

# Diarrheal Diseases

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Diarrheal diseases are a major cause of pediatric morbidity and mortality worldwide, with a median incidence of 3.2 episodes per child-year and 2.5 million deaths of children under 5 years of age estimated to occur annually.<sup>1</sup> If these statistics appear daunting, they should be compared with data from 1992, when 3.3 million annual deaths were estimated,<sup>2</sup> and 1982, when 4.6 million deaths were estimated.<sup>3</sup> The story underlying these statistics is the remarkable success of worldwide campaigns to treat acute diarrhea with oral rehydration therapy (ORT). The development of ORT is among the most successful collaborations ever between basic and applied biomedical research and one of the most significant applications of nutritional therapy to the management of acute disease. Interestingly, it is also a case of reverse technology transfer,<sup>4</sup> in which work originally carried out for benefit of those in countries with less developed economies has changed the standard of practice, even in industrialized settings.

It is, however, clear that the full benefits of the fluid, electrolyte, and nutritional therapy of acute diarrhea have not been realized. Shortcomings in treatment are significant, as they result in added morbidity and costs in both developing and industrialized societies. In the United States alone, acute gastroenteritis accounts for greater than 1.5 million outpatient visits, 200,000 hospitalizations, and roughly 300 deaths per year.<sup>5</sup> It has been reported that 13% of all childhood hospitalizations in the United States are associated with diarrhea, with a median hospital charge of nearly \$3,000.<sup>6</sup> It may be argued that the full implementation of ORT for treatment of acute diarrhea in countries with developed market economies has lagged behind its use in less developed countries, perhaps because of the ingrained use of intravenous therapy or the reduced appeal of a technologically simple solution.<sup>7</sup> In addition, it has been difficult to establish continued feeding during diarrheal episodes as normative therapy, in spite of a wealth of *in vitro* and *in vivo* data supporting the role of continued nutrition in improving measurements of gastrointestinal function, as well as anthropometric, biochemical, and clinical outcomes.<sup>8,9</sup> This chapter reviews the historical background and scientific basis of ORT and provides a framework for assessing and treating the dehydrated patient or the patient at risk for dehydration. The discussion focuses on common clinical scenarios and traditional practices,

especially with regard to feeding. The limitations of ORT are discussed, as well as areas of ongoing research.

## HISTORICAL BACKGROUND

Early attempts at treating dehydration resulting from diarrhea were first described in the medical literature in the 1830s, during epidemics of *Vibrio cholerae* infections.<sup>10,11</sup> It was not until 100 years later that the use of intravenous fluids became widespread. Accurate chemical analysis of diarrheal stools eventually permitted the formulation of physiologically appropriate replacement solutions, leading to the successful treatment of cholera with intravenous fluids by the 1940s.<sup>12</sup> Further research into intestinal electrolyte transport led to the development of oral solutions for rehydration.<sup>13,14</sup> In 1971, these were put to the test in the field with the large-scale treatment of refugees from the Bangladesh war of independence.<sup>15</sup> The remarkable success of oral solutions hastened the development of the World Health Organization (WHO) guidelines for ORT and production of standard packets of oral rehydration salts. It may be argued that the initial application of ORT to cholera epidemics in the developing world hindered the acceptance of this therapy's relevance in the United States and Europe. With time, however, ORT has become accepted as the standard of care for clinically efficacious and cost-effective management of acute diarrhea,<sup>5,16</sup> although it remains underused in settings in which parenteral rehydration has been the established practice.<sup>17–20</sup>

## PHYSIOLOGIC BASIS FOR THE USE OF ORAL REHYDRATION SOLUTIONS

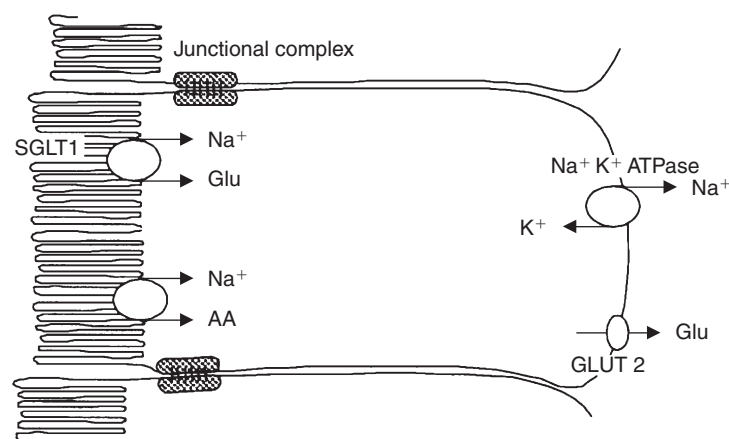
Fluid must be absorbed and reabsorbed for survival. Under the best of circumstances, the adult intestinal epithelium must handle 6,500 mL fluid per day, the combination of oral intake, salivary, gastric, pancreatic, biliary, and upper intestinal secretions. This is typically reduced to 1,500 mL by the distal ileum and is further reduced in the colon to stool output less than 250 mL/d.<sup>21</sup> Were it not for this ability for net absorption, there would be no balance of fluid to replace insensible losses and that necessary for renal filtration. During disease, the volume of intestinal

fluid output is remarkably increased, overwhelming reabsorptive capacity, leading to diarrhea.

Applied clinical research, first carried out among cholera patients, showed that diarrhea in cholera is not the result of a failure of intestinal reabsorption but a state of extreme output in which reabsorptive mechanisms remain intact.<sup>22</sup> Not only *V. cholerae* but many strains of *Escherichia coli*, *Shigella*, *Salmonella*, and other pathogenic bacteria have been shown to produce toxins that bind to enterocyte receptors, causing chloride-mediated secretion stimulated by second messengers, such as cyclic adenosine monophosphate, cyclic guanosine monophosphate, and calcium.<sup>23,24</sup> Even those infectious agents typically classified as causing osmotic diarrhea may, in some cases, also increase enterocyte secretion. *Rotavirus*, for instance, damages the villous brush border, causing osmotic diarrhea, but also produces an enterotoxin that causes a Ca<sup>2+</sup>-mediated secretory diarrhea.<sup>25,26</sup>

Basic scientific studies of intestinal solute transport mechanisms were also crucial in outlining the processes by which solute absorption is maintained. Water passively follows the osmotic gradient generated by the transcellular transport of electrolytes and nutrients. Although three principal mechanisms of sodium absorption have been described,<sup>21</sup> that essential to the efficacy of oral rehydration solutions (ORSs) was shown to result from the stoichiometric cotransport of sodium and glucose molecules at the intestinal brush border.<sup>27</sup> Figure 1 provides a schematic of the cotransport process. Cotransport across the luminal membrane is facilitated by the protein SGLT1.<sup>28</sup> Once in the enterocyte, the transport of glucose into the blood is facilitated by GLUT 2 in the basolateral membrane. The Na<sup>+</sup>-K<sup>+</sup> adenosine triphosphatase provides the gradient that drives the process. Clinical studies have demonstrated that this mechanism remains intact even in patients with severe diarrhea.<sup>22</sup>

In 1975, the WHO and the United Nations Children's Fund (UNICEF) agreed to promote a single solution (WHO-ORS) containing (in mmol/L) sodium 90, potassium 20, chloride 80, base 30, and glucose 111 (2%). This composition was selected to allow a single solution to be used among diverse populations in different countries. Although this solution performed well over 25 years, subsequent clinical research, documented



**Figure 1** Solute-coupled sodium absorption. AA = amino acid; ATPase = adenosine triphosphatase; Glu = glucose; SGLT1 = sodium glucose transporter-1. (Adapted from reference 5.)

in numerous controlled trials and summarized in a recent meta-analysis,<sup>29</sup> has favored the adoption of a lower osmolarity standard solution. Based on these findings, UNICEF and WHO organized an expert consultation on oral rehydration that recommended a reduced osmolarity solution.<sup>30</sup> In May 2002, WHO announced a new ORS formulation consistent with these recommendations, with sodium concentration 75 mEq/L, glucose 75 mmol/L, and total osmolarity 245 mmol/L<sup>31</sup> (see Table 1 for a comparison of the two solutions).

#### HOME MANAGEMENT OF ACUTE DIARRHEA

The simplicity of treatment based on ORSs makes possible the management of uncomplicated cases of diarrhea at home. As long as caretakers are properly instructed with regard to the need for clinical assessment when children appear significantly ill or appear to be failing treatment, then it is appropriate to begin therapy at home. Early intervention may reduce complications such as dehydration and poor nutrition. In developed, as in developing settings, early administration of

ORS may lead to fewer office or emergency room visits,<sup>32</sup> hospitalizations, or deaths.

In fact, it has always been the case that mothers and other caretakers begin treatment of diarrhea at home.<sup>33</sup> The advent of ORT allows a therapy that is more effective and less harmful than many traditional home therapies. All families should be encouraged to have a supply of ORS in the home at all times, much in the same way that acetaminophen and adhesive bandages are viewed as staples of the medicine chest. As soon as diarrhea begins, one of the commercially available products can be started at home. Although it is possible to produce a homemade solution with appropriate concentrations of glucose and sodium, possibilities for serious error abound, so that standard commercial oral rehydration preparations should be recommended where they are readily available and not prohibitively expensive. Regardless of the fluid used, an age-appropriate diet should be given as well.<sup>8</sup> The most crucial aspect underlying home management of diarrhea is the need to give increased volumes of fluid as well as to maintain adequate caloric intake. Infants should be offered more fre-

quent feeds at the breast or bottle, and children should also be given more fluids.

Caretakers should be educated to recognize signs of illness or treatment failure that necessitate medical intervention. Infants with acute diarrhea are more prone to become dehydrated than are older children because they have a higher body surface-to-volume ratio, a higher metabolic rate, and relatively smaller fluid reserves and depend on others for fluid. For this reason, parents should seek medical care promptly for infants with diarrhea, even before the first signs of dehydration are evident. Indications for prompt medical evaluation are summarized in Table 2. No guidelines have established a specific age under which evaluation is mandated, but, in general, infants should be evaluated by a health professional when there is risk of dehydration; in general, the smaller the child, the lower the threshold for hands-on evaluation. When fever is present, infants and children should be evaluated according to current guidelines. Naturally, underlying conditions, including history of prematurity, metabolic disorders, immune compromise, and recent recovery from surgical interventions, may prompt early evaluation, as may concurrent illness, even a concurrent respiratory infection. Children with dysentery (visible blood or mucus in stool) should be brought in for medical evaluation.

Naturally, parents or other caretakers cannot be assumed to have skills of assessment comparable to a clinician, but their report of any of the easily recognized signs of dehydration may indicate the need for immediate evaluation. Reports of changing mental status are particularly concerning. When the child's condition is in doubt, there should be a low threshold for recommending office or acute care evaluation. The hands-on visit provides an opportunity for physical assessment, including vital signs, more detailed history, and better family instruction.

**Table 1** Composition of Commercial Oral Rehydration Solutions as well as Commonly Consumed Beverages

Solution	CHO (g/L)	Glucose (mmol/L)	Na (mmol/L)	Na:Glu	K (mmol/L)	Cl (mmol/L)	Base* (mmol/L)	Osmolarity
WHO-ORS (2002)	13.5	75	75	1.1	20	65	10	245
WHO-ORS (1975)	20	111	90	0.8:1	20	80	10	311
ESPGHAN ORS	16	89	60	0.7:1	20	60	10	240
ReSoMal	22.5	125	45	0.4:1	40	70	21	300
Enfalyte <sup>#</sup>	30	167	50	0.3:1	25	45	34	200
Pedialyte <sup>†</sup>	25	139	45	0.3:1	20	35	30	250
Rehydralyte <sup>‡</sup>	25	139	75	0.5:1	20	65	30	305
Apple Juice <sup>‡</sup>	120	—	0.4	—	44	45	—	730
Coca Cola <sup>§</sup>	112	—	1.6	—	—	—	13.4	650
Gatorade <sup>  </sup>	58	—	23	—	3	17	3	330
Chicken Broth <sup>‡</sup>	8	—	260	—	0.5	260	—	450
Brewed Tea <sup>‡</sup>	4	—	—	—	6	—	—	6

Adapted from reference 5.

\*Actual or potential bicarbonate (eg, lactate, citrate, or acetate).

<sup>†</sup>Ross Laboratories, Columbus, OH. (Data for flavored and freezer pop pedialyte are identical.)

<sup>‡</sup>US Department of Agriculture.

<sup>§</sup>Coca-Cola Corporation, Atlanta, GA. (Figures do not include electrolytes, which may be present in local water used for bottling; base = phosphate.)

<sup>||</sup>The Gatorade Company, Chicago, IL.

<sup>#</sup>Mead-Johnson Laboratories, Princeton, NJ.

CHO = carbohydrate; ESPGHAN = European Society of Pediatric Gastroenterology, Hepatology and Nutrition; Glu = glucose; ORS = oral rehydration solution; WHO = World Health Organization.

**Table 2 Indications for Medical Evaluation**

- Young age, with low threshold for evaluating all children under 10 kg and lowest threshold for those under 6 months
- History of prematurity, underlying chronic medical conditions, or concurrent illness
- Fever  $\geq 38^{\circ}\text{C}$  for infants under 3 months,  $\geq 39^{\circ}\text{C}$  ages 3 to 36 months
- Visible blood in the stools
- High output, including large-volume diarrhea and persistent vomiting
- Caretaker's report of signs consistent with dehydration, including sunken eyes, decreased tears, and dry mucous membranes
- Poor apparent response to ORT already given or inability to administer ORT

Adapted from reference 5.

ORT = oral rehydration therapy.

## CLINICAL ASSESSMENT

Diarrhea may be characterized by the passage of three or more loose, watery stools per day. The volume of fluid lost through the stools can vary from 5 mL/kg/d (near normal) to 200 mL/kg/d or more.<sup>34</sup> Dehydration (loss of body water) and electrolyte losses follow untreated diarrhea and cause the primary morbidity of acute gastroenteritis. Loose stools may be among the presenting signs of nongastrointestinal illnesses, including meningitis, bacterial sepsis, pneumonia, otitis media, and urinary tract infection. Vomiting alone can be the first symptom of metabolic disorders, congestive heart failure, toxic ingestions, or trauma. To rule out other serious illnesses, a detailed history and physical examination should not be neglected in the diagnosis of acute gastroenteritis.

History taking should include questions about the onset, frequency, quantity, and character (including the presence of bile, blood, mucous) of vomiting and diarrhea. Recent oral intake, including food, fluids, and breast-feeding, as well as urine output, should be carefully noted and previous weight recorded, if known. Associated symptoms, including fever or changes in

mental status, should be noted. Past medical history should include questions regarding underlying significant medical problems, history of other recent infections, and human immunodeficiency virus (HIV) status, if known. Relevant social history may include the number and nature of caretakers and their ability to return for reevaluation, which may affect instructions regarding follow-up care.

As part of the complete physical examination, an accurate body weight must be obtained, along with temperature, heart rate, respiratory rate, and blood pressure. When premonitory weight is not known but a previous growth curve is available, an estimate of fluid loss may be obtained by subtracting current weight from expected weight based on previous weight-for-age percentile.<sup>35</sup> The quality of this estimate will vary, depending on the number and variability of prior data points. The general condition of the patient should be assessed, with special concern given to infants and children who appear listless, apathetic, or less reactive. The appearance of the eyes should be noted, including the degree to which they are sunken and the presence or absence of tears. The condition of the lips, mouth, and tongue may yield important clues as to the degree of dehydration, even if the patient has recently taken fluid. Deep respirations may be suggestive of metabolic acidosis. Faint or absent bowel sounds may suggest ileus. Extremities should not be neglected, as general perfusion, capillary refill, and skin turgor can help the assessment of dehydration. Visual examination of the stool can confirm abnormal consistency and determine the presence of blood or mucus.

The clinical signs and symptoms of dehydration are outlined in Table 3. A recently published comprehensive literature review found that the three most useful individual signs for predicting 5% dehydration in pediatric patients are abnormal capillary refill time, abnormal skin turgor, and an abnormal respiratory pattern.<sup>36</sup> The assessment of the anterior fontanel, though helpful in select instances, can be unreliable or misleading.<sup>37,38</sup> In infants and children, a fall in

blood pressure is a late sign that signifies the development of uncompensated shock and may correspond to fluid deficits greater than 10%. Increases in heart rate and slowed peripheral perfusion may be more sensitive indicators of moderate dehydration, although both may be difficult to interpret as both can vary with the degree of fever. Decreased urine output is a sensitive but nonspecific sign.<sup>35</sup> Urine output may be difficult to measure in infants with diarrhea, although increased urine-specific gravity may indicate dehydration when urinalysis is indicated.

Previous guidelines, including the CDC's 2003 recommendations<sup>5</sup> and the American Academy of Pediatrics (AAP) 2004 guidelines,<sup>16</sup> divide patients into subgroups for mild (3 to 5% fluid deficit), moderate (6 to 9% fluid deficit), or severe dehydration (>10% shock or near shock). Other classification schemes, including 2005 WHO<sup>39</sup> and 2001 European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines,<sup>40</sup> divide patients into those showing no signs of dehydration (<5%), some signs of dehydration (5 to 10%), and severe dehydration (>10%). Studies that have looked carefully at the correlation of clinical signs of dehydration with posttreatment weight gain suggest that the first signs of dehydration may not be evident until 3 to 4% dehydration, with more numerous clinical signs evident at 5% dehydration and those signs indicating severe dehydration not evident until fluid loss of 9 to 10%.<sup>35,37</sup> Because of this threshold effect, it may be difficult to distinguish between mild and moderate dehydration based on clinical signs alone. For this reason, Table 3 groups together patients with mild-to-moderate dehydration and notes that these signs may be seen over a relatively wide range of fluid loss, from 3 to 9%. The magnitude of ongoing losses and the patient's oral intake will determine the success of ORT as much as current status. The goal of assessment is not to determine the patient's hydration status once and for all but to provide a starting point for treatment and conservatively determine which patients may be safely sent

**Table 3 Signs of Dehydration**

	Minimal or No Dehydration	Mild-to-Moderate Dehydration	Severe Dehydration
Mental status	Well, alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious, floppy
Thirst	Drinks normally, may refuse	Thirsty, eager to drink	Drinks poorly, unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal, fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skinfold	Instant recoil	<2 s	>2 s
Capillary refill	Normal	Prolonged	Prolonged, minimal
Extremities	Warm	Cool	Cold, mottled, cyanotic
Urine output	Normal to decreased	Decreased	Minimal
Loss of body weight	<3%	3–9%	>9%

Adapted from reference 5.

**Table 4 Treatment of Acute Gastroenteritis—the “Seven Pillars of Good Treatment”**

- I. Use of ORS for rehydration
- II. Fast oral rehydration, over 3–4 h
- III. Rapid realimentation with age-appropriate unrestricted diet
- IV. Formula continuity: use of diluted formula is unjustified; special formula is usually not necessary
- V. Continuation of breast-feeding at all times
- VI. Additional ORS for ongoing losses
- VII. No unnecessary laboratory tests or medications

Adapted from reference 40.

ORS = oral rehydration solution.

home for therapy, which should remain for observation during therapy, and which should receive more intensive therapy immediately.

Supplementary laboratory studies in the assessment of the patient with acute diarrhea are usually unnecessary, including serum electrolytes.<sup>39</sup> Stool cultures are indicated in the case of dysentery but are generally not indicated in acute, watery diarrhea in the immunocompetent patient. Laboratory studies should not, however, be neglected where they may give important clues as to underlying or alternative causes of illness. For instance, urine cultures should not be neglected where there is reason to be concerned for urinary tract infection, and blood cultures and white blood cell count with differential are indicated where the clinical presentation suggests possible sepsis.

### THERAPY OF ACUTE GASTROENTERITIS BASED ON DEGREE OF DEHYDRATION

Table 4 outlines the “Seven Pillars of Good Treatment of Acute Gastroenteritis,” adapted from ESPGHAN guidelines,<sup>40</sup> and Table 5 provides a summary of specific treatment recommendations

synthesized from CDC, WHO, AAP, and ESPGHAN guidelines.<sup>5,39,16,40</sup> Although the first pillar, the use of ORS, should seem self-evident, one recent national survey of physicians in emergency care facilities in the United States showed that many would treat mild dehydration with intravenous therapy, and half would always or almost always use intravenous therapy for a moderately (5 to 10%) dehydrated child under age 2.<sup>20</sup> Treatment should include two phases: rehydration and maintenance. In the rehydration phase, the fluid deficit is replaced quickly, over 3 to 4 hours, and clinical hydration is attained. In the maintenance phase, maintenance calories and fluids are given. Rapid realimentation should follow rapid rehydration, with a goal of rapid return to an age-appropriate unrestricted diet, including solids. Gut rest is not indicated. If anything, diet should be increased as soon as tolerated to make up for lost caloric intake during the acute illness. Lactose restriction is generally not necessary, nor are changes in formula usually indicated. Full-strength formula is generally tolerated and allows more rapid return to full caloric intake. Breast-feeding should be continued at all times, even during the initial rehydration phases. In both phases, fluid losses from vomiting and diarrhea are replaced in an ongoing manner. No unnecessary medications should be used, and laboratory studies should be limited to those necessary to guide management.

### Minimal Dehydration

For those patients with minimal or no dehydration, treatment is aimed at replacing ongoing losses. Children with diarrhea must have increased fluid intake to make up for losses and to cover maintenance needs. In principle, 1 mL of fluid should be given for each gram output. In hospital settings, soiled diapers can be weighed (without urine) and the estimated dry weight of the diaper can be subtracted. When losses are not easily measured, a reasonable rule of thumb is that one may give 10 mL/kg additional fluid allotted for each watery

stool or 2 mL/kg for each episode of emesis. Nutrition should not be restricted. Instructions regarding dietary therapy are summarized in Table 5.

### Mild-to-Moderate Dehydration

Children who are found on assessment to have mild-to-moderate dehydration should have their estimated fluid deficit rapidly replaced, with additional fluid given for ongoing losses. Current guidelines recommend giving 50 to 100 mL ORS per kilogram over 2 to 4 hours to replace estimated fluid deficit, with additional ORS given to replace ongoing losses. WHO guidelines recommend a maximum rate of 20 mL/kg/h,<sup>39</sup> but the rate may be individualized. Using a teaspoon, syringe, or medicine dropper, small volumes of fluid (eg, one teaspoon) should be offered at first, with the amount gradually increased as tolerated. If a child appears to want more than the estimated amount of ORS solution, more can be offered. Although it is safe to give ORS very rapidly, vomiting may be increased with larger boluses. Frequent, small bolus feedings will generally be tolerated. Nasogastric (NG) feeding allows continuous administration of ORS at a slow, steady rate. Clinical experience supports the use of NG feedings even in vomiting patients. Rehydration via NG tube may be particularly useful in an emergency department setting where rapid correction of hydration may prevent unnecessary hospitalization. Although rapid intravenous hydration may also prevent unnecessary hospital admissions, one recent study showed that rapid NG rehydration was well tolerated, more cost-effective, and associated with fewer complications.<sup>41</sup>

### Outpatient Observation

Because a certain percentage of children with mild-to-moderate dehydration will fail to improve with ORT, it is prudent to observe dehydrated children until signs of dehydration subside. Similarly, children who do not show clinical signs of dehydration but who demonstrate unusually high

**Table 5 Summary of Treatment Plans**

Degree of Dehydration	Rehydration Therapy	Replacement of Losses	Nutrition
Minimal or no dehydration	N/A	1 mL ORS for each gram lost to vomiting or diarrhea or 10 mL/kg for each diarrheal stool, 2 mL/kg for each episode of emesis	Continue breast-feeding; resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance*
Mild-to-moderate dehydration	ORS 50–100 mL/kg over 3 to 4 h	Same as above	Same as above
Severe dehydration	LR or NS in 20 mL/kg IV boluses until perfusion and mental status improve. Then give 100 mL/kg ORS over 4 h or 100 mL/kg D5 ½ NS IV over 8 h	Same as above; if unable to drink, give via NG tube or give IV D5 ¼ NS with 20 mmol KC1/L	Begin oral or enteral feedings after initial hydration, acidosis corrected

Adapted from reference 5.

\*Overly restricted diets should be avoided during acute diarrhea. Breast-fed infants should continue to nurse ad libitum even during acute rehydration. Infants too weak to eat may be given breast milk or formula via NG tube. Full-lactose formulas are generally well tolerated. If lactose malabsorption appears clinically significant, lactose-free formulas may be used. Complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables are all recommended.

IV = intravenous; LR = lactated Ringer's; N/A = not applicable; NS = normal saline; ORS = oral rehydration solution.

output may be held for observation. Hydration status should be reassessed on a regular basis, with more frequent monitoring given to those patients whose status is more tenuous. This may be carried out in an emergency room, office, or other outpatient setting. Once dehydration is corrected, if ORT appears to be going well and if the child's caretakers demonstrate comprehension of home rehydration techniques, understand indications for returning for further evaluation, and have the means to do so, then further management may be carried out at home. Even among those whose illness appears uncomplicated on initial assessment, a small percentage may fail ORT, so that some plan for reassessment must be in place. Caretakers should be encouraged to return to medical attention should they have any concerns, if they are not sure that rehydration is proceeding well, or, naturally, should new or worsening symptoms develop.

### Management in the Hospital

Indications for management of the child in the hospital include (1) inability of caretakers to manage ORT at home; (2) significant difficulties administering ORT, including vomiting, ORS refusal, or inadequate intake; (3) concern for possible comorbidity, complicating course; (4) failure of treatment, including worsening diarrhea or dehydration in spite of ORT; (5) severe (>9%) dehydration; (6) social or logistical issues that may prevent return evaluation if necessary; (7) or any factors, for example, very young age, unusual irritability or drowsiness, progressive course of symptoms, or uncertainty of diagnosis, which may indicate close observation.

### Severe Dehydration

Severe dehydration constitutes a medical emergency. Intravenous rehydration should begin immediately. Twenty milliliters per kilogram boluses of lactated Ringer's (LR) solution, normal saline, or a similar isotonic solution should be given until pulse, perfusion, and mental status return to normal. This may require two intravenous lines or even alternative access sites (eg, intraosseous infusion, venous cutdown). The patient should be closely observed during this period and vital signs monitored on a regular basis. Where available, serum electrolytes, bicarbonate, blood urea nitrogen, creatinine, and serum glucose should be obtained, although it is safe to commence rehydration therapy without these results, as normal saline or LR infusion is the appropriate first step in either hyponatremic or hypernatremic dehydration. Hypotonic solutions should not be used for acute parenteral rehydration.<sup>42</sup>

The severely dehydrated patient may require several boluses, which may be carried out in short succession. Practically speaking, overly rapid rehydration is unlikely to occur as long as weight-based boluses are given with close observation. Errors occur most commonly in settings in which adult dosing is given to infants. (for example, "500 cm<sup>3</sup> normal saline intravenous bolus × ii")

would provide 200 mL/kg for the average 2-to 3-month-old.) Edema of the eyelids and extremities may indicate overhydration. Diuretics should not be given. Once the edema has subsided, the patient may be reassessed for continued therapy. With very frail or malnourished infants, it may be prudent to proceed with 10 mL/kg boluses because of their poorer ability to increase cardiac output and because it may be especially difficult to distinguish dehydration from sepsis in these patients. The smaller boluses will also facilitate closer evaluation (please see Chapter 13, "Protein-Energy Malnutrition: Pathophysiology, Clinical Consequences, and Treatment," for details). In general, frequent reassessment of hydration status should be performed to follow the adequacy of replacement therapy. Failure to respond to fluid bolus should raise the suspicion of alternative or concurrent diagnoses, including, as mentioned, septic shock, as well as metabolic, cardiac, or neurologic disorders.

As soon as the patient's level of consciousness returns to normal, therapy can often be changed to the oral route, with the patient taking by mouth the remaining estimated deficit. An NG tube may be helpful for patients too weak to drink adequately but with normal mental status. Although no studies have specifically documented increased aspiration risk with NG tube use in obtunded patients, intravenous therapy is ordinarily favored in these patients. If further intravenous therapy is necessary after initial resuscitation, ESPGHAN guidelines call for the use of 5% dextrose, 0.45% saline over 8 hours to replace calculated deficit, followed by 5% dextrose, 0.18% saline solution (with 20 mmol/L potassium once urine output is documented) for ongoing losses and maintenance.<sup>40</sup> Although it is reasonable to leave intravenous access in place in these patients should it be needed, early reintroduction of ORS is safer. The use of intravenous catheters is associated with frequent minor complications, including extravasation of intravenous fluid, and rare significant complications, including the inadvertent administration of inappropriate fluid, such as those containing excessive potassium. In addition, early ORS will likely encourage earlier resumption of feeding, and some recent data suggest that resolution of acidosis may be more rapid with ORS compared with intravenous fluid.<sup>41</sup>

### Dietary Therapy

Recommendations for maintenance dietary therapy depend on the age and diet history of the patient. Breast-fed infants should continue nursing on demand. Those on formula should continue their usual formula immediately upon rehydration in amounts sufficient to satisfy energy and nutrient requirements. Lactose-free or lactose-reduced formulas are usually not necessary. A meta-analysis of clinical trials shows no advantage of lactose-free formulas over lactose-containing formulas for most infants, although some infants with malnutrition or severe

dehydration recover more quickly when given lactose-free formula.<sup>43</sup> Patients with true lactose intolerance will have exacerbation of diarrhea when a lactose-containing formula is introduced. The presence of low pH (<6.0) or reducing substances (>0.5%) in the stool in the absence of clinical symptoms is not diagnostic of lactose intolerance. Although medical practice has often favored beginning feeds with diluted (eg, half or quarter strength) formula, there is insufficient evidence to justify this practice; in general, full caloric intake should be restored as soon as possible.

Soy formulas containing soy fiber, specifically Isomil<sup>®</sup> DF, have been widely marketed to physicians and consumers in the United States. Brown and colleagues showed that added soy fiber reduced liquid stools without changing overall stool output.<sup>44</sup> This "cosmetic" effect might have some benefits with regard to diminishing diaper rash and encouraging early resumption of normal diet but is probably not sufficient to merit its use as standard of care. A more recent trial by Burks and colleagues showed a reduction in the duration of antibiotic-associated diarrhea in older infants and toddlers fed soy formula with added soy fiber.<sup>45</sup>

Children receiving semisolid or solid foods should continue to receive their usual diet during diarrhea. Foods high in simple sugars should be avoided, as the osmotic load may worsen diarrhea. For this reason, large amounts of juice, gelatin desserts, and other highly sugared liquids should be avoided. Some guidelines have recommended avoiding fatty foods, but it is difficult to maintain adequate calories without some fat. Additionally, fat may in fact reduce intestinal motility. The practice of withholding food for 24 hours is inappropriate. Early feeding may decrease changes in intestinal permeability brought about by infection,<sup>46</sup> reduce illness duration, and improve nutritional outcomes.<sup>8,9</sup> Highly specific diets, such as the BRAT (bananas, rice, applesauce, and toast) diet, have been commonly recommended. Although one recent study has shown some benefit from green bananas and pectin in persistent diarrhea (PD),<sup>47</sup> the BRAT diet is unnecessarily restrictive and, like juice-centered diets, may provide suboptimal nutrition for the patient's nourishment and recovering gut.

Many children in poor countries have multiple episodes of diarrhea in a single season, so that diarrhea may contribute to poor nutrition, which may, in turn, worsen the course of subsequent episodes.<sup>48</sup> For this reason, ESPGHAN guidelines call for increased nutrition in the 2 weeks following an episode of diarrhea.<sup>40</sup> WHO guidelines recommend caloric supplements following episodes of diarrhea, such as added cereal in milk, oil in cereal, and foods with high nutrient density.<sup>39</sup> In general, current guidelines call for age-appropriate unrestricted diets, including complex carbohydrates, meats, yogurt, fruits, and vegetables. Children should maintain caloric intake during acute episodes as best possible and should subsequently receive additional nutrition to make up for any shortfalls arising during the illness.

### Limitations of ORT

Although ORT is recommended for all age groups and for diarrhea of any etiology, some restrictions to its use do exist. In children presenting in shock, the administration of oral solutions may be contraindicated, as airway-protective reflexes may be impaired. Likewise, patients with abdominal ileus should not be given oral fluids until bowel sounds are audible. It should be remembered that intestinal intussusception may present with diarrhea, including bloody diarrhea. Radiographic and surgical evaluations are warranted when the diagnosis is in question.

Stool output in excess of 10 mL/kg/h has been associated with a lower rate of success of oral rehydration.<sup>49</sup> No patient, however, should be denied ORT simply because of a high purging rate because most patients will respond well if given adequate replacement fluid.

A small proportion of infants with acute diarrhea experience carbohydrate malabsorption, with a dramatic increase in stool output following the administration of ORS. The presence of stool-reducing substances alone is not sufficient to make the diagnosis because this is a common finding in patients with diarrhea and does not in itself predict failure of oral therapy. Patients with true glucose malabsorption will also show an immediate reduction in stool output when ORS is replaced with intravenous therapy. The incidence of clinically significant glucose malabsorption during acute diarrhea is probably less than 1%, although rates as high as 8% have been reported in selected populations.<sup>50</sup>

Many patients with acute diarrhea have concomitant vomiting. Most, however, can be successfully rehydrated with oral fluids if small volumes of ORS (5 mL) are given every 5 minutes, with a gradual increase in the amount consumed. Administration via a spoon or syringe with close supervision helps guarantee a gradual progression in the amount taken. Often, correction of acidosis and dehydration lessens the frequency of vomiting. Continuous slow NG infusion of ORS via a feeding tube may be helpful. Even if some emesis occurs after NG administration of fluid, treatment may not be adversely affected.<sup>41</sup> The physician may characteristically meet some resistance in implementing NG rehydration in the vomiting child. Education of the hospital staff may be helpful, as the NG tube may not only help the initial rehydration but may also speed tolerance of refeeding, leading to improved patient disposition and quicker discharge.

### Hypernatremic Dehydration

Patients with hypernatremic dehydration respond well to ORT. Those with severe dehydration should first receive intravenous hydration, as outlined above. Subsequent hydration may be achieved with ORS.<sup>51</sup> As with normonatremic dehydration, ORS should be given both to replace the calculated deficit and for ongoing losses. ORS is safer than intravenous therapy because it is less likely to lead to a precipitous decline in serum

sodium, which may increase intracranial pressure.<sup>40</sup> ESPGHAN guidelines recommend slow intravenous rehydration only should ORT fail, replacing the calculated deficit with 5% dextrose/0.45% saline over 8 hours, followed by repeat plasma sodium. If the patient is still hypernatremic, then this may be repeated, followed by maintenance with 5% dextrose/0.18% saline.

## PHARMACOLOGIC THERAPY

### Antibiotics

Because viral agents are the predominant cause of acute diarrhea (eg, rotavirus, astrovirus, enteric adenovirus, norovirus, and sapovirus), the routine use of antimicrobial agents for the treatment of diarrhea wastes resources and may lead to increased microbial resistance. Especially in the hospital setting, bacterial causes of diarrhea are unusual. A survey of stool cultures submitted over several years to the microbiology laboratory at Children's Hospital in Boston, Massachusetts, revealed such infrequent occurrence of bacterial infections that the practice of sending stool cultures in patients who develop diarrhea while hospitalized has been abandoned.<sup>52</sup> Hospitalized patients and patients with a history of recent antibiotic use are, however, at risk for infections with *Clostridium difficile*. Infections with *C. difficile* documented by toxin assay should be treated with metronidazole 30 mg/kg divided three times daily given orally. Oral vancomycin is also effective but should be reserved as a second-line agent, given its expense and concern over the possible emergence of vancomycin-resistant *Enterococcus*.

Even when a bacterial cause is suspected, antibiotic therapy is generally not indicated because the majority of cases of acute diarrhea are self-limited and not shortened by antibiotics. In addition, antibiotics may cause harm. There is evidence that antibiotic use may increase the risk of hemolytic uremic syndrome from *E. coli* infections.<sup>53</sup> There remains some concern that treatment of *Salmonella enteritis* may increase the risk of the carrier state, although patients under 3 months old or with bacteremia should be treated.<sup>54</sup> Patients with underlying disorders, including immunodeficiency, provide exceptions to these rules. Detailed information regarding the appropriate use of antimicrobial therapy for infectious causes of acute diarrhea is beyond the scope of this chapter and is available in a variety of other resources.<sup>55-58</sup>

### Nonantibiotic Drug Therapies

The use of nonspecific antidiarrheal agents such as adsorbents (eg, kaolin-pectin), antimotility agents (eg, loperamide), antisecretory drugs, or toxin binders (eg, cholestyramine) is a common practice. Few data are available to support their efficacy. The side effects of these drugs are well known, in particular among the antimotility agents, including opiate-induced ileus, drowsiness, and nausea owing to atropine effects and

binding of nutrients and other drugs. One report from Pakistan detailed 18 cases of severe abdominal distention in association with use of loperamide, including at least 6 deaths.<sup>59</sup> Bismuth subsalicylate has shown some efficacy in traveler's diarrhea and other causes of acute gastroenteritis in children,<sup>60</sup> and although the side effects are less than antimotility agents, some theoretic concerns over the potential toxicity of salicylate remain. In any event, reliance on antidiarrheal agents shifts the therapeutic focus away from appropriate fluid, electrolyte, and nutritional therapy and adds unnecessarily to the economic cost of the illness.

It should be noted that none of the drugs mentioned above specifically address the underlying causes of diarrhea, specifically increased secretion by intestinal crypt cells. Racecadotril, an enkephalinase inhibitor, preserves the antisecretory activity of enkephalins, first discovered in 1975. It does not slow intestinal transit or promote bacterial overgrowth.<sup>61</sup> Its use has shown promise in two controlled clinical trials in children, significantly reducing acute watery diarrhea compared to placebo.<sup>62,63</sup> As long as its cost is reasonable and its use does not distract from ORT and education regarding home management of diarrhea, racecadotril may prove to be a useful adjunct to the treatment of watery diarrhea.

Similarly, the use of antiemetics may be warranted in some cases. Phenothiazines can interfere with oral rehydration by causing sleepiness. There are, however, two recent randomized, double-blind, placebo-controlled pediatric trials that have shown ondansetron, a 5HT<sub>3</sub> receptor antagonist, to be effective in decreasing vomiting and limiting hospital admission when administered either by oral<sup>64</sup> or by intravenous<sup>65</sup> route. A third trial showed that a single oral dose of ondansetron, given to pediatric emergency department patients with gastroenteritis and dehydration, significantly decreased the likelihood and frequency of vomiting. There was no significant decrease in the rate of hospitalization, however, the ondansetron group was significantly less likely to require intravenous hydration, had increased oral intake, and had a shorter mean length of stay in the emergency department.<sup>66</sup> The cost is not trivial, and nausea is frequently self-limited, but where admission or even the need for outpatient intravenous therapy is avoided, this intervention may be cost-effective.

### Functional Foods

Functional foods may be defined as those that have an effect on physiologic processes separate from their established nutritional function.<sup>67</sup> Probiotics, live microorganisms found in fermented foods and intended to promote intestinal health, are the classic functional food. The modern interest in probiotics may date from Metchnikoff's hypothesis that fermented milk products were responsible for the longevity of Bulgarian

peasants.<sup>68</sup> Although a number of recent reviews<sup>69</sup> and journal supplements<sup>70</sup> have more broadly evaluated their use, numerous recent studies have looked specifically at their use in reducing the severity or duration of diarrheal illnesses in children, especially those caused by *Rotavirus*<sup>71</sup> or associated with antibiotic use.<sup>72</sup> Generally, these have included various species of lactobacilli or bifidobacteria, or the nonpathogenic yeast *Saccharomyces boulardii*. The mechanism of action may include competition with pathogenic bacteria, either for receptor sites or for intraluminal nutrients, production of antibiotic substances, and enhancement of host immune defenses.<sup>73,74</sup>

One recently published meta-analysis concludes that *Lactobacillus* spp are both safe and effective as treatment for children with infectious diarrhea, reducing diarrhea duration by 0.7 days and diarrhea frequency by 1.6 stools per day.<sup>75</sup> A recent comprehensive review concluded that there is evidence for the efficacy of a wide variety of probiotics in acute gastroenteritis, especially *Rotavirus*.<sup>76</sup> A positive recommendation also emerges from a recent meta-analysis of probiotic use in antibiotic-associated diarrhea.<sup>77</sup> Probiotics may be effective in terms of prevention as well. A recent meta-analysis of studies predominately executed in developed countries concluded that probiotics reduced the risk of acute diarrhea among children by 57% and that of antibiotic-associated diarrhea by 52%.<sup>78</sup> In this analysis, the protective effect did not vary significantly among the variety of probiotic strains examined.

These reviews included some trials with limited sample size and are susceptible to potential publication bias, as it must be noted that trials with negative results may not have been published. Furthermore, as these products are generally not regulated, there is potential for great variability among products. As such, it may be difficult for the prescribing physician to make an informed recommendation. That being said, the safety and relatively low cost of probiotics may make recommendation of specific products worthwhile, especially where doing so may improve compliance with ORT.

Prebiotics differ from probiotics in that they are nutrients, rather than organisms, used to preferentially stimulate the growth of health-promoting intestinal flora.<sup>79</sup> Presumably, their use could be synergistic with probiotics. The oligosaccharides found in breast milk have been called the prototypic prebiotic in that they foster the growth of lactobacilli and bifidobacteria in the colon of breast-fed neonates.<sup>80</sup> The prebiotic effects of inulin and fructose oligosaccharides have been studied primarily in vitro and in animal model studies.<sup>81</sup> Two randomized, blinded trials on prebiotic-supplemented infant cereal in an urban, economically depressed area did not demonstrate a reduced incidence of diarrheal disease.<sup>82</sup> Specific recommendations regarding the use of prebiotics should await further well-controlled human trials. In the meantime, it should be noted that dietary fiber may serve both as a prebiotic and as a modifying agent of intestinal motility.

Current guidelines recommend fiber-containing fruits and vegetables as part of the diet of children recovering from acute gastroenteritis.

### Supplemental Zinc Administration

Many reports have linked diarrhea and abnormal zinc status,<sup>83</sup> including increased stool zinc loss,<sup>84</sup> negative zinc balance,<sup>85</sup> and reduced tissue levels of zinc.<sup>86</sup> It has long been observed that diarrhea may occur with severe zinc deficiency, as in acrodermatitis enteropathica, but the broader clinical question is whether more incremental deficiencies of zinc may play a role in childhood diarrhea and whether supplementation may be of benefit, either for improved outcomes in acute or chronic diarrhea or as prophylaxis against diarrheal disease.

A large number of studies have addressed these questions. One early study showed reduced duration of acute diarrhea in patients with low rectal zinc levels.<sup>86</sup> In Bangladesh, zinc supplements also improved markers of intestinal permeability in children with diarrhea.<sup>87</sup> In India, zinc supplementation was associated with a decrease in both the mean number of watery stools per day and the number of days with watery diarrhea.<sup>88</sup> More recently, prophylactic zinc supplementation in India was associated with substantially reduced incidence of severe and prolonged diarrhea, two of the most important determinants of malnutrition and diarrhea-related mortality.<sup>89</sup> In Nepal, this effect was shown to be independent of concomitant vitamin A administration, with very few side effects noted in a substantial number of patients, apart from a slight increase in emesis.<sup>90</sup> In Peru, zinc administration was also associated with a reduction in duration of PD when given during the illness<sup>91</sup> and a decreased incidence of diarrhea, dysentery, and other morbidity when given prophylactically.<sup>92</sup> In the latter study, zinc supplementation alone, compared to zinc supplementation and a multivitamin, had a greater decrease in morbidity. In two different pooled analyses of randomized, controlled trials in developing countries, the Zinc Investigators' Collaborative Group reviewed evidence that zinc supplementation is beneficial for the treatment of acute and Persistent diarrhea<sup>93</sup> and as a prophylactic supplement for decreasing the incidence of diarrheal disease and pneumonia. Among infants and young children who received supplemental zinc for 5 or 7 days per week for 12 to 54 weeks, the pooled odds ratio for diarrhea incidence was 0.82 [95% confidence interval (CI) 0.72 to 0.93] and that for pneumonia incidence was 0.59 (95% CI 0.41 to 0.83).<sup>94</sup>

WHO and UNICEF now recommend that all children with acute diarrhea receive zinc supplementation for a total of 10 to 14 days during and after diarrhea (10 mg/d for infants under 6 months of age and 20 mg/d for children greater than 6 months of age).<sup>39,95</sup> Zinc supplementation in more developed settings may not be as efficacious. A recent randomized, double-blind, placebo-controlled trial of zinc supplementation in breast-fed infants in the United States did not show a

significant difference in the frequency of diarrhea between the treatment and control groups.<sup>96</sup> Further research is needed to identify the mechanism of action and to determine optimal schemes for delivery of zinc to the neediest populations.

## OTHER CLINICAL SCENARIOS

### Acute Bloody Diarrhea (Dysentery)

Dysentery is defined as acute bloody diarrhea caused by invasive microbial infection. This does not include occult blood (detected by guaiac card only), streaks of blood on the surface of formed stool, or melena. The reader is referred to WHO guidelines, which discuss the evaluation and management of dysentery at length.<sup>34,39,97</sup> AAP,<sup>16</sup> CDC,<sup>5</sup> and ESPGHAN guidelines<sup>40</sup> do not specifically address dysentery.

The treatment of dehydration in dysentery follows the same principles as the treatment of acute watery diarrhea. The child with bloody diarrhea is at higher risk for complications, including sepsis and other systemic disease, so that the threshold for admission to the hospital for close observation is lower. Stool cultures are indicated in the setting of acute bloody diarrhea and are helpful for guiding therapy. Food should not be withheld in dysentery any more than in other cases of diarrhea. Because patients with dysentery may have significant anorexia, they should be coaxed to eat.<sup>34</sup> More frequent, smaller meals may be better tolerated. Children convalescing from dysentery should be given extra food to help them regain nutrition lost during the acute illness.

### Cholera

Cholera differs from other causes of acute diarrhea in that (1) it may occur in large epidemics involving adults and children; (2) it produces voluminous diarrhea, which may lead to shock and death by dehydration in a very short period; and (3) certain antibiotics may shorten the course.<sup>39</sup> Management of cholera may be carried out using the methods for assessment of dehydration and treatment plans outlined above and summarized in Tables 3, 4, and 5. The health worker must be prepared to deliver prodigious quantities of fluid, either by ORS or intravenously, to overcome ongoing losses. These losses should be quantified so that treatment may be updated and modified under continuous close observation. Unlike diarrhea from other causes, where cereal-based ORSs are equivalent to standard ORSs, there may be some advantages in using rice-based ORS in treating cholera.<sup>98</sup> Traditional wisdom held that sodium concentrations of ORS used in treating cholera should be higher than those for other causes of diarrhea (based on measured stool sodium losses), but a CHOICE study group trial showed no clinical difference between those treated with the lower osmolarity solution compared with a standard solution, apart from some increased incidence of asymptomatic hyponatremia.<sup>99</sup> In Bangladesh, a recently published study of over 50,000 monitored patients with

uncomplicated watery diarrhea found no evidence for an increase in symptomatic hyponatremia in those treated with reduced osmolarity ORS. In fact, the incidence rate of developing symptomatic hyponatremia was significantly lower in those treated the newer, reduced osmolarity formulation.<sup>100</sup>

### Persistent Diarrhea

Persistent diarrhea may be defined as diarrhea of acute onset that lasts more than 14 days in a child who either fails to gain or loses weight. Globally, PD accounts for a substantial proportion of diarrhea-related morbidity and between 36 and 54% of all diarrhea-related deaths.<sup>101</sup> A recent community-based study suggested that PD is experienced by roughly one in five young children per year in the United States, though with far less morbidity and mortality.<sup>102</sup>

In developing countries, the most important epidemiological risk factor for acquiring PD is malnutrition, further emphasizing the importance of aggressive nutritional therapy in the treatment of acute diarrhea. Other risk factors include immune status (including HIV), zinc deficiency, lack of breast-feeding, male sex, and infection with enteropathogenic or enteroaggregative *E. coli* or *Cryptosporidium*.<sup>103</sup> Malnutrition can also significantly increase mortality from PD, with a study of diarrheal deaths in Bangladesh demonstrating a 17-fold higher relative risk of death from PD in malnourished children compared to those with lesser degrees of malnutrition.<sup>104</sup>

The approach to the patient with PD should include assessing and treating diarrhea, as in the acute presentations. Worldwide, the most important predisposing factor is an acute diarrheal episode triggered by an enteric infection.<sup>103</sup> Particularly in the developing world, bacterial and parasitic infections are common and warrant aggressive diagnosis and therapy. In areas where HIV infection is endemic, chronic gastrointestinal infections with organisms such as *Cryptosporidium parvum* are even more likely.

When infection has been carefully excluded, other specific etiologies must be considered. These include food allergy and dietary protein intolerances, celiac disease, disaccharide (ie, lactose) intolerance, cystic fibrosis and other causes of pancreatic insufficiency, and inflammatory bowel disease. For further details on the diagnosis and nutritional management of these disorders, please refer to Chapters 48 (“Inflammatory Bowel Disease”), 50 (“Celiac Disease”), 51 (“Food Allergies”), 52 (“Exocrine Pancreatic Disease Including Cystic Fibrosis”), and 61 (“Carbohydrate Absorption and Malabsorption”).

In the developed world, chronic nonspecific diarrhea of childhood (or “toddler’s diarrhea”) is a common, nonpathologic phenomenon seen in children between the ages of 6 and 36 months. It is characterized by the passage of two or more loose, voluminous stools per day for over 4 weeks, in the absence of abdominal pain or growth

**Table 6 ORS for the Severely Malnourished Child**

Simple ORS for the Severely Malnourished Child	More Effective ORS for the Severely Malnourished Child
Dilute 1 L WHO-ORS to make 2 L	Dilute 1 L WHO-ORS to make 2 L
Add 45 mL KCl solution from stock solution containing 100 g KCl/L	Add the following salts:
Add and dissolve 50 g sucrose	3.6 g KCl
	1.3 g K citrate
Children given this solution should also receive:	1.2 g MgCl
2 mL 50% MgSO <sub>4</sub> solution (4 mEq Mg/mL) IM once	130 mg Zn acetate
Zinc chloride solution (10 g/L) 1 mL/kg/d until diarrhea stops	22 mg CuSO <sub>4</sub>
	0.44 mg NaSeO <sub>4</sub>
	0.20 mg KI
	Add and dissolve 50 g sucrose

Adapted from reference 39.

IM = intramuscularly; ORS = oral rehydration solution.

inhibition. Its pathophysiology remains unknown, but it will often respond to dietary alterations.<sup>105</sup> Diets either low in fat (which modulates intestinal motility), low in fiber (which may promote balanced intestinal flora) and/or high in high-osmolarity carbohydrate drinks, particularly sorbitol-containing fruit juice, may all contribute to PD in the developed world. In such cases, dietary modification should be attempted before undertaking an extensive diagnostic evaluation.

Attention to nutrition is critical in the treatment of PD, with restoration of a nutritious diet, including adequate calories, being a key element of therapy. As with acute diarrhea, recommended foods include age-appropriate unrestricted diets, including complex carbohydrates, meats, yogurt, fruits, and vegetables.<sup>5</sup> As previously discussed, zinc supplementation has been shown to be effective in reducing the duration and severity of PD and should be continued for prophylaxis against additional episodes after appropriate therapy is complete.<sup>94</sup> In cases of infectious etiologies, education regarding sanitation and hygiene may reduce rates of reinfection.

For details of PD in the setting of protein-energy malnutrition, please refer to Chapter 13, “Protein-Energy Malnutrition: Pathophysiology, Clinical Consequences, and Treatment.”

### Diarrhea with Severe Malnutrition

Assessment of the malnourished child is difficult because many of the signs outlined in Table 3 may be unreliable. Skin turgor may appear poor owing to the absence of subcutaneous fat. Eyes may be sunken from loss of periorbital fat. Irritability or apathy from malnutrition may complicate the assessment of mental status. When possible, malnourished children with diarrhea should be referred to a hospital. A severely malnourished child with signs of dehydration without a history of increased stool output should be treated for septic shock.<sup>39</sup> Because of the increased risk of bacteremia in severely malnourished children, and, in fact, in a broad range of children with diarrhea in a less developed setting,<sup>106</sup> the use of empiric antibiotics is not unreasonable where blood cultures cannot be obtained, although

the literature regarding choice of antibiotics, doses, and duration is sparse.

Because intravenous therapy may cause overhydration and heart failure in the severely malnourished child, except for treatment of shock, slow oral rehydration is the treatment of choice. An NG tube may be used for children who drink poorly. Rehydration should begin with 10 mL/kg over 2 hours. This rate may be adjusted based on the child’s thirst or ongoing stool losses. Increasing edema may be evidence of overhydration.

Full-strength WHO-ORS contains too much sodium and inadequate potassium for the severely malnourished child. WHO guidelines recommend modified solutions such as ReSoMal, as outlined in Tables 1 and 6. Feeding should begin as soon as possible once hydration has been achieved and should continue every 2 to 3 hours day and night. Malnourished children often exhibit anorexia and require coaxing to eat. For greater details, the reader is again referred to Chapter 13, “Protein-Energy Malnutrition: Pathophysiology, clinical consequences, and Treatment”.

### CHOICE OF ORS

Table 1 outlines the composition of several commonly available ORSs, as well as other beverages frequently used for inappropriate rehydration. The vast discrepancy between the composition of the WHO-ORS and beverages inappropriately recommended for rehydration should be noted. In July 2002, WHO and UNICEF recommended a significant change in ORS composition, including a reduction in sodium and glucose to maintain a 1:1 molar ratio and to decrease total osmolarity to 245 mOsm/L. The change was prompted by clinical trials showing that this solution resulted in less use of supplemental intravenous fluid therapy as well as lower stool output and less vomiting compared with the previous WHO standard ORS.<sup>29,107</sup> Although the differences in measured stool output resulting from different ORS formulations may be modest, reduction in intravenous fluid use is a substantial economic and health benefit of the new solution. The composition of the new solution is also more in line with solutions more commonly used in industrialized countries.

## New Solutions

Numerous improved ORSs have been attempted. These have generally included additional substrates for sodium cotransport (such as the amino acids glycine, alanine, and glutamine)<sup>108,109</sup> or, as reviewed by Fontaine and colleagues,<sup>98</sup> substituting complex carbohydrates for the glucose (rice and other cereal-based ORSs) to reduce osmolarity while preserving glucose–sodium cotransport. Given trials to date, the amino acid preparations do not appear to be more effective than traditional ORSs and are more costly. Rice-based ORS may be recommended where training is adequate and home preparation is preferable and appears to be particularly effective in treating diarrhea from cholera.<sup>98,110</sup> Nevertheless, given the simplicity and safety of ORS packets in developing countries and commercially available ORSs in developed countries, these remain the first choice for most clinicians.

A recent publication investigated the addition of recombinant human lactoferrin and lysozyme, two breast milk proteins with antimicrobial activity, to a cereal-based ORS. This novel ORS resulted in a decreased duration of acute diarrhea in Peruvian children compared to a mixed control of standard cereal- and rice-based ORS.<sup>111</sup>

Other potential additives to ORS include substances capable of liberating short-chain fatty acids. These include amylase-resistant starch derived from corn<sup>112</sup> and partially hydrolyzed guar gum.<sup>113</sup> The presumed mechanism of action is the enlistment of increased colonic sodium uptake coupled to short-chain fatty acid transport. Recently, a controlled trial of children with acute diarrhea demonstrated significantly decreased diarrhea duration in those given amylase-resistant starch-fortified ORS compared to those receiving the standard WHO-ORS formulation.<sup>114</sup>

Future possible ORS composition changes include the addition of probiotics, prebiotics, and zinc. Until further data are accumulated regarding all these additional substrates, no definitive recommendations can be made for their use.

## Barriers to ORT

Barriers to the use of ORS and continued nutrition during diarrheal disease include, among patients, cultural practices<sup>33</sup> and lack of information<sup>115</sup> and, among physicians, preference for intravenous hydration, even where evidence suggests improved results from oral rehydration.<sup>18,20,116</sup> At the other extreme from the development of the ultimate ORS, it remains distressingly common for patients, even at times under physician supervision, to attempt rehydration with solutions bearing no resemblance to physiologically based ORS. Table 1 includes a number of fluids commonly used in treating diarrhea which do not contain physiologically sound concentrations of carbohydrates and electrolytes. An informal survey of numerous hospital Web sites reveals outdated recommendations for the treatment of diarrhea that

include nonstandard fluids. A recent case report of one child whose care was compromised by following advice obtained from a prominent hospital's Internet site highlights the continued gap between knowledge and practice and the ongoing need to disseminate accurate information regarding oral rehydration.<sup>117</sup>

## CONCLUSION

The treatment of acute diarrhea has for many years been shown to rely on the simple but overwhelmingly effective therapy of oral rehydration. More recently, the important coprinciple of early refeeding of children immediately upon rehydration has also gained wider acceptance. The combination of oral rehydration and early nutritional support promises to safely and effectively guide a patient through a bout of diarrhea. If the principles of therapy outlined above are accepted by all levels of the medical community, and if education of parents includes beginning ORT at home, then numerous deaths and unnecessary hospitalizations can be avoided. Meanwhile, we await further technological breakthroughs (eg, improved vaccines, superior rehydration solutions) to better combat one of the most important public health problems today.

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