## REVIEW

# Paediatrics: how to manage viral gastroenteritis

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## Abstract

**Background:** Viral gastroenteritis is the most common diarrhoeal disorder seen in general practice and emergency departments. This article aims to provide a narrative updated review on the evaluation and management of viral gastroenteritis in children.

**Methods:** A PubMed search was performed with Clinical Queries using the key term 'viral gastroenteritis'. The search strategy included clinical trials, meta-analyses, randomized controlled trials, observational studies and reviews. The search was restricted to the English literature and the paediatric population.

**Results:** Acute viral gastroenteritis is usually self-limiting. However, it can lead to dehydration and electrolyte imbalance if not properly treated. Adequate fluids containing physiological concentrations of glucose and electrolytes should be provided to compensate for gastrointestinal losses and cover maintenance needs. Oral rehydration therapy is as effective as intravenous (IV) fluid therapy for rehydration for children with mild-to-moderate dehydration. Measurements of serum electrolytes, creatinine and glucose are usually not necessary and should only be considered in a subset of children with severe dehydration who require hospitalization and IV therapy. Judicious use of ondansetron can increase the success rate of oral rehydration therapy and minimize the need for IV therapy and hospitalization.

**Conclusion:** Acute viral gastroenteritis is associated with substantial morbidity in developed countries and significant mortality in developing countries. Physicians should educate caregivers on proper personal hygiene and handwashing to prevent faecal to oral transmission of the pathogen as well as the importance of rotavirus vaccine in the prevention of rotavirus gastroenteritis. Several norovirus vaccines are currently undergoing clinical trials with promising results. It is hoped that development of an effective norovirus vaccine will further reduce the incidence of viral gastroenteritis.

**Keywords:** dehydration, diarrhoea, gastroenteritis, ondansetron, oral rehydration, viral, vomiting.

## Introduction

Viral gastroenteritis is one of the most common causes of morbidity and mortality worldwide, especially in young children in developing countries.[1–5] Dehydration, which may be associated with electrolyte imbalance and metabolic acidosis, is the most frequent and dangerous complication.[6]

## Methods

This article provides a narrative updated review on the evaluation, diagnosis and management of viral gastroenteritis in children. A PubMed search was performed in November 2020 with Clinical Queries using the key term 'viral gastroenteritis'. The search strategy included clinical trials, meta-analyses, randomized controlled trials, observational studies and reviews published within the past 10 years. The search was restricted to the English literature and children. The information retrieved from the above mentioned search was used in the compilation of the present article.

## Aetiology

Worldwide, viruses account for approximately 75–90% of childhood acute gastroenteritis.[7] The most common viral pathogens are norovirus and rotavirus, followed by sapovirus,

enteric adenovirus and astrovirus.[4,5,8–16] Prior to routine rotavirus vaccination, rotavirus was the most common cause of gastroenteritis in the paediatric age group. Currently, norovirus is the most common cause of viral gastroenteritis in children.[8] Other less common viral pathogens include human bocavirus, torovirus, parechovirus, picobirnavirus, Aichi virus A and Safford virus.[17–23] Viral pathogens that are infrequent causes of acute gastroenteritis and that typically have extraintestinal manifestations include severe acute respiratory syndrome (SARS)-coronavirus, echovirus, coxsackievirus, influenza virus type B and poliovirus.[3,24,25]

## Epidemiology

Acute viral gastroenteritis is most common in children 5 years of age and younger.[26] The sex ratio is approximately equal.[27] The average child younger than 5 years of age experiences 2.2 diarrhoeal episodes per year in industrialized countries, with this rate being significantly higher in developing countries.[4,28] Worldwide, acute viral gastroenteritis accounts for over 200,000 child deaths per year, primarily in developing countries.[27]

Outbreaks of acute viral gastroenteritis occur most frequently during the winter.[29] The majority of viral pathogens are transmitted via the faecal–oral route through person-to-person contact and contaminated food and water.[27,29,30] Airborne transmission of norovirus, rotavirus and SARS-coronavirus has been suggested in some outbreaks.[24,31]

## Pathophysiology

The pathophysiology of viral gastroenteritis has been extensively studied with rotavirus.[12] Rotavirus preferentially infects enterocytes in the mature small intestine, leading to the destruction of these cells with impaired capacity for absorption of intestinal fluid and secondary disaccharidase deficiency.[12] The disaccharidase deficiency results in malabsorption of carbohydrates with resulting osmotic diarrhoea. Villous tips receive the most extensive damage with sparing of the crypts. Excessive secretion from the intestine may be secondary to the loss of villous tips and the filling of crypts with rapidly multiplying cells, leading to an imbalance between absorption and secretion and resulting in a net secretion (villous cells are largely absorptive and crypt cells are secretory).[12] In addition, the rotavirus non-structural protein 4 (NSP4) functions as an enterotoxin, which can lead to hypersecretion of intestinal fluid.[12,19]

## Clinical manifestations

The incubation period is usually 12–72 hours, depending on the causative viral pathogen.[1] The main clinical features of acute viral gastroenteritis include vomiting and diarrhoea, often accompanied by malaise, nausea, abdominal cramps, and fever.[1,4] It is interesting to note that children with gastroenteritis caused by norovirus or sapovirus may present with isolated vomiting in the absence of diarrhoea. Vomiting

is a prominent feature in most cases of rotavirus and norovirus gastroenteritis.[12,32] Stools are typically loose to watery. Mucous and gross blood are uncommon. In rotavirus gastroenteritis, stools have a distinct odour.[12] The severity of the disease depends on the virulence of the virus, the viral load, the host immune system and comorbidities.[1] Diarrhoea usually lasts less than 7 days, most often improving after 1–3 days, and does not last longer than 14 days.[24] Diarrhoea that lasts longer than 14 days is considered chronic and therefore does not fit into the definition of acute gastroenteritis.

Extraintestinal manifestations, such as respiratory symptoms, may occur with rotavirus infection and headache and myalgia may occur with norovirus infection.[1] Extraintestinal manifestations are especially common with gastroenteritis caused by SARS-coronavirus, echovirus, coxsackievirus, influenza virus type B and poliovirus.[3,24]

## Clinical evaluation

A detailed history and a thorough physical examination are essential to establish the diagnosis of acute gastroenteritis and to exclude other causes of vomiting and/or diarrhoea.[4] In viral gastroenteritis, the incubation period is usually longer than 12 hours, vomiting is prominent, fever is usually low grade, stools usually do not contain blood, and the entire illness usually lasts less than 7 days. However, the differentiation of viral gastroenteritis from bacterial gastroenteritis based on clinical manifestations alone is often difficult. Red-flag symptoms and clinical signs suggestive of acute bacterial gastroenteritis include bilious or bloody vomiting, blood or mucus in stool, excessive irritability, inconsolable crying, high fever, toxic appearance, tachypnoea, cyanosis, poor peripheral perfusion, petechial rash, neck stiffness and altered sensorium.[7]

### History

The history should focus on the age of the child and the onset, duration, number of episodes and quantity of the diarrhoea and vomiting as well as on the amount and type of fluid intake.[4,5,7] The character of vomiting (e.g. projectile, bilious) and diarrhoea (e.g. presence of blood and mucus) should be noted.

The child's weight before onset of the illness, associated symptoms (e.g. such as fever, abdominal cramps, tenesmus), overall activity level, consumption of contaminated foods or fluid, concurrent illness in family members, exposure to individuals with gastroenteritis, outbreak of gastroenteritis in the community, day-care attendance, medical history (e.g. comorbid disease, immunodeficiency), recent travel to a diarrhoea-endemic area, recent infection, recent use of antibiotics, duration of breastfeeding, and immunization status should be noted.[33–35]

### Physical examination

The general condition of the patient, vital signs (temperature, weight, heart rate, respiratory rate, blood pressure), and the

severity of dehydration should be assessed.[4,5,28] Although loss in body weight is a useful indicator of dehydration, it should always be corroborated by changes in clinical signs because weight measurement is susceptible to many potential errors (such as the use of different scales or unstandardized measurement techniques).[4] Additionally, weight may change significantly depending on whether the child has recently eaten, defecated or voided.[36] A thorough physical examination may help to exclude other causes of vomiting and/or diarrhoea.

## Diagnosis

The diagnosis of acute gastroenteritis is a clinical one based on the presence of diarrhoea (usually no blood in the stools), often accompanied by vomiting, fever and abdominal pain. Acute viral gastroenteritis refers to acute gastroenteritis caused by a viral pathogen. A presumptive diagnosis of acute viral gastroenteritis can be made in the absence of atypical features such as high fever, bilious vomiting, projective vomiting, gross blood or mucus in stool, persistence of diarrhoea more than 7 days without improvement, recent antibiotic use, severe dehydration, focal abdominal tenderness, marked abdominal distension, and absent bowel sounds.[24]

## Differential diagnosis

Acute viral gastroenteritis should be differentiated from bacterial causes of acute gastroenteritis (e.g. *Salmonella*, *Shigella*, diarrhoeagenic *Escherichia coli*, *Campylobacter jejuni*, *Clostridium difficile*), parasitic causes of acute gastroenteritis (e.g. *Giardia intestinalis*, *Entamoeba histolytica*, *Cryptosporidium* species), food poisoning, antibiotic-associated diarrhoea, acrodermatitis enteropathica, parenteral diarrhoea (e.g. otitis media, urinary tract infection), haemolytic uremic syndrome, malabsorption syndromes (e.g. celiac disease, cystic fibrosis, disaccharidase deficiency) and inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis).[24] Gross blood or mucus in the stool are unusual in viral gastroenteritis, the presence of which should prompt consideration of other aetiologies.

## Laboratory evaluation

Measurements of serum electrolytes, creatinine and glucose are usually not necessary in most immune-competent children with typical findings of acute viral gastroenteritis as the results do not change the management.[33,37] These tests should only be considered in a subset of children with severe dehydration who require hospitalization and intravenous (IV) therapy.[34,38] Routine aetiologic testing of viral pathogens is typically not necessary but may be employed during outbreaks for epidemiological purposes. Faecal leukocytes and stool cultures should be considered in children with bloody diarrhoea, high fever and severe abdominal cramps as these symptoms are

not consistent with uncomplicated viral gastroenteritis.[27,33] Complete blood cell count and appropriate cultures should be considered when sepsis is suspected.

## Complications

Dehydration and electrolyte imbalance are the most common complications. If the dehydration is severe enough, it can lead to shock, coma and even death. Children with poor nutrition status are at increased risk.[6] Shock and acute renal failure may result from severe dehydration.[39] Other complications include irritant diaper dermatitis, hypoglycaemia, carbohydrate intolerance, renal tubular damage, renal stone, hyperuricaemia, impaired liver functions and seizures.[40–47] Gastroenteritis is associated with enormous costs either directly through medical expenses or indirectly through loss of working hours by parents of sick children because of the frequency of the disease.[48,49]

## Management

### Rehydration therapy

The goal of treatment is to maintain adequate hydration of the child with gastroenteritis.[50,51] Adequate fluids should be provided to compensate for gastrointestinal losses and cover maintenance needs.[4] Children weighing <10 kg should receive 60–120 mL of an oral rehydration solution (ORS) per episode of vomiting or diarrhoeal stool whilst those weighing >10 kg should receive 120–240 mL of ORS per episode of vomiting or diarrhoeal stool in addition to their normal daily requirements.[24] The daily fluid maintenance requirement is 100 mL/kg for the first 10 kg, 50 mL/kg for the next 10 kg, and 20 mL/kg for each subsequent kilogram over 20 kg.[4]

It has been shown that oral rehydration therapy (ORT) is as effective as, if not better than, IV fluid therapy for rehydration for children with mild-to-moderate dehydration.[52–55] Compared with IV therapy, ORT is less traumatic, easier to administer, cheaper and can be administered in a variety of settings, including the home.[2,50,53,54]

ORSs containing physiological concentrations of glucose and electrolytes should be used.[36,37,56] Fluids containing non-physiological concentrations of glucose and electrolytes, such as carbonated drinks and sweetened fruit juices, are discouraged because these drinks have a high carbohydrate content, very low electrolyte content, and high osmolarity.[6,36] The administration of such hyperosmolar solutions in large amounts may produce osmotic diarrhoea. On the other hand, plain water should not be used for rehydration as intake of large amounts of plain water may lead to hypoglycaemia and hyponatraemia.[36] For infants who are breastfed, breastfeeding should be continued.[7,57] It is not necessary to dilute formula or to give lactose-free formula in refeeding non-breastfed infants.[34]

Children with mild-to-moderate dehydration can be managed as outpatients with ORT as mainstay of treatment.[2,7,58] For children refusing ORS, the key is to give small amounts of ORS at frequent intervals and the volume should be gradually increased until the child can drink as desired.[59] Using a dropper or syringe for very small infants and spoon for older infants and young children can significantly increase the success rate.[7,36] In a child who refuses to drink, squirting the ORS into the mouth with a syringe may help.[36] Flavoured ORS or ORS popsicles, which may be more acceptable to some children, may also be tried. If children refuse to drink by any of the above measures, nasogastric gavage should be considered before IV hydration is attempted.[60] Nasogastric rehydration provides the physiological benefits of enteral rehydration and avoids the potential complications of IV therapy.[61]

For children with severe dehydration, Ringer's lactate or normal saline (20 mL/kg) should be given intravenously over 1 hour.[37,62,63] Vital signs should be monitored and the patient reassessed on a regular basis. Boluses of IV fluid may have to be given until pulse, perfusion and mental status return to normal.[34] IV rehydration should also be considered in children with protracted vomiting despite small and frequent feedings and on those undergoing antiemetic treatment or with impaired consciousness, paralytic ileus, and severe acidosis.[34,37] Hypotonic saline solutions are inappropriate for IV rehydration as administration of large volume of hypotonic solution might lead to dilutional hyponatraemia.[4] ORT should be started when the child's condition is stable.[61]

## Early refeeding

Early refeeding with an age-appropriate diet has been shown to induce digestive enzymes, promote the recovery of disaccharidases, improve the absorption of nutrients, enhance enterocyte regeneration, decrease the intestinal permeability changes induced by infection, reduce the duration of diarrhoea, improve nutritional outcomes and maintain growth.[64,65] Foods high in complex carbohydrates (e.g. rice, cereals, bread, wheat and potatoes), fruits and vegetables, and lean meat are better tolerated than foods containing high levels of simple sugar and fats.[57] Foods high in simple sugars should be avoided as they may cause osmotic diarrhoea.[57] With the exception of a subset of children with transient secondary disaccharidase deficiency, most children with acute gastroenteritis are able to tolerate milk and lactose-containing diets.

## Antiemetic medications

Judicious use of ondansetron can increase the success rate of ORT and decrease the need for IV therapy and hospitalization.[58,64,66–68] In a meta-analysis of 24 randomized clinical trials comparing the antiemetic effects of ondansetron, dimenhydrinate, domperidone, granisetron, metoclopramide and dexamethasone, ondansetron was the only intervention that revealed an effect on the cessation of vomiting.[69] Compared to placebo, ondansetron increased the proportion of children with cessation of vomiting (OR 0.28; 95% CI 0.16–0.46; high quality of evidence) and decreased the proportion of children with the need for hospitalization (OR 0.93; 95% CI 1.69–6.18; moderate quality of evidence).[69] The recommended IV dose of ondansetron is 0.1–0.5 mg/kg, with a maximum of 4 mg.[4] The recommended oral dose is 2 mg for children weighing 8–15 kg, 4 mg for children weighing >15 kg to ≤30 kg, and 8 mg for children >30 kg.[70–72] A single dose of oral ondansetron is usually sufficient for the treatment of gastroenteritis-related vomiting.[64,66,71] The dose may be repeated if the child vomits within 15 minutes after taking the medication.[7] However, the use of ondansetron is associated with increased risk of diarrhoea.[54,73] Ondansetron should be avoided in children who are at risk for malignant hyperthermia and those with prolonged QT interval.[57,74] Other antiemetics such as dimenhydrinate, promethazine, metoclopramide, droperidol, domperidone, prochlorperazine, trimethobenzamide, and dexamethasone are not recommended for use in children either because of lack of efficacy data or because of the significant adverse events associated with their use.[2,57]

## Antidiarrhoeal medications

Racecadotril, an antisecretory drug, exerts its antidiarrhoeal effects by inhibiting intestinal endopeptidase (also known as enkephalinase), which helps to prevent the breakdown of enkephalins in the gastrointestinal tract and reduce the secretion of electrolytes and water into the gastrointestinal tract without affecting its motility.[75,76] A 2007 systematic review of three randomized controlled studies (238 children in the treatment group; 233 children in the control group) showed a reduction in the stool output and duration of diarrhoea in treated children with acute gastroenteritis.[76] In a 2018 systematic review and meta-analysis of 24 randomized controlled trials, racecadotril reduced the time to cessation of diarrhoea from 106.2 hours to 78.2 hours (mean reduction 28.0 hours; $p<0.0001$).[77] More studies are needed before the routine use of racecadotril in the treatment of acute gastroenteritis can be recommended.

Smectite/diosmectite, an adsorbent, has been used for the treatment of diarrhoea in many European countries.[57] A 2018 Cochrane systematic review of 18 randomized and quasi-randomized trials ($n$=2616 children) showed that smectite reduced the duration of diarrhoea by approximately 24 hours (mean difference −24.38 hours; 95% CI −30.91 to −17.85; 2,209 children, 14 studies; low-certainty evidence), increased clinical resolution at day 3 (RR 2.01; 95% CI 1.30–3.39; 312 children, 5 trials; low-certainty evidence) and reduced the output of stools (mean difference −11.37; 95% CI −21.94 to 0.79; 634 children, 3 studies; low-certainty evidence).[78,79] Based on the above low-certainty evidence, smectite might have a role in the treatment of diarrhoea in children with acute viral

gastroenteritis, pending on the results of future well-designed, randomized, placebo-controlled studies.[79] Other antidiarrhoeal medications such as bismuth subsalicylate, attapulgite, kaolin-pectin, diphenoxylate-atropine and loperamide are not recommended either because of lack of efficacy data or the potentially severe adverse events associated with their use.[57]

## Antimicrobial agents

Generally, antimicrobial agents are not indicated in the treatment of viral gastroenteritis.[57] Nitazoxanide, a broad-spectrum antiparasitic and antiviral agent, has been shown to reduce the duration of diarrhoea in children with viral gastroenteritis in several studies.[80–82] Well-designed, large-scale, randomized, double-blind and placebo-controlled studies are necessary to confirm the efficacy of nitazoxanide in order to make formal recommendations regarding their use in the management of viral gastroenteritis in children.

## Probiotics

Probiotics such as *Lactobacilli reuteri*, *Lactobacilli rhamnosus GG*, *Saccharomyces boulardii*, *Bifidobactium bifidum* and *Streptococcus thermophilus* have been used in the treatment of viral gastroenteritis with varying success.[83–86] Presumably, probiotics work by improving the barrier function of the intestine, competing for nutrients necessary for the survival of pathogens, competitive blockage of receptor sites, enhancement of the immune response and the production of substances that inactivate viral particles.[86] A 2020 systematic review and meta-analysis showed that, in patients with acute viral gastroenteritis, probiotics can shorten the duration of diarrhoea (mean difference 0.7 day; 95% CI 0.31–1.09 days; $n$=740, 10 trials) and the duration of hospitalization (mean difference 0.76 day; 95% CI 0.61–0.92 day; $n$=329, 4 trials).[87] Well-designed, large-scale, randomized, double-blind and placebo-controlled studies are necessary to determine the specific strains and optimal dosages of probiotics that are most helpful.

## Zinc supplementation

Zinc supplementation in children with diarrhoea in developing countries leads to reduced duration and severity of diarrhoea.[88–92] One way of administering zinc during acute diarrhoea is to mix it with ORS. The recommended dose is 20 mg zinc supplements per day for 10–14 days for children with acute diarrhoea (10 mg per day for infants younger than 6 months of age).[93] In a recent study conducted in India and Tanzania, 4500 children aged 6–59 months with acute diarrhoea were randomized to receive 5 mg, 10 mg and 20 mg of zinc sulphate orally for 14 days.[94] The mean number of diarrhoeal stool was 10.7, 10.9 and 10.8 in the 20-mg, 10-mg and 5-mg groups, respectively. Vomiting within 30 minutes after administration of zinc sulphate occurred in 19.3%, 15.6% and 13.7% of children in the 20-mg, 10-mg and

5-mg groups, respectively. The authors concluded that lower doses of zinc have non-inferiority efficacy for the treatment of children with acute diarrhoea and have less vomiting than the standard 20-mg dose.[94] A 2016 Cochrane review found that zinc supplementation may be of benefit in the treatment of diarrhoea in children aged 6 months and older in areas where the prevalence of zinc deficiency or malnutrition is high.[95] The current evidence does not support the routine use of zinc supplementation in children less than 6 months of age, in well-nourished children and children in areas at low risk of zinc deficiency.[95] Given the effectiveness of traditional ORS and the increased cost of zinc supplementation, zinc supplementation is not routinely recommended in developed countries.[4]

## Human immunoglobulin

A preliminary study showed that oral administration of human serum immunoglobulin to hospitalized immunocompromised children with acute diarrhoea reduced stool output by 50%.[96] Well-designed, large-scale, randomized controlled trials are needed to support the routine use of oral human serum immunoglobulin in hospitalized immunocompromised children with acute diarrhoea.

# Prevention

Good personal hygiene is of utmost importance to prevent the spread of pathogens. This includes frequent handwashing with soap, careful diaper disposal, and proper preparation and storage of food and drinking water. Contaminated objects and surfaces should be properly disinfected.

Breastfeeding is recommended for the first year of life with exclusive breastfeeding for the first 6 months.[35] Human milk may reduce the incidence of gastroenteritis and shorten the duration of diarrhoea.[7]

Studies have shown that rotavirus vaccination is both efficacious and effective in the prevention of rotavirus-related diarrhoea and rotavirus-related hospitalizations as well as in the reduction of diarrhoea-associated healthcare utilization and costs.[97–100] The rotavirus vaccination was licensed in 2006;[97] 10 years after vaccine licensure, a systematic review of 57 articles from 27 countries showed that emergency department visits and hospitalizations due to rotavirus gastroenteritis were reduced by a median of 67% overall and 60%, 59% and 71% in countries with high, medium and low child mortality, respectively.[97] Universal immunization of infants as early as 6 weeks of age and completion of the schedule by 8 months of age with rotavirus vaccine is recommended and will substantially reduce the incidence of rotavirus gastroenteritis and associated morbidity and mortality.[101] A novel multiepitope subunit vaccine is under development for the prevention of norovirus gastroenteritis and the outlook is promising.[102] The vaccine still requires

validation to ensure its safety and effectiveness against norovirus gastroenteritis. Several norovirus vaccines are currently undergoing clinical trials with promising results.[103–109] It is hoped that development of an effective norovirus vaccine will further reduce the incidence of viral gastroenteritis.

## Prognosis

The prognosis is good. In most cases, acute viral gastroenteritis is self-limited. Mortality does occur in very young, malnourished or immunodeficient children and in children who do not have access to medical care.[27]

## Conclusion

Acute viral gastroenteritis is associated with substantial morbidity in developed countries and has a significant mortality in developing countries. Norovirus has surpassed rotavirus as the most common aetiologic agent in regions where rotavirus vaccination is included in the routine childhood immunization programmes. Physicians should educate caregivers on proper personal hygiene and handwashing to prevent the faecal–oral transmission of the pathogen as well as on the importance of rotavirus vaccine in the prevention of rotavirus gastroenteritis.

## Key practice points

- The main clinical features of acute viral gastroenteritis include vomiting and diarrhoea, often accompanied by malaise, nausea, abdominal cramps, and fever.
- Diarrhoea usually lasts <7 days, improving after 1–3 days, and does not last >14 days; diarrhoea that lasts >14 days is considered chronic.
- Respiratory symptoms may occur with rotavirus infection; headache and myalgia may occur with norovirus infection.
- Rehydration therapy with fluids containing physiological concentrations of glucose and electrolytes is required to compensate for gastrointestinal losses and cover maintenance needs.
- Oral rehydration therapy is as effective as intravenous (IV) fluid therapy for rehydration for children with mild-to-moderate dehydration.
- Measurements of serum electrolytes, creatinine and glucose should only be considered in children with severe dehydration who require hospitalization and IV therapy.
- Antiemetic medications such as ondansetron can increase the success rate of oral rehydration therapy and minimize the need for IV therapy and hospitalization.
- The recommended IV dose of ondansetron is 0.1–0.5 mg/kg, with a maximum of 4 mg. The recommended oral dose of ondansetron is 2 mg for children weighing 8–15 kg, 4 mg for children weighing >15 to ≤30 kg, and 8 mg for children >30 kg. A single dose is usually sufficient but may be repeated if the child vomits within 15 minutes after administration.
- Antidiarrhoeal medications are not currently recommended in children.
- The antimicrobial nitazoxanide requires further study to be recommended for use in children.
- Proper personal hygiene and handwashing to prevent faecal to oral transmission of the pathogen is required.
- Norovirus is currently the most common cause of viral gastroenteritis in children; an effective norovirus vaccine should further reduce the incidence of viral gastroenteritis.

# References

1. Bányai K, Estes MK, Martella V, Parashar UD. Viral gastroenteritis. *Lancet*. 2018;392(10142):175–186. https://doi.org/10.1016/S0140-6736(18)31128-0

2. Chow CM, Leung AKC, Hon KL. Acute gastroenteritis: from guidelines to real life. *Clin Exp Gastroenterol*. 2010;3:97–112. https://doi.org/10.2147/ceg.s6554

3. Dennehy PH. Viral gastroenteritis in children. *Pediatr Infect Dis J*. 2011;30(1):63–64. https://doi.org/10.1097/INF.0b013e3182059102

4. Leung AKC. Viral gastroenteritis. In: Leung AKC, ed. *Common Problems in Ambulatory Pediatrics: Specific Clinical Problems*. Vol. 1. New York: Nova Science Publishers, Inc., 2011;223–232.

5. Leung AKC. Pediatric viral gastroenteritis. British Medical Journal Point of Care. http://online.epocrates.com/u/2911794/Viral. Accessed November 28, 2020.

6. Elliott EJ. Acute gastroenteritis in children. *BMJ*. 2007;334(7583):35–40. https://doi.org/10.1136/bmj.39036.406169.80

7. Hartman S, Brown E, Loomis E, Russell HA. Gastroenteritis in children. *Am Fam Physician*. 2019;99(3):159–165.

8. Akdag AI, Gupta S, Khan N, Upadhayay A, Ray P. Epidemiology and clinical features of rotavirus, adenovirus, and astrovirus infections and coinfections in children with acute gastroenteritis prior to rotavirus vaccine introduction in Meerut, North India. *J Med Virol*. 2020;92(8):1102–1109. https://doi.org/10.1002/jmv.25645

9. Bozkurt D, Selimoğlu MA, Otlu B, Sandıkkaya A. Eight different viral agents in childhood acute gastroenteritis. *Turk J Pediatr*. 2015;57(1):68–73.

10. Desselberger U. Viral gastroenteritis. *Medicine*. 2017;45(11):690–694. https://doi.org/10.1016/j.mpmed.2017.08.005

11. Huang H, Liao D, Zhou G, Zhu Z, Cui Y, Pu R. Antiviral activities of resveratrol against rotavirus in vitro and in vivo. *Phytomedicine*. 2020;77:153230. https://doi.org/10.1016/j.phymed.2020.153230

12. Leung AKC, Kellner JD, Davies HD. Rotavirus gastroenteritis. *Adv Ther*. 2005;22(5):476–487. https://doi.org/10.1007/BF02849868

13. Nguekeng Tsague B, Mikounou Louya V, Ntoumi F, Adedoja A, Vouvoungui CJ, Peko SM, et al. Occurrence of human astrovirus associated with gastroenteritis among Congolese children in Brazzaville, Republic of Congo. *Int J Infect Dis*. 2020;95:142–147. https://doi.org/10.1016/j.ijid.2020.02.056

14. Olortegui MP, Rouhani S, Yori PP, Salas MS, Trigoso DR, Mondal D, et al. Astrovirus infection and diarrhea in 8 countries. *Pediatrics*. 2018;141(1):e20171326. https://doi.org/10.1542/peds.2017-1326

15. Page N, Groome MJ, Murray T, Nadan S, Netshikweta R, Keddy KH, et al. Sapovirus prevalence in children less than five years of age hospitalised for diarrhoeal disease in South Africa, 2009–2013. *J Clin Virol*. 2016;78:82–88. https://doi.org/10.1016/j.jcv.2016.03.013

16. Zaraket R, Salami A, Bahmad M, El Roz A, Khalaf B, Ghssein G, et al. Prevalence, risk factors, and clinical characteristics of rotavirus and adenovirus among Lebanese hospitalized children with acute gastroenteritis. *Heliyon*. 2020;6(6):e04248. https://doi.org/10.1016/j.heliyon.2020.e04248

17. Bergallo M, Galliano I, Montanari P, Rassu M, Daprà V. Aichivirus in children with diarrhea in Northern Italy. *Intervirology*. 2017;60(5):196–200. https://doi.org/10.1159/000487051

18. Chhabra P, Payne DC, Szilagyi PG, Edwards KM, Staat MA, Shirley SH, et al. Etiology of viral gastroenteritis in children <5 years of age in the United States, 2008–2009. *J Infect Dis*. 2013;208(5):790–800. https://doi.org/10.1093/infdis/jit254

19. Desselberger U. Global issues related to enteric viral infections. *Virusdisease*. 2014;25(2):147–149. https://doi.org/10.1007/s13337-014-0223-y

20. Gubbay J, Al-Rezqi A, Hawkes M, Williams L, Richardson S, Matlow A. The role of torovirus in nosocomial viral gastroenteritis at a large tertiary pediatric centre. *Can J Infect Dis Med Microbiol*. 2012;23(2):78–81. https://doi.org/10.1155/2012/134961

21.   La Rosa G, Della Libera S, Iaconelli M, Donia D, Cenko F, Xhelilaj G, et al. Human bocavirus in children with acute gastroenteritis in Albania. *J Med Virol*. 2016;88(5):906–910. https://doi.org/10.1002/jmv.24415

22.   Rivadulla E, Varela MF, Romalde JL. Epidemiology of Aichi virus in fecal samples from outpatients with acute gastroenteritis in Northwestern Spain. *J Clin Virol*. 2019;118:14–19. https://doi.org/10.1016/j.jcv.2019.07.011

23.   Vandesande H, Edman K, Rondahl E, Falkeborn T, Serrander L, Lindberg AM. Saffold virus infection in elderly people with acute gastroenteritis in Sweden. *J Med Virol*. https://doi.org/10.1002/jmv.26452

24.   O'Ryan M. Acute viral gastroenteritis in children in in resource-rich countries: clinical features and diagnosis. In: Edwards MS, Li BUK, eds. *UpToDate*. Waltham, MA. https://www.uptodate.com/contents/acute-viral-gastroenteritis-in-children-in-resource-rich-countries-clinical-features-and-diagnosis. Accessed November 28, 2020.

25.   Xiong LJ, Zhou MY, He XQ, Wu Y, Xie XL. The role of human coronavirus infection in pediatric acute gastroenteritis. *Pediatr Infect Dis J*. 2020;39(7):645–649. https://doi.org/10.1097/INF.0000000000002752

26.   Monroe SS. Control and prevention of viral gastroenteritis. *Emerg Infect Dis*. 2011;17(8):1347–1348. https://doi.org/10.3201/eid1708.110824

27.   Stuempfig ND, Seroy J. Viral gastroenteritis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020.

28.   Nutrition and Gastroenterology Committee, Canadian Paediatric Society. Oral rehydration therapy and early refeeding in the management of childhood gastroenteritis. *Paediatr Child Health*. 2006;11:527–531.

29.   Wikswo ME, Kambhampati A, Shioda K, Walsh KA, Bowen A, Hall AJ; Centers for Disease Control and Prevention (CDC). Outbreaks of acute gastroenteritis transmitted by person-to-person contact, environmental contamination, and unknown modes of transmission--United States, 2009–2013. *MMWR Surveill Summ*. 2015;64(12):1–16. https://doi.org/10.15585/mmwr.mm6412a1

30.   Li J, Gao X, Ye YL, Wan T, Zang H, Mo PH, et al. An acute gastroenteritis outbreak associated with person-to-person transmission in a primary school in Shanghai: first report of a GI.5 norovirus outbreak in China. *BMC Infect Dis*. 2018;18:316. https://doi.org/10.1186/s12879-018-3224-4

31.   Bonifait L, Charlebois R, Vimont A, Turgeon N, Veillette M, Longtin Y, et al. Detection and quantification of airborne norovirus during outbreaks in healthcare facilities. *Clin Infect Dis*. 2015;61(3):299–304. https://doi.org/10.1093/cid/civ321

32.   Robilotti E, Deresinski S, Pinsky BA. Norovirus. *Clin Microbiol Rev*. 2015;28(1):134–164. https://doi.org/10.1128/CMR.00075-14

33.   D'Agostino J. Considerations in assessing the clinical course and severity of rotavirus gastroenteritis. *Clin Pediatr*. 2006;45(3):203–212. https://doi.org/10.1177/000992280604500301

34.   King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 2003;52(RR-16):1–16.

35.   Leung AKC, Sauve RS. Breast is best for babies. *J Natl Med Assoc*. 2005;97(7):1010–1019.

36.   Leung AKC, Robson WL. Acute diarrhea in children. What to do and what not to do. *Postgrad Med*. 1989;86(8):161–174. https://doi.org/10.1080/00325481.1989.11704505

37.   American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Practice parameter: the management of acute gastroenteritis in young children. *Pediatrics*. 1996;97(3):424–435.

38.   Carson RA, Mudd SS, Madati PJ. Clinical practice guideline for the treatment of pediatric acute gastroenteritis in the outpatient setting. *J Pediatr Health Care*. 2016;30(6):610–616. https://doi.org/10.1016/j.pedhc.2016.04.012

39.   Kira S, Mitsui T, Zakoji H, Aoki T, Sawada N, Miyamoto T, et al. Postrenal failure due to urinary stones associated with acute viral gastroenteritis: three case reports. *Case Rep Urol*. 2016;2016:1375923. https://doi.org/10.1155/2016/1375923

40.   Fujinaga S, Nishino T. Acute kidney injury due to rotavirus gastroenteritis-associated obstructive uric acid stones in a Japanese infant harboring a heterozygous W258X mutation. *Pediatr Nephrol*. 2016;31(12):2379–2380. https://doi.org/10.1007/s00467-016-3477-3

41.   Kucuk O, Ugras M, Bicer S, Col D, Giray T, Erdag GC, et al. Hypertransaminasaemia in children with viral gastroenteritis. *Infez Med*. 2016;24(1):32–37.

42.   Kuge R, Morikawa Y, Hasegawa Y. Uric acid and dehydration in children with gastroenteritis. *Pediatr Int*. 2017;59(11):1151–1156. https://doi.org/10.1111/ped.13366

43.   Morita T, Fujieda M. Acidosis with hyperuricemia and renal tubular damage in viral gastroenteritis. *Pediatr Nephrol*. 2011;26(12):2259–2260. https://doi.org/10.1007/s00467-011-2003-x

44.   Ochi F, Furuno K, Chong PF, Tezuka J, Mizuno Y, Aoki T, et al. Bilateral hydronephrosis due to obstructive ureteral stone associated with norovirus gastroenteritis. *Clin Case Rep*. 2017;5(6):936–938. https://doi.org/10.1002/ccr3.952

45.   Qadori M, Flem E, Bekkevold T, Døllner H, Gilje AM, Rojahn A, et al. Hypoglycaemia was common in acute gastroenteritis in a prospective hospital-based study, but electrolyte imbalances were not. *Acta Paediatr*. 2018;107(8):1455–1460. https://doi.org/10.1111/apa.14318

46.   Tsukida K, Goto M, Yamaguchi N, Imagawa T, Tamura D, Yamagata T. Rotavirus gastroenteritis-associated urinary tract calculus in an infant. *Turk J Pediatr*. 2018;60(6):769–770. https://doi.org/10.24953/turkjped.2018.06.025

47.   Ueda H, Tajiri H, Kimura S, Etani Y, Hosoi G, Maruyama T, et al. Clinical characteristics of seizures associated with viral gastroenteritis in children. *Epilepsy Res*. 2015;109:146–154. https://doi.org/10.1016/j.eplepsyres.2014.10.021

48.   Baral R, Nonvignon J, Debellut F, Agyemang SA, Clark A, Pecenka C. Cost of illness for childhood diarrhea in low- and middle-income countries: a systematic review of evidence and modelled estimates. *BMC Public Health*. 2020;20(1):619. https://doi.org/10.1186/s12889-020-08595-8

49.   Barker SF, Zomer E, O'Toole J, Sinclair M, Gibney K, Liew D, et al. Cost of gastroenteritis in Australia: a healthcare perspective. *PLoS One*. 2018;13(4):e0195759. https://doi.org/10.1371/journal.pone.0195759

50.   Leung AKC, Darling P, Auclair C. Oral rehydration therapy: a review. *J R Soc Health*. 1987;107(2):64–67. https://doi.org/10.1177/146642408710700210

51.   Leung AKC, Leung AAM, Wong AHC, Hon KL. Travelers' diarrhea: a clinical review. *Recent Pat Inflamm Allergy Drug Discov*. 2019;13(1):38–48. https://doi.org/10.2174/1872213X13666190514105054

52.   Bellemare S, Hartling L, Wiebe N, Russell K, Craig WR, McConnell D, et al. Oral rehydration versus intravenous therapy for treating dehydration due to gastroenteritis in children: a meta-analysis of randomized controlled trials. *BMC Med*. 2004;2:11. https://doi.org/10.1186/1741-7015-2-11

53.   Fonseca BK, Holdgate A, Craig JC. Enteral vs intravenous rehydration therapy for children with gastroenteritis: a meta-analysis of randomized controlled trials. *Arch Pediatr Adolesc Med*. 2004;158(5):483–490. https://doi.org/10.1001/archpedi.158.5.483

54.   Freedman SB, Pasichnyk D, Black KJ, Fitzpatrick E, Gouin S, Milne A, et al. Gastroenteritis therapies in developed countries: systematic review and meta-analysis. *PLoS One*. 2015;10(6):e0128754. https://doi.org/10.1371/journal.pone.0128754

55.   Issenman RM, Leung AK. Oral and intravenous rehydration of children. *Can Fam Physician*. 1993;39:2129–2136.

56.   Leung AK, Taylor PG, Geoffroy L, Darling P. Efficacy and safety of two oral solutions as maintenance therapy for acute diarrhea. A double-blind, randomized, multicenter trial. *Clin Pediatr*. 1988;27(8):359–364. https://doi.org/10.1177/000992288802700801

57.   O'Ryan M. Acute viral gastroenteritis in children in in resource-rich countries: management and prevention. In: Edwards MS, Li BUK, eds. *UpToDate*. Waltham, MA. https://www.uptodate.com/contents/acute-viral-gastroenteritis-in-children-in-resource-rich-countries-management-and-prevention. Accessed November 28, 2020.

58.   Brady K. Acute gastroenteritis: evidence-based management of pediatric patients. *Pediatr Emerg Med Pract*. 2018;15(2):1–25.

59.   Leung AKC, Robson WL. In children with vomiting related to gastroenteritis, are anti-emetic medications an effective adjunct to fluid and electrolyte therapy? Part B: clinical commentary. *Paediatr Child Health*. 2008;13(5):393–394. https://doi.org/10.1093/pch/13.5.393

60.   Nager AL, Wang VJ. Comparison of nasogastric and intravenous methods of rehydration in pediatric patients with acute dehydration. *Pediatrics*. 2002;109(4):566–572. https://doi.org/10.1542/peds.109.4.566

61.   Brandt KG, Castro Antunes MM, Silva GA. Acute diarrhea: evidence-based management. *J Pediatr*. 2015;91(6 Suppl. 1):S36–S43. https://doi.org/10.1016/j.jped.2015.06.002

62.   Iro MA, Sell T, Brown N, Maitland K. Rapid intravenous rehydration of children with acute gastroenteritis and dehydration: a systematic review and meta-analysis. *BMC Pediatr*. 2018;18(1):44. https://doi.org/10.1186/s12887-018-1006-1

63.   Toaimah FH, Mohammad HM. Rapid intravenous rehydration therapy in children with acute gastroenteritis: a systematic review. *Pediatr Emerg Care*. 2016;32(2):131–135. https://doi.org/10.1097/PEC.0000000000000708

64.   Leung, AKC. Oral rehydration therapy and early refeeding in the management of childhood gastroenteritis. In: Overton LT, Ewente MR, eds. *Child Nutrition Physiology*. New York, NY: Nova Biomedical Books, 2008, pp. 271–289.

65.   Sandhu BK, European Society of Paediatric Gastroenterology, Hepatology and Nutrition Working Group on Acute Diarrhoea. Rationale for early feeding in childhood gastroenteritis. *J Pediatr Gastroenterol Nutr*. 2001;33(Suppl. 2):S13–S16. https://doi.org/10.1097/00005176-200110002-00003

66.   Leung AKC, Robson WL. Acute gastroenteritis in children: role of anti-emetic medication for gastroenteritis-related vomiting. *Paediatr Drugs*. 2007;9(3):175–184. https://doi.org/10.2165/00148581-200709030-00006

67.   Roslund G, Hepps TS, McQuillen KK. The role of oral ondansetron in children with vomiting as a result of acute gastritis/gastroenteritis who have failed oral rehydration therapy: a randomized controlled trial. *Ann Emerg Med*. 2008;52(1):22–29. https://doi.org/10.1016/j.annemergmed.2007.09.010

68.   Tomasik E, Ziółkowska E, Kołodziej M, Szajewska H. Systematic review with meta-analysis: ondansetron for vomiting in children with acute gastroenteritis. *Aliment Pharmacol Ther*. 2016;44(5):438–446. https://doi.org/10.1111/apt.13728

69.   Niño-Serna LF, Acosta-Reyes J, Veroniki AA, Florez ID. Antiemetics in children with acute gastroenteritis: a meta-analysis. *Pediatrics*. 2020;145(4):e20193260. https://doi.org/10.1542/peds.2019-3260

70.   Freedman SB, Fuchs S. Antiemetic therapy in pediatric emergency department. *Pediatr Emerg Care*. 2004;20(9):625–632. https://doi.org/10.1097/01.pec.0000139748.61838.ad

71.   Freedman SB, Adler M, Seshadri R, Powell EC. Oral ondansetron for gastroenteritis in a pediatric emergency department. *N Engl J Med*. 2006;354:1698–1705. https://doi.org/10.1056/NEJMoa055119

72.  Freedman SB. Acute infectious pediatric gastroenteritis: beyond oral rehydration therapy. *Expert Opin Pharmacother*. 2007;8(11):1651–1665. https://doi.org/10.1517/14656566.8.11.1651

73.  Lalani N, Gaco D. Ondansetron for gastroenteritis in children and adolescents. *Am Fam Physician*. 2015;91(7):Online.

74.  Hoffman RJ, Alansari K. Effect of intravenous ondansetron on QTc interval in children with gastroenteritis. *Am J Emerg Med*. 2018;36(5):754–757. https://doi.org/10.1016/j.ajem.2017.10.004

75.  Sáez J, Cifuentes L. Is racecadotril effective for acute diarrhea in children? First update. *Medwave*. 2016;16(Suppl. 2):e6438. https://doi.org/10.5867/medwave.2016.6438

76.  Szajewska H, Ruszcznski M, Chmielewska A, Wieczorek J. Systematic review: racecadotril in the treatment of acute diarrhea in children. *Aliment Pharmacol*. 2007;26(6):807–813. https://doi.org/10.1111/j.1365-2036.2007.03444.x

77.  Eberlin M, Chen M, Mueck T, Däbritz J. Racecadotril in the treatment of acute diarrhea in children: a systematic, comprehensive review and meta-analysis of randomized controlled trials. *BMC Pediatr*. 2018;18(1):124. https://doi.org/10.1186/s12887-018-1095-x

78.  Campbell J. Smectite for acute infectious diarrhoea in children: a Cochrane review summary. *Int J Nurs Stud*. 2020:103645. https://doi.org/10.1016/j.ijnurstu.2020.103645

79.  Pérez-Gaxiola G, Cuello-García CA, Florez ID, Pérez-Pico VM. Smectite for acute infectious diarrhoea in children. *Cochrane Database Syst Rev*. 2018;4(4):CD011526. https://doi.org/10.1002/14651858.CD011526.pub2

80.  Rossignol JF, Abu-Zekry M, Hussein A, Santoro MG. Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. *Lancet*. 2006;368(9530):124–129. https://doi.org/10.1016/S0140-6736(06)68852-1

81.  Rossignol JF, El-Gohary YM. Nitazoxanide in the treatment of viral gastroenteritis: a randomized double-blind placebo-controlled clinical trial. *Aliment Pharmacol Ther*. 2006;24(10):1423–1430. https://doi.org/10.1111/j.1365-2036.2006.03128.x

82.  Teran CG, Teran-Escalera CN, Villarroel P. Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. *Int J Infect Dis*. 2009;13(4):518–523. https://doi.org/10.1016/j.ijid.2008.09.014.

83.  Saavedra JM, Bauman NA, Oung I, Perman JA, Yolken RH. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. *Lancet*. 1994;344(8929):1046–1049. https://doi.org/10.1016/s0140-6736(94)91708-6

84.  Thomas DW, Greer FR; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. *Pediatrics*. 2010;126(6):1217–1231. https://doi.org/10.1542/peds.2010-2548

85.  van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics*. 2002;109(4):678–684. https://doi.org/10.1542/peds.109.4.678

86.  Vandenplas Y, Salvatore S, Viera M, Devreker T, Hauser B. Probiotics in infectious diarrhea in children: are they indicated? *Eur J Pediatr*. 2007;166(2):1211–1218. https://doi.org/10.1007/s00431-007-0497-9

87.  Ansari F, Pashazadeh F, Nourollahi E, Hajebrahimi S, Munn Z, Pourjafar H. A systematic review and meta-analysis: the effectiveness of probiotics for viral gastroenteritis. *Curr Pharm Biotechnol*. 2020;21(11):1042–1051. https://doi.org/10.2174/1389201021666200416123931

88.  Bahl R, Bhandari N, Saksena M, Strand T, Kumar GT, Bhan MK, et al. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. *J Pediatr*. 2002;141(5):677–682. https://doi.org/10.1067/mpd.2002.128543

89.  Bhatnager S, Bahl R, Sharma PK, Kumar GT, Saxena SK, Bhan MK. Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. *J Pediatr Gastroenterol Nutr*. 2004;38(1):34–40. https://doi.org/10.1097/00005176-200401000-00010

90.  Goldman RD. Zinc supplementation for acute gastroenteritis. *Can Fam Physician*. 2013;59(4):363–364.

91.  Patel AB, Dhande LA, Rawat, MS. Therapeutic evaluation of zinc and copper supplementation in acute diarrhea in children: double blind randomized trial. *Indian Pediatr*. 2005;42(5):433–442.

92.  Patro B, Golicki D, Szajewska H. Meta-analysis: zinc supplementation for acute gastroenteritis in children. *Aliment Pharmacol Ther*. 2008;28(6):713–723. https://doi.org/10.1111/j.1365-2036.2008.03787.x

93.  Kouame KS, Verga ME, Pittet A, Rey-Bellet CG, Gehri M, Fontaine O, et al. Zinc and diarrhea in children under 5 years: WHO recommendations implemented in Switzerland [In French]. *Rev Med Suisse*. 2012;8(344):1244–1247.

94.  Dhingra U, Kisenge R, Sudfeld CR, Dhingra P, Somji S, Dutta A, et al. Lower-dose zinc for childhood diarrhea – a randomized, multicenter trial. *N Engl J Med*. 2020;383(13):1231–1241. https://doi.org/10.1056/NEJMoa1915905

95.  Lazzerini M, Wanzira H. Oral zinc for treating diarrhoea in children. *Cochrane Database Syst Rev*. 2016;12(12):CD005436. https://doi.org/10.1002/14651858.CD005436.pub5

96.  Alexander E, Hommeida S, Stephens MC, Manini ML, Absah I. The role of oral administration of immunoglobulin in managing diarrheal illness in immunocompromised children. *Paediatr Drugs*. 2020;22(3):331–334. https://doi.org/10.1007/s40272-020-00389-0

97. Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. *J Infect Dis*. 2017;215(11):1666–1672. https://doi.org/10.1093/infdis/jix186

98. Getachew HB, Dahl RM, Lopman BA, Parashar UD. Rotavirus vaccines and health care utilization for diarrhea in US children, 2001 to 2015. *Pediatr Infect Dis J*. 2018;37(9):943–948. https://doi.org/10.1097/INF.0000000000001988

99. Lamberti LM, Ashraf S, Walker CL, Black RE. A systematic review of the effect of rotavirus vaccination on diarrhea outcomes among children younger than 5 years. *Pediatr Infect Dis J*. 2016;35(9):992–998. https://doi.org/10.1097/INF.0000000000001232

100. Pietsch C, Liebert UG. Rotavirus vaccine effectiveness in preventing hospitalizations due to gastroenteritis: a descriptive epidemiological study from Germany. *Clin Microbiol Infect*. 2019;25(1):102–106. https://doi.org/10.1016/j.cmi.2018.03.046

101. Gibory M, Dembinski JL, Flem E, Haltbakk I, Dudman SG. Effect of rotavirus vaccine implementation on the prevalence of coinfections with enteric viruses in Norway. *J Med Virol*. 2020;92:3151–3156. https://doi.org/10.1002/jmv.26013

102. Ahmad I, Ali SS, Zafar B, Hashmi HF, Shah I, Khan S, et al. Development of multi-epitope subunit vaccine for protection against the norovirus' infections based on computational vaccinology. *J Biomol Struct Dyn*. 2020;10:1–12. https://doi.org/10.1080/07391102.2020.1845799

103. Atmar RL, Baehner F, Cramer JP, Song E, Borkowski A, Mendelman PM; NOR-201 Study Group. Rapid responses to 2 virus-like particle norovirus vaccine candidate formulations in healthy adults: a randomized controlled trial. *J Infect Dis*. 2016;214(6):845–853. https://doi.org/10.1093/infdis/jiw259

104. Baehner F, Bogaerts H, Goodwin R. Vaccines against norovirus: state of the art trials in children and adults. *Clin Microbiol Infect*. 2016;22(Suppl. 5):S136–S139. https://doi.org/10.1016/j.cmi.2015.12.023

105. Bernstein DI, Atmar RL, Lyon GM, Treanor JJ, Chen WH, Jiang X, et al. Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. *J Infect Dis*. 2015;211(6):870–878. https://doi.org/10.1093/infdis/jiu497

106. Lindesmith LC, Ferris MT, Mullan CW, Ferreira J, Debbink K, Swanstrom J, et al. Broad blockade antibody responses in human volunteers after immunization with a multivalent norovirus VLP candidate vaccine: immunological analyses from a phase I clinical trial. *PLoS Med*. 2015;12(3):e1001807. https://doi.org/10.1371/journal.pmed.1001807

107. Sundararajan A, Sangster MY, Frey S, Atmar RL, Chen WH, Ferreira J, et al. Robust mucosal-homing antibody-secreting B cell responses induced by intramuscular administration of adjuvanted bivalent human norovirus-like particle vaccine. *Vaccine*. 2015;33(4):568–576. https://doi.org/10.1016/j.vaccine.2014.09.073

108. Treanor JJ, Atmar RL, Frey SE, Gormley R, Chen WH, Ferreira J, et al. A novel intramuscular bivalent norovirus virus-like particle vaccine candidate – reactogenicity, safety, and immunogenicity in a phase 1 trial in healthy adults. *J Infect Dis*. 2014;210(11):1763–1771. https://doi.org/10.1093/infdis/jiu337

109. Cates JE, Vinjé J, Parashar U, Hall AJ. Recent advances in human norovirus research and implications for candidate vaccines. *Expert Rev Vaccines*. 2020;19(6):539–548. https://doi.org/10.1080/14760584.2020.1777860