Complementary, Holistic, and Integrative Medicine: A Review of Therapies for Diarrhea

Deepika Mittra, MSc,*
Cecilia Bukutu, PhD,*
Sunita Vohra, MD, FRCP, MSc*

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This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Introduction
In 2002, diarrhea was ranked as the seventh leading cause of death in the world. (1) Estimates from the World Health Organization (WHO) 2000–2003 report show that worldwide, diarrhea accounts for 18% of deaths in children younger than the age of 5 years. (2) Diarrhea commonly is defined as loose or liquid stools that are passed frequently. (3) Although diarrhea acts as a defense mechanism in the body, quickly eliminating infective organisms, it can cause dehydration, especially in malnourished or immuno-suppressed individuals. (3)

This review examines published scientific literature on the use of common complementary and alternative medicines (CAM) that have been used to prevent and treat childhood diarrhea that is infectious, acute, or persistent. Due to the high prevalence of this disease in developing nations, much of the literature in this review stems from these regions.

Natural health products (NHPs) are used widely for the prevention, treatment, or relief of various conditions, as well as for promotion of personal well-being. NHPs include vitamins and minerals, amino acids, probiotic products (ie, a live microbial culture), homeopathic remedies, and traditional medicines.

Dietary Supplements
Zinc
Zinc is an essential mineral; without it, immune function is compromised and rates of infectious disease can increase. (4) The role of zinc in childhood diarrhea has been studied extensively.

A 2008 meta-analysis of 22 studies, 16 addressing acute diarrhea (n=15,231) and 6 examining persistent diarrhea (n=2,968), found that zinc supplementation reduced average stool frequency by 18.8% compared with a 12.5% reduction with placebo. (5) Zinc supplementation and placebo reduced the duration of diarrhea by 15.0% and 15.5%, respectively.

Positive findings also were noted in an earlier review that included 25 published and 17 unpublished trials (7 prevention trials, 5 therapeutic trials for acute diarrhea, and 5 for persistent diarrhea) of preschool-age children in developing countries (n=5,362). (4) Pooled analysis of the seven prevention trials found that zinc supplementation reduced the incidence of diarrhea by 18% (95% confidence interval [CI]=7% to 28%) and the prevalence of diarrhea by 25% (95% CI=12% to 37%). Pooled analysis of three of the acute diarrhea trials demonstrated that diarrheal episodes were 15% less likely to continue (95% CI=5% to 24%) in the zinc-supplemented group than in the control groups. Furthermore, pooled analysis of four trials of persistent diarrhea revealed that children receiving a zinc supplement reduced their risk of continuing persistent diarrhea by 24% (95% CI=9% to 37%). Pooled analysis also revealed a 42% reduction in treatment failure and death rates (95% CI=10% to 63%) in children given zinc supplements.

Most of the trials and meta-analyses involving supplemental zinc for childhood diarrhea demonstrated its effectiveness. However, systematic reviews can overlook important details of the randomized, controlled trials (RCTs) included in their analyses. For example, many of the trials may have used different forms of zinc supplement or varied dosages for...
differing periods of intervention. Of note, many of the trials have been conducted in areas where children may not be receiving adequate amounts of zinc in their diets and, therefore, results may not be transferable to developed nations.

A common adverse effect (AE) of zinc supplementation is increased vomiting. There also are concerns that the cumulative long-term consumption of high doses of zinc may lead to impaired copper absorption. (6) The WHO (2006) recommends a 10- to 14-day course of zinc in combination with increased intake of fluids, along with breastfeeding and other measures, for the treatment of all episodes of childhood diarrhea. (7)

**Vitamin A**

Several studies have examined the role of vitamin A in preventing or treating diarrhea, with conflicting results. A meta-analysis of eight RCTs (n=45,199) investigated the effect of vitamin A supplementation on children ages 6 months to 7 years suffering from respiratory tract infections and diarrhea. (8) Of the eight studies, two reported a statistically significant protective effect of vitamin A for diarrhea, and one found that vitamin A caused AEs, specifically, a slightly increased risk of developing respiratory infections. When the eight trials were assessed together, vitamin A supplementation had no protective effect on the incidence of diarrhea (relative risk [RR]=1.00, 95% CI=0.94 to 1.07).

Findings from two studies conducted after the previously noted meta-analysis are contradictory. The first, a Turkish study in which 120 adequately nourished children (6 to 12 months old) hospitalized for acute diarrhea received either a single oral high dose of vitamin A (100,000 international units) or placebo, found no effect of vitamin A on the duration of acute diarrhea. (9) The second, a Tanzanian RCT, examined the incidence and duration of diarrheal episodes and respiratory tract infections during the year after discharge from the hospital for pneumonia in 574 children ages 6 to 60 months.

(10) Children ingested either vitamin A or placebo at baseline and at 4 and 8 months. Compared with the placebo group, the vitamin A group had a significantly smaller risk of severe watery diarrhea (95% CI=0.32 to 0.99, P=0.04), with an increased risk of cough and rapid respiratory rate (95% CI=1.17 to 2.36, P=0.004). Children whose growth was stunted and normally nourished children taking vitamin A had an increased risk of acute diarrhea, but vitamin A had a protective effect for children who had wasting disease (P=0.01). Human immunodeficiency virus (HIV)-negative children were found to have a higher risk than HIV-positive children for developing a respiratory tract infection (P=0.07). The results of this study suggest that vitamin A interventions may be useful against morbidity in HIV-infected and undernourished children, but supplementation may cause AEs in nourished children.

There is some indication that vitamin A may be beneficial for children who are malnourished, but no conclusions can be drawn regarding the role of vitamin A in children who have diarrhea but are otherwise healthy. Vitamin A is fat soluble and, thus, is retained by the body. Excessive intake can lead to acute and chronic hypervitaminosis A, which has several known hazards, including nausea, vomiting, headaches, and bone pain. (11)

**Zinc and Vitamin A**

Additional diarrhea studies have examined the role of zinc in combination with vitamin A. (12)(13)(14)(15) The results of identified vitamin A and zinc RCTs for childhood diarrhea do not reach consensus. The diversity of results among these studies may be due, in part, to the variance in study locations, methodology, subject factors (such as age), and research questions of each trial. No conclusive evidence supports the concurrent use of vitamin A and zinc to treat childhood diarrhea.

**Nucleotide Supplements**

Dietary nucleotides have important effects on the growth and development of cells that have a rapid turnover, such as those in the immune system and the gastrointestinal tract. (16) A 12-month double-blind study completed in Taiwan assessed the effect of fortified nucleotide formula (NF) (72 mg/L) compared with control formula (CF) on the incidence of diarrhea in 1- to 7-day-old infants. (17) Compared with infants fed CF (n=166), infants fed
NF (n=166) for the first postnatal year had a significant reduction in the incidence of diarrhea from 8 to 28 weeks of age and a trend for reduction in the incidence of diarrhea from 8 to 48 weeks of age. In this study, 63 AEs (mostly mild to moderate) were observed, but they were deemed unrelated to the study formulas by the authors. These findings are supported by an earlier 3-month study conducted in Chile of healthy infants (n=392) of low socioeconomic status living in poor sanitary conditions. (18) The children fed formula that had a low nucleotide concentration (14.2 mg%) had reduced diarrheal illness compared with infants fed CF. No information regarding randomization of study participants or AEs was provided.

Nucleotide supplementation generally is considered to be safe. To date, no nucleotide supplementation AEs have been reported. One report has noted increased severity to allergic response in mice in a nasal allergy model study. To assess nucleotide supplementation safety, tolerability, and potential AEs better, additional long-term human studies are needed. (16)

Amino Acids: Glutamine
Glutamine is an essential amino acid and, thus, is important for protein synthesis. Glutamine is believed to be helpful in treating diarrhea caused by irritation of the intestinal lining. One RCT assessed the efficacy of glutamine supplementation in reducing the duration and severity of diarrhea in 6- to 24-month-old, otherwise healthy Turkish children. (19) In addition to standard therapy, children either received oral glutamine (0.3 g/kg per day) (n=63) or placebo (n=65) for 1 week. The mean duration of diarrhea was significantly shorter in the glutamine group than in the placebo group (3.40 versus 4.57 days, 25.7% reduction, P=0.004). No other differences between groups were found, and no AEs were observed.

When taken by healthy individuals and preterm infants at recommended dosages (0.1 to 0.3 g/kg per day), glutamine is believed to be safe. (19) However, individuals who are hypersensitive to monosodium glutamate should use glutamine with caution because it is metabolized into glutamate. A case report has suggested that high doses of glutamine could trigger manic episodes in susceptible individuals. (20)

Partially Hydrolyzed Guar Gum (PHGG)
PHGG is a natural, water-soluble dietary fiber. Added to the diet in the treatment of persistent diarrhea, PHGG is believed to help improve colonic function. (21) PHGG has been used in cereals, juices, shakes, yogurt, and soups. (21) One RCT examined the effects of PHGG in the treatment of persistent diarrhea (>14 days) in 116 boys ages 4 to 18 months living in Bangladesh. (22) WHO oral rehydration solution (ORS) with or without (control group) 20 g/L of PHGG was provided to the children in a randomized trial. Boys randomized to WHO ORS with PHGG had reduced duration of diarrhea compared with boys who received WHO ORS alone (74±37 hours versus 90±50 hours, P=0.03). No AEs were observed.

Potential AEs of dietary fiber (eg, PHGG) include reduced absorption of vitamins, minerals, proteins, and calories. The recommended safe daily consumption of PHGG for adults is 20 g/d. (21) More research is needed to determine a safe PHGG dosage for children.

Probiotics
Probiotics refer to “friendly” nonpathogenic microorganisms intended to benefit the host by improving the properties of indigenous microflora. The safest forms of probiotic bacteria are found in many common fermented foods (ie, yogurt, buttermilk). The evidence presented here reviews supplemental forms of probiotics only.

Probiotics for the treatment of acute infectious diarrhea of viral origin have been studied extensively in RCTs in children. These trials include a number of probiotic species, both alone and in combination, and have demonstrated decreased severity and duration of diarrhea in a range of socioeconomic populations when administered individually or with oral rehydration therapy. A meta-analysis of nine randomized, controlled trials examined the therapeutic effects of Lactobacillus (including L acidophilus, L bulgaris, L GG, and L reuteri) in children who had acute infectious diarrhea. (23) Lactobacillus reduced the duration of acute infectious diarrhea by approximately 1 day in children, with trials of L GG (n=4) providing the most substantial contribution to the overall results. However, a 2003 RCT found L GG to be ineffective in children who had severe diarrhea and were admitted to the hospital. (24) The authors hypothesized that prior intestinal colonization from probiotic use may be important, resulting in greater benefits in preventing rather than treating virally induced diarrhea. (24)

The prevention of acute diarrhea (ie, antibiotic-associated diarrhea [AAD], infectious diarrhea, nosocomial diarrhea) using probiotics also has been studied in RCTs involving infants. In these trials, Bifidobacterium bifidum, together with Streptococcus thermophilus and L GG, have demonstrated benefit in preventing nosocomial diarrheas. (25)(26) Further, a meta-analysis of
masked, randomized, placebo-controlled trials (n=34) has found sufficient evidence for the efficacy of probiotics in the prevention of acute diarrhea in the general population (adults and children). (27) The 12 trials in children demonstrated a 0.43 RR (95% CI=0.29 to 0.65). RCTs involving monostrains of *B lactis*, *L GG*, (25) and *L reuteri* (28) have demonstrated favorable results for the prevention of acute diarrhea in children.

Two recent meta-analyses have evaluated the effectiveness of probiotics in the prevention of AAD in pediatric patients and found them to be modestly effective. (29)(30) The objective of these studies was to assess the efficacy of probiotics (of any specified strain or dose) for the prevention of AAD in children. The first, a 2006 meta-analysis of six RCTs (707 children), found that probiotics reduced the risk of AAD by 16.6% compared with placebo (28.5% versus 12%, RR=0.43, 95% CI=0.31 to 0.58). (29) This finding indicates that treatment of seven patients with probiotics will prevent one case of AAD. The second, a 2007 meta-analysis of 10 RCTs, assessed the efficacy of probiotics with either *Lactobacillus* sp, *Bifidobacterium* sp, *Streptococcus* sp, or *Saccharomyces boulardii* alone or in combination for the prevention of AAD in 1,986 children. (30) Significant results for probiotics compared with placebo (RR=0.43, 95% CI=0.25 to 0.75) were observed. The review authors suggested that future studies involve probiotic strains and doses that have the most promising evidence. No serious AEs were observed in these trials.

**Homeopathy**

Homeopathy is based on the premise that “like cures like,” meaning that small, highly diluted quantities of medicinal substances are given to cure symptoms. The same substances given at higher or more concentrated doses would cause those symptoms.

A meta-analysis of three small RCTs conducted by the same research group, one in Nepal and two in Nicaragua, evaluated the use of individualized homeopathic treatment for acute childhood diarrhea. (34) The meta-analysis included 242 children 6 months to 5 years of age randomized to receive individualized homeopathic remedies or placebo. The combined analysis found the duration of diarrhea to be shorter in the homeopathic group compared with the control group at 3.3 and 4.1 days, respectively (P=0.008).

A double-blind RCT conducted in Honduras assessed the efficacy of homeopathic combination therapy in treating 292 children (5 months to 6 years of age) who had acute diarrhea. (35) Children were randomized to receive either homeopathic tablets (consisting of the five most common homeopathic remedies used for childhood diarrhea: *Arsenicum album*, *Calcarea carbonica*, *Chamomilla*, *Podophyllum*, and sulfur) or placebo treatment. Children were followed until diarrhea subsided or for 7 days (whichever came first). Homeopathy had no significant effect on the duration or severity of diarrhea.

Homeopathy has been associated with mild AEs, including exacerbations of eczema, headaches, and fever in children. Homeopathy also is believed to aggravate or worsen symptoms for several hours after taking homeopathic medicine in approximately 20% of patients. (36)
Traditional Chinese Medicine (TCM)

Most articles investigating the effectiveness of TCM in treating diarrhea in children are in Chinese; only two complete English articles were identified. In a clinical study, Yang (37) randomly divided children (4 days to 3 years old) suffering from chronic protracted diarrhea into two groups: Chinese herbal medicine (HM) \( (n=115) \) and Western medicine (WM) \( (n=47) \). In the HM group, xiang cheng san was applied externally to the umbilicus of patients; in the WM group, western drugs (digestants, antidiarrheals, antibiotics, folic acid) were administered routinely. The trial found that 53% of HM and 30% of WM patients were cured, 27% versus 36% had improved symptoms, and 20% versus 34% showed no effect. These between-group differences were statistically significant \( (P<0.05) \).

Lin and associates (38) compared the treatment of diarrhea in children (1 to 35 months of age) by shallow needling or drugs. The children were randomized into one of the following groups: Group 1 \( (n=354) \) had shallow needling performed on head acupoints, Group 2 \( (n=350) \) received shallow needling techniques on body acupoints, and Group 3 \( (n=57) \) received one or more of the following agents: gentamicin, aminobenzylpenicillin, compound sinomin, furazolidone, and berberine. No significant differences were found between groups 1 and 2 \( (P>0.05) \), but results for both were significantly superior to the treatment given to group 3 \( (P<0.01) \).

Acupuncture rarely results in serious AEs, although cases of skin infections, pneumothorax, and injury to the central nervous system have been reported. (39) Based on information from these two studies, the safety and efficacy of TCM as an intervention for childhood diarrhea cannot be determined. More research is needed in this area before wider use can be recommended.

Conclusion

Many studies have examined the use of CAM for childhood diarrhea. Of the research presented in this review, both probiotics and zinc show effectiveness in treating and preventing childhood diarrhea. For all other therapies reviewed (vitamin A, nucleotide supplements, glutamine supplements, PHGG, chamomile, homeopathy, and TCM), the evidence is limited or inconclusive and requires additional study to determine efficacy and safety before use can be recommended. Most of the literature presented in this review stems from research conducted in developing nations; caution must be extended when using the information provided to ensure that it is applicable to a given population.

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