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New Developments in Acute Diarrhea

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Introduction

Diarrhea is defined as excess stool water, usually greater than 200 gm/day (or greater than 10 gm/kg/day in infants). Frequency per se, is not indicative of diarrhea, although they often coexist. Indeed, breast-fed infants may have up to 12 stools/day, and formula-fed infants, up to seven stools/day. The presence of undigested food particles merely indicates fast transit. Acute infective diarrhea is usually an obvious increase over the baseline with nausea, vomiting, fever, and abdominal pain variably present.

Although most of the episodes in children are self-limited, diarrhea continues to be a major global problem, accounting for up to 3.5 million deaths in children less than 5 years old worldwide. In the United States, 220,000 patients are hospitalized per year, accounting for 10.6% of admissions in this age group, whereas most of the 300 to 400 deaths per year attributed to diarrhea occur in the first year. The established pathogens of pediatric diarrhea are listed in Table 1. In up to 40% of presumed acute infective diarrhea, no pathogen is isolated.

Epidemiology is important in predicting likely pathogens, especially in terms of age, geography, season, water source, travel, and day-care exposure. The current approach to diarrhea in childhood is to establish whether we are dealing with a secretory or osmotic (malabsorptive) process. The immediate problem is to avoid or correct dehydration. High fever, particularly with bloody diarrhea, requires investigation for possible bacteremia and sepsis. Furthermore, documentation of the causative organism, bacterial, viral, or parasitic, is mandatory in infants. The susceptibility of young infants to bacterial toxins is becoming more apparent. On the one hand, the greater susceptibility of infants to enterotoxigenic Escherichia coli is due to higher density of guanylate cyclase–associated receptors in the small intestinal enterocytes. On the other hand, Shiga toxin of shigellosis does not affect the infant as much because of underdeveloped glycolipid receptors on the enterocytes. Unusual organisms in the stool, like persistent cryptosporidium might raise the suspicion of AIDS and immunodeficiency. Nonspecific diarrhea may be a symptom of infection elsewhere, such as pneumonia, otitis media, and appendicitis, and is generally not dehydrating unless it coexists with anorexia and vomiting.

Noninfectious causes such as dietary indiscretion, especially overfeeding and the use of large quantities of fruit juices that include fructose, sorbitol, and sucrose may precipitate diarrhea, and food poisoning from preformed toxins tend to cause brief problems (botulism an important exception) and may be suspected from the history. Ingestion of drugs and chemicals, for example, heavy metals, should always be considered. Many proprietary antipyretical elixirs contain sig-

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New Developments

TABLE 1. Agents causing acute diarrhea and their relative frequency

|                | United States (%) | Developing countries (%) |
|----------------|-------------------|-------------------------|
| **Viral**      |                   |                         |
| Rotavirus      | 8-50              | 4-45                    |
| Enteric adenovirus | 5-15         | 5-15                    |
| Norwalk agent  | 5-15              | 1-2                     |
| Pestivirus     | <10               |                         |
| Astrovirus     | 1-5               |                         |
| Calicivirus    | 1-2               |                         |
| Coronavirus    | <1                |                         |
| **Bacterial**  |                   |                         |
| Campylobacter jejuni | 1-7          | 1-7                     |
| Salmonella     | 2-4               | 0-15                    |
| Enterotoxigenic E. coli | 1-4        | 7-50                    |
| Enterohemorrhagic E. coli | 1-3      | *                       |
| Shigella       | 1-3               | 3-16                    |
| Yersinia       | 1-3               | *                       |
| Clostridium difficile | 1-2          | *                       |
| Aeromonas      | <1                | *                       |
| Pleisomonas    | <1                | *                       |
| Vibrio cholera and other species | 1-6 | |
| **Parasitic**  |                   |                         |
| Giardia        | High              | 4-20                    |
| Cryptosporidium parvum | High | 4-8                    |
| Entamoeba histolytica | <1        | 2-15                    |
| Dientamoeba fragilis | <1           | *                       |
| Balantidium coli | <1              | *                       |
| Strongyloides stercoralis | <1     | *                       |
| **Food poisoning** |               |                         |
| Staphylococcus aureus | 1           | *                       |
| Clostridium perfringens | 1           | *                       |
| Bacillus cereus | <1               | *                       |

*Incomplete data.

**Significant amounts of sucrose and sorbitol and may confuse the presentation of a febrile illness by inducing diarrhea. Recent additions to the list of organisms causing diarrhea, new insights into pathogenesis, and current approaches to improved management will be discussed. We are against the use of most antidiarrheal medication; the mainstay is rehydration and, occasionally, antimicrobials if sepsis is present.**

**Recently Discovered Pathogens**
Although several "new" pathogens have been associated with diarrhea for the last few years, only recently have some of these become implicated more conclusively.

**Viral (Table 1)**
Although rotavirus is considered the main viral pathogen, recently enteric adenoviruses have been recognized as a major cause of diarrhea. Better characterization of enteric adenoviruses with serotypes 40 and 41, subgroup F, has allowed
differentiation from other nonenteric adenoviruses in stool and by serologic testing. They have been strongly implicated in pediatric diarrheal disease both in the United States and in developing countries. In a day-care setting enteric adenoviruses were found to be the third most common pathogen identified. The pathogenesis remains poorly understood. The illness is similar to rotaviral diarrhea, including associated respiratory symptoms. Vomiting is less common, but prolonged duration of diarrhea is more often seen and may lead to greater nutritional insult. Electron microscopy or stool enzyme-linked immunosorbent assay are available for diagnosis. Pestivirus has recently been shown to be associated with childhood diarrhea in the United States and may prove to be an important pathogen. Mucosal injury has been well documented, with deficiency in disaccharidases recently found to be more common in HIV-positive infants than controls. Not only is the diarrhea debilitating, the cachexia seen with AIDS diarrhea may be attributed to anorexia in addition to malabsorption.

**Bacterial (Table 2)**

*E. coli* demonstrates the complete spectrum of host-parasite relationships, with normal colonization at one extreme to pathogenicity at the other, by mechanisms as diverse as possible. They may either primarily attack the colon or the small intestine, using direct invasion, toxins, adhesion, and possibly affecting motility. Of the five different *E. coli*, enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroinvasive, and enterohemorrhagic *E. coli* are well-documented pathogens; the role of recently proposed enteroadherent or enteroaggregative strains, also recently found to be more common in HIV-positive infants than controls, remains inconclusive. Worldwide, EPEC (early infancy) and ETEC (infants and children and travelers' diarrhea) are major pathogens, whereas EHEC (*E. coli* O157:H7) has greater notoriety in the United States, particularly as the cause of hemolytic-uremic syndrome.

Noncholera vibrios and other members of the Vibrionaceae family, particularly *Aeromonas* and *Pleisomonas* spp., have reemerged as probable pathogens, in early childhood. *Aeromonas*-associated diarrhea is seen in children less than 3 years of age, with significant morbidity in early infancy. *Aeromonas* are ubiquitous in surface waters in the United States, including saltwater and chlorinated drinking water, and have been associated with up to 10% of diarrheal episodes in children. Pathogenesis may be mediated by any of the several mechanisms documented in vitro, including cholera-like toxins, adherence, and invasion. Indeed, three clinical patterns are seen: (1) self-limited acute watery diarrhea, (2) chronic diarrhea, and (3) acute or chronic diarrhea with blood and mucus. Specific antibiotic treatment, such as cotrimoxazole, has been used for chronic diarrhea or in immunocompromised patients to prevent systemic spread, but controlled studies are lacking. The evidence for *Pleisomonas* diarrhea is less convincing.

The enterotoxigenic bacteria (Table 2) that have a definite toxin are cholera, *E. coli* (ST), *E. coli* (verotoxin), *Clostridium difficile*, and *Shigella*. Others have been shown to produce toxins, although the clinical impact is unproved.

Diarrhea is common in AIDS patients, and an important factor in morbidity and mortality. Several organisms such as atypical mycobacteria are implicated, usually leading to chronic diarrhea. Acute watery, dehydrating diarrhea is also seen, for example, with parasites like *Cryptosporidia* and *Microsporidia*. 
TABLE 2. Pathogenesis of bacterial and protozoal diarrhea

| Pathogenesrs | Age | Site | Features |
|--------------|-----|------|----------|
| 1. Enterotoxic |     |      |          |
| ETEC         | All; i & c | sb | Secretory, watery diarrhea, traveler's; nosocomial; ST1 worse than ST2 |
| Cholera      | All  | sb  | Secretory |
| Aeromonas    | i & c |      | Role of toxins in pathogenesis unclear |
| Pleisomonas  |      |      | As above |
| C Diff (Toxin A) |      |      | As above |
| Yersinia     |      |      | As above |
| 2. Cytotoxic |     |      |          |
| EHEC         | i & c, aged | c | Hemorrhagic colitis; common source outbreaks; hamburgers, apple juice; HUS and TTP |
| C Diff (Toxin B) | All  | c  | Pseudomembranous colitis, most postantibiotic asymptomatic carriage common in infants |
| Shigella     | Preschool | sb, c | Watery diarrhea, then colitis |
| EPEC (some)  | Infants |      | Shiga-like cytotoxin |
| 3. Invasive  |     |      |          |
| EIEC         | Preschool | sb, c | Acute colitis, colitis, sepsis |
| Shigella     | Preschool | Distal sb, c | Acute enterocolitis |
| Salmonella   | Preschool | sb, c | Acute enterocolitis |
| Campylobacter| i & adolesc | sb, c | As above, mild in preschoolers |
| Yersinia     | Preschool | Distal sb, c | Acute and chronic diarrhea |
| 4. Adherence |     |      |          |
| EAEC         | Infants | sb | Adherent; microvillus damage, mucosal injury chronic malabsorption, traveler's diarrhea |
| Giardia      | Preschool | Upper sb | Adherent; microvillus damage, patchy villous atrophy; acute and chronic diarrhea |
| Cryptosporidiun | Preschool | sb, c | Acute and chronic diarrhea |
| EPEC         | Infants | sb | Local adherence by enteroadhesive factor, destruction of microvilli |

i, infants; c, children; ado/, adolescents; sb, small bowel; c, colon; C diff, Clostridium difficile; for ST1, ST2, EIEC, EPEC, ETEC, EAEC, and EHEC, see text.

**Parasites**

Cryptosporidium, *Isospora belli*, sarcocystis, and microsporidium are recent additions as pathogens, especially in AIDS. Cryptosporidium is the only one that commonly infects a normal host. Feco-oral transmission, including that from other mammals, or from food, water (even chlorinated), and fromites may occur. Daycare outbreaks are common. Although usually short and self-limited, watery diarrhea with cramps is seen, and chronic, often secretory diarrhea, with persistent infection and mucosal injury with malabsorption can ensue. Antibiotics, such as spiramycin and erythromycin, reduce shedding and symptoms but do not eradicate the organism. In AIDS it can pose a major threat, leading to a rapidly dehydrating diarrhea and marked wasting. Hyperimmune bovine colostrum was claimed to be useful.
TABLE 3. Differences between osmotic and secretory diarrhea

| Stools | Osmotic diarrhea | Secretory diarrhea |
|--------|------------------|--------------------|
| Electrolytes | Na⁺ <70 mmol/L | Na⁺ >70 mmol/L |
| Osmotic gap | >100 mOsm | <50 mOsm |
| pH | <5 | >6 |
| Reducing substance* | Present | Absent |
| Volume | <20 ml/kg/day | >20 ml/kg/day |
| After fasting | <10 ml/kg/day | >20 ml/kg/day |
| Blood/pus/fat | Present or absent | Absent |

*Hydrolysis required for sucrose.

Mechanism of Diarrhea

It is becoming clear that several different mechanisms may be used by the same organisms and shared by different organisms. After ingestion, multiplication and attachment or adhesion to cells must occur. Toxin production, invasion, adhesion with brush border membrane damage, and increasing motility are some of the factors that lead to gastrointestinal dysfunction. Table 2 reviews some of these. The important role of membrane receptors and immune mediators in effecting enterocyte dysfunction is becoming more clear. Table 3 lists some of the features differentiating secretory from osmotic diarrhea.

Secretory Diarrhea

Receptor-Mediated Secretory Diarrhea

The generalized concept of receptor-mediated secretory diarrhea includes three steps: (1) toxin binding to its microvillus membrane receptor; (2) an intracellular response to the toxin-receptor interaction (signal transduction); and (3) altered enterocyte function, either directly or through a mediator, such as prostaglandin E₂.

Toxigenic diarrhea involves binding to specific cell receptors and subsequent triggering of cellular events. Of the heat-labile and heat-stable (ST1 and ST2) toxins of toxigenic E. coli, the former uses the same receptor as cholera, that is, the GM1 glycolipid receptor on enterocytes. Binding allows the active component to enter the cell and by signal transduction through cyclic AMP leads to chloride and water secretion in the crypt or reduced water and electrolyte absorption in the villus. The heat-stable toxin (ST1) causes a cyclic GMP-mediated secretory state by a very similar mechanism.

The role of development on the susceptibility of the infant intestine to different bacterial pathogens has been noted clinically for a long time. Although anatomic considerations suggest diminished colonic capacity for reabsorption than in older children and adults, other factors must be important. Intriguing cell membrane level correlation with developmental changes have been noted. The receptor density for ETEC ST1 toxin, which is high within the first few months of life, then diminishes and probably accounts for the greater susceptibility limited to early infancy. The receptor is a member of the guanylate cyclase family of transmembrane proteins. Conversely, Shiga toxin of Shigella dysenteriae, binds to a receptor (glycolipid Gb3) that appears to be underdeveloped in the immature intestine and probably explains the relative resistance in neonates. Likewise C. difficile toxin A-producing strains may be present in 50% of infants.
but do not result in toxicity, probably because of a lack of receptors\textsuperscript{23} and possibly because of reduced responsiveness of the receptors.\textsuperscript{24}

**Other Mechanisms**

Damage to villus enterocytes as seen in rotavirus diarrhea leads to impaired sodium chloride absorption, leaving the crypt cell Cl\textsuperscript{−} secretion unaffected. Net secretory loss has been documented in laboratory models and concurs with clinical observations. Bile acids and excess fatty acids are known to exert a secretory effect on enterocytes and may be important in intestinal resections, bacterial overgrowth, and motility disorders.

**Osmotic Diarrhea**

**Receptor-Mediated Invasion**

Intact bacterial invasion of nonphagocytic cells may also be receptor mediated. *Salmonella typhimurium* has recently been shown to induce cell invasion by stimulation of the epidermal growth factor receptor.\textsuperscript{25} It is unclear whether it binds to the receptor or stimulates it indirectly. Such bacterium-specified endocytosis is also seen with *Yersinia pseudotuberculosis*, where binding to integrin receptors results in internalization.\textsuperscript{26} On reaching the lamina propria, inflammatory response is triggered. Indeed, inhibition of such a response attenuates the diarrhea.\textsuperscript{27}

**Immune System Mediation**

Diarrhea is a key manifestation of intestinal inflammation. A bewildering array of soluble mediators alter enterocyte ion and water transport.\textsuperscript{28} There seem to be many checks and balances regulating enterocyte function within the complex interactions of immune mediators with nervous and endocrine systems, as may be expected to allow cohabitation with such diverse a flora as is found in the gut. As a general rule, with some exceptions, individual soluble mediators are proinflammatory and secretory, whereas endocrine mediators, such as somatostatin and cortisol are antiinflammatory and enhance absorptive processes.

Bacterial infections that involve direct invasion of the epithelium can provoke a reaction in several ways. After acute infection, luminal antigens, bacterial cell wall components—especially lipoprotein polysaccharides, and bacterial F-Met oligopeptides can activate lamina propria phagocytic cells and recruit neutrophils and mucosal mast cells to secrete proteases; cytokines, including interleukin 1 (IL-1), IL-6; and systemic tumor necrosis factor \( \alpha \) and eicosanoids that can then lead to increased net secretion directly, as well as through increased motility and release of neurotransmitters.

Recently, cytokines such as IL-8 have been shown to be released by enterocytes in cell culture.\textsuperscript{29} These would then initiate a response by chemotaxis of neutrophils. Indeed, the role of the enterocyte as an unconventional antigen-presenting cell may be pivotal in such infections.

Multiple mechanisms may be important with the same pathogen. Rotavirus-induced damage leads to malabsorption, as well as secretion mentioned above; carbohydrate fermentation leads to increased fatty acid delivery to the colon. Short-chained fatty acids are the preferred fuel for the colonocyte and are titrated by and, indeed, probably exchanged for HCO\textsubscript{3}\. leading to acidosis. Cholera is a classic example of toxin-mediated secretory diarrhea resulting from increased
chloride and water loss from crypt cells and reduced water and electrolyte absorption by villus cells in the small intestine. It is now apparent that it has several other actions, including reducing colonic absorption and thus diminishing colonic salvage.

Management of Acute Diarrhea

The history and clinical examination often need to be focused initially on assessment of clinical dehydration, based on World Health Organization or American Academy of Pediatrics guidelines (Table 4). An important addition to these is the use of capillary refill time (2 to 3 seconds approximates a 50 to 90 ml/kg deficit; greater than 3 seconds, a 100 ml/kg or more deficit) and, where possible, a core peripheral temperature gap, a more accurate indicator of perfusion. Hypernatremic dehydration tends to result in better turgor for degree of deficit with thickened doughy skin; parched, shriveled tongue; and hyperirritability. Blood pressure and sensorium are better maintained than in hyponatremic dehydration. Abdominal distention and ileus suggest hypokalemia, whereas tachypnea and air hunger are seen with acidosis.

At the initial assessment differentiation of type of diarrhea may be made (e.g., presence of mucus, gross blood, and pus cells on smear in small frequent stools suggests a colitic process; large volume stools are characteristically seen with small intestinal pathologic conditions). Frothy, acid stools suggest associated

| Signs and symptoms | Mild dehydration | Moderate dehydration | Severe dehydration |
|--------------------|------------------|----------------------|-------------------|
| General appearance | Thirsty, alert,  | Thirsty; restless or| Drowsy; limp, cold, |
| and condition:     | restless          | lethargic but        | sweaty, cyanotic   |
| infants and young  |                  | irritable to touch  | extremities; may   |
| children           |                  | or drowsy           | be comatose        |
| Older children and | Thirsty, alert,  | Thirsty, alert,     | Usually conscious; |
| adults             | restless          | postural hypotension| apprehensive;      |
|                    |                  |                     | cold, sweaty,      |
| Radial pulse       | Normal rate and  | Rapid and weak      | cyanotic extremities; |
|                    | strength         |                     | wrinkled skin of   |
| Respiration        | Normal           | Deep, maybe rapid   | fingers and toes;  |
| Anterior fontanel  | Normal           | Sunken               | muscle cramps      |
| Systolic blood     | Normal           | Normal or low        | Rapid, febrile,    |
| pressure           |                  |                     | sometimes          |
| Skin elasticity    | Pinch retracts   | Pinch retracts slowly| Deep and rapid     |
|                    | immediately      |                     | Very sunken        |
| Eyes               | Normal           | Sunken (detectable) | <30 mm Hg; may     |
| Tears              | Present          | Absent               | be unrecordable    |
| Mucous membranes   | Moist            | Dry                  | Pinch retracts very|
| Urine flow         | Normal           | Reduced amount and   | slowly (>2 sec)    |
| % Body weight loss | 4-5              | dark                 | Grossly sunken     |
| Estimated fluid    | 40-50            | 6-9                  | Absent             |
| deficit (ml/kg)    |                  | 60-90                | Very dry           |
|                    |                  |                      | None passed for    |
|                    |                  |                      | several hours;     |
|                    |                  |                      | empty bladder      |
|                    |                  |                      | 10 or more         |
|                    |                  |                      | 100-110            |
New Developments

carbohydrate malabsorption, whereas watery stools should be further analyzed for secretory electrolyte and osmolality profile (Table 3). Continuation of diarrhea largely unabated despite adequate bowel rest is a hallmark of secretory diarrhea.

Indications for hospitalization need to be individualized. Most mild to moderately dehydrated infants and children with intact thirst can be successfully treated as outpatients, even with vomiting, with close attention to detail. Social and family circumstances should be evaluated as they relate to outcome. Clinical or laboratory evidence for electrolyte imbalance, altered mental status, anorexia, intractable vomiting, as well as the severely dehydrated or toxic-looking patients should signal hospital admission. Children with large stool outputs, especially if greater than 10 ml/kg/hr, likely will need intravenous fluids. The threshold for admission should be lower for young infants.

**Osmotic and Malabsorptive Diarrheal Therapy**

Pharmacotherapy with antidiarrheals (Table 5) targeted toward slowing motility, antisecretory effects, or antimicrobials, for example, are not recommended be-

| Drug category          | Examples                      | Mechanism of action                                         | Some side effects                     |
|------------------------|-------------------------------|-------------------------------------------------------------|---------------------------------------|
| Adsorbents             | Kaolin-pectin                 | Absorption of gut fluid, firming of stool consistency        | May increase fecal electrolyte losses |
|                        | Cholestyramine                | Binding of bile salts and toxins                             |                                       |
|                        | GM1, ganglioside              | Binds bacterial toxins, inhibits gut motility                |                                       |
|                        | Attapulgite                   |                                                             |                                       |
| Anticholinergics       |                               |                                                             |                                       |
| Opiates                | Morphine, codeine, diphenoxylate| Altered gut motility, increased electrolyte absorption | Urinary retention, headache, blurred vision |
| Antiinflammatory agents| Aspirin, bismuth subsalicylate| Inhibition of prostaglandin synthesis                       | Hypotension, respiratory depression, ileus, addiction, drug abuse |
| Calcium/calcmodulin regulators | Chlorpromazine, verapamil, nifedipine, aluminum, bismuth | Intracellular binding of calcium, blockage of calcium into cells, occupation of binding sites | Gastrointestinal discomfort, peptic ulceration, gastrointestinal hemorrhage |
| Neurotransmitters      | Adrenergic agents; clonidine, Lindamine, dopamin, bromocriptine, somatostatin | Stimulation of sodium and chlorine absorption | Cardiovascular effects such as arrhythmias, heart block, and postural hypotension |

TABLE 5. Antidiarrheal drugs
cause of proven and theoretical risks.\textsuperscript{31} We are against opiates, including loperamide and diphenoxylate, calcium/calmodulin regulators, such as chlorpromazine and verapamil, and neurotransmitter modulators such as clonidine. Occasionally in older children adsorbents, such as kaolin-pectin and cholestyramine, and antiinflammatory agents, such as bismuth subsalicylate, can be used primarily for social reasons. In special situations, such as in immunodeficiency, including infants less than 2 months of age, antimicrobials may be indicated. The mainstay, however, is good hydration with prompt readministration of nutrients.

**Secretory Diarrhea**

Cholera, ETEC, and Shigella are the likely pathogens in secretory diarrhea. Mucosal structure and absorptive capacity is intact. The diarrhea is usually milder in the latter two and does not need specific therapy. Cholera can result in enormous fluid losses, hypokalemia, shock, and rapid death. Hypoglycemia and convulsions can occur in children. Close attention to detail in rehydration and maintenance fluids can lead to successful oral therapy. Tetracycline or cotrimoxazole in children less than 9 years old shortens the duration of diarrhea. Oral furazolidone is sometimes preferred because it is not absorbed but clears the organism more slowly. Sensitivities should be confirmed as resistance is emerging. Severe purging may respond to chlorpromazine, although care is needed in view of sedation and hypotension that may result. Table 6 lists some of the modalities and putative agents for secretory diarrhea.

**Prevention of Dehydration**

If hydration and electrolyte balance can be maintained, the disease is self-limiting. It is important, therefore, for intervention to be instituted at the onset. This entails anticipatory guidance and education and maintenance of a supply of oral rehydration solution (ORS), keeping in mind that the most vulnerable pe-

| TABLE 6. Antisecretory agents* |
|--------------------------------|
| **Increased absorption** | **Decreased secretion** |
| Nutrients | Phenothiazines |
| Glucose, glucose polymers | Chlorpromazine |
| Amino acids | Trifluoperazine |
| α-Adrenergic agonists | Opiates |
| Epinephrine | Codeine |
| Clonidine | Diphenoxylate |
| Antiinflammatory agents | Loperamide |
| Glucocorticoids | Alkaloids |
| Indomethacin | Berberine |
| Aspirin | Others |
| Hormones | Propranolol |
| Somatostatin | Nicotinic acid |
| Aldosterone | Verapamil |
| Enkephalins | Heavy metals |
| Aluminum | Lanthanum |

*Used by permission from Rubino A. Secretory diarrhea in infants and children. In: Lebenthal E (ed). Textbook of gastroenterology and nutrition in infancy, 2nd ed. New York, Raven Press, 1989:1159-70.
period is early infancy. In the first instance, replacement of all high-carbohydrate drinks with a commercial ORS, administration of an extra 3 to 4 ounces of a commercial ORS or water per stool, and an ounce per emesis may suffice. Withholding formula milk for no more than 24 hours may help maintain hydration. Solids should be continued in small but frequent amounts, avoiding high-sugar or high-fat foods. Bananas, cereals, rice, and potato noodles are good examples. Homemade ORSs and commercial drinks also should be avoided because sodium and sugar concentrations, as summarized in Table 7, are so critical.

**Treatment of Dehydration**

Although shown to be very successful, the aggressive enteral rehydration as recommended by the World Health Organization and recently reiterated by the Centers for Disease Control and Prevention\(^{32}\) is not generally practiced in the United States.\(^{33}\) Rehydration using ORS for up to 4 or 6 hours with volumes up to 100 ml/kg can be achieved in most patients, even when vomiting is present. Nasogastric tubes may be needed, especially when constant bedside attention and small, frequent oral feeding is not feasible. The limitations of available ORS solutions are that they do not change the frequency, volume, and duration of diarrhea or the severity of vomiting. They are not palatable, have a low caloric density (Table 7), and are not accepted in full by mothers and physicians alike. Intravenous hydration is necessary for shock, diminished level of consciousness, intractable vomiting, or massive stool outputs greater than 10 ml/kg/hr. Breast milk should be continued, and solids restarted after rehydration is achieved as outlined above. The regular formula milk, even if lactose based, may be reinstalled within 24 hours. Only in the few cases where purging rates increase significantly in the presence of significant reducing substances in the stool should lactose-free formulas be considered. In severe cases, usually in young infants with rotavirus, a severe mucosal injury may be suspected and may need further measures such as sucrose-free formula, hydrolyzed formula, or even parenteral fluid and nutrition.

Isotonic, hypotonic, and hypertonic dehydration and acidosis can all be successfully managed with ORS. Greater care must be taken with intravenous hydration, particularly in hypertonic (hypernatremic) states. Reduction of sodium concentration should not exceed 10 mmol/L/day for fear of cerebral edema.

**TABLE 7. Comparison between commonly used solutions for rehydration and standard oral rehydrating solutions**

| Liquid       | Na (mmol/L) | K (mEq/L) | HCO₃/urate (mEq/L) | % Glucose and other sugars | Osmolality (mOsm/L) | Calories (100 ml) |
|--------------|-------------|-----------|--------------------|---------------------------|---------------------|-------------------|
| Cola         | 2           | 0.1       | 13                 | 5-15                      | 550                 | 550               |
| Ginger ale   | 3           | 1         | 4                  | 5-15                      | 540                 | 540               |
| Apple juice  | 3           | 20        | 0                  | 10-15                     | 700                 | 700               |
| Gatorade     | 20          | 3         | 3                  | 4.5                       | 330                 | 330               |
| Tea          | 0           | 0         | 0                  | 0                         | 5                   | 5                 |
| Chicken broth| 250         | 5         | 0                  | 0                         | 450                 | 450               |
| WHO ORS      | 90          | 20        | 30                 | 2.0                       | 330                 | 8                 |
| Pedialyte    | 45          | 20        | 30                 | 2.5                       | 260                 | 10                |
| Rehydralyte  | 75          | 20        | 30                 | 2.5                       | 305                 | 10                |
| Riceleyte    | 50          | 25        | 34                 | 3.0 (polymers)            | 210                 | 12                |
| Amylyte*     | 70          | 20        | 7.5 (polymers)     | 34                        | 315                 | 42.5              |

*Rice-based clear ORS undergoing trials*
Super ORS
A limiting factor for glucose in ORS is the osmolality (must not exceed 330 mOsm). Amino acids and oligopeptides can increase water absorption by sodium-coupled transport. Digestion and absorption is largely intact in acute diarrhea. Thus several improvements to the standard ORS can be envisioned. Although amino acid-containing solutions, especially alanine, show some promise, cereal-based solutions offer several of these advantages. Caloric intake can be increased without increasing the osmolality of the solution by using starches instead of glucose or sucrose. The duration and severity of diarrhea are also improved in high output diarrhea, presumably because sodium-coupled transport with amino acids and oligopeptides, for example, add to the water absorption. The use of cereal-based solutions is within the repertoire of most traditions and may only need guidance in terms of electrolytes and osmolality. Commercial, cereal-based solutions may soon be marketed. Hydrolyzed cereal-based solutions may offer even more calories while maintaining a clear liquid state and offer the possibility of maintaining a respectable caloric intake even during the rehydration phase. Multicenter trials of such solutions based in our institute are already in progress.

Specific Nutrients
Vitamin A deficiency concomitant with diarrhea is associated with poor immunity, poor mucosal healing, and increased morbidity and mortality from infections in general. The problem is not restricted to the developing countries and should be corrected. Zinc, important for cell replication and maturation, may be deficient in acute diarrhea, and supplementation may shorten duration of diarrhea. Glutamine is the preferred fuel for small bowel enterocytes. Trials of ORS with high glutamine content are under way to assess whether mucosal healing is augmented. All three of these nutrients may be important adjuncts to a “super ORS.” Finally, short-chain fatty acids are the preferred fuel of colonocytes and have potential use in augmenting colonic mucosal healing after an infective colitis.

Vaccines
Currently, there are studies looking at vaccines against the major pathogens causing diarrhea. However, practically none are currently available for regular use. Complex factors determine virulence and pathogenicity. Often, the role of the immune response in the pathophysiology is uncertain. Creating vaccines then remains a difficult task. The primary agent to vaccinate against is rotavirus because improved hygiene does not reduce attack rates. Several candidate vaccines have been tried with varying degrees of success that have not been confirmed in the field in developing countries. Thus bovine, rhesus, and reassortants of rhesus rotavirus expressing serotype 1 or 2 show high protection rates from severe disease. Candidate vaccines with human type outer capsid protein of types 1, 2, 3, and 4 may be more effective. Side effects, predominantly fever, need to be contained. A useful form of rotavirus vaccine should be available in a few years. Other vaccines, such as against Shigella, are likely to take longer. Other strategies include the use of antifimbrial antibodies to prevent adhesion of E. coli, the first step in pathogenesis, and fusion proteins containing the B subunit of the heat-labile enterotoxin to elicit a blocking antibody.

Acute diarrhea is a significant cause of morbidity in the United States and morbidity together with mortality in developing countries. The practical approach is to rehydrate the child as soon as possible because of the rapidity, severity,
and complexity of the fluid and electrolyte loss in early life. The practicing physician should encourage the use of ORS despite the limitations in palatability, acceptability, and the fact that the duration, frequency, and volume of diarrhea are not altered with ORS. Furthermore, if the dehydration is not corrected and there is suspicion of sepsis, parenteral fluids will be needed as soon as possible.

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