

Amylase-Resistant Starch as Adjunct to Oral Rehydration Therapy in Children with Diarrhea

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ABSTRACT

Background: Oral rehydration solution (ORS) for treatment of diarrhea relies on enhancement of small intestinal sodium and fluid absorption to correct dehydration. Amylase-resistant starch added to ORS significantly reduced the duration and severity of diarrhea in adults with cholera, presumably by generation of short-chain fatty acids in the colon and enhancement of colonic sodium and fluid absorption. The present study was initiated to determine whether addition of amylase-resistant starch to standard World Health Organization glucose-ORS (G-ORS) would reduce the duration of diarrhea and fecal fluid losses in children with acute diarrhea.

Methods: One hundred eighty-three children (6 months to 3 years) with acute watery diarrhea were randomized to receive either standard treatment with G-ORS or G-ORS with additional amylase-resistant starch, HAMS (HAMS-ORS, 50 g/L). Stool weight and consistency were monitored serially until development of formed stool or development of treatment failure defined as either the need for unscheduled intravenous fluid therapy or diarrhea longer than 72 hours.

Results: Five of the subjects were lost to follow up. In 178 remaining children (87 HAMS-ORS and 91 G-ORS) with evaluable data, time from enrolment to last unformed stool was significantly less in children receiving HAMS-ORS (median, 6.75 hours; 95% confidence interval, 4.27–9.22) than in children treated with G-ORS (12.80 hours, 8.69–16.91) ($P = 0.0292$). Time to first formed stool was also significantly shorter in children receiving HAMS-ORS (median, 18.25 hours; 95% confidence interval, 13.09–23.41) compared with children receiving G-ORS (median, 21.50 hours; 95% confidence interval, 17.26–25.74) ($P = 0.0440$). The total amount of ORS consumed was similar in both groups. There was a trend toward lower mean stool weight in first 24 hours ($P = 0.0752$) as well as total diarrheal stool weight ($P = 0.0926$) in patients in the HAMS group compared with the G-ORS group. **Conclusion:** In children with acute diarrhea, the addition of amylase-resistant starch to glucose ORS significantly shortened duration of diarrhea compared with standard treatment. *JPGN* 42:362–368, 2006. **Key Words:** Children—Diarrhea—Rotavirus—Oral rehydration solution—Amylase—Resistant starch. © 2006 by Lippincott Williams & Wilkins

INTRODUCTION

Watery diarrhea continues to be a major cause of childhood mortality in developing countries, with an estimated 1.5 million children younger than 5 years dying each year of diarrhea (1,2). This figure has greatly reduced from approximately 5 million diarrheal deaths annually 20 years ago (3), a phenomenon often attributed to the utilization of oral rehydration solution (ORS) (3). The introduction of ORS, hailed as one of the most significant medical advances of the twentieth century, allowed correction of dehydration and prevention of mortality (4). The physiological basis for ORS is that glucose-stimulated sodium and fluid absorption is not inhibited by cyclic 3',5'-adenosine monophosphate

(cAMP). However, the conventional glucose-based ORS does not reduce duration or severity of diarrhea and may in fact paradoxically increase fecal fluid losses (5). This drawback associated with its usage has led to continuing attempts to improve ORS composition to create a more effective ORS or "super-ORS."

Bhan et al. (6) in 1994 compiled a summary of several such attempts: rice-based ORS, maltodextrin- and amino acid-containing ORS were not superior to glucose-based ORS for acute noncholera diarrhea, provided that feeding was promptly resumed after initial rehydration of the child. A meta-analysis of 13 clinical trials suggested that compared with glucose-ORS (G-ORS), rice-ORS reduced stool output by about 18% in children with noncholera diarrhea (7). Meta-analysis also suggested that most of the effectiveness of rice- or other cereal-based ORS was because of the low osmolality of the ORS used. Hypo-osmolar ORS was particularly effective in the subgroup without rotavirus. A meta-analysis of trials using reduced

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osmolarity ORS concluded that compared with World Health Organization (WHO) standard ORS, hypo-osmolar ORS was associated with fewer unscheduled intravenous fluid infusions, lower stool volumes, and less vomiting (8). The WHO recently recommended a change in the composition of ORS to a low-sodium and low-glucose solution (9).

All previous attempts at improving ORS have sought to optimize small intestinal fluid absorption. In health, the major function of the colon is to dehydrate colonic fluid content, and this function becomes critical in diarrheal disease. Thus, diarrhea has been interpreted as a failure of colonic salvage of fluid (10). Short-chain fatty acids (SCFAs) are the major colonic luminal anion with concentrations as high as 130 mmol/L and enhance sodium absorption from both normal and secreting colon as a result of the demonstrated failure of cAMP to inhibit SCFA-stimulated sodium absorption (11,12). Preservation of SCFA-linked sodium absorption in diarrhea may result from SCFA stimulation of sodium absorption via sodium hydrogen exchanger isoform 2 (NHE-2), which is not inhibited by cAMP, whereas bicarbonate-linked sodium absorption occurs only through NHE-3, which is inhibited by cAMP (13). SCFAs also appear to inhibit chloride secretion in the colon (14,15). SCFAs are formed in the colon by the fermentation of nonabsorbed carbohydrates, including amylase-resistant starch (ie, starch that is relatively resistant to amylase digestion), by the anaerobic bacterial flora (16). In a randomized clinical trial in adults with cholera, the group that received amylase-resistant (high-amylase maize, HAMS) starch had significantly reduced stool volumes and duration of illness compared with those patients treated with standard therapy consisting of G-ORS and early refeeding (17).

Although cholera may be the most important dehydrating diarrhea in adults in developing countries, children often have diarrhea due to causes other than cholera. There have been 2 studies of the use of dietary substances that are potentially fermented to SCFAs added to ORS in the treatment of acute noncholera diarrhea in children. In one study, partially hydrolyzed guar gum, given as the SCFA precursor, significantly reduced the duration of diarrhea in children with noncholera acute diarrhea, compared with standard G-ORS (18). In another recent study, a mixture of nondigestible carbohydrates was used as the SCFA precursor but did not reduce either the duration or volume of diarrhea in children with noncholera diarrhea (19). The present study was designed to assess the effect of HAMS-ORS compared with standard WHO-ORS in the treatment of acute diarrhea in children younger than 3 years.

METHODS

Consecutive children presenting to the outpatient clinics or the pediatric emergency services of the Department of Child Health, Christian Medical College and Hospital, Vellore,

India, were offered entry into the study if they fulfilled inclusion and exclusion criteria and consented to the study (Table 1). The study was conducted between January 2001 and June 2004 by a team with prior experience in ORS trials. Children were included if they were boys aged 6 months to 3 years and had diarrhea defined as more than 3 watery stools in the past 24 hours with clinically detectable dehydration. Children were excluded from the study if they had diarrhea of duration longer than 7 days; blood and mucus in stool; experienced a previous episode of diarrhea in the last 4 weeks; concurrent pneumonia, meningitis, or infections requiring antibiotics; or severe (grades III and IV) malnutrition. Children with severe dehydration at presentation were hydrated with intravenous fluids for 6 hours as per WHO treatment plan C (20) and then included in the study if intravenous fluids could be discontinued at this stage. Children with severe dehydration who were not adequately hydrated at the end of 6 hours of administration of intravenous fluids were not included in the study.

Children were randomly allocated to 1 of 2 treatment groups. The contents of the packets containing the formulations of 2 ORSs were made up to be dissolved in 200 mL of water. The composition of G-ORS reflected the WHO recommendations at the time the study was initiated in 2001 (Na, 90 mEq/L; K, 20 mEq/L; Cl, 80 mEq/L; citrate, 10 mmol/L; glucose, 111 mmol/L; osmolarity, 311 mOsm/kg). HAMS-ORS packets contained 2 separate sachets, one with sufficient G-ORS (with the same electrolyte, glucose concentration, and osmolarity as standard WHO ORS) for 200 mL of water, and the other containing 10 g HAMS. When the contents of the 2 sachets were dissolved in 200 mL of water it resulted in a cloudy suspension containing 50 g/L of HAMS. Twenty packets of each ORS were randomly packed in sealed opaque covers bearing serial study numbers. The study numbers for each arm of the study were generated using a table of random numbers in blocks of 40 patients, and the randomization code was retained by the Pharmacy Department. The identity of the ORS used in individual patients was not revealed

TABLE 1. Baseline Characteristics of Children Recruited into the Study

	HAMS-ORS	G-ORS
Total number of children	87	91
Number of children 12 months or older	36	32
Age (mo), mean ± SE	12.0 ± 0.6	11.5 ± 0.6
Body weight (kg), mean ± SE	8.2 ± 0.2	8.2 ± 0.2
Duration of diarrhea before admission (h), mean ± SE	46.5 ± 3.1	52.1 ± 2.5
Degree of dehydration at entry		
Mild	49	43
Moderate	38	48
Treatment received before admission		
Antibiotics	32	27
Intravenous fluids	28	31
Pathogen		
Rotavirus	28	30
<i>Vibrio cholerae</i>	5	6
Other*	3	4

Numbers shown are those who were included in the final analysis.

*Other organisms identified include *Cryptosporidium parvum* in 2 children in the G-ORS group, *Shigella boydii* in 1 subject receiving HAMS-ORS, and *Giardia* in 1 subject each receiving HAMS-ORS and G-ORS. Pathogenic forms of *Escherichia coli* were not sought.

to the clinicians caring for the patients or to the investigators evaluating the patients. At admission into the study, each child was assigned the next available serial number by the physician recruiting the patient, and the nurse member of the team was responsible for providing the cover with the ORS therapy assigned for that specific child. The ORS was then mixed and administered by 1 of the 4 nurses who were responsible for supervising the study. Addition of HAMS to G-ORS created a cloudy suspension that was physically distinctive in appearance from G-ORS. Therefore, mixing and administration of the ORS was performed solely by the study nurses and never in the presence of the pediatricians responsible for clinical decisions or for grading stool consistency. The study nurses did not determine which specific study group any individual patient entered; this was accomplished by providing sealed opaque covers (bearing serial numbers in random order) with 1 of the 2 test ORSs. The study pediatricians were not aware of the specific ORS treatment that the child was receiving. However, the study was designed such that 1 of 2 pediatricians was primarily responsible for assessment of hydration and the clinical care of the child. Because there was a possibility that this pediatrician might accidentally become aware of the treatment that the patient was receiving, the other pediatrician was responsible for assessing stool consistency.

At entry, stool was examined by dark-field microscopy, stool culture, and rotavirus enzyme-linked immunoassay. Before the start of this study HAMS-ORS was administered orally to 6 children with acute diarrhea and found to be well tolerated. HAMS-ORS did not induce vomiting or significant increase in diarrhea and was ingested by the children in the quantities offered. HAMS-ORS was administered as a suspension without cooking because cooking was likely to alter the amylase-resistant properties of the starch. Children were admitted to a diarrhea ward where ORS was administered by a team of study nurses in the quantities recommended in WHO treatment plan B. Children in both treatment arms received identical treatment, as per WHO guidelines, other than the type of ORS. Oral intake of water was allowed ad libitum and encouraged. Children were fed after the initial rehydration period of 6 hours. Refeeding consisted of breast milk feeding alternating with the ORS in infants, a weaning mixture for children 6 to 12 months and a regular south Indian diet (3 meals in 24 hours) in children older than 1 year. Blood tests were performed as clinically indicated. Urine was collected separate from stool using a urine pouch. The stool was collected in preweighed diapers, the weight measured, and the time of stool collection and consistency of each stool recorded. Weight of stool and volume of urine in relation to the child's body weight were recorded every 6 hours. Consistency of the stool was graded as watery, loose, semi-loose, pasty, or formed, a grading system that had been used in earlier ORS studies from this hospital (17). Initial standardization of the grading of stool consistency was reestablished by the pediatricians. To avoid bias, the assessment of consistency was performed by a study physician who was blinded to the specific ORS administered to the child. The

time from first administration of ORS to the last unformed stool was recorded as well as the time to the first formed stool.

Clinical decisions regarding management and need for intravenous fluids were based solely on the state of hydration of the child (as per the WHO guidelines) and were made by the pediatrician on call or the attending pediatrician during ward rounds, without reference to the type of ORS being received by the child. Children were discharged from the hospital when they had a formed stool. Body weight was recorded at entry and after 4, 12, 24, and 48 hours. Informed written consent was obtained from the parent. The study design, patient information sheet, and consent form were approved by the Ethics Committee (Institutional Review Board) of the Christian Medical College.

The study was designed as a randomized trial that would allow comparison between an established form of therapy (G-ORS) and HAMS-ORS. The primary end points or variables assessed for comparison were stool weight in the first 24 hours, total stool weight until cessation of diarrhea, and duration of diarrhea (defined as time from onset of oral rehydration therapy until the last unformed stool). "Treatment failure" was defined as either the need for unscheduled intravenous fluid therapy or the persistence of diarrhea beyond 72 hours, which was also a secondary end point. The study ended in each individual patient either when there was a formed stool or when there was treatment failure.

Treatment with G-ORS was chosen as the control group because this is the ORS that has been tested most widely. Although rice-ORS, in a number of different forms, is now widely used, the inclusion of rice-ORS as an additional treatment group would have resulted in the need to recruit a substantially greater number of patients for the study. Data were analyzed using GraphPad InStat Version 3.06 for Windows. The continuous variables were expressed as means with 95% confidence intervals. Significance of differences between means of groups was measured using the Mann-Whitney *U* test. Survival curves displaying time to termination of diarrhea and time to first formed stool were compared using Breslow test, which provides greater weight to the earlier part of the curves where more observations are available. *P* values (2-tailed) were considered significant if they were less than 0.05.

RESULTS

Based on sample size calculations derived from another published study (21), we originally intended to recruit 232 children into this study allowing for dropouts. An interim analysis was performed with blinded data for safety monitoring. Based on the mean and SD of the fecal weight and duration of diarrhea for the entire population of children with diarrhea, it was calculated that the total number of children that would be required to be recruited could be reduced to 160 cases with 80% power to detect a 25% difference in duration of diarrhea between the 2 groups, whereas approximately 200 cases would be needed to detect a 20% difference in stool volume with 80% power. Because recruitment of patients into the study was

slower than anticipated, the study was discontinued before the initial targeted recruitment. The decision to terminate the study was taken jointly by the 3 principal investigators (P.R., B.S.R., and H.J.B.) as the number of patients studied would allow conclusions to be drawn regarding the effect of HAMS-ORS on the duration of diarrhea, and the charts were reviewed for analysis at a time when the 3 principal investigators were all present in Vellore.

Of the 183 children that were recruited, 3 were excluded because of withdrawal of consent and 2 because of incomplete entry in the case record form (Fig. 1). Unscheduled intravenous fluid therapy had a priori been designated as an end point terminating the study. Fifteen children (9 in G-ORS group and 6 in HAMS-ORS group) required unscheduled intravenous fluids within 12 hours of enrolment, and stool collection and recording was terminated in these children before actual cessation of diarrhea. Four children (2 in each study group) had diarrhea persisting beyond 72 hours, and data were available up to this point. Data from these children were included in the intention-to-treat analysis until the time of discontinuation at which point they became censored observations. Nineteen children (8 in G-ORS group and 9 in HAMS-ORS group) had no stool output during the initial 24 hours after entry into study, and they were

discharged at 24 hours. Data from these children were included in intention-to-treat analysis with the assumption that time from enrolment to last unformed stool was 0 hours and time from enrolment to first formed stool was 24 hours. It is possible that those receiving an unscheduled intravenous were the most ill and therefore most likely to be followed for a long period without terminating diarrhea or observing the first formed stool. Hence, sensitivity analysis (ie, changing the censoring time from their time of discontinuation to the full 72 hours' follow-up) was done, which did not significantly alter study conclusions.

The total amount of ORS consumed was similar in both groups (Table 2) ($P = NS$). The mean stool output in the first 24 hours was 31% lower in the HAMS-ORS group compared with the G-ORS group, and this difference showed a trend toward statistical significance (Table 2). Total diarrheal stool output was 29% lower in the HAMS-ORS group compared with the G-ORS group, and again this difference showed a trend toward statistical significance. Analysis of the subgroup of children with rotavirus infection did not reveal any significant difference in stool volume between the 2 treatment groups.

The time from enrolment into the study to the last unformed stool was significantly shorter in children

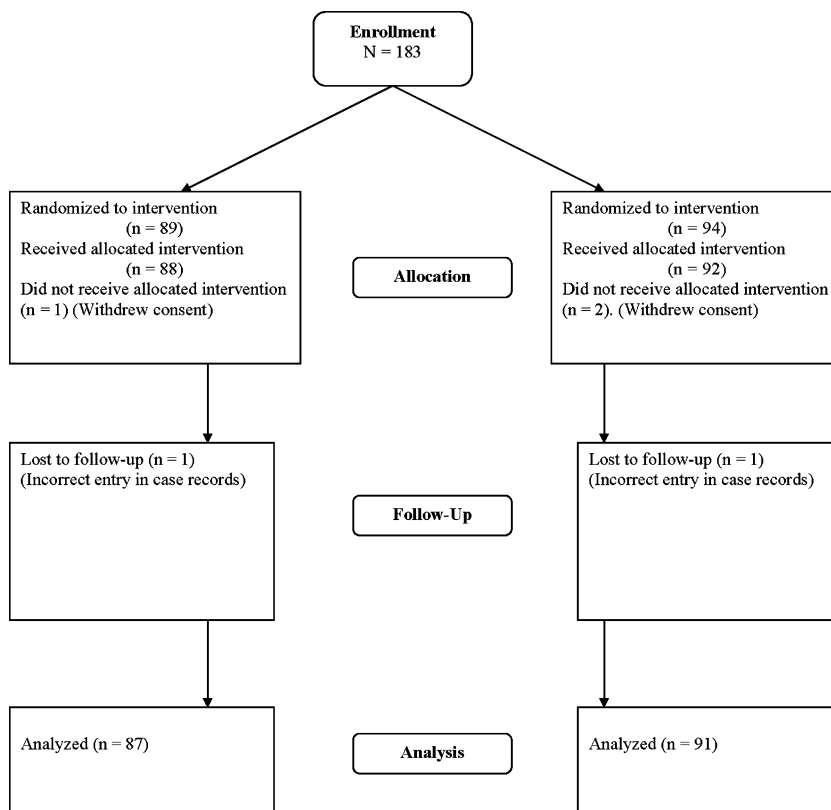


FIG. 1. Flow chart of patients through the study and analysis.

TABLE 2. Outcome Variables in Children Treated with HAMS-ORS Compared with Those Treated with G-ORS

Variable	HAMS-ORS	G-ORS	P
Total ORS consumed (mL/kg body weight)			
Mean	79.6	87.3	NS
95% CI	67.1–92.1	74.1–100.4	
Stool weight in initial 24 h (g/kg body weight)			
Mean	35.5	51.3	0.07
95% CI	26.8–44.3	40.0–62.7	
Total stool weight until last unformed stool (g/kg body weight)			
Mean	44.8	63.5	0.09
95% CI	31.7–57.9	47.2–79.9	
Time from enrolment until last unformed stool (h)			
Mean	6.75	12.8	0.03*
95% CI	4.27–9.23	8.69–16.91	
Time from enrolment until first formed stool (h)			
Mean	18.25	21.50	0.04*
95% CI	13.09–23.41	17.26–25.74	
Unscheduled intravenous fluids	6	9	NS**
Diarrhea persisting beyond 72 h	2	2	NS**

NS indicates not significant.

P values shown are 2-tailed values using Mann-Whitney U test, *Breslow test, or ** χ^2 test.

treated with HAMS-ORS than in children treated with G-ORS (Table 2 and Fig. 2). The median time from enrolment into study to the last unformed stool in children receiving HAMS-ORS (6.75 hours) was significantly lower than that in children receiving G-ORS (12.8 hours) ($P = 0.03$). The median duration of time from enrolment to the first formed stool was predictably longer in both groups, but again was significantly lower in the HAMS-ORS group (median, 18.25 hours) compared with the G-ORS group (median, 21.5 hours) ($P = 0.04$). Diarrhea lasting longer than 24 hours was observed in 19 of 91 children randomized to G-ORS compared with 13 of 87 children treated with HAMS-ORS ($P = NS$). When the subgroup of children with rotavirus infection was separately analyzed, the differ-

ence in duration of diarrhea between the 2 groups was not statistically significant.

DISCUSSION

Improvement in the composition of ORS continues to be a major research effort in the treatment of acute diarrhea as there is no universal rehydration solution that is equally effective in all types of diarrhea. Cholera and other severe dehydrating diarrheas are associated with high fecal losses of sodium and water, whereas rotavirus and other diarrheas common in children have much smaller losses of sodium. Any new ORS must be established to decrease the duration of diarrhea as well as reducing fecal fluid losses. It is expected that such

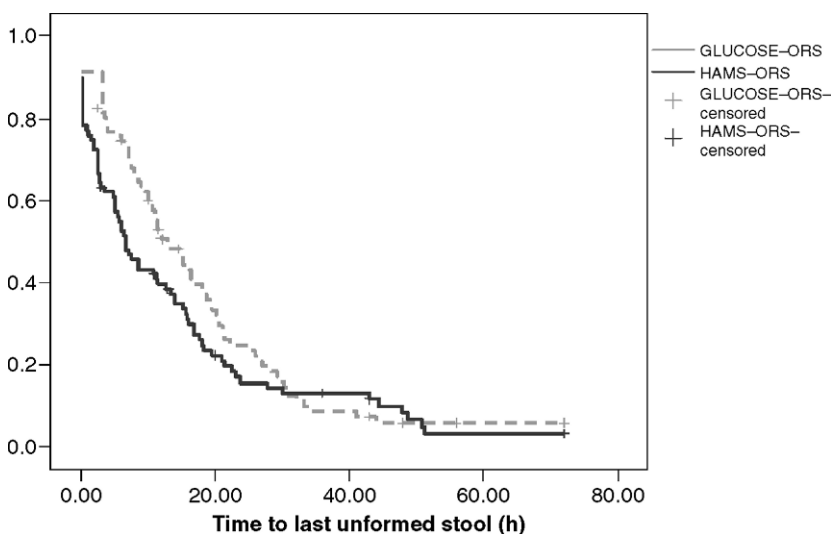


FIG. 2. Kaplan-Meier survival analysis related to proportion of children continuing to have diarrhea at different time intervals. The data plotted are for time from entry into study until last unformed stool and are shown for 178 children (91 G-ORS and 87 HAMS-ORS). Details of the analysis are given in the Results section.

objective measures of efficacy will be translated into increased acceptability by caregivers of patients with diarrhea. The present study demonstrates that starch that is relatively resistant to amylase digestion (or resistant starch) significantly reduced the duration of diarrhea in children with acute diarrhea that was predominantly because of causes other than cholera. The primary outcomes that were evaluated were whether the new ORS reduced stool volume and duration of diarrhea compared with the standard G-ORS, attributes that we believed any new ORS must possess. The secondary outcome was the need for unscheduled intravenous fluid therapy, which indicates the therapeutic efficacy of the test-ORS compared with the standard-ORS. The use of amylase-resistant starch was associated with a trend to lower stool weight during the first 24 hours.

Despite its efficacy in correcting dehydration and preventing mortality, ORS has not achieved the widespread use that was initially expected. Although this may be due in considerable part to lack of knowledge or appreciation of the effects of ORS, caregivers in the community have been reluctant to use ORS when it does not palpably reduce diarrhea (22). The G-ORS is associated with persistence of diarrhea during ORS administration, whereas hypo-osmolar ORS may reduce diarrhea to some extent. Green bananas and pectin have been shown to reduce duration of diarrheal illness and hasten recovery in children with persistent diarrhea in Bangladesh (23). Green bananas contain amylase-resistant starch, and the assumption is that the starch is fermented to SCFAs in the colon, which, besides salvaging sodium and water from the colon, also enhance mucosal function and recovery. Amylase-resistant starch is poorly digested in the small intestine, but is fermented in the colon to SCFAs by the luminal bacterial flora. SCFAs increase Na absorption from the secreting colon. The model of SCFA stimulation of sodium absorption requires a Na-H exchange, similar to that for HCO₃ stimulation of Na absorption. Although cAMP inhibits HCO₃-dependent sodium absorption as a result of inhibition of Na-H exchange, SCFA-dependent sodium absorption is not inhibited by cAMP. This apparent paradox is likely explained by the observation that SCFA-dependent sodium absorption may occur via either NHE-2 or NHE-3, whereas HCO₃-dependent sodium absorption is only dependent on NHE-3. Cyclic nucleotides inhibit the NHE-3 isoform but increase NHE-2 isoform activity. In addition, it has been shown that SCFAs inhibit chloride secretion (the primary driving force for fluid secretion in cholera and other secretory diarrhea) in the colon. Amylase-resistant starch had earlier been shown to reduce significantly both fluid losses and the duration of diarrhea in adults with cholera (17). The present study extends this earlier observation and shows that amylase-resistant starch is also useful in the treatment of noncholera diarrhea in children.

This reduction in the duration of diarrhea occurred despite early refeeding of children in both treatment

groups. It is clear from prior studies that early refeeding significantly shortens the duration of diarrhea (5,6). Refeeding introduces complex carbohydrates in children ingesting a normal diet and thus provides substrate for SCFA generation in the colon. Starch in the colon is a substrate that is rapidly fermented to SCFAs and preferentially fermented to butyrate. It is, therefore, likely that the additional benefit provided by amylase-resistant starch is because of increased generation of SCFAs, possibly butyrate. A recent multicenter study carried out by ESPGHAN in 8 centers enrolled 144 boys with acute diarrhea and examined the addition of a mixture of nondigestible carbohydrates to ORS on the course of diarrhea. In these children, the addition of a mixture of nondigestible carbohydrates (soy polysaccharide, cellulose, gum arabic, fructo-oligosaccharide, inulin, and a small amount of resistant starch) to ORS did not provide any significant reduction of diarrhea duration, fecal volume, or unscheduled intravenous fluid therapy (19). It is likely that this lack of benefit was because of the nature of the specific carbohydrates used and/or to the low concentration of nondigestible carbohydrate administered. In that study 10 g/L of unabsorbed carbohydrate was administered, compared with approximately 25 g/L of resistant starch (expected to enter the colon), which was administered in the present study. In another study of 150 male children with acute diarrhea, addition of partially hydrolyzed guar gum significantly reduced duration of diarrhea, and reduced stool volume on day 7 of diarrhea (18). These somewhat contrary observations suggest that the concentration of nondigestible carbohydrate as well as the absolute amount of nondigestible carbohydrate could be important in determining its effect on the duration of diarrhea.

The use of reduced osmolarity ORS has been in wide practice in the past few years largely because some children developed hypernatremia when receiving conventional G-ORS. This study used the old WHO ORS as the reference treatment because this was the recommended therapy at the time of the start of the trial. As a result of studies performed in several centers worldwide, the World Health Organization revised its recommendation for ORS composition in mid-2002 and now recommends a lower sodium and glucose concentration for the treatment of diarrhea (24,25). In countries where cholera is common, it is expected that the use of a single or universal reduced osmolarity ORS for all kinds of diarrhea will likely result in problems related to hyponatremia (26). We have shown in whole gut perfusion studies in animals (unpublished observations) that amylase-resistant starch significantly enhances sodium absorption from a hypo-osmolar ORS. The present study suggests that clinical trials in adults and children with diarrhea to determine the effect of adding amylase-resistant starch to reduced osmolarity ORS would be appropriate.

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REFERENCES

- Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet* 2003;361:2226–34.
- Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease as estimated from studies published between 1992 and 2000. *Bull World Health Organ* 2003;81:197–204.
- Snyder JD, Merson MH. The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. *Bull World Health Organ* 1982;60:605–13.
- Editorial. Water with sugar and salt. *Lancet* 1978;2:300–1.
- Greenough WB 3rd. A simple solution: curing diarrhea. *J Diarrhoeal Dis Res* 1993;11:1–5.
- Bhan MK, Mahalanabis D, Fontaine O, Pierce NF. Clinical trials of improved oral rehydration salt formulation: a review. *Bull World Health Organ* 1994;72:945–55.
- Gore SM, Fontaine O, Pierce NF. Impact of rice based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials. *Br Med J* 1992;304:287–91.
- Hahn S, Kim S, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. *Cochrane Database Syst Rev* 2002;1:CD002847.
- Duggan C, Fontaine O, Pierce NF, Glass RI, Mahalanabis D, Alam NH, Bhan MK, Santosham M. Scientific rationale for a change in the composition of oral rehydration solution. *JAMA* 2004;291:2628–31.
- Read NW. Diarrhea: the failure of colonic salvage. *Lancet* 1982;2:481–3.
- Binder HJ, Mehta P. Characterization of butyrate-dependent electroneutral NaCl absorption in rat distal colon. *Pflugers Arch* 1990;417:365–9.
- Ramakrishna BS, Nance SH, Roberts-Thomson IC, Roediger WEW. The effect of enterotoxins and short chain fatty acids on water and electrolyte fluxes in ileal and colonic loops in vivo in the rat. *Digestion* 1990;45:93–101.
- Krishnan S, Rajendran VM, Binder HJ. Apical NHE isoforms differentially regulate butyrate-stimulated Na absorption in rat distal colon. *Am J Physiol Cell Physiol* 2003;285:C1246–54.
- Dagher PC, Egnor RW, Taglietta-Kohlbrecher A, Charney AN. Short-chain fatty acids inhibit cAMP-mediated chloride secretion in rat colon. *Am J Physiol* 1996;271:C1853–60.
- Vidyasagar S, Ramakrishna BS. Effects of butyrate on active sodium and chloride transport in rat and rabbit distal colon. *J Physiol* 2002;539:163–73.
- Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. *Proc Nutr Soc* 2003;62:67–72.
- Ramakrishna BS, Venkataraman S, Srinivasan P, Dash P, Young G, Binder HJ. Amylase-resistant starch plus oral rehydration solution for cholera. *N Engl J Med* 2000;342:308–13.
- Alam NH, Meier R, Schneider H, Sarker SA, Bardhan PK, Mahalanabis D, Fuchs GJ, Gyr N. Partially hydrolyzed guar gum-supplemented oral rehydration solution in the treatment of acute diarrhea in children. *J Pediatr Gastroenterol Nutr* 2000;31:503–7.
- Hoekstra JH, Szajewska H, Zikri MA, Micetic-Turk D, Weizman Z, Papadopoulou A, Guarino A, Dias JA, Oostvogels B. Oral rehydration solution containing a mixture of non-digestible carbohydrates in the treatment of acute diarrhea: a multicenter randomized placebo controlled study on behalf of the ESPGHAN working group on intestinal infections. *J Pediatr Gastroenterol Nutr* 2004;39:239–45.
- The treatment of diarrhoea: a manual for physicians and other senior health workers. *WHO/CDR/95.3*. Geneva: World Health Organization; 1995.
- Pizzarro D, Posada G, Sandi L, Moran JR. Rice-based oral electrolyte solutions for the management of infantile diarrhea. *N Engl J Med* 1991;324:517–21.
- Desjeux JF, Briend A, Butzner JD. Oral rehydration solution in the year 2000: pathophysiology, efficacy and effectiveness. *Baillieres Clinical Gastroenterology* 1997;11:509–27.
- Rabbani GH, Teka T, Zaman B, Majid N, Khatun M, Fuchs GJ. Clinical studies in persistent diarrhea: dietary management with green banana or pectin in Bangladeshi children. *Gastroenterology* 2001;121:554–60.
- Anonymous. *Reduced osmolarity oral rehydration salts (ORS) formulation*. Geneva: World Health Organization; 2002.
- Application to change the composition of oral rehydration salts (ORS) in the WHO Model List of Essential Medicine (April 2003). Available at: <http://www.who.int/medicines/organization/par/edl/expcom13/expcom03change.shtml>.
- Nalin DR, Hirschhorn N, Greenough WB III, Fuchs GJ, Cash RA. Clinical concerns about reduced osmolarity oral rehydration solution. *JAMA* 2004;291:2632–5.