Abstract:
Acute gastroenteritis remains a major cause of morbidity and mortality in children around the world, especially in children younger than 5 years. The severity of the disease varies widely depending on the volume of fluid loss the child experiences through vomiting and diarrhea. Preventing the development of dehydration and rehydration therapy are the mainstay of emergency department treatment. A variety of therapies have been proposed to achieve these aims in children with acute gastroenteritis by alleviating vomiting and diarrhea. This review will describe the most recent developments in the literature related to acute gastroenteritis. Special emphasis will be placed on the emerging evidence for innovative therapeutic interventions.

Keywords:
gastroenteritis; vomiting; diarrhea; dehydration; oral rehydration; antiemetics; ondansetron; probiotics; zinc; subcutanous rehydration

*Pediatric Emergency Medicine, Department of Pediatrics, Dana Children's Hospital, Tel-Aviv University, Israel; †Divisions of Paediatric Emergency Medicine and Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, The University of Toronto, Canada.
Reprint requests and correspondence: Ayelet Rimon, MD, Pediatric Emergency Medicine, Department of Pediatrics, Dana Children's Hospital, Tel-Aviv University, Israel 64239.
ayeletr@tasmc.health.gov.il

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Recent Advances in the Treatment of Acute Gastroenteritis

Ayelet Rimon, MD*,
Stephen B. Freedman, MDCM, MSc†

The American Association of Pediatrics; the European Society for Pediatric Gastroenterology, Hepatology and Nutrition; and the World Health Organization all recommend oral rehydration solution (ORS) as the treatment of choice for children with mild to moderate gastroenteritis in both developed and developing countries. This recommendation is based on the results of dozens of randomized controlled trials (RCTs) and several large meta-analyses. One such analysis, which included 16 trials and 1545 children with mild to moderate dehydration, found that compared with intravenous rehydration, children treated with ORS had a significant reduction in length of hospital stay and fewer adverse events, including seizures and death.[1] Nonetheless, therapies that decrease the volume of diarrhea and increase the success of oral rehydration therapy are constantly being sought. The ultimate goal of these interventions is to reduce fluid loss and improve oral intake.

PHARMACOLOGIC THERAPIES

Antidiarrheal Agents

A range of antidiarrheal agents have been evaluated for use in children with acute gastroenteritis. *Adsorbent agents* such as clay minerals (kaolin or smectite) and charcoal have been used. Kaolin has only been evaluated in a single quasi-RCT study that showed no differences in the duration of acute diarrhea or in the number of stools per day between children receiving kaolin in addition to rehydration therapy and those receiving rehydration therapy

alone.[2] Smectite has been much more extensively evaluated, and a systematic review that included 9 RCTs and 1238 participants found that its administration to children resulted in a reduction in the frequency of diarrhea (2 studies included).[3] However, this benefit only appeared 48 hours after the initiation of therapy, with the duration of therapy ranging from 3 to 5 days. Children in the intervention group were also more likely to experience a more rapid resolution (6 studies) of diarrhea (–23 hours; 95% confidence interval [CI], –25 to –21). The review found no statistically significant differences between the smectite and control groups in the number of episodes or duration of vomiting. The studies did not report any significant increase in adverse effects. Nonetheless, its routine use is not recommended because the majority of the studies performed to date had significant methodological limitations.[4]

One RCT of children with acute gastroenteritis and severe dehydration compared treatment with activated charcoal in addition to rehydration (oral and intravenous) with rehydration therapy alone.[5] The study found that the group receiving the activated charcoal had a shorter mean duration of diarrhea (mean, 2.1 days) than the control group (mean, 3.0 days) (95% CI, –1.5 to –0.3 days). The study did not demonstrate a difference in the amount of intravenous rehydration therapy required between the groups; and it suffered from a poor description of the method of randomization, allocation concealment, and follow-up.

Bismuth subsalicylate (BSS) has a number of properties that may be important in reducing diarrhea, including inhibition of intestinal fluid secretion, suppression of intestinal inflammation, and a bactericidal action. Evidence from RCTs evaluating the effectiveness of BSS in the treatment of diarrhea is inconclusive. Data from 2 small RCTs showed that children with acute diarrhea receiving BSS in addition to ORS solution had a significantly reduced duration of diarrhea, duration of hospital stay, and need for fluid therapy.[6,7] However, results from a third RCT, which had a large sample size, did not show a statistically significant reduction in the duration of diarrhea, in the incidence of persistent diarrhea, or in the total intake of ORS solution in the group of children treated with BSS compared with the placebo group.[8]

Antimotility agents such as loperamide may reduce diarrhea by increasing intestinal transit time and hence absorption. Clinical trials using loperamide have demonstrated a significant antidiarrheal effect in children with gastroenteritis. A meta-analysis reported that children receiving loperamide experienced less stool output and had a reduction of the duration of diarrhea when compared with children that did not receive the drug.[9] However, serious adverse events such as drowsiness, abdominal distension, and ileus only occurred in the children receiving loperamide. Hence, despite its beneficial effect, use is generally not recommended as part of the routine management of children with acute gastroenteritis.

Antisecretory drugs such as racecadotril, a selective enkephalinase inhibitor that works by reducing intestinal water and electrolyte secretion, have emerged as potentially promising drugs in the treatment of acute infectious diarrhea in children. A recent systematic review combined the results of RCTs that compared racecadotril with placebo or no intervention (Table 1).[10-13] The duration of treatment in the 3 eligible studies was 5 to 7 days. Data from these trials demonstrated a significant reduction in stool output in children with acute gastroenteritis treated with racecadotril. Pooled standardized mean difference for all patients was –0.67 (95% CI, –0.90 to –0.44). The duration of diarrhea was significantly reduced in all trials; but because of the reporting of different outcome measures, data

TABLE 1. Description of racecadotril studies.

Study	N	Age	Inclusion Criteria	Racecadotril Dose	Placebo
Salazar-Lindo et al[11]	135	3-35 mo	Hospitalized, 3 diarrheal stools within past 24 h, 1 diarrheal stool within 4-6 h after admission	1.5 mg/kg Q8h	Yes
Cezard et al[12]	172	3-48 mo	Hospitalized, 3 watery stools/d for at least 72 h	1.5 mg/kg Q8h	Yes
Cojocaru et al[13]	166	3-36 mo	Hospitalized and outpatients, >3 loose stools within past 12 h	Weight <9 kg: 10 mg Q8h Weight 9 kg: 20 mg Q8h	No
Santos et al[14]	189	3-36 mo	Outpatients, 3 loose stools within past 24 h	Weight <9 kg: 10 mg Q8h Weight 9-13 kg: 20 mg Q8h Weight 13 kg: 30 mg Q8h	No

could not be pooled. Achievement of a cure by day 5 was not significantly different between the racecadotril group and the control group (relative risk [RR], 1.1; 95% CI, 0.97-1.21).

A more recent prospective, randomized, open-label clinical trial compared racecadotril plus oral rehydration vs oral rehydration alone in children with acute gastroenteritis.[14] No significant differences were found in the number of bowel movements 48 hours after initiating treatment (4.1 ± 2.7 in the oral rehydration group vs 3.8 ± 2.4 in the racecadotril plus oral rehydration group), and no differences were found in the average duration of gastroenteritis (4.7 ± 2.2 days in the oral rehydration group vs 4.0 ± 2.1 days in the racecadotril plus oral rehydration group; $P = .15$). No significant increase in the frequency of adverse events has been reported with racecadotril use. Nevertheless, caution is advocated in children with carbohydrate intolerance because of the presence of saccharose as an excipient and in children younger than 2 years because of the potential for central nervous system depression. Thus, at this time, further research is needed to determine the effectiveness, safety, and costs associated with racecadotril use.

Antiemetic Agents

Many children with acute gastroenteritis experience vomiting, particularly in the early phase of the illness. In addition to causing distress to both child and caregiver, vomiting is a major factor in leading to the use of intravenous rehydration.[15] Various antiemetic agents have been used to prevent or reduce vomiting in children with acute gastroenteritis in the effort to reduce the use of intravenous fluid administration.

Phenothiazines, such as promethazine, are dopamine antagonists that act centrally by blocking the chemoreceptor trigger zone. Although promethazine use in gastroenteritis has undergone a very limited evaluation, it has not been found to be effective.[16] In addition, severe dystonic reactions and respiratory depression may occur with their use. Thus, there exists a black-box warning regarding use in children younger than 2 years.[17]

Metoclopramide has activity that closely resembles that of the phenothiazines, but it also acts directly on the gastrointestinal tract. Thus, it theoretically may be more effective than the phenothiazines for vomiting associated with gastroduodenal disease. To date, 2 studies have evaluated its effectiveness in hospitalized children with gastroenteritis. Whereas one study found that it was more effective than placebo at reducing the symptoms of nausea and vomiting,[18] the other did not.[19] Thus, there is a lack of high-quality evidence demonstrating the effectiveness of metoclopramide. Given that, as with the phenothiazines, metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms, oculogyric crises, drowsiness, cough, and tremor, its use is not justified at present.

Ondansetron is a specific 5-hydroxytryptamine-3 antagonist that blocks receptors in the gastrointestinal tract and the central nervous system. It initially was found to be effective in the treatment of vomiting in patients receiving chemotherapy and radiation therapy. Recently, 7 RCTs have evaluated its effectiveness in pediatric gastroenteritis (Table 2).[19-25] Meta-analyses of these RCTs concluded that oral ondansetron reduces vomiting during oral rehydration (RR, 0.45; 95% CI, 0.33-0.62), the need for intravenous fluids (RR, 0.41; 95% CI, 0.28-0.62), and immediate hospital admission (RR, 0.52; 95% CI, 0.27-0.95).[26] In a cost-effectiveness analysis performed by the National Institute for Health and Clinical Excellence (United Kingdom), ondansetron administration was found to be a dominant strategy that was insensitive to parameter uncertainty.[4] This was because the magnitudes of the effect sizes are so large that they are unlikely to be due to chance. In addition, the costs of hospitalization and intravenous therapy are high relative to ondansetron. It should be noted that, following ondansetron administration, there is a clinically insignificant increase in diarrheal episodes.[20,22,24,25] Two studies have evaluated the use of multiple doses of ondansetron. In 2002, Ramsook et al[20] reported their experience with administering a total of 6 doses of ondansetron or placebo. They found that, compared with placebo, following emergency department (ED) discharge, children administered ondansetron experienced an increase in diarrhea, no reduction in vomiting, and an increase in ED revisits. In 2010, Yilmaz et al[25] administered 3 doses of ondansetron or placebo. They found that, 24 hours following enrollment, the proportion of still-vomiting patients was lower; however, the ability to tolerate oral hydration was similar between groups. In addition, at 24 hours, the rate of return visits to the ED did not differ significantly between groups; and the ondansetron group experienced an increase in the number of episodes of diarrhea (5.0 vs 4.3, $P = .04$). Thus, multiple-dose ondansetron is not recommended at present. Lastly, a recent case report described the possible occurrence of malignant hyperthermia in a

TABLE 2. Description of ondansetron studies.

Study	N	Age	Inclusion Criteria	Antiemetics Used	Route	Outcomes
Cubeddu et al[19]	36	6 mo-8 y	Hospitalized, vomited ≥2 within 1 h	Single dose of ondansetron, metoclopramide, or placebo	IV	The elimination of emesis was significantly greater (P = .04) with ondansetron (58%) than placebo (17%). Fewer treatment failures were observed with ondansetron (17%) than placebo (33%) and metoclopramide (42%).
Ramsook et al[20]	145	6 mo-12 y	ED, vomited ≥5 within past 24 h	Ondansetron or placebo q8h ×6 doses	PO	Less vomiting while in the ED in ondansetron group (87% vs 65%), no difference at 48 h. Less IV fluids (P = .02), less hospitalization (P = .007) in ondansetron group. Higher revisit rate in ondansetron group at 24 h (5% vs 0%).
Reeves et al[21]	107	1 mo-22 y	ED, vomited ≥3 within past 24 h	Single dose of ondansetron or placebo	IV	More patients stopped vomiting in the ondansetron group (70% vs 51%, P = .04). Fewer admissions of subgroup of first-time patients with measured serum CO_2 ≥15 in the ondansetron group (7% vs 23%, P = .04). No difference in all patient analysis.
Freedman et al[22]	214	6 mo-10 y	ED, vomited ≥1 within past 4 h	Single dose of ondansetron or placebo	PO	Less vomiting (RR = 0.40) and IV fluids (RR = 0.46) in ondansetron group. No difference in hospitalization rates, returns, or adverse events at 72-h follow-up.
Stork et al[23]	137	6 mo-12 y	ED, vomited ≥3 within past 24 h	Single dose of ondansetron, dexamethasone, or placebo	IV	Less hospitalization (4% vs 21%, P = .02) in ondansetron group. More patients tolerated oral hydration in ondansetron group (87% vs 67%; RR = 1.3). No difference in vomiting or revisit at 24 and 72 h.
Roslund et al[24]	106	1-10 y	ED, failed oral challenge	Single dose of ondansetron or placebo	PO	Fewer patients required IV fluids and hospitalization in ondansetron group (22% vs 55%, $P < .001$). No difference in diarrhea or revisit rates at 1 wk.
Yilmaz et al[25]	109	5 mo-8 y	ED, vomited ≥4 within past 6 h	Ondansetron or placebo q8h ×3 doses	PO	Patients in ondansetron group were less likely to vomit at 8 h (RR = 0.33, NNT = 2) and 24 h (RR = 0.15, NNT = 2).

IV indicates intravenous; PO, by mouth; NNT, number needed to treat.

child with a known myopathy and prior episode of malignant hyperthermia who was administered ondansetron. Thus, pending further investigations into this possible association, its use is discouraged in at-risk children.[27]

Dimenhydrinate is a salt of 2 drugs, diphenhydramine and 8-chlorotheophylline, a chlorinated derivative of theophylline. The benefits of its rectal administration in children with vomiting were recently evaluated in a multicenter RCT of 243 children with presumed gastroenteritis and no/mild dehydration.[28] Weight change, the primary outcome, did not differ between children who received dimenhydrinate or placebo. However, the secondary outcome of mean number of vomiting episodes was reduced in the dimenhydrinate group (0.64 vs 1.36 episodes, P = .001). There were no differences between groups in the hospital admission rate, fluid intake, or general well-being. The authors concluded that the overall benefit associated with dimenhydrinate use is low because it does not improve oral rehydration and clinical outcomes.

ADJUNCTIVE THERAPIES

Because medications are not routinely recommended for use in children with acute gastroenteritis, other treatment options are being sought to reduce the burden of disease.

Probiotics

Probiotics are defined as viable microbial preparations that have a beneficial effect on the health and well-being of the host by achieving a normal balanced intestinal microbiota. Much research has been directed toward examining the potential benefit of a variety of probiotics in the treatment of infectious gastroenteritis. The possible mechanisms of action include competition with pathogens for binding sites and substrates, lowering of intestinal luminal pH, production of bacteriocins, promotion of mucin production, up-regulation of genes mediating immunity, and production of trophic short-chain fatty acids that promote mucosal cell growth and differentiation.[29]

In 2003, a Cochrane Database Systematic Review, which included 23 RCTs, examined the effectiveness of probiotics compared with controls in the treatment of infectious diarrhea.[30] The included studies enrolled a total of 1917 participants. Of these, 1449 were children, almost all of whom were hospitalized. Although all the studies enrolled participants with acute diarrhea, outcome criteria were not uniform across the studies. In addition, 14 of the studies were carried out in developing countries; and although many did not comment on the nutritional status of the participants, children with underlying severe or chronic illnesses were excluded. The review concluded that probiotic administration reduced the risk of ongoing diarrhea at day 3 (RR, 0.66; 95% CI, 0.55-0.77) and the mean duration of diarrhea by 31 hours (95% CI, 19-43 hours). This and other reviews however are limited by significant heterogeneity that is not fully accounted for by probiotic(s) tested, diarrhea etiology, and age of the participants. The data however do seem to indicate that the beneficial effects are strain and dose dependent, being generally greater with doses larger than 10^{10} to 10^{11} colony-forming units, highly significant for rotaviral gastroenteritis but not for invasive bacterial diarrhea, more evident when treatment is initiated early in the course of disease and more evident in children in developed than in developing countries.[31]

Lactobacillus rhamnosus GG (LGG) is the most extensively evaluated probiotic. A recent meta-analysis that included 8 RCTs concluded that, compared with placebo, it had no effect on total stool volume.[32] However, it was associated with a reduction in diarrhea duration (weighted mean difference [WMD], −1.1 days; 95% CI, −1.9 to −0.3), particularly that induced by rotavirus (WMD, −2.1 days; 95% CI, −3.6 to −0.6). There was no reduction in the number of stools at any time interval. In the first North American ED study of probiotic use, 155 children 6 months to 6 years of age with a complaint of diarrhea were randomized to receive LGG or inulin twice daily for 5 days; 129 patients completed the study.[33] A return to normal stools during the study period occurred in 79% of the LGG group and 70% of the placebo group (P = .21). There was no significant difference in the median (interquartile range) time to normal stool (LGG 60 hours [37-111] vs placebo 74 hours [43-120], P = .37) or the number of diarrheal stools during the study period (LGG 5.0 [1-10] vs placebo 6.5 [2-14], P = .19).

Five RCTs, evaluating *Saccharomyces boulardii* in a total of 619 patients, were included in a recent meta-analysis.[34] The combined data showed that *S boulardii* significantly reduced the duration of diarrhea (WMD, −1.1 days; 95% CI, −1.3 to −0.8) and the risk of diarrhea lasting more than 7 days (RR, 0.25; 95% CI, 0.08-0.83) compared with controls.

In general, probiotics are considered to be safe; however, little is known about minor adverse effects that have rarely been reported in outpatients. More serious safety issues are related to the risks of bacterial translocation, sepsis, and the introduction of antibiotic resistance transposons. Potential at-risk children include those with central venous lines, those with congenital heart disease, and those who are immunosuppressed. Although the evidence supporting probiotic use in pediatric gastroenteritis is strong, the scientific community needs to ensure access to strains with supporting evidence, sufficient viable dose, and better knowledge of efficacy in outpatients. Lastly, large clinical trials in outpatients with meaningful outcomes are needed to overcome the limitations expressed by the authors of all meta-analyses performed to date.

Zinc

Zinc is an important trace element that is necessary to maintain gastrointestinal structure and function. It is involved in maintaining epithelial barrier integrity and enhancing tissue repair and immune function.[35] In developing countries, zinc deficiency may be common owing to inadequate food intake, reduced availability in animal food

sources, and the high phytate content in the diet that results in impaired absorption.[36] The World Health Organization recommends that infants and children receive a dietary supplement of zinc for up to 2 weeks after the onset of acute gastroenteritis.[37] This is based on early studies conducted in developing countries that demonstrated a reduction in stool frequency and duration in children who received zinc supplementation.[38,39]

A recent Cochrane review[40] included 18 RCTs comparing oral zinc supplementation (5 mg/d for any duration) with placebo in children aged 1 month to 5 years with acute or persistent diarrhea, including dysentery. Among children with acute diarrhea, zinc administration resulted in a shorter diarrhea duration (mean differences, −12.3 hours; 95% CI −23.0 to −1.5) and less diarrhea at day 3 (RR, 0.69; 95% CI, 0.59-0.81), 5 (RR, 0.55; 95% CI, 0.32-0.95), and 7 (RR, 0.71; 95% CI, 0.52-0.98). Subgroup analyses by age showed no benefit to zinc administration to children younger than 6 months. This finding may be explained by the fact that (1) breast milk is an adequate source of zinc up until 6 months of age, (2) zinc deficiency usually only develops after 6 months of age, and (3) zinc administration is likely only beneficial in the setting of zinc deficiency. None of the included trials reported any serious adverse events, but vomiting was more common in zinc-treated children (RR, 1.7; 95% CI, 1.3-2.3).

The National Institute for Health and Clinical Excellence UK conducted a meta-analysis excluding trials with persistent diarrhea or malnutrition.[4] The analysis, which included 8 studies,[38,41-46] did not find a statistically significant reduction in duration or frequency of diarrhea in zinc-supplemented children when compared with the controls. Based on these results, there is insufficient evidence to justify recommending zinc supplementation for well-nourished children with acute gastroenteritis. In developing countries, however, the routine use of zinc continues to be recommended.

Recombinant Human Hyaluronidase (Hylenex)–Enabled Subcutaneous Rehydration

Although oral rehydration remains the recommended therapy in children with mild to moderate dehydration,[47] physicians, particularly in North America, often choose to administer intravenous rehydration. However, obtaining intravenous access to treat dehydrated infants and youths can be a challenge.[48] Potential alternatives include nasogastric rehydration, which has been demonstrated to be effective,[49] and subcutaneous rehydration. A systematic review of 9 small articles (2 RCTs) in an elderly population analyzed the effectiveness of subcutaneous fluid administration.[50] The review concluded that hypodermoclysis is as effective as intravenous rehydration in older adults with mild to moderate dehydration. However, it is infrequently used in North America for a variety of reasons including the slow absorption of fluids and drugs administered by this route.

Recombinant human hyaluronidase (rHuPH20, Hylenex [Baxter International, Deerfield, IL]) is a human, DNA-derived, hyaluronidase enzyme. After being administered subcutaneously, it can facilitate the infusion of subcutaneous fluids.[51] One study compared the rate of subcutaneous administration of lactated Ringers with and without rHuPH20.[52] The study found that, in adult volunteers, a greater volume of fluid (up to 500 mL/h) can be delivered subcutaneously when rHuPH20 is administered compared with placebo (150 mL/h).

A follow-up study suggested that subcutaneous rehydration is a viable alternative in children with mild to moderate dehydration.[53] Children were administered 1 mL of rHuPH20 subcutaneously through a needle followed by continuous, pump-facilitated, subcutaneous infusion of 20 mL/kg of isotonic fluid followed by additional fluids as needed. The efficacy end point, discharge home from the ED, with the investigator attributing this success to the use of rHuPH20-facilitated subcutaneous rehydration, was achieved in 84% of subjects. Fifty-nine percent required a flow rate decrease. Adverse effects were not insignificant, with 57% developing a swelling of at least 5 cm in diameter, 53% of children younger than 3 years having an Objective Pain Rating Scale Score of at least 5 (maximal score = 10), and 8% having adverse effects that were deemed to be unacceptable. In addition, 20 hours following discharge, one child developed cellulitis at the infusion site requiring admission for intravenous antibiotics.

This study did show that subcutaneous access can be achieved with fewer attempts than is often required to achieve intravenous access with initial subcutaneous catheter placement being successful in 46 (90%) of 51 patients. Ninety-six percent of physicians found the procedure easy to perform, and parental satisfaction with the procedure was excellent.

At present, it is clear that greater evidence supporting the efficacy of rHuPH20, its safety, and its role in pediatric gastroenteritis is necessary. Subcutaneous rehydration may eventually play a role in children who do not tolerate oral/nasogastric rehydration and in whom intravenous access is very difficult to achieve.

SUMMARY

The treatment of children with acute gastroenteritis remains an important responsibility of pediatric emergency health care providers. A considerable amount of effort is required to successfully achieve oral rehydration; hence, we are constantly searching for a means to enhance our success and minimize the morbidity experienced by our patients. Recent research has demonstrated that some pharmacologic and adjunct therapies should be incorporated into ED treatment guidelines for children with acute gastroenteritis. Ondansetron has emerged as a beneficial antiemetic agent with the capability of reducing the need for intravenous fluids administration and hospital admission. Probiotics may shorten the duration of diarrhea and reduce the stool frequency following ED discharge, but greater data in the outpatient population are required before its routine use should be adopted. Emergency departments should update their management strategies to ensure that patients are treated in the most efficient and effective manner. ✚

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