

Zinc and childhood infections: From the laboratory to new treatment recommendations

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ABSTRACT

Zinc is an essential nutrient particularly important for growing children and for those who experience frequent infections. Many children in developing countries have inadequate zinc nutrition that impairs their immune system. Diarrhea and pneumonia are among the leading causes of morbidity and mortality in children of low-income countries. Zinc deficiency increases the susceptibility to these infections and administration of zinc to children with diarrhea and, possibly, pneumonia speeds up recovery. Furthermore, zinc given to otherwise healthy children also reduces the incidence of diarrhea and pneumonia. Thus, thousands of lives can be saved every year by giving zinc to prevent childhood infections or by providing zinc to children with ongoing infections. This paper gives a brief outline of the history of zinc research and reviews existing evidence from clinical trials on the prophylactic and therapeutic effect of oral zinc on childhood pneumonia and diarrhea.

A BRIEF HISTORY OF ZINC NUTRITION AND RESEARCH

More than 70 years ago scientists demonstrated that adequate zinc nutrition is important for health in mammals (1). Zinc deficiency was not, however, considered a problem in humans. In the early sixties, Prasad showed that zinc deficiency caused stunted growth and delayed sexual maturation in Iranian and Egyptian adolescents (2). In 1974 the Food and Nutrition Board of the US National Academy of Sciences declared zinc an essential nutrient and established recommended dietary allowances (RDA) for humans. Later, zinc was included in total parenteral nutrition fluids, which without a doubt have saved many lives. In 1988, Sachdev demonstrated that zinc given to Indian children with diarrhea reduced the severity of the diarrheal episode. Since then several clinical trials have confirmed the therapeutic effect of zinc given during diarrhea. The evidence is now so convincing that zinc will be included in the routine treatment for acute diarrhea in children of developing countries. Furthermore, routine zinc supplementation to apparently healthy children reduces the incidence of diarrhea, the risk of acquiring severe illness, and the risk of acute lower respiratory infections (ALRI). The available evidence will be discussed below.

DIARRHEA AND ALRI IN DEVELOPING COUNTRIES

Diarrhea and pneumonia remain important causes of morbidity and mortality in children of developing countries. Among those under 5 years of age these diseases are responsible for approximately 40% of the

annual 10 million deaths. Diarrhea may be classified into three syndromes; dysentery, acute diarrhea, and persistent diarrhea. Persistent diarrhea is defined as diarrhea of a presumed infectious cause with acute onset that lasts for at least 14 days (3). Almost half of all diarrhea related deaths is attributed to this syndrome and it is now the leading cause of diarrheal deaths (3). Reduction in the proportion of diarrheal episodes that become persistent may accordingly bring down the number of diarrhea related deaths. Pneumonia and other ALRIs kill more than two million children every year. The majority of these deaths occur in the developing world (4,5). The very young, the elderly, and those with conditions that interfere with immunity such as sickle-cell disease and HIV infection are particularly at high risk of severe disease (6). Pneumonia is usually treated successfully with inexpensive antibiotics. The high disease burden in many developing countries may to a large extent be ascribed to unavailability of adequate health care as well as to impaired immunity due to malnutrition (7).

WHY ZINC?

Zinc is an essential trace element important for almost all biological systems. It is required for cellular division, differentiation and growth. Organs that are dependent on continuous cell division for proper function, such as the immune system and the gut, are particularly sensitive to zinc deficiency. Inadequate zinc intake has profound effects on almost all facets of the immune system, on the mucosal integrity, and on epithelial function (8,9). In humans, severe zinc deficiency is seen in those with the rare inherited disease *Acrodermatitis enteropathica* (AE), which is caused

by impaired zinc absorption. Individuals with this disease have impaired growth and increased susceptibility to infections, particularly those causing diarrhea. AE is effectively treated with high doses of oral zinc.

Absorption of zinc depends on the amount and its solubility in the intestinal lumen. Phytic acid reduces the solubility of zinc in the gut and impairs its absorption (10-15). Phytic acid is present in legumes (e.g. beans, peas, lentils and ground nuts) and cereals (e.g. corn and sorghum), foods that are frequently consumed in many low-income countries. Meat and other animal products are generally rich in zinc, contain amino acids that promote zinc absorption, and are accordingly good sources of bioavailable zinc (10). Furthermore, the demand for zinc is high in individuals with a rapid growth rate, i.e. fetuses, children and adolescents (8). Zinc is excreted in the stools and substantial amounts of zinc is lost during diarrhea (16). Thus, zinc nutriture is likely to be suboptimal in many children of developing countries and contributes to their impaired growth, an increased susceptibility to infections and possibly to their high mortality.

ASSESSMENT OF ZINC STATUS

Plasma zinc and serum zinc are currently the most commonly used indicators of zinc status in humans. However, these markers are of limited value because less than 1% of the total body zinc circulates in the plasma and because plasma zinc concentration is affected by several conditions such as hypoalbuminemia, hemoconcentration, and the acute phase response (17). In fact, the reduction in plasma zinc seems to reflect the severity of the infection (18,19) and may be observed early during the illness, even before signs of infection, such as fever, appear (20). Due to lack of adequate biomarkers, zinc supplementation trials are essential in understanding the epidemiology of zinc deficiency and to explore a causal effect between zinc deficiency and increased morbidity.

PREVENTION OF DIARRHEA WITH ZINC

Clinical trials in children, usually from relatively marginalized strata of developing countries, have shown that routine zinc supplementation reduces the incidence and prevalence of diarrhea (Table 1, Figure 1) (21-28). A pooled analysis of zinc supplementation trials used published and unpublished data from 10 developing countries to assess the efficacy of daily zinc administration on diarrheal morbidity (29). This analysis concluded that zinc-supplemented children had an 18% (95% CI 7%, 28%) lower incidence rate and a 25% (95% CI 12%, 37%) lower prevalence of diarrhea compared to children that were not given zinc. This publication also included a pooled analysis from three trials that used short-term zinc supplementation. In these studies the children were supplemented with 2-4 RDA (30) zinc for two weeks and then observed for

another 2 to 3 months. The combined pooled effect of these short courses of zinc supplementation on the prevalence (odds ratio [OR] 0.66, 95% CI 0.52, 0.83) and incidence rate (OR 0.89, 95% CI 0.62, 1.28) of diarrhea was similar to what was seen in the trials supplementing children with zinc throughout the observation period. After this pooled analysis was published, large studies have confirmed this reduction in diarrheal morbidity both in routine (21,22) and in short term zinc supplementation trials. Bhandari and coworkers conducted the largest of these trials, which included 2,500 Indian children (22). They showed that four months of routine zinc supplementation to children aged 6 to 30 months reduced the incidence of severe and prolonged diarrhea. Furthermore, in a recent trial the investigators showed that even only a weekly dose substantially reduced the incidence of diarrhea (31). This study also demonstrated a substantial effect of zinc on pneumonia (see below).

TREATMENT OF DIARRHEA WITH ZINC

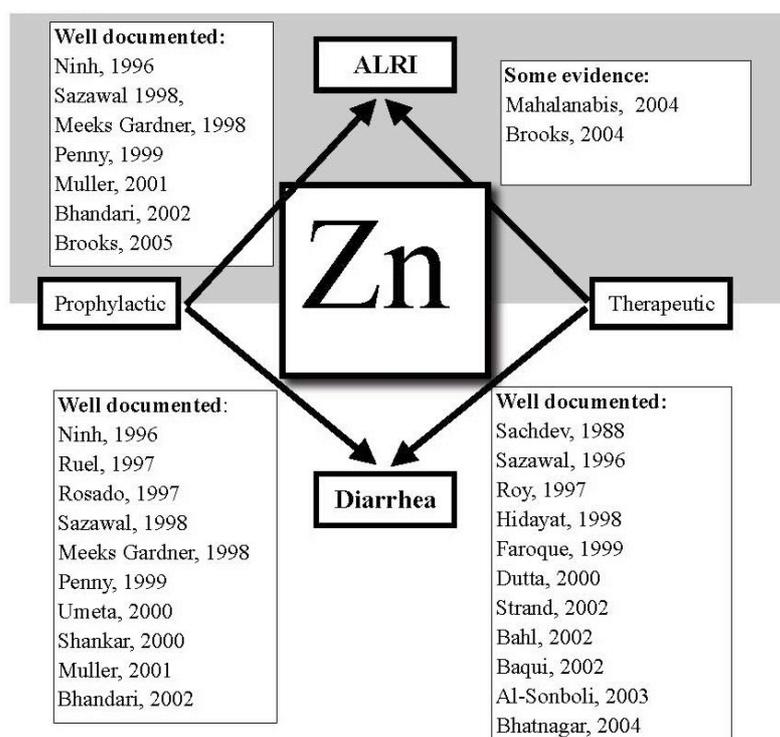
Sachdev and coworkers were the first to assess the therapeutic effects of zinc on diarrhea (32). In a study on acute diarrhea they found that children who were given 40 mg of elemental zinc daily had shorter duration of diarrhea and lower stool frequency than the controls. Following this publication, several trials on zinc administration during acute and persistent diarrhea have been conducted and the results from these trials have been summarized in two pooled analyses (33). The analysis that included children with acute diarrhea demonstrated that there was an overall and statistically significant 15% reduction of the duration in children receiving zinc (Hazard ratio 0.85, 95% CI 0.76, 0.95). In the trials that enrolled children with persistent diarrhea, therapeutic zinc reduced the time till recovery of diarrhea by 24% (Hazard ratio 0.76, 95% CI 0.63, 0.91) and the risk of treatment failure or death (OR 0.61, 95% CI 0.26, 1.46).

Table 1. Effects of zinc on preventing childhood diarrhea and pneumonia.

Author, year (reference no)	Country	n	Diarrhea ¹	ALRI ¹
Ninh, 1996 (23)	Vietnam	146	44 ²	44 ²
Rosado, 1997 (49)	Mexico	219	37	
Ruel, 1997 (25)	Guatemala	89	18 ²	
Sazawal, 1998 (40)	India	609	8	43 ²
Penny, 1999 (41)	Peru	173	12 ²	15
Shankar, 2000 (50)	Papua New Guinea	274	12	
Umeta, 2000 (51)	Ethiopia	200	55 ²	
Muller, 2001 (21)	Burkina Faso	685	16 ²	57
Bhandari, 2002 (43)	India	2482		26 ²
Bhandari, 2002 (22)	India	2500	12 ²	
Brooks, 2005 (31)	Bangladesh	1665	6 ²	17 ²

¹ % lower incidence or risk of disease among those given zinc.

² Statistically significant, i.e. $p < 0.05$



ALRI: Acute lower respiratory infection

Figure 1. Existing evidence for the effect of zinc (prophylactic and therapeutic) on the two most common causes of death due to infections in children of low-income countries.

Table 2. Studies evaluating therapeutic effects of zinc supplementation in the treatment of acute diarrhea.

Author, year (reference no)	Country	n	Dose *	Difference † (95% CI)	Odds ratio episode >7 days ††
Sachdev, 1988 (52)	India	50	40 mg	-0.4 (-1.4, 0.6)	
Faruque, 1999 (53)	Bangladesh	681	14.2 / 40 mg	-1.0 (-1.8, -0.2)	
Dutta, 2000 (54)	India	80	40 mg	-1.4 (-1.6, -1.1)	
Al Soboni, 2001 (37)	Brazil	74	22.5 / 45 mg	-1.3 (-1.9, -0.6)	
Relative Hazards (95% CI)					
Sazawal, 1996 (24)	India	937	20 mg	0.79 (0.69, 0.90)	0.85 (0.60, 1.19)
Roy, 1997 (55)	Bangladesh	111	20 mg	0.85 (0.57, 1.28)	0.77 (0.33, 1.79)
Hidayat, 1998 (56)	Indonesia	1398	4.5 mg/kg	0.92 (0.83, 1.02)	0.72 (0.48, 1.07)
Bahl, 2002 (35)	India	805	15 / 30 mg	0.89 (0.80, 0.99)	0.61 (0.33, 1.12)
Strand, 2002 (36)	Nepal	1792	15 / 30 mg	0.79 (0.68, 0.93)	0.57 (0.38, 0.86) **
Baqui, 2002 (34)	Bangladesh	1252	20 mg	0.77 (0.65, 0.90)	
Bhatnagar, 2004 (57)	India	168	15 / 30 mg	0.77 (0.59, 0.99)	

* elemental zinc

† mean difference in days

** relative risk

†† odds of having an episode in those who received zinc compared to the placebo group

After these pooled analyses were published, more studies on the therapeutic use of zinc in diarrhea have been completed (34-37). The results of these studies were presented in a WHO meeting in New Delhi in 2001 and the report from this meeting (38) concludes: "Based on the results of this review, it is concluded that there is now enough evidence demonstrating the

efficacy of zinc supplementation on the clinical course of diarrhoea, with regard to the severity and duration of the episode".

The results from a trial we undertook in 1,792 Nepalese children aged 6 to 35 months with acute diarrhea were included in this report (36). In this trial the risk of persistent diarrhea was reduced from 5.2%

to 2.7%, corresponding to an absolute risk reduction of 2.5% (95% CI 0.2%, 5%) in those who received zinc (39). An almost 50% reduction in the risk of persistent diarrhea is promising and this finding is supported by a cluster-randomized trial in Bangladeshi children (34). In this trial 40 non-injury fatalities were reported and the risk of such deaths was 51% (95% CI 5%, 75%) lower among children belonging to clusters that were offered zinc as adjunct therapy for acute diarrhea.

PREVENTION OF ACUTE LOWER RESPIRATORY INFECTIONS (ALRI) WITH ZINC

The above-mentioned pooled analysis of preventive zinc supplementation trials also included data for ALRI from four trials (29) (Table 1, Figure 1). This analysis of data from India (40), Vietnam (23), Peru (41), and Jamaica (42) showed that routine zinc supplementation reduced the odds of getting pneumonia by 41% (95% CI 17%, 69%). Later, Bhandari and coworkers confirmed this reduction in the incidence of clinical pneumonia in 2,500 Indian children that were given zinc on a daily basis (43). Zinc appeared to confer largest protection to those with severe illness. This finding was supported by the recently published trial where 1665 Bangladeshi children were given 70 mg zinc or placebo weekly (31). In this study only infants between 2 and 12 months of age were included. The incidence of pneumonia was 17% lower (95% CI: 5%, 27%) among those given zinc compared to the placebo recipients. Even more important, the study reported a strong effect of zinc on mortality; 10 of the children in the placebo group died, whereas only 2 of the children in the zinc group died during the observation period. This corresponds to an 85% reduction in mortality. Respiratory infections was the main cause of death.

TREATMENT OF LOWER RESPIRATORY INFECTIONS WITH ZINC

There is limited information on zinc as adjunct therapy for ALRI and pneumonia (Figure 1). One published trial that included children with measles related pneumonia showed no effect (44). However, two other studies showed an impact of zinc on the duration of the illness, in one of which only an effect in boys was observed (45). The largest and the most recent of these two trials demonstrated a 30% reduction in the duration of the episode (RH 0.70, 95% CI 0.51, 0.98) (46) with no gender differences. However, the therapeutic effect of zinc administration on pneumonia might be more difficult to measure compared to the effect of zinc on diarrhea. This is partly because the study participants also have to be offered effective antibiotics that dilute the possible effect zinc. The three trials mentioned above were relatively small and totally they

included only 508 children. More and larger clinical trials should accordingly be undertaken.

MORTALITY AND ZINC

In a trial on low birth weight babies in North India, placebo or 5 mg elemental zinc as zinc sulfate was given daily between 30 and 284 days of age. There were five fatalities among the zinc supplemented and 15 among the placebo recipients. The relative risk of dying between those in the zinc group and those in the placebo group was accordingly 0.32 (95% CI 0.12, 0.89). The results from this trial, the trial that demonstrated a reduced death risk in children belonging to clusters that received zinc as adjunct therapy for acute diarrhea (34), and the trial that showed an 85% reduction in infant mortality of children given weekly zinc (31) are promising. Thus, zinc administration can reduce childhood mortality – probably through the reduction in severe episodes of pneumonia and diarrhea.

CONCLUSION

Seventy years of zinc research have resulted in new treatment recommendations for acute diarrhea. Zinc might also be beneficial when given during pneumonia, and children that are given zinc regularly have a reduced burden of diarrhea and pneumonia, both important causes of childhood death. Around half of the world's population and 95% of the South Asian population are at risk of low zinc intake (47). Zinc administration reduces the burden of diarrhea and pneumonia, and according to a recent publication in the *Lancet* by Jones and coworkers, therapeutic and prophylactic zinc administration have the potential of reducing almost 10% of the under 5 mortality, mainly through a reduction of the incidence and severity of diarrhea and pneumonia (48).

There is a need to develop and implement strategies to improve zinc nutriture. The delayed effect of short-term zinc administration is promising. Short courses of zinc administration in order to reduce the burden of zinc deficiency is attractive compared to long-term administration that can interfere with current breastfeeding recommendations. This downstream effect of zinc needs, however, to be explored further. The doses that have been used for the treatment of pneumonia and to induce a downstream effect are similar to those recommended to treat diarrhea. Thus, when zinc is available for the treatment of acute diarrhea, other indications for its use should be easy to implement.

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