Treatment of Acute Diarrhea in Children

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Acute diarrhea is a common cause of childhood morbidity in both developed and developing countries; it is the second most important cause of mortality in the latter. Acute watery diarrhea causes water, electrolyte, and acid-base imbalance. Nutrient malabsorption and decreased food intake during diarrhea may lead to growth faltering. Acute dysentery may additionally lead to complications such as encephalopathy, hemolytic-uremic syndrome, toxic megacolon, seizures, hypoglycemia, and intestinal perforation. Furthermore, children with diarrhea who have severe malnutrition often have hypothermia, hypoglycemia, associated systemic infections, and high case fatality, which makes the management of diarrhea much more difficult and challenging.

The wide promotion of acute diarrhea case management strategy based on oral rehydration therapy, continued anti-microbial treatment for dysentery and cholera during acute diarrhea, together with decline in rates of severe malnutrition have greatly reduced diarrhea associated hospitalizations and deaths. In 1980, an estimated 4.6 million children under 5 years of age died annually from acute diarrheal diseases, predominantly in low-income countries. In 1990, child deaths from diarrhea decreased to 3.2 million. In 2000, this number is estimated to be 1.3 million (1). While this is understandably a major accomplishment, the limitations of the current management approach based on oral rehydration are that it does not achieve all the desired goals of therapy (Table 1).

There is a strongly felt need among physicians and caretakers of children for

<table>
<thead>
<tr>
<th>TABLE 1. Potential goals of therapy in acute diarrhea</th>
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<tr>
<td>• Reduce average duration, stool output and prevent dehydration</td>
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<tr>
<td>• Identify and correct dehydration and electrolyte and acid-base imbalance</td>
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<tr>
<td>• Prevent acute episodes from becoming persistent</td>
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<tr>
<td>• Prevent and when present promptly identify and treat infection and non-infection complications due to associated malnutrition</td>
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<tr>
<td>• Prevent bacteremia in the high-risk host, e.g., young infant, low birth weight and malnourished with simple acute diarrhea</td>
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<tr>
<td>• Maximize nutrient availability to facilitate mucosal recovery; growth and development</td>
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additional modalities of treatment that would reduce the duration and severity of the illness, treatment failure rates, and need for intravenous fluids. Some of these newer therapeutic modalities currently under evaluation include new generation oral rehydration solutions, probiotics, micronutrients, and alternate feeding regimens. This review summarizes established treatments and describes the current status of the newer therapeutic modalities.

**FLUID AND ELECTROLYTE REPLACEMENT**

**Assessment of a Child With Diarrhea for Hydration Status**

Fluid and electrolyte replacement therapy depends on classification of a child with diarrhea as having no, some, or severe dehydration. The World Health Organization (WHO) proposed this revised scheme of classification against the earlier one of no, mild, moderate, or severe dehydration, particularly for use in developing country programs (2). This revised scheme categorizes children with fluid deficits of 3% to 5%, who were previously classified as mild dehydration as having some dehydration, thereby ensuring that oral rehydration therapy is given to them at treatment facilities before they are sent home. Accordingly, a child with two of the four features would be considered to have some dehydration: restless or irritable, sunken eyes, drinks eagerly—thirsty, and skin pinch goes back slowly (2). Furthermore, the assessment of thirst is now used as a sign by observing whether the child drinks eagerly when offered a suitable liquid such as oral rehydration salts solutions. Assessment of affected patients should also include a search for features of hyponatremia or hypernatremia, hypokalemia, and acidosis, wherever feasible.

The global community has now fully accepted the efficacy of oral rehydration solution (ORS) to prevent dehydration, to correct some dehydration, and to limit the duration of intravenous fluid therapy in children with severe dehydration. This followed several randomized controlled efficacy trials and vast clinical experience with oral rehydration therapy in hospitals as well as in less supervised clinical settings (1,3–5). Training programs worldwide for physicians, nurses, and peripheral health workers also contributed to increasing confidence in oral rehydration therapy.

The WHO-ORS is effective in correcting dehydration in all but a small proportion of cases of some dehydration within 3 to 6 hours. Intravenous fluids are required in treatment failures associated with high frequency of stools, uncontrolled vomiting, or poor oral intake due to associated infection.

Initial treatment of children with severe dehydration is always intravenous fluid therapy using an isotonic electrolyte solution similar to plasma in composition, such as isotonic saline or lactated Ringer. In the initial phase, 20 to 30 ml of such a solution is given as a bolus and repeated a second or third time until the patient is hemodynamically stable. This initial therapy applies to hyponatremic, hypernatremic, or isotonic dehydration. In case of hypernatremia, the extra sodium administered during this phase has little effect on the sodium levels. The subsequent phase of therapy is focused on continued replacement of existing deficit, provision of
TREATMENT OF ACUTE DIARRHEA IN CHILDREN

maintenance fluid and electrolytes, and replacement of ongoing losses over two 8-hour periods. In developed countries, at this stage laboratory results are available to plan the subsequent therapy.

In the WHO protocol, the 100 ml per kg body weight intravenous fluid is recommended to be given over a shorter time than is usual; 6 hours for infants below 12 months and 3 hours for those 12 months to 5 years. Some ORS (about 5 ml/kg/hour) is offered, when the children can drink without difficulty even when they are getting intravenous fluids, usually within 3 to 4 hours for infants and 1 to 2 hours for older children. The WHO recommended schedule for oral rehydration and intravenous therapy has remarkably reduced long hospitalizations and inpatient care. However, it is important that the confidence in oral rehydration not lead to avoidance of intravenous therapy when it is really needed such as in severe cholera and infants who are unable to drink effectively and in required amounts to compensate for large stool losses.

There are concerns that the formulation designed originally for the treatment of cholera is not optimal for prevention of dehydration for severely malnourished children and young infants. Research to improve the safety and efficacy of WHO oral rehydration solution has continued over the years and some of the important findings are reviewed later in this chapter.

Improved Oral Rehydration Formulations

The composition of WHO-ORS was initially based on studies in adults suffering from cholera. The sodium concentration of 90 mEq/l in the solution corresponds to the stool electrolyte composition in toxin-mediated diarrheas. This solution has nevertheless worked well even in young children with non-cholera diarrhea both in developing and developed countries when used according to recommended guidelines with ready access to plain water during oral rehydration.

Several developments have lead to the clinical evaluation of oral rehydration solutions with a reduced osmolarity. Initially, the main concern was the potential risk of hypernatremia with WHO-ORS (4,6). There was also the recognition that the WHO-ORS may provide too much sodium to edematous children (7). It has been pointed out that at a rate of 100 ml/kg/day, the WHO solution can provide as much as 9 mEq/kg/day of sodium, whereas edematous children, especially if they have anemia, can develop heart failure on diets that provide 6 mEq/kg/day of sodium (8,9). In later years, there were reports of recurrent dehydration in young infants treated with WHO-ORS on a weight-to-volume basis as replacement of ongoing stool losses that was promptly reversed on nil orally intravenous fluid regimens (10,11). It was postulated that in some infants, glucose malabsorption may be relatively severe and oral fluid replacement in response to stool output simply leads to a vicious cycle with recurrent dehydration. Finally, reduced osmolarity solutions were reported to promote water and sodium absorption more efficiently than the WHO-ORS (9).

A number of oral rehydration solutions with osmolarity ranging from 210 to 268
mosmol/l and sodium ranging from 50 to 75 mEq/l have been assessed for efficacy in randomized controlled trials in adults with cholera and in children with cholera and non-cholera diarrhea (12–24). The findings of these studies are summarized in Tables 2 and 3 (WHO-ORS, 2001). The study children had acute diarrhea (duration <7 days) with dehydration, they were aged 3 months to 5 years and included malnourished and well-nourished subjects. In a combined analysis of these studies in non-cholera diarrhea, stool output was reduced by 20%, incidence of vomiting by about 30%, and unscheduled intravenous fluid therapy by 39% in children treated with reduced osmolarity (210 to 268 mosmol/l) as compared to those treated with WHO-ORS (22).

When low osmolarity solutions with sodium less than 75 mEq/l and those with sodium ≥75 mEq/l were independently compared with standard WHO-ORS in the treatment of acute diarrhea with dehydration, there was a distinct trend toward greater efficacy of the former, particularly in terms of stool output and vomiting (Table 3). The number of subjects was however not sufficient to ensure adequate study power for a firm conclusion on this issue.

A recent review of these findings by a WHO task force has led to the recommendation of a reduced osmolarity ORS containing 75 mEq/l sodium and 75 mmol/l glucose (total osmolarity 245 mosmol/l) as the preferred universal solution for prevention and treatment of diarrheal dehydration to replace the current WHO-ORS, irrespective

### TABLE 2. Results of meta-analysis comparing reduced osmolarity ORS with standard ORS in children with diarrhea

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unscheduled IV</td>
<td>9</td>
<td>0.61 (0.47, 0.81)</td>
</tr>
<tr>
<td>Stool output</td>
<td>12</td>
<td>0.81 (0.74, 0.88)*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>0.71 (0.55, 0.92)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3</td>
<td>1.45 (0.93, 2.26)</td>
</tr>
</tbody>
</table>

*a Ratio of geometric means. CI, confidence interval; IV, intravenous; ORS, oral rehydration solution.

From Hahn et al. (22).

### TABLE 3. Results of meta-analysis of all randomized controlled trials comparing reduced osmolarity ORS with standard ORS in children with diarrhea

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reduced osmolarity ORS (OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;75 mEq/l sodium</td>
</tr>
<tr>
<td>Unscheduled IV</td>
<td>0.65 (0.41, 1.00)</td>
</tr>
<tr>
<td>Stool output</td>
<td>0.69 (0.49, 0.98)*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.49 (0.27, 0.91)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>No event reported</td>
</tr>
</tbody>
</table>

*a Ratio of geometric means. CI, confidence interval; IV, intravenous; ORS, oral rehydration solution.

From WHO, Division of Child Health and Development (24).
of age, etiology, or disease severity (Table 4). The recommendation was based on several considerations (i) improved efficacy in non-cholera diarrhea in infants and children, (ii) comparable efficacy in adults with cholera with only a marginally elevated risk of asymptomatic hyponatremia, and (iii) the programmatic advantages of preserving a single formulation for treatment and prevention of all types of diarrheas. While it is likely that a more appropriate solution for non-cholera diarrhea is one with even lower osmolarity, the risks of hyponatremia when such a solution is used in cholera may be greater and perhaps unacceptable. The WHO recommended a range that includes all acceptable ORS formulations including the standard ORS (24).

The findings of studies of clinical trials of amino acid-fortified ORS, of rice and other cereal-based oral rehydration solutions in acute diarrhea and dehydration have been previously reviewed (5,25-29). Rice-based ORS is clearly superior to WHO-ORS in efficacy in adults with cholera but the two solutions were found to be similar in efficacy in non-cholera diarrhea based on the most updated meta-analysis (27). Oral solutions fortified with amino acids such as l-alanine, glycine, glutamine, or with dipeptides were similarly more efficacious in adult cholera but not in non-cholera diarrhea in children, presumably due to the high osmolarity of these fortified solutions.

**SPECIAL CONSIDERATIONS IN TREATING DEHYDRATION IN THE SEVERELY MALNOURISHED**

The high sodium content of the WHO-ORS may lead to fluid and electrolyte disturbances in the child with severe malnutrition especially in those with edema. Dehydration tends to be overdiagnosed and its severity overestimated in severely malnourished children. The WHO has therefore recommended that the intravenous route not be used for rehydration of severely malnourished children except in cases of shock (7,30).

Severely malnourished children have low total body potassium content, which is associated with increased mortality. Such children benefit from potassium supplements (8). Potassium concentration of the standard WHO-ORS may be too low to adequately replace stool losses during diarrhea. Diluting ORS to reduce sodium leads
TABLE 5. Treatment of dehydration in severely malnourished children with ReSoMal

<table>
<thead>
<tr>
<th>ReSoMal rehydration fluid, administered orally or by nasogastric tube, much more slowly than for well-nourished children</th>
</tr>
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<tbody>
<tr>
<td>• 5 ml/kg every 30 min for the first 2 hr</td>
</tr>
<tr>
<td>• 5–10 ml/kg/hr for the next 4–10 hr depending on how much the child wants and the volume of stool loss</td>
</tr>
</tbody>
</table>

From Khin-Maung et al. (29).

to further reduction in potassium. A new formulation with sodium concentration of 45 mEq/l and potassium of 40 mEq/l, which also provides buffered magnesium, zinc, and copper (ReSoMal), is recommended by WHO for use in severely malnourished children (Tables 4 and 5) (29). ReSoMal is not commercially available in many developing countries but can be prepared in a hospital formulary.

In south and southeast Asia and other regions where grossly edematous forms of malnutrition are infrequent, the reduced osmolarity ORS now recommended by the WHO (osmolarity 245 mmol/l) is likely to be as well tolerated as a solution with electrolyte contents similar to ReSoMal if it were administered at a slower rate than that recommended for well-nourished children and with added potassium (3 to 4 mEq/kg/day) and magnesium (0.4 to 0.6 mmol/kg/day). This view is based on recent studies in this region as well as extensive experience in diarrhea treatment units. In Bangladesh, rice-based oral rehydration solution with sodium 90 mmol/l when used for treatment of dehydration in severely malnourished children was not associated with heart failure (31). Vitamins and micronutrients particularly vitamin A, zinc (2 mg/kg/day), copper (0.3 mg/kg/day), and folic acid (5 mg on day 1, then 1 mg/day) are also recommended. Advantage of this reduced osmolarity ORS formulation for general use including malnutrition is that a single formulation would be promoted for all ages, irrespective of etiology or nutritional status.

Further research is required to standardize assessment and treatment of dehydration in malnourished children.

RESISTANT STARCH AS AN ADJUVANT TO ORAL REHYDRATION SOLUTION

Short-chain fatty acids promote water and electrolyte absorption in the colon. Starch is fermented in the colon by anaerobic bacteria resulting in production of short-chain fatty acids, acetate, propionate, and butyrate.

Ramakrishna and colleagues studied a glucose-based oral rehydration solution modified by the addition of an amylase-resistant starch that is poorly digested in the small intestine of adults with cholera (32). Starch that is resistant to amylase in the small intestine is found in small quantities in many cereals and is a good substrate for colonic fermentation. High amylase maize starch, obtained from a specific variety of corn, is rich in resistant starch, and when eaten uncooked, 50% to 70% of the starch is not digested in the small intestine (32). The researchers anticipated that
the indigestible starch would reach the colon without being absorbed in the small intestine and be metabolized there by colonic bacteria into short chain fatty acids. The use of resistant starch may provide another absorption mechanism in the colon in addition to glucose-mediated absorption in the small intestine. This may be particularly important in cholera, as in addition to intestinal secretion, there is decreased absorption of fluid from the large intestine, a phenomenon that can be reversed by short-chain fatty acids.

In the adult cholera trial, treatment with resistant starch reduced the amount of diarrhea and shortened the duration of illness. Data in non-cholera diarrhea in children are lacking. The physiologic principle demonstrated by these studies is important. The practical implications will become apparent, when more clinical evaluation is carried out. In the trial by Ramakrishna et al. antibiotics were withheld for 1 day, which is not the usual practice (32). Timely effective antibiotics reduce the volume of stool and duration of diarrhea by about 50%. Further, the effects achieved with resistant starch are already available through rice-based and other cereal-based oral solutions, which are routinely used for treatment of adult cholera in countries such as Bangladesh. It appears that the clinical effects of rice-based solutions appear earlier than effects with resistant starch, probably reflecting the site of action as small intestine rather than only colon for the former. The real test would be to compare the efficacy of rice-based ORS and resistant starch-based standard ORS to assess whether the new product is a practical advance in therapy.

ANTI-MICROBIAL THERAPY

There is a wide gap between evidence of efficacy and clinical practice when it comes to antimicrobial therapy for infectious diarrhea. Whether a patient is infected with a pathogen amenable to antimicrobial therapy depends on many factors including age, geographic location, and clinical presentation. Further, many antibiotics that show potent activity in vitro have little or no efficacy in vivo. Among bacterial infections, the value of antibiotics can be extremely high (Shigella and Vibrio cholerae), questionable (Campylobacter), or none at all (Salmonella) (33).

Almost 90% of diarrheal illnesses have been placed in the category of simple diarrhea manifested by watery diarrhea, low-grade fever, mild malaise, abdominal cramps, nausea, and occasional vomiting. In developing country children, Enterotoxigenic Escherichia coli and rotavirus are the two predominant positive organisms, while viral agents account for most of such illnesses in industrialized countries.

On these bases, it has been rightly recommended that such episodes not be treated with antibiotics with the exception of travelers from developed countries in whom diarrhea develops, when they visit the less developed areas; enterotoxigenic and other diarrheogenic E. coli account for up to half of these illnesses and early therapy with antibiotics such as trimethoprim-sulfamethoxazole significantly improves the clinical illness.

Antibiotics clearly shorten pathogen excretion, hasten recovery, and reduce case fatality rates in dysentery. Patients with dysentery are identified by the presence of
gross blood and mucus in stools or sheets of polymorphonuclear leukocytes in a
smear stained with methylene blue. Shigella is the commonest pathogen associated
with dysentery and the one that causes the most severe illness. Choice of antibiotics
in dysentery is therefore, based on local sensitivity patterns of Shigella isolates.
Although trimethoprim-sulfamethoxazole is the recommended first-line drug, resis-
tance is so common in many parts of the world that this drug is being replaced by
nalidixic acid, norfloxacin, ciprofloxacin, or newer quinolones. Recent studies show
that short-term therapy with ofloxacin and cefixime are nearly as efficacious as 5
days of therapy with the same agent against shigellosis (34-36). This should reduce
costs and improve compliance. Drugs that are not clinically efficacious include
neomycin, cephalixin, cefaclor, furazolidine, and intramuscular aminoglycosides. It
is still not understood why antibiotics that have excellent activity in vitro against
Shigella are not efficacious in patients.

Antibiotics significantly reduce the duration of diarrhea, the total diarrheal stool
volume, and the duration of excretion of vibrios. Tetracycline is the most superior
oral antibiotic in cholera and is the recommended treatment of choice where strains
are sensitive to this drug. The course of therapy is short and therefore, the accumula-
tion of tetracycline in the teeth is not a significant concern in children. Other effica-
cious drugs in cholera include doxycycline, erythromycin, cotrimoxazole, and chlor-
amphenicol (37).

Antimicrobial therapy is indicated for clearly established *Giardia lamblia*
parasites. The drugs that appear highly effective include metronidazole, furazolidone,
tinidazole, quinacrine, and nitazoxenide (33,38,39). Metronidazole is effective
against *Entamoeba histolytica* trophozoites. If a patient continues to be an asymp-
tomatic passer of amebic cysts after successful treatment of acute illness drugs such
as diloxanide furoate may be required.

Amoebiasis is a very infrequent cause of acute dysentery in young children. Fur-
ther recent studies show that infection with non-invasive *E. dispar* is more common
than *E. histolytica* so that it may be worthwhile to differentiate the two by readily
applicable enzyme-linked immnosorbert assay tests before considering therapy.

Protozoal agents such as *Cryptosporidium*, microsporidia, and *Isospora belli* are
common causes of diarrhea in immunocompromised individuals. Among microspori-
dia, human infection has been reported for *Enterocytozoon bieneusi*, *Encephalito-
zone cuniculi*, and *Septata intestinalis*. Multiple stool examinations may be required
to detect these protozoal agents. *Isospora* is amenable to treatment with antibiotics,
specifically sulfonamides and pyrimethamine. In microsporidiasis, metronidazole
and albendazole appear encouraging.

The majority of acute infections with these protozoa is self-limited; most treatment
trials have been done in chronic infections in patients with acquired immunodefi-
ciency syndrome (AIDS). Many agents were used to treat isosporiasis, but a 10-day
course of trimethoprim-sulfamethoxazole treats the protozoa in immunologically
normal patients and in those with AIDS. Pyrimethamine-sulfadoxine/sulfadiazine,
although used less frequently, provides a prompt response. Pyrimethamine used
alone is effective in patients with sulfonamide allergies. Macrolide antibiotics have
marginal efficacy in treating isosporiasis (40,41). Trimethoprim-sulfamethoxazole has also been reported to effectively treat *Cyclospora* infections. Little information on clinical experience in therapy of human microsporidiasis is available. Descriptive case series suggest that microsporidial *S. intestinalis* infection can be cured with albendazole. No therapy has proved to be beneficial for *E. bieneusi*, although there is some evidence that albendazole may improve the clinical status without eradicating the protozoa from the stools or the small bowel (42).

There is an abundance of anecdotal data regarding the use of numerous agents for cryptosporidiosis; however, most are ineffective (43–45). Spiramycin, chloroquine, trimethoprim-sulfamethoxazole, and metronidazole failed to show a beneficial effect. Ornithine decarboxylase inhibitor, alfa-difluoremethylnornithine, has shown modest efficacy, but its usefulness is limited by bone marrow and gastrointestinal toxicity. Equivocal reports have been obtained with the use of hyperimmune bovine colostrum. Both uncontrolled case series and a randomized controlled trial indicate that paromomycin may be effective in treating chronic intestinal cryptosporidiosis (46). The response rate varies from 30% to 70% and is associated with decreased intensity of infection and improved intestinal function and morphology. Newer semi-synthetic macrolide antibiotics such as clarithromycin and azithromycin have shown promise in small therapeutic trials but larger studies are required (47,48). In a recent study, clarithromycin and rifabutin were highly protective against the development of cryptosporidiosis in human immunodeficiency virus infection (HIV) (48). There is some preliminary evidence of benefits of treatment of cryptosporidiosis with nitazoxanide, a 5-nithrothiazole compound also found to be effective against a broad range of parasites, almost all anaerobic obligate and facultative bacteria, and some aerobic bacteria (49). There have been some reports of resolution of cryptosporidial diarrhea with the use of zidovudine in HIV-infected patients. Recently, combination anti-retroviral therapy, which includes at least one HIV-1 protease inhibitor, has been used for improving immunity to *E. bieneusi* and *C. parvum* in a small number of HIV-1–infected patients. The treatment resulted in complete immediate microbiologic, clinical, and histologic responses, but failed to eradicate the infection, as evidenced by a rapid relapse rate (50). Another case report has documented effective treatment and successful eradication of *Cryptosporidium* with indinavir, a protease inhibitor, in an HIV-infected person.

**NUTRITIONAL SUPPORT**

In the past 15 years, there is a major improvement in our understanding of what is optimal with regard to feeding during acute diarrhea. There has been a shift from food withdrawal, as a means of allowing the intestine to rest, to the now widely accepted view that continued availability of nutrients promotes absorption of water and electrolytes, hastens recovery, and promotes weight gain without increased risk of treatment failure (51–55). Experimental and clinical studies have demonstrated that refeeding with breast milk during the peak of diarrhea can stimulate intestinal repair and recovery of
function. Khin-Mang et al. showed that breastfeeding reduces stool output in comparison to ORS alone in acute diarrhea. In formula-fed babies, the risk of hypernatremia is higher than in breastfed infants (56).

The importance of early refeeding with semi-solid foods or infant formula is well established. Children receiving full component of calorie intake during diarrhea had better weight gain and similar treatment failure rates than those receiving half their requirement (54,55).

There is also ample evidence to support the use of lactose-containing diets; the rate of treatment failure on lactose-containing diets during acute diarrhea was similar to that on lactose-free diet in studies done over the past 15 years (52,53). Even infants below 6 months of age, taking non-human milk after initial rehydration, had a similar clinical course to that in controls using half-strength milk. In children consuming large quantities of milk as the main dietary component, lactose burden may need to be reduced by adding cereals to milk, which ensures that energy density is not decreased.

Using rice as a cereal to be mixed with milk may have additional advantages as a fraction from rice has been identified that inhibits the response of intestinal epithelial crypt cells to adenosine 3'5'-cyclic mono-phosphate, a major intracellular mediator of secretion (57).

The effect of dietary fiber has been investigated in acute diarrhea. Soya polysaccharide fiber was shown to reduce the duration of diarrhea, but there was no such effect on stool output or nutritional status (58).

The bulk of cereal-based diets may limit intake, particularly when children are anorexic as in acute diarrhea. Addition of amylase-rich flour from germinated wheat, malting, and fermentation reduces viscosity of cereal gruels and increases energy intake in severely malnourished children during and after diarrhea. The main effect of these technologies is to reduce viscosity. In clinical practice, optimal intakes from cereal diets can be readily achieved by increasing the feeding frequency to five to seven times a day (59).

**MICRONUTRIENTS IN THE TREATMENT OF ACUTE DIARRHEA**

The rationale for the use of specific nutrients as treatment of acute diarrhea is based on their effects on immune function or on intestinal structure or function and on the epithelial recovery process during diarrhea.

Zinc deficiency has been found to be widespread among children in developing countries, and occurs in most of Latin America, Africa, the Middle East, and South Asia. Zinc has been identified to play a critical role in metallo-enzymes, polyribosomes, the cell membrane, and cellular function, leading to the belief that it also plays a central role in cellular growth and in the function of the immune system. Intestinal zinc losses during diarrhea aggravate preexisting zinc deficiency (60). The zinc-depleting effects of diarrhea are most distinctly seen in adults receiving parenteral nutrition: intravenous zinc required to achieve positive zinc balance averaged 13 mg in patients with ongoing diarrheal fluid losses compared with 2.5 mg in
patients without such losses (60,61). Although the theoretical basis for a potential role of zinc in the treatment of acute diarrhea has been postulated for quite some time, convincing evidence for its clinical importance has come from recent randomized controlled trials of zinc supplementation (62–67).

The results of pooled analyses by Sazawal and Black of zinc treatment trials in children with acute diarrhea and the findings of three subsequent studies are summarized in Table 6. The main features of these trials include the randomized placebo-controlled design, subjects' age between 6 months and 3 years, and daily elemental zinc dose ranging from 10 to 30 mg per day (67).

In the trials subjected to meta-analysis, zinc-supplemented children had 16% faster recovery time (95% CI, 6% to 22%). Zinc treatment also resulted in a 20% reduction (95% CI, 2% to 38%) in the odds of acute episodes lasting longer than 7 days. The analyses concluded that zinc supplementation given along with appropriate fluids and food during acute diarrhea reduces the duration of the illness and its severity (67).

The findings of the subsequent trials are consistent with the conclusions of the meta-analysis. The study by Bhatnagar et al. is of interest as it was hospital-based, involved cases of acute diarrhea with dehydration, and measured impact on stool output. In the zinc-treated children, the total stool output was reduced by 28% (95% CI, 3% to 50%) more than in the placebo group (68). In another Indian study by Bahl et al. the efficacy of 40 mg elemental zinc mixed with a liter of standard ORS solution was compared with ORS without zinc and with zinc syrup administered separately from ORS. While zinc-ORS was superior to ORS alone, it was less efficacious in reducing duration of the episode than zinc supplements given separately from the ORS solution (70).

Several other observations from these trials are noteworthy (71). The effect of

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of continuation of diarrhea</td>
<td></td>
<td>Relative hazards</td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>1252/1194</td>
<td>0.85 (0.76 to 0.95)</td>
</tr>
<tr>
<td>Bhatnagar et al. (68)</td>
<td>132/134</td>
<td>0.77 (0.59 to 0.99)</td>
</tr>
<tr>
<td>Strand et al. (69)</td>
<td>442/449</td>
<td>0.79 (0.68 to 0.93)</td>
</tr>
<tr>
<td>Bahl et al. (70)</td>
<td>404/401</td>
<td>0.89 (0.80 to 0.99)</td>
</tr>
<tr>
<td>Diarrhea lasting &gt;7 days</td>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>1252/1194</td>
<td>0.78 (0.56 to 1.09)</td>
</tr>
<tr>
<td>Strand et al. (69)</td>
<td>442/449</td>
<td>0.57 (0.68 to 0.86)</td>
</tr>
<tr>
<td>Bahl et al. (70)</td>
<td>404/401</td>
<td>0.61 (0.33 to 1.12)</td>
</tr>
<tr>
<td>Stool output</td>
<td></td>
<td>Difference in means or ratio of geometric means</td>
</tr>
<tr>
<td>Roy et al. (63)</td>
<td>57/54</td>
<td>−91 g</td>
</tr>
<tr>
<td>Dutta et al. (21)</td>
<td>44/36</td>
<td>−900 g (−1200 to −590)</td>
</tr>
<tr>
<td>Bhatnagar et al. (68)</td>
<td>132/134</td>
<td>0.73 (0.52 to 1.02)</td>
</tr>
</tbody>
</table>
zinc did not vary significantly with age or nutritional status assessed by anthropometry. The effects were not dependent on the type of zinc salts: zinc sulfate, zinc acetate, or zinc gluconate. The optimal dose is yet to be determined but there seems to be little gain in efficacy when the commonly used 20-mg daily dose of elemental zinc was increased to 30 to 40 mg daily (71). The majority of the studies so far were conducted in South Asia, where zinc deficiency is common. Finally, there are relatively few data on children aged less than 6 months to allow any conclusions about efficacy in this age group.

The therapeutic benefits in acute diarrhea may be attributed to effects of zinc on various components of the immune system and its direct gastrointestinal effects. Zinc deficiency is associated with lymphoid atrophy, decreased cutaneous delayed hypersensitivity responses, lower thymic hormone activity, a decreased number of antibody-forming cells, and impaired T killer cell activity (60). Zinc deficiency has also been recently shown to affect the differentiation of CD4 response towards Th1 rather than Th2 pathway (72). The direct intestinal effects of zinc deficiency include decreased brush border activity, enhanced secretory response to cholera toxin, and altered intestinal permeability, which is reversed by supplementation (60,63).

The results of trials with vitamin A treatment in acute diarrhea are summarized in Table 7. The trials were all randomized placebo-controlled, the subjects were aged 6 months to 5 years and a 100,000 IU dose of vitamin A was administered to children between 6 and 12 months, and 200,000 IU to children older than 1 year. Overall, the results indicate that vitamin A has no impact on overall diarrhea duration or stool frequency, but there is a significant reduction in episodes that become persistent i.e. lasting 14 or more days. It thus appears that while the effects of treatment with zinc become apparent early in illness, effects of a vitamin A large dose take many days to manifest, possibly reflecting differences in the way they affect the gastrointestinal tract during acute infection (73–77).

It is still not known whether other micronutrients or combinations of micronutrients have greater effects during acute diarrhea than those achieved with zinc alone.

**TABLE 7. Randomized controlled trials evaluating the effect of vitamin A administered during acute diarrhea on episode outcome**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henning <em>et al.</em> (73)</td>
<td>41/42</td>
<td>No effect on mean duration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No effect on severity</td>
</tr>
<tr>
<td>Bhandari <em>et al.</em> (75)</td>
<td>451/444</td>
<td>No effect on mean duration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marked effect on risk of persistence of diarrhea ≥14 d, rate ratio 0.3 (95% CI 0.1–0.92)</td>
</tr>
<tr>
<td>Faruque <em>et al.</em> (76)</td>
<td>341/340</td>
<td>No effect on mean duration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possibility of an effect on risk of persistence of diarrhea ≥14 days, rate ratio 0.66 (95% CI 0.24–1.85)</td>
</tr>
<tr>
<td>Hossain <em>et al.</em> (74)</td>
<td>42/41</td>
<td>Effect on proportion of children clinically not cured by day 5, risk ratio 0.68 (95% CI 0.5–0.93)</td>
</tr>
</tbody>
</table>

CI, Confidence interval.
Bahl et al. recently compared the efficacy of a combination of micronutrients including zinc, vitamin A, folic acid, vitamin B12, vitamin D, selenium, and manganese in children with acute diarrhea with zinc alone (78). This study showed that zinc alone was as efficacious as these multiple micronutrients in reducing the severity of acute diarrhea, but the authors recognized that with the available end study power, only large differences in diarrheal duration and stool frequency could have been detected.

In summary, there is convincing evidence that zinc treatment leads to a modest reduction in duration and severity of acute diarrhea, but the role of other micronutrients needs more evaluation.

PROBIOTICS IN THE TREATMENT OF ACUTE DIARRHEA

Probiotics have been used for a long time in the treatment of acute diarrhea, although their efficacy has been frequently questioned.

The rationale for their use in acute diarrhea is based on one or more of several of their postulated effects. These include competition for nutrients with pathogenic microorganisms, inhibition of adhesion of pathogens to intestinal epithelial cells, production of antimicrobial substances, modification of toxins or toxin receptors and enhanced immune responses to pathogens (79–89). A systematic review of randomized, placebo-controlled trials of probiotics in the treatment of acute diarrhea was recently carried out by Szajewska and Mrukowicz (Table 8) (83). In these trials, acute diarrhea was defined as the passage of more than three loose or watery stools per 24 hours in infants and children. The use of probiotics as compared to placebo was associated with a significant reduction in the duration of diarrhea when compared to placebo: the pooled, weighted mean difference was -20.1 hours (95% CI, -26.1 to -14.2). Four of the ten trials used Lactobacillus GG, two each Lactobacillus reuteri and Lactobacillus acidophilus LB, another trial used Saccharomyces boulardii, and another S. thermophilus with L. acidophilus and L. bulgaricus.

The authors interpreted the data to show that the most consistent effect was with lactobacillus GG, although other probiotic strains may also be effective. The available data are not sufficient to allow any firm conclusions with regard to the efficacy by the type of strain used in these trials.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>Odds ratio difference in means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea lasting &gt;3 d</td>
<td>8</td>
<td>0.40 (0.28, 0.57)</td>
</tr>
<tr>
<td>Diarrhea lasting &gt;3 d</td>
<td>3</td>
<td>0.38 (0.19, 0.77)</td>
</tr>
<tr>
<td>(Studies with Lactobacillus GG only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diarrhea (hr)</td>
<td>8</td>
<td>-20.1 (-26.1 to -14.2)</td>
</tr>
<tr>
<td>Duration of rotavirus diarrhea (hr)</td>
<td>5</td>
<td>-24.8 (-31.8 to -17.9)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
From Szajewska et al. (83).
Overall, the evidence is consistent with a modest but significant benefit of probiotics in the treatment of acute gastroenteritis in infants and children. Unfortunately, none of the studies in the review reported stool output data and a firm recommendation on the practical importance of this treatment must await trials that measure its impact on this important outcome. Future trials should use carefully selected and precisely defined probiotic strains to allow judgment on individual products.

CONCLUSIONS

The challenge ahead is to implement more widely the current treatment package. Efforts must also continue to discover a clinically useful anti-secretory agent for all cases of diarrhea, newer agents against cholera, shigella and protozoal diarrheas. The recent interventions reported here represent a useful change in the current treatment package but not a major leap forward. In deciding the relevance of new interventions in developing country programs, several factors need consideration. These include the likelihood that their introduction will displace oral rehydration solutions in a cost competition and on the other hand, potential reduction in unwarranted antibiotic use.

REFERENCES


256 TREATMENT OF ACUTE DIARRHEA IN CHILDREN


57. The zinc investigators’ collaborative group. Therapeutic effects of oral zinc in acute and persistent


Dr. Abdul Majid Molla: What complexity are you referring to?

Dr. M. K. Bhan: I think ReSoMal has been developed for severely malnourished children based on a consensus. I wish some more research had been done before recommending it. My own sense is that for South East Asia, low osmolarity ORS and the promotion of an electrolyte (potassium containing) micronutrient mixture to be given with feeds rather than with ORS is a more practical approach. ReSoMal in being proposed by agencies who are working in the refugee population and there they need something already mixed; if ReSoMal can be shown to be more efficacious, then its use is feasible in such a setting. In the 1990s, according to published literature, there has not been a sufficient decline in case fatality in severely malnourished children and something needs to be done about it. What we are currently doing is not enough and this accounts, among other factors, for the stagnant child death rates in developing countries. We need to work faster towards improving the quality of initial stabilization and rehabilitation of severely malnourished children. Today a high percent of patients have incurable diseases and a severely malnourished child with diarrhea finds it difficult to get admitted despite probability of cure, while complicated patients spend weeks in hospitals with lesser rates of ultimate success. We need to press the point about greater objectivity in hospital admission policies. Domiciliary care of the severely malnourished is theoretically feasible but in practice difficult.

Dr. George Fuchs: I just would endorse your call for more research. The ReSoMal is being promoted. I can see and understand why it is being promoted, because of a sense of urgency to do something. However, it has not been subjected to a lot of testing. We completed a study in it and the manuscript has been submitted, it hasn’t been peer viewed yet, just to let you know that, but what we found was that in fact on clinical outcomes, there was no difference between ReSoMal and standard WHO-ORS and most of our patients had marasmus, which I think is the distribution that most centers face, a lot more marasmus than kwashiorkor. They have a significantly better potassium status, which is understandable and quite positive, but there was more hyponatremia in the marasmic kids that got the ReSoMal and one child had a seizure, a hyponatremic seizure. It was just one case and so you can’t say that it was significantly associated with ReSoMal, but there is a great need for further definition of this and given the scope of the problem, I’m not so sure why there aren’t more studies. It’s an easy thing to study and I would just endorse your call for more research.

Dr. B. S. Ramakrishna: There are 2 practical questions I wanted to ask you just for clarification. You mentioned the use of unselective antibiotics in severely malnourished children with diarrhea. If I’m not mistaken, it’s a combination of 3 antibiotics, gentamicin, erythromycin, and metronidazole. Am I right?

Dr. M. K. Bhan: When we say unselective antimicrobials, we are really talking of aminoglycosides and may be ampicillin or an acceptable alternative, for all admitted severely malnourished children. The earlier studies in which metronidazole and oral gentamicin was used as a strategy to combat luminal bacteria have not been substantiated. Studies in India and Lima found no effect of these two agents in comparison to placebo in malnourished children with persistent diarrhea. They related anaerobic and aerobic bacterial counts with nitrogen, fat, carbohydrate absorption and found no relationship. It is only colonization with enterobacteriae that correlated with stool output; these are specific pathogens we are talking about here. I am not recommending metronidazole or oral gentamicin. I think we have overused metronidazole for everything under the sun and now 80% of the Helicobacter pylori in India are resistant to this agent.
Dr. B. S. Ramakrishna: Probiotics in a child with bloody diarrhea? Now would you like to know whether this child had enterohemorrhagic coli or shigella, before you give antibiotics, or would you just use clinical criteria to give the antibiotic?

Dr. M. K. Bhan: I would use clinical criteria first because if there is visible blood, then I think the assumption is that antibiotics would help deal with shigella infection but also help many of the other causative pathogens. Your concern that giving antibiotics to enterohemorrhagic E. coli might increase the risk of hemolytic-uremic syndrome is theoretically sound but not a major practical issue. In the entire South East Asia, there are a handful of isolations of enterohemorrhagic E. coli reported in diarrhea cases. They are present but not in humans as yet, and my suspicion is that it is related to the way we cook meat. Maybe with time these pathogens become important. The value of culture in isolating shigella is when clinical response is poor and related to resistant strains.

Dr. Roger J. Glass: I want to just follow up on one epidemiologic conundrum and that is that as I understand malnutrition in the subcontinent has the epidemiologic feature that the rates of malnutrition go up with increasing age. So the children who are breastfed in the first few months of life or the first 6 months of life are least likely to be malnourished and it progresses. At the same time, you made the observation that deaths from diarrheal disease are primarily in children under 6 months of age and the age range of diarrheal deaths is coming down. So my question is that if malnutrition is responsible for these diarrheal deaths, you have an age distribution of malnourished children, which is much older than the age distribution of the diarrheal death children, which is much younger. How do you account for that?

Dr. M. K. Bhan: In South East Asia, 30% have low birth weight and 9% of children are wasted at age 3 to 6 months. If you look at vitamin A levels or zinc levels, 30% to 50% of kids have low levels as early as 3 to 4 months. Many older infants and children have severe malnutrition. The interventions that were promoted during the last decade have had greater impact on deaths in children than in young infants. Below 6 months, diarrheal disease deaths have reduced to a lower extent during early infancy. Of the low-birthweight kids who are still undernourished some get into problems with severe infections like diarrhea. At that age ORS usage rates are the lowest, mixed illnesses are common as are systemic infections or other complications. Even deaths due to dysentery are common during first 6 months of life. We analyzed a birth cohort in Delhi recently. There were five per 1,000 deaths due to dysentery in the first year of life; 80% of them were in the first 6 months. The incidence is high here because exclusive breastfeeding is low. The exclusive breastfeeding rates are only 10% to 40% in India. In fact, in a recent community-based trial where we introduced an exclusive breastfeeding promotion program, there was a 20% reduction in hospitalizations for diarrhea for 6 months.

Dr. Mirdula Chatterjee: My question is very simple. Instead of preparing two different ORS for children and adults, why don’t you dilute the present ORS in a larger amount of water say in 1.25 l of water for children?

Dr. M. K. Bhan: It reduces potassium, and there was one point that I may differ with George. Marasmic children have normal serum potassium, but they have total body potassium deficiency and what increases the risk of death is what’s happening in the cell. Having two different types of instructions for preparing ORS may cause confusion. Secondly, now that we know that low osmolarity ORS is better for everyone, there is no reason why we should dilute anything, but I agree with you that a single formulation makes sense and that would be the NA75/Glucose75. As a discussion point the best-reduced osmolarity formulation is
probably not one with Na75/Glucose75 but a formulation with even lower sodium and glucose and thereby osmolarity.

*Dr. Mirdula Chatterjee:* Breast milk contains sufficient potassium. In a small child who is breastfed and is not malnourished, why can’t we dilute WHO-ORS and give it alternately with breast milk? Don’t you think it will be worth something especially at community level?

*Dr. M. K. Bhan:* I think the current concentration of potassium in the WHO-ORS is probably just adequate even for a normal child. I quote Majid Molla who has published on this. If 20 mEq is low and we wouldn’t like any more reduction by dilution.

*Dr. George Fuchs:* I didn’t communicate it very well, but I agree fully with your statements about potassium, and in our study the ReSoMal group had much better potassium status and so I don’t want people to go away thinking that there was any discrepancy there. That was actually a dramatic, positive finding for the ReSoMal, and I think based on that one study, the formulation you had with the lower ORS with added potassium may be actually a better combination than ReSoMal, which seems to be a work in progress, but you’re absolutely right about the potassium.

*Dr. M. K. Bhan:* I’m not endorsing this at all. I would like to see reduced osmolarity ORS that’s suitable for everyone. That’s the sole objective.

*Dr. Gareth Williams:* You mentioned that when IV fluids are given, you use hypotonic saline. I can’t really see the rationale for that physiologically, because if you give isotonic saline to a child that’s dehydrated, you’re already giving a fluid that is relatively hypotonic. Has there been a proper evidence-based comparison of hypotonic versus isotonic saline given intravenously to the kids that need the intravenous method, and secondly, what do the children die of? Do they die of cerebral edema or respiratory distress syndrome both of which could be caused by giving hypotonic fluid to somebody in that setting?

*Dr. M. K. Bhan:* What the WHO manual proposes is that we use and continue to use Ringer’s lactate and as another option, if Ringer lactate is not available, use half-strength saline rather than full-strength saline. I am unaware of a direct comparison in the severely malnourished children. Your second question is what do they die of. They die of cardiac failure, which may be diagnosed as pneumonia. This is not our experience in South East Asia with marasmus. We find that with only subtle changes in current regimens, the results are good. However, the experience in Africa is that this is not the case and so there may be some fundamental differences between the kids in Asia and those in Africa who are more often edematous. The truth is that a lot of these recommendations came from a consensus meeting, where everybody had to agree not to disagree so as to make some progress on an important problem.