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I, 5. Treatment of viral gastroenteritis

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Introduction

Every child in the world is infected with gastroenteritis viruses during their first years of life. In the developed world, the result is substantial morbidity (Glass et al., 1996) and expense while in developing countries hundreds of thousands of children die (Medicine, 1986). A good deal of the difference in outcomes is due to differences in the availability of treatment. Viral gastroenteritis (mainly after rotavirus infection) directly causes death through dehydration. Thus, treatment and prevention of dehydration is the first goal in caring for infants with gastroenteritis. Viral gastroenteritis can also inflict considerable nutritional insult on children due to anorexia, vomiting, malabsorption, and traditional therapies in which nutritionally poor diets are offered (Jelliffe, 1987). Finally, a bout of viral gastroenteritis can serve as trigger point for an extended downward spiral of chronic diarrhea and malnutrition (Haffejee, 1990b). The optimal solution to the disease burden of viral gastroenteritis would be prevention via effective vaccines but that option remains several years away. In this section, I will discuss the treatment of the deficiencies of fluid, electrolytes and nutrients. While there are already very good cost-effective strategies for correcting the sequelae of viral gastroenteritis, there is little yet available to effectively treat the acute symptoms of vomiting and diarrhea. Several potential modes of symptomatic therapy for viral gastroenteritis are discussed below including probiotics, antivirals, passive immunotherapy, and antidiarrheals.

Traditional therapy of diarrheal disease has often been based on the empiric observation that withholding feeds and fluids results in less stooling (Jelliffe, 1987). Obviously this may lead to disastrous consequences in severe gastroenteritis with dehydration. The first major advance in treatment of dehydration was the development of effective intravenous rehydration therapy in the 1950’s. Intravenous therapy requires sophisticated and relatively expensive equipment and expertise; thus, effective rehydration therapy remained unavailable to most of the world’s children. Initial attempts at producing solutions for oral rehydration therapy (ORT) contained excess glucose and led to frequent osmotic diarrhea and hypernatremic dehydration (Paneth, 1980). The legacy of these early solutions lives on as concern about hypernatremia with ORT, even with
its improved formulations. The development of effective ORT in the late 1960’s was an offshoot of increasing knowledge of intestinal absorptive physiology — essentially the idea of glucose coupled sodium transport as a fundamental mechanism of sodium and water absorption (Hirschhorn, 1968). Further advances in rehydration include the realization that rapid rehydration and prompt refeeding improve outcomes.

**Rehydration**

Although much debate and speculation continue about the relative contribution of various pathophysiologic mechanisms in viral gastroenteritis, the net result of moderate to severe disease is a deficit of body water and sodium known as dehydration. The relative deficits of sodium and water determine whether the child has hypo-, normo-, or hypernatremic dehydration. The first step in treatment is assessing the degree of dehydration. Table 1 lists some of the signs and symptoms used in the assessment of mild, moderate, and severe dehydration. Unlike adults, children tend to maintain blood pressure until very advanced states of hypovolemia are reached. If the child is in or nearly in shock or is otherwise obtunded, rehydration commences with rapid intravenous administration of 20-40 ml/kg of isotonic fluid such as normal saline or lactated Ringers solution (130 mEq/L Na⁺, 4 mEq/L K⁺, 109 mEq/L Cl⁻, 28 mEq/L HCO₃⁻). The great majority of infants are not in shock and may commence ORT.

| Signs and Symptoms         | Mild Dehydration | Moderate Dehydration | Severe Dehydration |
|----------------------------|------------------|----------------------|--------------------|
| Body weight loss (%)       | 3-5%             | 6-9%                 | 10% or greater     |
| Appearance                 | Alert, thirsty   | Irritable, lethargic, thirsty | Limp, lethargic |
| Pulse                      | Normal           | Rapid, weak          | Rapid, feeble      |
| Blood pressure             | Normal           | Normal               | Decreased to undetectable |
| Capillary refill           | Normal           | +/-2 Seconds         | >3 Seconds         |
| Respiration                | Normal           | Deep, +/-rapid       | Deep and rapid     |
| Skin turgor                | Normal           | Decreased            | Poor               |
| Mucous membranes           | Moist            | Dry                  | Very dry           |
| Fontanel/eyes               | Normal           | Sunken               | Very sunken        |
| Urine output               | Normal           | Decreased            | Absent             |
Various ORT formulations have been studied and are in use (Table 2). Modern ORT solutions generally contain 45-90 mEq of sodium per liter and approximately equimolar carbohydrate as glucose or glucose polymer. The World Health Organization recommends ORT with a glucose to sodium molar ratio of no greater than 1.4. Glucose polymers have the advantage of lowering the solution osmolarity although a meta-analysis of treatment of non cholera (mostly rotavirus) diarrhea suggested only a slight advantage for rice-based polymer solutions (Gore et al., 1992). Some ORT solutions utilize traditional complex carbohydrate sources such as those found in rice water to produce a low osmolarity solution which may be more culturally acceptable. Most solutions contain approximately 20 mEq of potassium to make up for enteral losses in form of acetate, bicarbonate or citrate. At least one authority suggests the base content is not critical for successful rehydration (Walker-Smith, 1992). Solutions not designed as ORT such as sports drinks, soft drinks, and broths are inappropriate and dangerous due to either excessive carbohydrates or salt. The compositions of some appropriate and inappropriate solutions are shown in Table 2. Additional substances such as amino acids have been added to ORT in attempts to capitalized on other intestinal co-transporter systems, but these have not proven clinically superior to glucose based ORT (Bhan, 1994).

| Solution/drink | Glucose (mEq/L) | Sodium (mEq/L) | Glucose/Sodium ratio | Potassium (mEq/L) | Base (mEq/L) | Osmolarity (mMol/L) | Appropriate for ORT |
|----------------|-----------------|----------------|----------------------|-------------------|--------------|---------------------|-------------------|
| WHO ORT        | 111             | 90             | 1.2                  | 20                | 30           | 310                 | YES               |
| Pedialyte      | 140             | 45             | 3.1                  | 20                | 30           | 250                 | YES               |
| Rehydrolyte    | 140             | 75             | 1.9                  | 20                | 30           | 310                 | YES               |
| Infalyte       | 70              | 45             | 1.4                  | 25                | 30           | 200                 | YES               |
| Gatorade       | 255             | 20             | 13                   | 3                 | 3            | 330                 | NO                |
| Apple juice    | 690             | 3              | 230                  | 32                | 0            | 730                 | NO                |
| Cola           | 700             | 2              | 350                  | 0                 | 13           | 750                 | NO                |
| Chicken broth  | 0               | 250            | 8                    | 0                 | 500          | NO                  |                   |

ORT can be administered by bottle, cup, spoon, or nasogastric tube. Vomiting can be minimized by administering ORT slowly. The goal is to achieve rehydration within the first four hours of therapy. The fluid deficit is calculated as 10ccORT/kg body
weight for each one percent of estimated dehydration or body weight loss (Table 1). One simple but practical recommendation is to administer one teaspoon (5 ml) of ORT each minute. For a typical 10 kg infant this would provide 120cc/kg over the first 4 hours of therapy. Properly administered ORT has been shown repeatedly to be effective in hypo-and hypernatremic dehydration with lower incidence of seizures observed than with intravenous therapy (Pizarro, 1983; Pizarro, 1984). After rehydration has been achieved, regular feedings are resumed with ORT offered after each stool to compensate for ongoing fluid and salt losses until the diarrhea episode resolves.

In both developing and developed worlds, slow refeeding is an established tradition. This practice was derived from the observation that stooling is increased immediately after a feeding. Recently, a number of studies in developing and developed countries have shown that the duration and nutritional impact of acute gastroenteritis is reduced by offering a reasonable age appropriate diet as soon as rehydration is complete (Hjelt et al., 1989; Quak et al., 1989). Breastfed infants are nursed throughout the rehydration period. To the surprise of older clinicians, a number of studies have shown that most infants with gastroenteritis tolerate lactose-containing diets quite well although the occasional infant may develop severe osmotic diarrhea due to acquired lactase deficiency (Armitstead et al., 1989; Haffejee, 1990b; Szajewska et al., 1997).

There has been considerable interest in whether specific nutritional interventions could accelerate recovery from diarrheal illness. Recent studies in Bangladesh have shown that cooked green banana or pectin added to a normal diet can hasten resolution of chronic diarrhea (Rabbani, 2001). Micronutrients have also been examined as possible therapies for acute diarrhea. Vitamin A when given prophylactically in areas of the world where children are at risk for deficiency, seems to decrease childhood mortality/morbidity from diarrhea and respiratory illness (Rahman, 2001). Results of vitamin A therapy during acute diarrhea have been less impressive (Dewan, 1995; Yurdakok, 2000; Khatun, 2001). Zinc supplements have been shown to hasten the resolution of acute watery diarrhea in the developing world (Bhutta, 2000). Whether such supplements would be effective in developed nations where deficiencies are much less common is not known.

Probiotics are live cultures of nonpathogenic bacteria which are administered as therapy or prophylaxis. As a rule, the strains do not stably colonize the gut, thus continuous dosing is required. Some strains are not easily recovered in stools. A variety of strains of bacteria and some yeast have been used to treat or prevent diarrhea. Many strains are lactobacilli such as are found in yogurts, others (bifidobacteria) are derived from the flora of breast fed infants, and Saccharomyces bouladi is a non-pathogenic yeast. Excellent safety profiles have been observed. The mechanisms by which these probiotics protect the gut remain unclear. Hypotheses include; change in luminal pH due to local fermentation, competition with pathogens for mucosal receptors, and stimulation of the local immune system by activating enterocytes to secrete specific cytokines (Marteau, 2001). There is evidence that probiotic therapy does enhance the IgA response to rotavirus (Majamaa et al., 1995). Lactobacillus GG has been shown to reduce the duration of rotavirus excretion. Probiotics have been studied extensively in rotavirus gastroenteritis with Lactobacillus spp. most widely used. In one large
(300 subjects), double-blinded, European, multicenter study, *Lactobacillus* GG or placebo were administered in ORT to children with acute diarrhea (Guandalini *et al.*, 2000). Most of the patients had relatively mild symptoms. Rotavirus-infected children who were treated experienced about 20 hours less diarrhea than those who received placebo. Ten percent of placebo-treated infants had symptoms longer than one week compared to 2 percent of the *Lactobacillus*-treated infants. A recent meta-analysis of *Lactobacillus* as therapy for childhood diarrhea concluded that it is an effective treatment but the clinical significance of reducing duration of stooling by less than one day remains questionable (Van Niel *et al.*, 2002). Perhaps new, well powered trials with early intervention might examine more relevant endpoints such as determining whether probiotic therapy can prevent hospitalization or the need for intravenous rehydration. Most studies of probiotics for acute infantile diarrhea have taken place in developed countries. There is a need to extend these studies to the developing world where the need is most acute and the baseline intestinal microflora is quite different.

Antiviral drug therapy for viral gastroenteritis has been explored mainly in the laboratory. A number of compounds have been shown to be inhibitory to rotavirus replication *in vitro*, including ribavirin, isoflavines, and other adenosine analogues (Smee, 1982; De *et al.*, 1984; Kitaoka *et al.*, 1986). They probably owe their anti-rotavirus activity to inhibition of S-adenosylhomocysteine hydrolase, a key enzyme in regulating methylations including those that are required for the maturation of viral mRNA. Results using these drugs in animal experiments have been largely unimpressive (Schoub, 1977; Smee, 1982; Kitaoka *et al.*, 1986). A number of herbal and tea extracts have also been reported to inhibit rotavirus *in vitro* (Husson *et al.*, 1991; Clark *et al.*, 1998; Kudi and Myint, 1999). An essential question for antiviral therapy in gastroenteritis is whether much clinical benefit can be expected if rotavirus has already done most of its damage prior to the onset of symptoms in a disease with a natural duration of only a few days.

Several other approaches to inhibiting rotavirus infection have been examined. Protease inhibitors administered enterally can prevent the trypsin-mediated cleavage of VP4 which is essential for rotavirus replication and increases its infectivity (Vonderfecht *et al.*, 1988). Unfortunately, severe inhibition of gut luminal proteases leads to severe protein maldigestion, and thus this is not a practical therapy. Another approach has been the administration of glycoproteins or lipids which may function as pseudo-receptors or receptor competitors for the virus. Such entities have been identified in human breast milk and intestinal mucins (Yolken *et al.*, 1992; Yolken *et al.*, 1994; Kiefel *et al.*, 1996; Reading *et al.*, 1998). None of these approaches have been reported in clinical trials.

Passive immunotherapy has been examined for both prevention and treatment of viral gastroenteritis. Antibodies of human, bovine or egg yolk derivation have been administered enterally to infants with rotavirus diarrhea. Many of these studies have shown some decrease in stooling in treated infants. Human serum immunoglobulin containing rotavirus-specific antibodies administered orally to immunocompromised children with chronic rotavirus infection was able to associate with rotavirus in the gut, resulting in the formation of large immune complexes rather than free virus. Antigen
shedding was significantly reduced after antibody therapy, although the virus was not eliminated in all cases (Losonsky et al., 1985). Enteric administration of antibody has shown some efficacy in normal children. A single dose of human immunoglobulin preparation that had a high neutralization titer against rotavirus (800-3,200) significantly accelerated the rate of virus clearance and recovery from diarrhea in children infected with rotavirus (Guarino et al., 1994). However, another similar study showed no significant effect of orally administered immunoglobulin (Ventura et al., 1993). Bovine immunoglobulin against rotavirus has been produced by hyperimmunizing cattle with human rotaviruses (Brüssow et al., 1987). Either the milk of hyperimmunized cattle or serum immunoglobulins resuspended in milk formula significantly reduced the incidence of rotavirus illness in 3 to 7 months old children when orally administered. Results of treatment of active disease with bovine antibodies has also produced conflicting results. In some studies no effect was observed (Hilpert et al., 1987) while in others diarrhea was reduced (Sarker et al., 1998).

An alternative means of producing anti-rotavirus immunoglobulins is to harvest specific immunoglobulins from the yolks of eggs laid by chickens that had been immunized with rotavirus. Egg yolks contain large quantities of specific immunoglobulin following intramuscular immunization of hens, and the antibody remains stable for long periods of time. Oral dosing of mice and calves with these immunoglobulins significantly reduces overall disease (Ebina et al., 1990; Kuroki et al., 1994; Kuroki et al., 1997). In mice, this protection was directly associated with reduced rotavirus antigen distribution within the intestinal tract, suggesting that replication of the virus has been inhibited. Recent human trials in Bangladesh suggested that such egg yolk preparations may have potential therapeutic value in human infants as well (Sarker, 2001).

Cytokines and hormones play an important role in host defense and self regulation and have been examined as potential therapeutic agents for viral gastroenteritis. Interferons are cytokines which were discovered and named for their antiviral properties. Rotavirus and astrovirus are sensitive in vivo to the effects of class I and class II interferons (IFN) as well as Interleukin 1 (Bass, 1997). However in mice, treatment with IFN had no effect on rotavirus replication or disease (Angel et al., 1999). Knockout mice lacking receptors for class I IFN and IFN gamma negative mice cleared virus as easily as their normal counterparts. These results hint at mucosal host defense systems with multiple levels of redundancy. In calves IFN has been reported as efficacious in suppressing rotavirus disease (Schwers et al., 1985). Cytokines and hormones which affect intestinal epithelial integrity such as epithelial growth factor, TGF 1, hydrocortisone, and thyroid hormone have been tested experimentally as therapeutic aids for viral enteritis. Despite improvement in functional assays of the infected epithelium, epidermal growth factor and TGF failed to decrease diarrhea or increase weight gain in infected swine (Zijlstra, 1994; Rhoads et al., 1988). Corticosteroids lead to early maturation of the suckling mouse gut and prevented symptomatic murine rotavirus (EDIM) infection (Wolf et al., 1981). Corticosteroid treatment of suckling pigs infected with transmissible gastroenteritis virus lead to improved villous structure and improved sodium transport in intestinal mucosa (Rhoads et al., 1988). In vivo experiments have suggested that prostaglandins may exert an antiviral effect on rotaviruses (Superti et al., 1998).
Therapies aimed against symptoms of viral gastroenteritis have not been very useful in young children who typically have the most severe disease. Some compounds such as kaolin, smectite, and psyllium fiber change the consistency of stools by binding the free water but do not really alter the net fluid loss. Antiemetics are ineffective in gastroenteritis in young children and cause frequent dystonic reactions in dehydrated infants. Bismuth subsalicylate has some effect on clinical symptoms, probably due to antisecretory effects (Soriano et al., 1991), but has not been recommended routinely largely because of concerns about potential metabolic toxicity, such as concern for triggering Reye's syndrome. Cholestyramine, an anion exchange resin which binds bile salts, appeared to decrease clinical symptoms in a small study (Vesikari and Isolauri, 1985). Currently available antidiarrheal medications have been disappointing in efficacy for viral enteritis in young children. Most of the antidiarrheals are based on narcotics or narcotic analogues which act mainly by altering intestinal motility. Narcotics such as tincture of opium are inappropriate for young children with acute gastroenteritis. Loperamide is a synthetic opioid which is relatively free of central effects and has virtually no abuse potential. Loperamide has been found ineffective for the treatment of early childhood diarrhea in several studies (Owens et al., 1981; Kassaem et al., 1983; Vesikari and Isolauri, 1985) and has been known to cause life threatening ileus and central nervous system intoxication in children with gastroenteritis (Bhutta and Tahir, 1990; Minton and Henry, 1990; Schwartz and Rodríguez, 1991).

Racecadotril is a new class of antidiarrheal medication which inhibits the degradation of endogenous opioid-like enkephalins. Animal studies showed that racecadotril had much less tendency to cause small intestinal bacterial overgrowth and far less CNS toxicity than loperamide (Duval-Iflah, 1999). In preliminary studies in children and adults it is remarkably well tolerated with no CNS effects, no increase in vomiting, and only one pediatric ileus reported to date. Racecadotril has been reported to decrease stool output in young children with rotavirus diarrhea by approximately 50% and duration of diarrhea from 72 hours to 23 hours (Salazar-Lindo et al., 2000; Cezard, 2001). Thus far, racecadotril appears to be a very promising adjunctive therapy to ORT in viral gastroenteritis (See also Lundgren and Svensson, Section I, Chapter 3 of this book).

In summary, current recommended therapy for viral gastroenteritis in children is limited to rehydration and nutritional support. Current and potential therapies are summarized in Table 3. It is hoped that safe, effective and affordable treatments will be developed in coming years.
Table 3
Therapies for Viral Gastroenteritis

| Treatment                  | Efficacy     | Safety     | cost          |
|----------------------------|--------------|------------|---------------|
| ORT                        | Excellent    | Excellent  | Low           |
| Early Feeding              | Good         | Good       | Low           |
| Probiotics                 | Fair-good    | Good       | Moderate      |
| Zinc                       | Fair (developing world) | Good       | Low           |
| Immunoglobulin             | Fair         | Good       | High          |
| Antiviral                  | Poor         | Unknown    | High          |
| Antiemetics                | Poor         | Poor       | Moderate-high |
| Antidiarrheal-opiate       | Poor         | Poor       | High          |
| agonists (loperamide, diphenoxylate) |             |            |               |
| Cytokines/hormones         | Not known    | ??????     | High          |
| Racecadotril               | Possibly good| Possibly good | Not yet available |

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