effects have also been noted with malaria, with zinc supplemented children having 32% fewer clinical visits for malaria than non supplemented children [38]. In zinc supplementation areas children had a 51% lower risk of non-injury deaths compared to those in areas where zinc was not available [18,38].

#### **IV-5. Safety and dosages**

Supplementation of zinc in the treatment of diarrhea is safe, effective and inexpensive [6, 42]. The only known adverse effect is vomiting, and this can be attributed to a metallic taste in the supplement [6, 30]; and a slight drop in plasma copper concentrations [42]. The dosage is 10mg once per day in children less than 6 months, and 20mg once per day in children above 6 months. The tablets could be dissolved in breast milk, ORS, or clean water.

#### **IV-6. Zinc and malnutrition**

The usefulness and benefits of zinc in malnutrition is controversial. In a randomized double-blind To evaluate the potential benefit of dietary supplementation of a rice-lentil (khitchri) and yogurt diet with 3 mg/kg/day of elemental zinc in 87 hospitalized malnourished children 6 to 36 months, The overall weight gain, stool volume, stool frequency, as well as the time taken for diarrheal recovery or steady weight gain, were comparable for both supplemented children and controls. Although there was satisfactory recovery in malnourished children with persistent diarrhea receiving the khitchri-yogurt diet, there was no evidence of improved weight gain or acceleration of recovery from diarrhea with zinc supplementation. In contrast, the reduction in plasma copper levels in zinc-supplemented malnourished children suggests that caution should be exercised in supplementing severely malnourished children with zinc alone [43].

In a randomized, double-blind trial to measure the effects of zinc supplementation on catch-up growth in severe protein-energy malnutrition, in 141 children aged between 6 months and 3 years in a nutritional rehabilitation unit in Dhaka, Bangladesh, and randomly assigned to receive elemental zinc by mouth, 1.5 mg/kg for 15 days, 6.0 mg/kg for 15 days, or 6.0 mg/kg for 30 days, and thereafter were followed-up for a total of 90 days. It was noted that higher zinc doses were not associated with significant change in any anthropometric measurement, but mortality was significantly greater in children who received high-dose zinc. Possible explanations to this was that high dose-zinc may have a direct detrimental effect on the immune system during sepsis; high-dose zinc supplementation could aggravate deficiencies of other minerals by decreasing their intestinal absorption, and also that zinc inhibits copper absorption aggravating copper deficiency which can coexist with severe protein-energy malnutrition. Copper deficiency is also associated with an impaired immune response, specifically, a reduction in the antibody response to T cell-dependent antigens and a decrease in the microbiocidal activity of phagocytes [5, 44].

#### **IV-7. Mode of action of zinc in diarrhea**

Despite the several clinical observations of the efficacy of Zn in the treatment of acute diarrhea, the mechanism(s) by which Zn acts as an antidiarrheal agent are understood poorly. All of these successful clinical studies concluded that the possible mechanism for the beneficial effect of Zn treatment on the duration of diarrhea included the following:

1. improved absorption of water and electrolytes by the intestine (by a yet undefined or poorly defined mechanism),
2. faster regeneration of gut epithelium,
3. increased levels of enterocyte brush border enzymes,
4. an enhanced immune response leading to increased clearance of the pathogen(s) Responsible for diarrhea from the intestine [3,45].

However, the physiologic effect of zinc on intestinal ion transport has not yet been established thoroughly. Neither are there reports of whether zinc induces cation absorption and/or inhibits anion secretion, which are all properties of most anti-diarrheal drugs. Furthermore, it has not yet been well established whether Zn deficiency potentiates secretory diarrhea [3]. There is experimental evidence in rats that zinc inhibits cAMP-stimulated Cl secretion by selectively inhibiting a cAMP-activated basolateral K channel. These observations suggest that Zn may be effective in other cAMP-mediated secretory diarrheal disorders and that other K-channel blockers may have the potential for development as anti-diarrheal agents [3, 46].

#### V- CONCLUSION

Reduced osmolarity ORS and zinc supplementation have proven to be the cornerstone of management of diarrhea in children. As recommended by UNICEF/WHO and key expert partners, a comprehensive strategy encompassing interventions as breastfeeding and hygiene, reduced ORS, zinc supplementation and rotavirus vaccines can be a highly effective way to reduce childhood diarrheal diseases in developing countries. Sensitizing and educating policy makers, health workers, and parents on the use of zinc and reduced osmolarity ORS can achieve a remarkable and sustainable impact on childhood mortality ■

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