

# Clinical Concerns About Reduced-Osmolarity Oral Rehydration Solution

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**D**EMONSTRATION OF THE BENEFITS OF ORAL THERAPY for cholera in 1968<sup>1</sup> soon led to application of the method to all forms of infectious diarrheal diseases.<sup>2</sup> The original oral rehydration solution (ORS) formulation developed by the World Health Organization (WHO) (TABLE) struck a compromise between the ideal solutions for these diverse disorders to meet the programmatic goal of a single formulation and packaging for global use in cholera and noncholera diarrheas, in both adults and children. Recently, WHO recommended a new oral solution (Table) for all acute diarrheas, including cholera. This new formula would replace the original ORS, which saved millions of lives, with a new formulation containing less sodium and glucose.<sup>3</sup> This change was ostensibly to reduce gross stool volume and use of unscheduled intravenous therapy by lowering solution osmolality. However, the reduced-osmolality formulation is particularly unsuitable for universal use because it contains an amount of sodium insufficient to maintain sodium balance in cholera patients, in whom its use induces negative sodium balance and may lead to hyponatremia,<sup>4,5</sup> polyuria,<sup>4</sup> and a small but clinically significant risk of neurologic complications. The new reduced-osmolality formulation stretches the original compromise to the breaking point. It may be time to promote use of different solutions for patients with cholera, beginning in controlled settings such as cholera treatment centers and hospitals.

Therapy of acute watery diarrhea requires replenishing water and electrolyte losses (rehydration phase) and maintaining water and electrolyte balance after rehydration until diarrhea ceases (maintenance phase). Oral rehydration is successful when hourly oral intake matches or modestly exceeds fluid losses (regardless of gross stool rate). When the solution contains appropriate amounts of sodium, potassium, and bicarbonate or base-precursor, electrolyte balance

is also restored and maintained. Dehydrated patients in shock need rapid intravenous rehydration followed by oral maintenance. If intravenous fluids or skilled personnel are unavailable, oral rehydration and maintenance can be effective even in hypotensive patients.<sup>6</sup> With lesser degrees of dehydration, most patients respond without intravenous fluids, and dehydration can be prevented by early oral maintenance therapy.

Cholera patients have the highest purging rates, stool sodium concentrations, and loss of body sodium; adult losses exceed those of children, who have lower stool sodium concentrations, the latter linked to greater stool potassium losses.<sup>7</sup> Patients with noncholera diarrhea generally have lower purging rates.<sup>8</sup> In early studies of adults with cholera, use of oral maintenance solutions with glucose and 100 mEq/L of sodium resulted in an average negative sodium balance of 50 mEq, ranging as low as -200 mEq.<sup>9,10</sup> The original WHO formulation containing 90 mEq/L of sodium could not offset sodium losses in adult cholera patients (120-140 mEq/L of cholera stool). The reduced sodium formulation (75 mEq/L) would further aggravate these sodium losses. In a randomized double-blind trial of 300 adults with cholera, more patients given the new solution developed hyponatremia (sodium <130 mEq/L) than those given the standard WHO ORS (odds ratio, 2.1; 95% confidence interval [CI], 1.1-4.1).<sup>5</sup> There were no differences in diarrheal duration or volume, vomiting, or use of unscheduled intravenous fluids between patients receiving standard or reduced-sodium ORS.

The concern that hyponatremia may result from use of the reduced-osmolality formulation is not restricted to adults with cholera. In the multicenter CHOICE study of 675 children with acute watery diarrhea,<sup>11</sup> which helped inform the decision to change the sodium content of the WHO ORS, more children given the reduced sodium solution had hyponatremia than those given the standard solution (serum sodium levels <130 were 11% vs 9% and <125 mEq/L were 4% vs 2%, respectively), but these differences were not statistically significant. However, 1 of the 373 children (0.3%) with hy-

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**Financial Disclosures:** Dr Nalin is a consultant to Merck & Co and Dr Greenough is a scientific advisor to and shareholder in Cera Products Inc, a manufacturer of rice-based oral rehydration solution.

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ponatremia who received the reduced-osmolarity solution had a generalized seizure. Such seizures are not benign.<sup>12</sup>

One rationale for the new ORS was to reduce stool output by lowering solution osmolarity because families and physicians were believed to be reluctant to use the solution if gross stool output increased. The CHOICE study<sup>11</sup> showed no significant difference in stool output or duration of illness among children who received reduced-osmolarity solution vs those who received standard ORS. A difference in use of unscheduled intravenous fluids was reported (10% vs 15%; odds ratio, 0.6; 95% CI, 0.4-1.0.) However, in both groups, patients given unscheduled intravenous fluids had twice the volume of stool output of those who did not receive intravenous fluids. This suggests that transient glucose malabsorption may have played a role in this outcome, and chance overallocation of several patients with glucose malabsorption to the group that received the standard ORS could explain the difference. (There is no evidence that oral solution sodium concentration affects glucose tolerance.)

In a meta-analysis of 15 trials comparing use of the 2 solutions in children hospitalized with dehydration associated with diarrhea,<sup>13</sup> use of unscheduled intravenous fluids was reported to be lower in those children who received the lower-osmolarity solution. However, only 9 of 15 trials reviewed were included in the analysis of unscheduled intravenous fluid needs, and in 5 of these 9, including the largest trial, the odds ratios hovered near 1.0. The meta-analysis also reported a reduction in stool output among those receiving the reduced-osmolarity solution, but its magnitude could hardly be noticed except by measuring stool volume.<sup>14</sup> Stool output comparisons showed close to zero difference in 8 of 12 trials analyzed. In addition, only 3 trials in the meta-analysis included children with cholera. Moreover, the largest trials included showed the smallest differences.<sup>5,11</sup> Finally, none of the 15 studies prestratified patients by diarrhea rates before randomized allocation,<sup>13</sup> which may explain the high inter-study variability in outcomes, since the initial rate of stool loss determines overall diarrhea rate and volume.<sup>15</sup>

No studies comparing outcomes of the standard WHO ORS to the new reduced-osmolarity formulation have measured net sodium and potassium losses. The impact of the reduced-osmolarity solution on sodium and potassium balance is therefore unknown. Previous studies have shown that standard WHO ORS inadequately replaces stool potassium losses,<sup>16</sup> and hyponatremia aggravates urine potassium losses.<sup>17</sup> The new formulation aggravates sodium deficits in cholera more than the original formulation.<sup>4,5</sup> In some studies the 2 solutions performed similarly because both induce negative sodium balance. Earlier oral solutions for cholera contained 100 to 120 mEq/L of sodium, matched stool electrolyte levels more closely, and promoted modest positive sodium balance without hyponatremia or hypernatremia.<sup>1,18</sup>

Pediatric and adult cholera patients typically lose 100 to 135 mEq of sodium per liter of diarrhea, respectively.<sup>19</sup> The reduced-osmolarity solution with 75 mEq/L of sodium would there-

**Table.** Composition of Oral Rehydration Solutions

Component	Standard WHO (1975)	Reduced-Osmolarity WHO (2002)	Glucose Plus Glycine*
Glucose, mmol/L	111	75	110
Sodium, mEq/L	90	75	120
Potassium, mEq/L	20	20	15
Chloride, mEq/L	80	65	72
Base	10†	10†	48‡ (15§)
Glycine, mmol/L			110
Osmolarity, mOsm/L	311	245	510

Abbreviation: WHO, World Health Organization.

\*See also reference 30.

†Citrate in mmol/L.

‡The base was bicarbonate in the original study.<sup>18</sup>

§Potassium citrate.

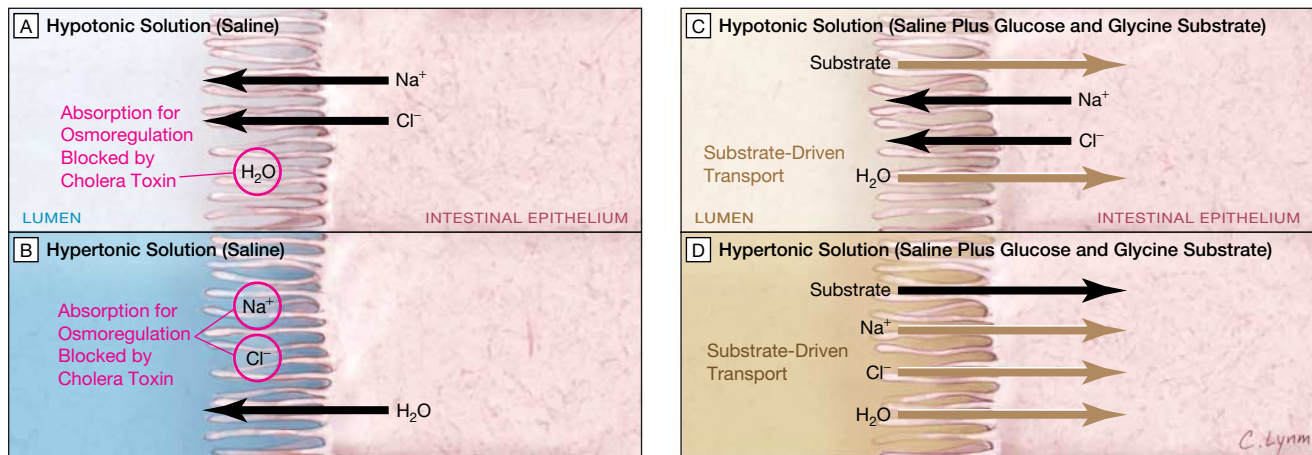
fore induce a negative sodium balance of -25 to -60 mEq/L ingested when matching intake to output. Adult diarrhea rates in severe cholera approach 1 L/h, so losses of up to 300 mEq of sodium can accrue within 5 hours of such treatment, enough to sharply lower blood sodium levels. Even with antibiotics, oral maintenance usually lasts 24 to 44 hours in adult cholera patients,<sup>18,20,21</sup> enough to induce massive sodium deficits using the low-sodium solution. Moreover, to expand intravascular volume rapidly, patients must drink more of a low-sodium solution, which may lead to fatigue and treatment failure.<sup>17</sup>

In malnourished patients with chronic hyponatremia and multiple diarrhea episodes, very low-sodium oral solutions (45 mEq/L) also aggravate hyponatremia (1 of 65 patients had seizure).<sup>22</sup> Use of reduced-osmolarity solution in these patients should be relatively contraindicated, but the new recommendations do not address this point.<sup>3</sup>

Another difficulty is that all studies of the new formulation involved single-incident diarrheal episodes. Where effective oral therapy programs exist, children may receive therapy for multiple diarrhea episodes. Surveys in several countries have shown more than 7 episodes of varied etiologies per child annually.<sup>23,24</sup> The risk of aggravated hyponatremia might exist when such patients, already sodium depleted, present for treatment of incident episodes. This deserves study to determine the safety of low-sodium solutions in such patients. When programs are not yet developed, the fluids given at home are also often associated with hyponatremia (and other electrolyte disorders), which remain undetected until hospitalization.<sup>25</sup>

The studies that led to modification of the WHO ORS formulation have several key limitations. First, resumption of intravenous fluids was based on clinical criteria, with objective confirmation by measuring plasma specific gravity in only 1 study.<sup>11</sup> The methods of measuring intake and output, and quality control procedures, were omitted or incompletely reported in all but 1 study.<sup>11</sup> In another study,<sup>4</sup> instead of matching oral intake to fluid losses, patients who received low-sodium ORS drank twice their volume of stool loss, and those who received standard ORS drank 3 times their stool volume losses. In the 1 higher-quality study,<sup>11</sup> 125 of 676 children (18%) discontinued or were excluded, which might partly explain why groups

**Figure.** Net Water and Ion Movement During Intestinal Osmoregulation in the Presence of Cholera Toxin



Intestinal absorption of sodium, chloride, and water is severely impeded in cholera. Osmoregulation of luminal fluids occurs chiefly by net sodium and chloride movement into hypotonic saline solutions (A) and by net water movement into hypertonic solutions (B). In A, water losses are slowed but sodium losses are heightened; in B, water losses are massively increased and diarrhea worsens. In C and D, addition of substrates, which enhance active sodium transport, increases net sodium, chloride, and water absorption and promotes rehydration. In C, however, net sodium deficits occur because sodium enters luminal fluids when its concentration is below plasma levels.<sup>18,28,29</sup>

with generally similar diarrhea duration and volume differed in the administration of unscheduled intravenous fluids. In studies of adult patients with cholera, those who received the new ORS had increased risk of hyponatremia and polyuria but no significant reduction in rates of unscheduled intravenous fluids. Lower diarrhea rates were reported among those who received the new formulation in a small study,<sup>4</sup> but this outcome was not confirmed in a large randomized trial.<sup>5</sup> Published data on pediatric cholera patients are sparse. No difference in 24-hour stool volume was seen in 1 study (n=26); in 2 others (n=19 each) stool output was reduced by 30% in those who received the new formulation, but there was also an increase in rates of hyponatremia.<sup>11,26,27</sup>

**Consequence of a Lower-Sodium Solution**

The normal small bowel adjusts luminal tonicity by both secretion and absorption. Sodium enters the lumen according to its plasma-to-lumen chemical gradient, regardless of luminal fluid tonicity. Water enters the lumen when the luminal fluid is hypertonic and is absorbed from the lumen when the luminal fluid is hypotonic. Cholera toxin causes high-output diarrhea by interfering with the absorption of sodium and water, leading to a defect in small intestinal osmoregulation, demonstrated in the canine cholera model.<sup>28</sup> Osmoregulation is then achieved only by changing the rate of net secretion of salt or water into the lumen. Hypotonic luminal contents are then adjusted by increased secretion of sodium into the lumen and reduced secretion of water; hypertonic solutions are adjusted by increased movement of water and sodium entering the lumen (FIGURE A, B). Thus, in experimental models, after application of cholera toxin, luminal plain water can slow water secretion but causes a drastic increase in sodium loss into the lumen.<sup>28</sup> Two chol-

era patients treated with 0 to 50 mEq/L sodium solutions with substrate rapidly lost more than 300 mEq of sodium and developed hyponatremia.<sup>29</sup> Similarly, 34 adult cholera patients<sup>4</sup> randomly allocated to low-sodium solution had 29% less stool output but 44% higher urine output (19.9 vs 13.8 L of urine/48 h). Hyponatremia causes polyuria by suppressing antidiuretic hormone. Three of these patients had serum sodium levels lower than 125 mEq/L at 24 hours.<sup>4</sup> Urine volumes in studies of an earlier formulation with osmolarity of 380 mOsm/L were typically 1.6 L during 30 hours' mean therapy.<sup>21</sup> Among the 34 adult recipients of reduced-sodium ORS, 12% needed unscheduled intravenous fluid vs 24% among 29 standard ORS recipients; this difference was not significant (P=.19). The standard ORS recipients had a higher diarrhea rate in the preoral period, probably accounting for the observed difference.<sup>4</sup> In a much larger study,<sup>5</sup> no difference in diarrhea rate was seen.

The absorptive component of osmoregulation in cholera is restored by substrates promoting sodium absorption. Indeed, the most hypertonic solution yet tested, 510 mOsm/L, containing electrolytes and glucose plus glycine, was also the most effective in reducing both diarrhea rate and duration in adult and pediatric cholera patients<sup>18,30</sup> (Table). Likewise, oral solutions containing rice-based substrate, which has a high glycine content, reduce cholera diarrhea output.<sup>31</sup> Thus, in cholera, osmolarity per se does not determine changes in diarrhea rates or in net absorption associated with different oral formulations; absorbability of the components contributing to osmolarity, and their effects on sodium and water transport, are key (Figure C, D).

However, glucose with glycine or rice-based solutions do not have the same enhanced efficacy in noncholera diarrheas (except those sharing the cAMP [cyclic adenosine mono-

phosphate] diarrheagenic mechanism). A possible explanation is that substrate-induced active transport, previously believed to be intact in cholera, may actually be enhanced by the increased cAMP induced by cholera toxin. This was demonstrated in intestinal cells and oocytes of rabbits expressing mammalian sodium-glucose transporters.<sup>32</sup>

### Experience With the Original WHO ORS

The original WHO formulation with 90 mEq/L of sodium and 111 mmol/L of glucose (Table) proved a safe, effective formulation for all age groups and cholera or noncholera diarrhea.<sup>2,7,9,16,25</sup> However, failure to communicate the information needed to ensure correct solution preparation, concentration, and appropriate drinking volumes can lead to electrolyte imbalance, whatever the formulation. Thus, inaccuracies in home-mixing of solutions led to hypernatremia in Egypt, a situation that was reversed with detailed instructions broadcast via television and taught in rehydration clinics.<sup>33</sup>

Practical clinical recommendations using the original formulation offered safe and effective variations on the basic regimen in noncholera areas, including early feeding and allowing extra oral water, for example, the 2:1 regimen.<sup>16,25</sup> Mild, transient elevations of serum sodium levels occurred in a minority of patients without cholera who were receiving the original formulation (without extra water), without any adverse events.<sup>16</sup> In fact, the original formulation was found safe and effective for treating hypernatremic dehydration<sup>34</sup> but was less successful in correcting hyponatremic dehydration.<sup>16</sup>

### Conclusions

In conclusion, studies leading to the recommendation for the reduced-osmolarity ORS for noncholera diarrhea therapy had variable outcomes. Reduction in diarrhea rate, if real, is minimal; diarrhea duration is unaffected. The need for unscheduled intravenous fluids was not laboratory confirmed, and in the largest study<sup>11</sup> it was not paralleled by reduced stool losses. For these reasons, and the risk of induction of hyponatremia, it remains unclear whether the new solution favorably alters the benefit-to-risk ratio for pediatric and adult diarrhea patients without cholera. Additional, more rigorous studies are needed to determine the optimal solution for such patients. What is clear is that the reduced-osmolarity ORS increases the risk for hyponatremia during therapy in adults with cholera but offers them no clinical advantages. Moreover, clinical findings in small numbers of pediatric patients with cholera were contradictory.

The goal of reducing rates of unscheduled intravenous fluids and diarrhea rate and duration in patients with cholera and nonvibrio cholera<sup>8</sup> is best met in controlled settings with a separate oral solution, such as that containing glucose plus glycine or rice-based substrate, with electrolyte concentrations that maintain electrolyte balance and avoid hyponatremia. Such solutions are clearly more effective in cholera patients than either of the WHO solutions.

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