

Carol Rees Parrish, R.D., MS, Series Editor

# Oral Rehydration Solution: A “Low-Tech” Oft Neglected Therapy



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The concept of oral rehydration solutions arose from concerns in the public health community regarding the high worldwide mortality occurring as a result of infectious diarrheas. This was primarily in the Third World where death rates were as high as 5 million in the 1980's. This clinical setting and the discoveries related to the physiology of membrane structure and function led to the most rapid successful clinical application of basic science principles that has been experienced in modern medicine. Yet, this life-saving therapy has been slow to be accepted by Western medicine. This review explores the underlying physiologic principle of oral rehydration solution, discusses some of the critical literature in the field and provides some of the practical application of oral rehydration in medical practice today.

## INTRODUCTION

Oral rehydration solution (ORS) represents the clinical application of some of the most basic concepts of cellular physiology. It offers a therapy that is inexpensive and simple with very few potential complications. ORS does not involve the genetic recombinant

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technology that is so much a part of advanced medicine today. This likely belies the obstacle for acceptance in the western world today! Indeed, several years ago, a patient from Bolivia who had a severe chronic diarrheal illness came to my office with a small packet of *sales de rehidratacion* saying “Doctora Kelly, you must have something better here in the US” but we did not at that time. This low-tech, inexpensive treatment had to come to us from the third world!

## HISTORY: THE SCIENCE BASIS OF ORS

The ORS story begins with very basic understanding of physiologic characteristics of biological membranes

*(continued on page 55)*

(continued from page 51)

that evolved over the course of three centuries, with marked advances in the mid-20th century. As early as 1938, a cell surface consisting of proteins and lipids was proposed as a barrier to diffusion into cells (1). Membranes consist of a bimolecular leaflet made up of a double layer of phospholipids with their hydrophilic heads oriented toward the outsides and the hydrophobic fatty acid chains oriented inwards (2). Embedded within these lipids are proteins that act as enzymes and antigens, as well as carriers and channels for transport of electrolytes, nutrients and water.

### MECHANISMS OF FLUID AND ELECTROLYTE ABSORPTION

Within the small intestine absorption and secretion occur as a result of specialized mechanisms located within the cells of the villus tips and the crypt cells, respectively. The basolateral membranes of the enterocytes have unique transport features that differ from those of the luminal surface. In all intestinal cells, there is a sodium-potassium activated ATPase pump embedded in the basolateral membrane that maintains the low intracellular sodium concentration by pumping sodium out toward the circulation and potassium into the enterocytes. Simultaneously, the basolateral membrane allows sodium and potassium to enter the cells via a sodium-potassium-chloride co-transport mechanism, and a potassium channel allowing potassium to leave the cells into the blood. In the secretory cells there is a luminal cyclic-AMP chloride channel that is responsible for chloride secretion into the intestinal lumen. The synchronization of these transport mechanisms is critical to the maintenance of chloride secretion.

Electrolyte absorption by the enterocytes of the villus tips involves luminal permeability to sodium resulting from various mechanisms. Each segment of the intestine has somewhat different characteristics of permeability. Within the jejunum, ileum and proximal colon there is coupling of sodium absorption with extrusion of hydrogen ions into the intestinal lumen. Because the sodium-potassium-ATPase pump in the basolateral membrane maintains the steep inwardly directed sodium gradient, net sodium absorption is favored. Additionally, within the small intestinal cells there is a co-transport system linking sodium transport

to that of glucose and amino (3,4,5). A carrier within the luminal membrane transfers one sodium ion along with a single glucose molecule. A similar sodium-amino acid carrier has been identified in intestinal cells. Maintenance of a downhill sodium gradient by the basolateral sodium-potassium-ATPase pump is critical for the proper transport of these nutrients. Conversely, one can think of these organic compounds as driving forces for sodium absorption. Water is transported paracellularly as a result of the osmotic gradient. The osmolarity of ions and molecules in stool water is identical to that of plasma (6).

When glucose is present within the intestinal lumen, sodium and water absorption is increased. This transport is stimulated up to a glucose concentration of about 50 mM, a level at which jejunal sodium absorption is increased by fourfold and water absorption by six fold (7,8,9). Within the ileum this concentration of glucose increases sodium and water absorption by two to three times (7).

### THE CHOLERA STORY

Cholera is the most severe diarrheal disease known to man. The first pandemic of cholera occurred in 1817 in the Indian subcontinent. By the 1830s, another pandemic had reached western Europe, and in 1866 there was an epidemic in New York (10). It is endemic in Southeast Asia, the Indian subcontinent, Africa and most recently in South America where it is found in aquatic environments. Summertime seafood-associated cholera cases occur sporadically in the United States.

Cholera occurs as a result of the bacterium *Vibrio cholerae*. The *Vibrio* releases a protein toxin that binds irreversibly to a ganglioside receptor of intestinal epithelial cells and does not enter the blood stream (11). The result of the toxin is stimulation of chloride and bicarbonate secretion via its effect on cyclic AMP within the enterocytes. Of clinical importance, the glucose-sodium co-transport of enterocytes is not altered by the toxin.

Cholera is characterized by vomiting and by voluminous diarrhea, often called rice-water diarrhea, as it has the appearance of water arising from soaking rice. Fluid losses in these cases can amount to 500–1000 mL/hour (10). Severe dehydration results and about half of untreated severe cases succumb from vascular

**Table 1: WHO/Unicef ORS Recommendations and Composition of ORS and Other Fluids\***

	<i>Carbohydrate (Gm/L)</i>	<i>Sodium mEq/L</i>	<i>Potassium mEq/L</i>	<i>Base mEq/L</i>	<i>Osmolarity (mosm/L)</i>
<b>WHO/UNICEF ORS Formulae</b>					
“Standard Formula”	20 (glucose)	90	20	30	310
“Reduced-Osmolarity Formula”	13.5 (glucose)	75	20	30	245
<b>Rehydration Solutions</b>					
CeraLyte 70 (Cera Products)	40 (rice starch polymers)	70	20	30	220–235
CeraLyte 90		90	20	30	260
Equalyte (Ross)	30 (dextrose, fructooligosaccharide)	78.2	22.3	30	290
Jianas Brothers ORS	20 (glucose)	90	20	10	300+
Liquilyte (Gerber)	25 (dextrose)	45	20	30	250
Pedialyte (Ross)	25 (glucose or dextrose, fructose)	45	20	30	250
Rehydralyte (Ross)	25 (dextrose)	75	20	30	310
<b>Other Fluids</b>					
Gatorade (powdered)	58 (fructose, sucrose, & glucose)	20	3	3	330–380
Prune Juice	(fructose, glucose, sucrose)	0	0	0	1265
Apple Juice	(fructose, glucose, sucrose)	3	32	0	680
Colas Regular	(fructose, sucrose)	2	0	13	550–700
Colas Diet	0	2	0	13	0
Tea	0	0–10	0	0	18
Water	0	0–10	0	0	0–18

\*Note: Normal plasma osmolarity 275–295.

collapse, which can occur within hours of onset. Rapid, appropriate rehydration is the mainstay of therapy of cholera. In those with severe volume contraction, intravenous fluids are given rapidly. Even with intravenous fluid replacement, mortality may occur in up to 30% of cases. For those with less severe degrees of dehydration, oral fluid replacement can be used. The worldwide threat of cholera epidemics and of the resulting mortality led to the development of a research laboratory in Dacca, Pakistan (SEATO Pakistan Cholera Research Lab—later called the International Centre for Diarrhoeal Disease Research, Bangladesh). This endeavor was sponsored by the National Institutes of Health, the National Naval Medical Center and the Agency for International Development, in collaboration with the World Health Organization (WHO). The center was interested in a treatment that would be available from household food staples in the third world.

### THE INTRODUCTION OF ORAL REHYDRATION SOLUTIONS (ORS)

There are reports of oral replacement solutions being used in diarrheas for centuries with variable success. Some of these are described in ancient Hindu texts (12). The modern era of oral replacement of fluid and electrolytes in pediatric diarrheas had its beginnings in reports from Baltimore using sodium, potassium, chloride and lactate to replace losses in infantile diarrheas in the 1950's (13) with subsequent addition of sugar to spare protein. The science of ORS was advanced when Phillips and colleagues determined the composition of fluid lost in diarrhea (14). Addition of excessive amounts of carbohydrate to commercially available mixtures resulted in hypernatremia, probably as a result of their high osmolarity (15).

(continued on page 58)

(continued from page 56)

As the understanding of the sodium glucose co-transporter developed, the true role of carbohydrate in the early oral replacement fluids could be appreciated. The addition of glucose improved absorption of sodium (thus of water transport) to effectively treat the diarrheas encountered in children. Perfusion studies of the effect of enteral glucose and electrolyte solutions in patients with cholera demonstrated that these solutions decreased stool output (16,17). Subsequently, oral rehydration therapy was proposed as a viable alternative for cholera in areas of the world with short supplies of intravenous fluids and needles forcing clinicians to deliver oral solutions to those with cholera. This reduced mortality rates to only 3% compared to 30% of those treated in other camps with intravenous fluids (18). Based on this evidence, WHO and UNICEF recommended a single standard ORS formula (Table 1) for all ages. Critical to these fluids was not only the concentration of carbohydrate and electrolytes, but also the osmolarity (~300 mosm/L). The dry ingredients were available in packets that were manufactured in more than 60 countries and were available to 30% of children who developed acute diarrhea, as of the early 1990's (19). In the US, more commonly premixed fluid forms slowly became available. It has been estimated that deaths due to diarrhea decreased by as much as 50% after introduction of ORS.

### REFINEMENTS OF ORS FORMULAS

Adding more glucose to standard ORS was initially thought to further increase sodium and electrolyte absorption, but it was found to be counterproductive and, frankly, dangerous given the effects of the high osmotic load in the small intestine. The intestine from the pylorus to the rectum acts as a dialysis membrane when one observes fluid shifts (6). Consequently, the high osmotic activity of various fluids actually increases diarrhea. (Case in point, the osmolarity of prune juice is ~1265 mosm/L!)

The role of osmosis as a driving force for intestinal absorption was incorporated into ORS formulations (20). The substitution of polymers of glucose for simple glucose would decrease the osmolarity of the solution while providing favorable ratios of glucose to sodium. Subsequently, research focused on the use of various starches as a source of glucose. Rice powder

has been shown to effectively replace the standard glucose in ORS, decreasing stool output, duration of diarrhea, and requirements for intravenous fluids compared to the WHO ORS formula (21,22). Rice syrup solids have also been shown to promote greater absorption and retention of fluids and electrolytes than the glucose-based ORS (23). Because the hydrolysis of starch is relatively slow in the intestinal lumen compared to that of maltose or sucrose, starch provides a continuous supply of glucose for absorption under isosmotic conditions (dubbed a "glucose battery" by Field) (24).

In contrast to sucrose, starch provides the glucose to drive sodium and water absorption, but not at the expense of a large osmotic load that would actually cause fluid shifts into the lumen. It appears that the starch or glucose polymers not only replace fluid losses, but they also lessen diarrhea (24). Other grains, such as lentils (25) and wheat (26) have been tested. In the latter study, stool output of children with acute diarrheal illnesses was decreased significantly in those using ORS based on either rice or wheat when compared to glucose-ORS, but there is concern with the wheat based solution for those with co-existing celiac disease.

The addition of other substrates for enhanced sodium co-transport has been proposed including glutamine (27), alanine and glycine (29), but none of these has a therapeutic advantage in decreasing fluid output (thus diarrheal volumes) over standard ORS. This may be in part due to the increased osmolarity that occurred with such additions. The addition of proteins would also be expected to work similarly, but at much greater expense.

### THE "NEW" WHO ORS

Recent developments in ORS formulas are related to concern that the sodium concentration of the standard ORS was too high at 90 mEq/L and was occasionally associated with hyponatremia. The European Society of Paediatric Gastroenterology and Nutrition recommended an ORS containing 60 mEq/L of sodium and an osmolarity between 200 and 250 for children in developed countries who are not malnourished (29). Subsequently WHO recommended a replacement for the standard ORS using a new formulation containing 60–75 mEq/L sodium and glucose ranging from 75–90

mmol/L (Table 1) (30). The 1:1 molar ratio of sodium to glucose was maintained but at a lower osmotic activity. This new reduced-osmolarity ORS while as effective at reducing diarrhea in cholera had an increased risk of hyponatremia (odds ratio 2.1) (31). This new ORS was associated with a generalized seizure in one child with hyponatremia among 341 who received the new formula (32). This complication has led to controversy regarding this new formula (33,34).

### ORS: NOT JUST A THIRD WORLD ANSWER

Application to ORS in North America has been reported in only a few publications, mainly applying it to acute diarrhea of childhood. Clinicians have been admonished for years, because they have not applied the treatment of the third world as a simple solution for acute diarrheal diseases (35). Indeed, only 14 years after the introduction of ORS for cholera, Carpenter (36) wrote “We physicians all presumably accept the ‘primum no nocere’ principle. On the basis of . . . studies . . . this principle would dictate that oral rehydration be accepted not only as an equal, but perhaps as the superior means of treating acute diarrheal illnesses in the sophisticated and sanitized medical centers of the Western world as well as in rural Bangladesh.”

### Short Bowel Syndrome

One of the earliest applications of ORS to a patient with short bowel syndrome utilized a low osmolarity solution (~210 mosm/L) consisting of ~50 mmol/L sodium and 70 mmol/L of a glucose polymer and also a commercially produced ORS containing rice starch (37). With the combination of these mixtures, a low disaccharide diet, and aggressive anti-diarrheals, the patient had marked reduction of stool volume and sodium output, as well as increased urine output. A second application in “un-adapted” short bowel syndrome (3 to 9 weeks post-resection) compared a glucose ORS with an iso-osmotic glucose polymer ORS enriched with glutamine, demonstrated no difference between the two formulae. (27). No comparisons were made to fluid outputs prior to ORS use. We studied the effects of magnesium gluconate added to a rice-based commercial ORS and found that magnesium absorp-

**Table 2**

#### Lessons Learned from the Literature: Suggested Features of ORS

- Osmolarity in the range of 200 to 300 mosm/L
- Sodium of 60–90 mEq/L
- Potassium of ~20 mEq/L
- Rice starch polymers preferred glucose source
  - Maximizes absorptive capacity without an osmotic load
- Carbohydrate:Sodium ratio of 1:1

tion could be enhanced with this dosing regimen compared to giving the magnesium in equivalent bolus doses (38).

A very recent report described discontinuation of long-term parenteral nutrition in three patients with short bowel syndrome by using nocturnal enteral infusions of ORS (39). Many reviews of the treatment of short bowel syndrome fail to even raise the topic of ORS.

### PRACTICAL APPLICATION OF ORS

We try to tailor our selection and use of ORS based on the principles demonstrated by the literature (Tables 2, 3). ORS plays an integral part in our clinical practice of gastroenterology and nutrition. We use it with particular success in treatment of high stomal outputs of patients who have undergone recent intestinal resections. In many of these individuals it is possible to avoid turning to parenteral solutions to maintain fluid

**Table 3**

#### Lessons Learned from Practice to Improve Compliance with ORS Therapy

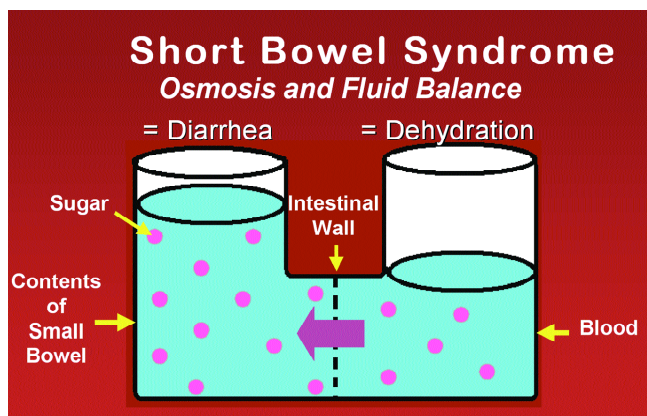
- Sodium concentrations in excess of 70 mEq/L are difficult to get patients to drink
- Initially further dilution of the formula is helpful in “acquiring a taste” for ORS
- Flavoring is almost essential
- Artificially pre-sweetened flavorings may be too sweet (titrate the sweetener)
- Avoid addition of sugar
- Avoid addition of salt (rarely desired!)
- Avoid addition of ice (unless made from ORS)
- Time spent discussing rationale with patients and appropriate educational materials help compliance
- Introduce the concept of sipping not “glugging”

**Table 4**  
**Potential Uses For Oral Rehydration therapy**

- Infectious diarrheas
- Short bowel syndrome
- Excessive ostomy losses
- Diarrheal illness in nursing home residents
- Pediatric viral illnesses
- AIDS
- Salt wasting nephropathies

balance. Typically, we place these individuals on a low free sugar diet (low osmolarity), optimize anti-diarrheals (both with respect to amount and timing—specifically 30 minutes before meals and at bedtime) and start an ORS, titrating volume requirements as needed to produce a urine output of at least one liter daily. One important point of the anti-diarrheals is that crushing tablets or opening capsules before dosing them is helpful in improving effectiveness. Elixirs of anti-diarrheals can also be used, but care must be taken to recognize which of the medications include sorbitol as a sweetener, thus worsening diarrhea!

Typically we discuss various options of ORS with the patient (Table 1), as well as other fluids that are less desirable. Although the literature suggests that 90 mEq/L sodium is the critical concentration of ORS in short bowel syndrome (40), this recommendation is based on data defining the jejunal efflux in short bowel syndrome (41). Based on our clinical experience, these high sodium solutions are very poorly accepted by



**Figure 1.** Cartoon used for teaching patients about the rationale for ORS use. This animated frame depicts osmosis, relating it to the mechanism of fluid shift in short bowel syndrome.

patients (Table 3). Often we find that even 70 mEq/L sodium solutions must be diluted initially to allow the patient to adapt to the taste. Various flavored, artificial beverage powders are helpful in making the solutions more acceptable, however some patients find them too sweet and prefer to add sucralose or aspartame sweeteners to the unsweetened beverage packet.

We train patients in the use of ORS using a self-developed set of cartoons (see example in Figure 1) that explains the concept of intestinal adaptation, a re-introduction to osmolarity, a discussion of sodium absorption, and techniques to increase palatability. Most patients can follow this discussion with the use of simple slides, and thus, we feel, have more likelihood of compliance. Finally, for most patients continual encouragement and recognition of adequate intakes are required for success with the ongoing use of ORS. See Table 4 for potential uses of ORS.

### ORS: THE FINAL WORD AS OF 2004

ORS has been called the most important advance in twentieth century (Anon, 1978). It has been credited as the major therapy responsible for decreasing deaths due to diarrhea from 5 million per year in 1980 to 2.2 million in 1999 (42). This simple application of basic intestinal physiology has not been so readily accepted in the US. It has been estimated that the cost of NOT using ORS in acute diarrhea in the United States exceeds \$1 billion in direct medical costs annually (43). Added to this is its potential use in decreasing morbidity in such circumstances as chronic diarrheal diseases, as a replacement for intravenous fluids and TPN in some patients with short bowel syndrome, and to decrease dehydration and the hospital length after colectomy. Our neglect of this inexpensive therapy is a costly omission in western medicine!

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(continued on page 62)

(continued from page 60)

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