

## Zinc: Role in the management of diarrhea and cholera

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### Abstract

Diarrhea and cholera are major health problems. *Vibrio cholera*, the causative agent of cholera, infects the small intestine, resulting in vomiting, massive watery diarrhea and dehydration. Reduced water and electrolyte absorption is also due to zinc deficiency. Zinc has an important role in recovery from the disease. The combination of zinc with cholera vaccine and oral rehydration solutions has a positive impact on cholera and diarrhea. It has led to a decrease in the mortality and morbidity associated with diarrhea.

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**Key words:** Diarrhea; Cholera; *Vibrio cholera*; Zinc; Oral rehydration solutions

**Core tip:** In diarrhea and cholera, reduced water and electrolyte absorption is due to zinc deficiency. Therefore, zinc has an important role in recovery from the symptoms. The use of zinc with cholera vaccine and oral rehydration solutions has been shown to affect positive impacts in cholera and diarrhea.

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### INTRODUCTION

Diarrhea and cholera are major global health problems. Cholera toxin produced by the causative agent increases cyclic adenosine monophosphate (cAMP) production. This result in massive electrolyte and water secretion into the intestinal lumen, resulting in severe dehydration<sup>[1]</sup>. *Vibrio cholera*, the causative agent of cholera, infects the small intestine. Vomiting, massive watery diarrhea and dehydration (Figure 1) are associated with cholera and may lead to death if not managed properly<sup>[2]</sup>. Reduced water and electrolyte absorption is also due to zinc deficiency<sup>[3]</sup>. Zinc has an important role in recovery from the disease<sup>[4]</sup> and can reduce the morbidity and mortality, associated with diarrhea, in the population<sup>[5]</sup>.

### ZINC WITH CHOLERA VACCINE

Clinically, zinc has positive effect in children with complications of diarrhea<sup>[6]</sup>. Young children are immunized with oral inactivated whole cell cholera vaccine containing recombinant cholera toxin B subunit. This vaccine induces T-cell responses that are further enhanced by zinc supplementation<sup>[7]</sup>. Zinc combined with oral cholera vaccine shows increased vibriocidal antibody effects and suppresses cholera toxin antibody response<sup>[8]</sup>. Zinc supplementation enhances oral cholera vaccine efficacy and also improves seroconversion to vibriocidal antibody<sup>[9]</sup>. Oral administration improves immune response to antigens applied to mucosal surfaces and also improves antibacterial response in serum and reduces antitoxin levels<sup>[10]</sup>.

Administration of two doses of oral inactivated cholera vaccine, containing cholera B subunit and killed cholera vibriosis, combined with zinc supplementation, to 6-8 mo old children was found to be safe and immunogenic<sup>[11]</sup>.

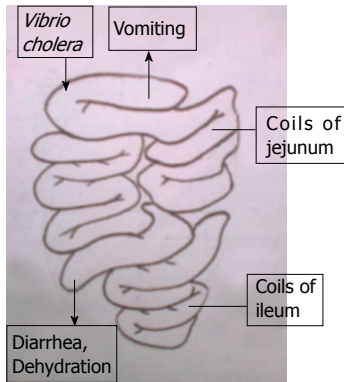


Figure 1 Effect of *Vibrio cholera* on small intestine.

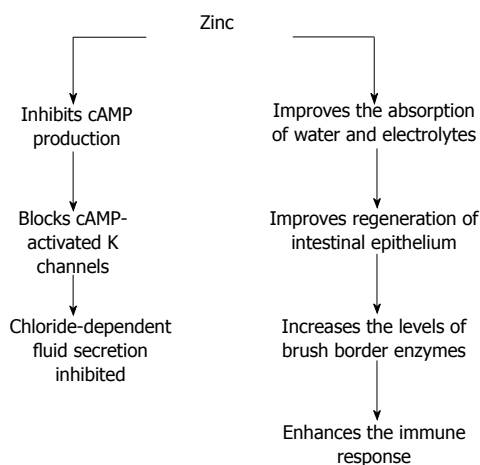


Figure 2 Physiological effects of zinc. cAMP: Cyclic adenosine monophosphate.

## ZINC WITH ORAL REHYDRATING SOLUTIONS

Diarrhea and cholera are major global health problem and have caused seven pandemics. Cholera toxin produced by *Vibrio cholera* increases cAMP production. This results in massive electrolyte and water secretion into intestinal lumen, leading to severe dehydration. The World Health Organization emphasises the use of oral rehydration solutions (ORS) in the treatment of diarrhea. Various modifications have been made to standard ORS, to treat non cholera diarrhea<sup>[12]</sup> and cholera diarrhea. These include addition of zinc, amino acids and amylase-resistant starch<sup>[1]</sup>, to decrease the morbidity and mortality associated with acute diarrhea<sup>[12]</sup>. Zinc with ORS is an attempt to improve ORS for cholera diarrhea management<sup>[1]</sup>. The presence of zinc in ORS improves physiological condition, reduces the risk of recurrent diarrhea attacks<sup>[4]</sup> and also has positive effects in dehydrating acute diarrhea in malnourished children<sup>[13]</sup>. Studies in various countries showed that the duration and severity of diarrhea can be reduced by zinc addition and this also allows limitation of the use of antibacterials and antimicrobials<sup>[14]</sup> (Figure 2).

## WATER SOLUBLE ACTIVE ZnTe NANOCOMPOSITES

Water soluble active ZnTe nanocomposites (average size range of 2.9-6.0 nm) show potential against enteropathogenic bacteria including enterotoxigenic *Escherichia coli* (*E. coli*) and *Vibrio cholera* serogroup 01, having positive effects in diarrhea and cholera without toxic effects on humans<sup>[15]</sup>.

## EFFECT OF ZINC

A study on an animal model showed that zinc deficiency in the intestine resulted in reduced water and electrolyte absorption<sup>[3]</sup>. Cholera toxin increases cAMP production, thereby causing electrolyte and water secretion<sup>[1]</sup>. Zn reduces cAMP concentration and cholera toxin-induced ion secretion, as well as increasing ion absorption, but does not inhibit *E. coli* heat stable enterotoxin-induced ion secretion<sup>[16]</sup>.

In children suffering from acute diarrhea and persistent diarrhea, the effect of zinc on intestinal integrity is unknown. However, in patients with acrodermatitis enteropathica infection, zinc induced more mucosal repair. Zinc also effects excretion of urinary probe sugars, increasing lactulose excretion and decreasing mannitol excretion<sup>[17]</sup>.

## EFFECT OF SCHEDULED DOSES OF ZINC

Children and older patients both show zinc deficiency in cholera<sup>[18]</sup>. Zinc supplementation showed beneficial impact on diarrhea in infants but its impact was masked by the protective action of breastfeeding<sup>[19]</sup>.

Zinc supplementation administered on a daily or weekly schedule is effective in decreasing diarrhoeal morbidity without adverse reactions<sup>[20]</sup>.

Children with cholera supplemented with zinc show reduction in stool output and in the duration of diarrhea. Children with diarrhea may benefit from zinc supplementation but its cost effectiveness and optimal mode of delivery are not yet clear<sup>[21]</sup>.

## CONCLUSION

In diarrhea and cholera, reduced water and electrolyte absorption is due to zinc deficiency. Therefore, zinc has an important role in recovery from the symptoms. Zinc combined with cholera vaccine and ORS has been shown to have positive impacts in cholera and diarrhea.

## REFERENCES

1. **Atia A**, Buchman AL. Treatment of cholera-like diarrhoea with oral rehydration. *Ann Trop Med Parasitol* 2010; **104**: 465-474 [PMID: 20863435 DOI: 10.1179/136485910X12786389891164]
2. **Roy SK**, Hossain MJ, Khatun W, Chakraborty B, Chowdhury S, Begum A, Mah-e-Muneer S, Shafique S, Khanam M, Chowdhury R. Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial. *BMJ* 2008; **336**: 266-268 [PMID: 18184631 DOI: 10.1136/

- bmj.39416.646250]
- 3 **Roy SK**, Tomkins AM, Ara G, Jolly SP, Khatun W, Chowdhury R, Chakrabarty B. Impact of zinc deficiency on vibrio cholerae enterotoxin-stimulated water and electrolyte transport in animal model. *J Health Popul Nutr* 2006; **24**: 42-47 [PMID: 16796149]
  - 4 **Altaf W**, Perveen S, Rehman KU, Teichberg S, Vancurova I, Harper RG, Wapnir RA. Zinc supplementation in oral rehydration solutions: experimental assessment and mechanisms of action. *J Am Coll Nutr* 2002; **21**: 26-32 [PMID: 11838884 DOI: 10.1080/07315724.2002.10719190]
  - 5 **Gupta DN**, Rajendran K, Mondal SK, Ghosh S, Bhattacharya SK. Operational feasibility of implementing community-based zinc supplementation: impact on childhood diarrheal morbidity. *Pediatr Infect Dis J* 2007; **26**: 306-310 [PMID: 17414392 DOI: 10.1097/01.inf.0000258692.65485.d9]
  - 6 **Dutta P**, Mitra U, Dutta S, Naik TN, Rajendran K, Chatterjee MK. Zinc, vitamin A, and micronutrient supplementation in children with diarrhea: a randomized controlled clinical trial of combination therapy versus monotherapy. *J Pediatr* 2011; **159**: 633-637 [PMID: 21592508 DOI: 10.1016/j.jpeds.2011.03.028]
  - 7 **Ahmed T**, Arifuzzaman M, Lebens M, Qadri F, Lundgren A. CD4+ T-cell responses to an oral inactivated cholera vaccine in young children in a cholera endemic country and the enhancing effect of zinc supplementation. *Vaccine* 2009; **28**: 422-429 [PMID: 19837094 DOI: 10.1016/j.vaccine.2009.10.032]
  - 8 **Qadri F**, Ahmed T, Wahed MA, Ahmed F, Bhuiyan NA, Rahman AS, Clemens JD, Black RE, Albert MJ. Suppressive effect of zinc on antibody response to cholera toxin in children given the killed, B subunit-whole cell, oral cholera vaccine. *Vaccine* 2004; **22**: 416-421 [PMID: 14670323 DOI: 10.1016/j.vaccine.2003.07.005]
  - 9 **Albert MJ**, Qadri F, Wahed MA, Ahmed T, Rahman AS, Ahmed F, Bhuiyan NA, Zaman K, Baqui AH, Clemens JD, Black RE. Supplementation with zinc, but not vitamin A, improves seroconversion to vibriocidal antibody in children given an oral cholera vaccine. *J Infect Dis* 2003; **187**: 909-913 [PMID: 12660937 DOI: 10.1086/368132]
  - 10 **Karlsen TH**, Sommerfelt H, Klomstad S, Andersen PK, Strand TA, Ulvik RJ, Ahrén C, Grewal HM. Intestinal and systemic immune responses to an oral cholera toxoid B subunit whole-cell vaccine administered during zinc supplementation. *Infect Immun* 2003; **71**: 3909-3913 [PMID: 12819076 DOI: 10.1128/IAI.71.7.3909-3913.2003]
  - 11 **Ahmed T**, Svennerholm AM, Al Tarique A, Sultana GN, Qadri F. Enhanced immunogenicity of an oral inactivated cholera vaccine in infants in Bangladesh obtained by zinc supplementation and by temporary withholding breast-feeding. *Vaccine* 2009; **27**: 1433-1439 [PMID: 19146904 DOI: 10.1016/j.vaccine.2008.12.036]
  - 12 **Atia AN**, Buchman AL. Oral rehydration solutions in non-cholera diarrhea: a review. *Am J Gastroenterol* 2009; **104**: 2596-2604; quiz 2605 [PMID: 19550407 DOI: 10.1038/ajg.2009.329]
  - 13 **Dutta P**, Mitra U, Datta A, Niyogi SK, Dutta S, Manna B, Basak M, Mahapatra TS, Bhattacharya SK. Impact of zinc supplementation in malnourished children with acute watery diarrhoea. *J Trop Pediatr* 2000; **46**: 259-263 [PMID: 11077932 DOI: 10.1093/tropej/46.5.259]
  - 14 **Sur D**, Bhattacharya SK. Acute diarrhoeal diseases--an approach to management. *J Indian Med Assoc* 2006; **104**: 220-223 [PMID: 17058565]
  - 15 **Ghosh S**, Ghosh D, Bag PK, Bhattacharya SC, Saha A. Aqueous synthesis of ZnTe/dendrimer nanocomposites and their antimicrobial activity: implications in therapeutics. *Nanoscale* 2011; **3**: 1139-1148 [PMID: 21218228 DOI: 10.1039/c0nr00610f]
  - 16 **Canani RB**, Cirillo P, Buccigrossi V, Ruotolo S, Passariello A, De Luca P, Porcaro F, De Marco G, Guarino A. Zinc inhibits cholera toxin-induced, but not Escherichia coli heat-stable enterotoxin-induced, ion secretion in human enterocytes. *J Infect Dis* 2005; **191**: 1072-1077 [PMID: 15747242 DOI: 10.1086/428504]
  - 17 **Roy SK**, Behrens RH, Haider R, Akramuzzaman SM, Mahalanabis D, Wahed MA, Tomkins AM. Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. *J Pediatr Gastroenterol Nutr* 1992; **15**: 289-296 [PMID: 1432467 DOI: 10.1097/00005176-199210000-00010]
  - 18 **Chowdhury F**, Khan AI, Harris JB, LaRocque RC, Chowdhury MI, Ryan ET, Faruque AS, Calderwood SB, Qadri F. A comparison of clinical and immunologic features in children and older patients hospitalized with severe cholera in Bangladesh. *Pediatr Infect Dis J* 2008; **27**: 986-992 [PMID: 18833030 DOI: 10.1097/INF.0b013e3181783adf]
  - 19 **Sur D**, Gupta DN, Mondal SK, Ghosh S, Manna B, Rajendran K, Bhattacharya SK. Impact of zinc supplementation on diarrheal morbidity and growth pattern of low birth weight infants in Kolkata, India: a randomized, double-blind, placebo-controlled, community-based study. *Pediatrics* 2003; **112**: 1327-1332 [PMID: 14654605 DOI: 10.1542/peds.112.6.1327]
  - 20 **Gupta DN**, Mondal SK, Ghosh S, Rajendran K, Sur D, Manna B. Impact of zinc supplementation on diarrhoeal morbidity in rural children of West Bengal, India. *Acta Paediatr* 2003; **92**: 531-536 [PMID: 12839279]
  - 21 **Alam NH**, Ashraf H. Treatment of infectious diarrhea in children. *Paediatr Drugs* 2003; **5**: 151-165 [PMID: 12608880 DOI: 10.1111/j.1651-2227.2003.tb02501.x]

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