Current Infectious Disease Reports (2020) 22: 4
https://doi.org/10.1007/s11908-020-0713-6

PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Acute Infectious Diarrhea and Gastroenteritis in Children

Ivan D. Florez[1,2] · Laura F. Niño-Serna[2,3] · Claudia P. Beltrán-Arroyave[2]

Published online: 28 January 2020

Abstract

Purpose of Review We aimed to summarize the most current evidence on the main aspects of the diarrheal diseases in children. The following key elements were addressed: definitions, etiology, pathogenesis, diagnosis, dietary management, pharmacological treatments, and prevention. We covered the following questions: What are the most important clinical and laboratory features of the disease? What are the best approaches for the dietary management? What is the best way to classify the hydration status, and to prevent and treat the dehydration? What are the most effective and safe interventions for reducing the diarrhea and vomiting?

Recent Findings Diarrheal diseases are one of the most common diseases in childhood. The most common cause is rotavirus. A key element in the approach of a child with diarrhea is determining their hydration status, which determines the fluid management. Laboratory tests are nor routinely required, as most of the cases, they do not affect the management and it should be indicated only in selected cases. Several treatments have been studied to reduce the duration of the diarrhea. Only symbiotics and zinc have shown to be effective and safe with high certainty on the evidence. Rest of the interventions although seem to be effective have low to very low quality of the evidence. The only effective and safe antiemetic for controlling vomiting is ondansetron. A list of antimicrobials indications according to the identified microorganisms is provided.

Summary We summarized the most current evidence on diagnosis, management, and prevention of diarrhea in children. More research is needed in some areas such as dehydration scales, rehydration management, antidiarrheals, and antibiotic treatments.

Keywords Gastroenteritis · Diarrhea · Rotavirus · Dehydration · Antidiarrheals · Antiemetics · Pediatrics

Introduction

Diarrheal diseases accounted for more than half-million deaths of children under 5 years old in 2013 [1, 2]. Most of these deaths occur in low- and middle-income countries (LMIC). In high-income countries (HIC), meanwhile, the disease is rarely fatal, but it is a leading cause of visits to the emergency department and hospitalizations [3]. The World Health Organization (WHO) defines acute diarrhea as the passage of three or more loose or liquid stools per day, for 3 or more days, and less than 14 days [4]. On the other hand, the American Academy of Pediatrics (AAP) defines acute gastroenteritis as a diarrheal disease of rapid onset, with or without additional symptoms and signs, such as nausea, vomiting, fever, or abdominal pain [5]. When literature focuses on the impact of the disease in children in LMIC, the preferred terms are "acute diarrhea" or "diarrheal disease," whereas when literature focuses on children in HIC, the most common term is "acute gastroenteritis." Although based on different definitions, all these terms are describing the same disease: a gastrointestinal infection caused by specific microorganisms such as rotavirus, norovirus, *Salmonella*, *E. coli*, and *Campylobacter* [6]. In this narrative review, we use the term "diarrhea," but we aimed to capture the most relevant information regardless of the context (acknowledging the potential differences of the disease in children from LMIC and HIC),

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

✉ Ivan D. Florez
ivan.florez@udea.edu.co

Laura F. Niño-Serna
fernanda.nino@udea.edu.co

Claudia P. Beltrán-Arroyave
claudia.beltran@udea.edu.co

[1] Department of Health Research Methods, Evidence and Impact, McMaster University, Juravinski Site. G Wing, 2nd Floor; 711 Concession Street, Hamilton, ON L8V 1 C3, Canada

[2] Department of Pediatrics, University of Antioquia, Medellin, Colombia

[3] Department of Pediatrics, Hospital Pablo Tobón Uribe, Medellin, Colombia

and therefore, we aimed to update the evidence on acute infectious diarrhea and gastroenteritis in children.

Classifications

According to the WHO, the disease can be classified in acute watery diarrhea, acute bloody diarrhea (dysentery), persistent diarrhea, and diarrhea with severe malnutrition [4]. We focus on the first two as they are the most common in either LMIC or HIC. Persistent diarrhea is a complex condition in which a diarrheal episode does not resolve appropriately and lasts more than 14 days [4]. This condition requires a separate review, and it is out of the scope of this article. Diarrhea in children with severe malnutrition also requires a different approach because these children are at high risk of severe complications (electrolytes disturbances, infections and death). These cases should be managed following specific guidelines for severe malnutrition [7].

Chronic diarrhea is another term worth mentioning. Some authors use this term interchangeably with persistent diarrhea, but most commonly is used for those diarrheal episodes that last more than 4 weeks [7]. Chronic diarrhea occurs in children with long-lasting diarrhea that is not preceded by acute onset, and as a manifestation of genetic, structural or inflammatory diseases (e.g., cystic fibrosis, inflammatory bowel disease, or short-bowel syndrome). This disease is also out of the scope of this review.

Etiology and Epidemiology

Viruses are the leading causes of diarrhea in children accounting for approximately 70–90% of cases [8, 9]. Bacteria as *Shigella*, *Salmonella*, *Campylobacter* and, enterotoxigenic *E. coli* (ETEC), and less frequently enteroinvasive *E. coli* (EIEC), are causative agents in 10–20% of cases [10]. Anaerobic bacteria can cause diarrhea mediated by toxins. *Clostridium difficile* toxins produce antibiotic-associated diarrhea (AAD) and is a leading cause of disease in hospitalized children and adults [11]. Some authors have investigated the role of *Bacteroides fragilis* enterotoxin in children with diarrhea in LMIC [12]. However, this association remains controversial since *B. fragilis* can be isolated in healthy children as well [13].

Although viruses are the leading causes in most of the cases, the relative frequency of both viruses and bacteria varies according to the context: viruses have higher frequency rates in children from HIC than in those from LMIC [14]. Parasites are present in less than 5% of cases, mainly *Cryptosporidium*, *Giardia*, and *E. histolytica* [15]. Similar to bacteria, parasites are more frequent in LMIC [10].

Rotavirus was the leading cause of viral diarrhea and also the main cause of hospitalizations and severe disease, but after the introduction of rotavirus vaccines (RV), rotavirus-related hospitalizations and deaths have significantly decreased [14, 16, 17]. Currently, in countries that have introduced RV, norovirus has become the leading cause of moderate to severe disease, traveler's diarrhea and outbreaks due to food poisoning in children younger than 2 years old [8, 10, 18].

Pathogenesis

The most common modes of transmission of enteropathogens are via person-to person, by fecal–oral route, or by ingestion of contaminated food or water. Incubation periods usually range between 1 h (toxin-producing bacteria: *S. aureus*) and 7 days (invasive bacteria as *Shigella)* [19]. However, for some bacteria, incubation periods can be up to 14 days (*Salmonella*) and for some parasites up to weeks or months (*E. histolytica*) [20].

Diarrhea is secondary to excessive intestinal secretion or to impaired fluid and electrolytes absorption across the intestinal epithelium [21]. Watery diarrhea is commonly caused by cytolytic microorganisms or by toxin-producing bacteria. Viruses produce a cytolytic effect in the intestinal epithelium, inflammation, and cytokine liberation, which produce a decrease in the absorption of water, and in the disaccharides' digestion. In secretory diarrhea (e.g., *V. cholerae* and ETEC), the stimulation of water and electrolytes secretion due to the activation of the adenylate cyclase, which raises the intracellular cAMP and/or cGMP, and calcium, turns epithelial cells to an active secretion of chloride state [21]. Inflammatory diarrhea is caused by microorganisms that produce cytotoxins (e.g., *Shigella* and STEC) or invade and disrupt the intestinal epithelium (e.g., *Salmonella*, *Campylobacter*) producing inflammation and necrosis of epithelium and microabscesses [19].

Clinical Assessment

An episode of acute watery diarrhea is characterized by loose or liquid stools, which can be accompanied by hyporexia, vomiting, fever, and abdominal pain [22]. Common causes are viruses (rotavirus, norovirus, adenovirus) or non-invasive bacteria (ETEC, non-typhoidal *Salmonella* and *Campylobacter).* Less frequently, the disease can present as dysentery: bloody diarrhea associated with high fever and toxicity. These episodes are caused by *Shigella*, EIEC, and some strains of *Salmonella* and *Campylobacter.* Parasitic infections can present as explosive and mucus or bloody stools, cramping, tenesmus (*E. histolytica*), or as a malabsorption syndrome (*Giardia*) [23].

Table 1 Classification of the hydration status according to three different scales

Classification of dehydration and studies' characteristics	WHO [4]	CDS [27]	Gorelick scale (4-item model) [28]	Gorelick scale (10-item model) [28]
No dehydration	No signs of dehydration (< 5% fluid deficit): -Well, alert -Normal eyes -Drinks normally, not thirsty -Skin fold goes back quickly	Score 0 (< 3% fluid deficit): -Normal general appearance -Normal eyes -Moist mucous membranes -Tears	-Alert -Normal capillary refill -Tears present -Moist mucous membranes	-Alert -Normal capillary refill -Tears present -Moist mucous membranes -Normal eyes -Normal breathing -Normal pulses -Instant recoil of skin -Normal heart rate -Normal urine output
Mild dehydration	Some dehydration (5–10% fluid deficit): -Restless, irritable, sunken eyes -Thirsty, drinks eagerly -Skin fold goes back slowly	Score 1–4 (3–6% fluid deficit): -Thirsty, restless, or lethargic but irritable when touched -Slightly sunken eyes -Sticky -Decreased tears		
Moderate dehydration		Score 5–8 (> 6% fluid deficit):	-Restless, lethargic, unconscious -Prolonged capillary refill -Tears absent -Dry or very dry mucous membranes Note: Deficit varies according to the number of the above signs present in the child*	-Restless, lethargic, unconscious -Prolonged capillary refill -Tears absent -Dry or very dry mucous membranes -Sunken eyes -Deep and rapid breathing -Thready, weak, or impalpable pulses -Recoil of skin slowly -Tachycardia -Reduced urine output Note: Deficit varies according to the number of the above signs present in the child†
Severe dehydration	Severe dehydration (> 10% fluid deficit): Lethargic or unconscious -Sunken eyes -Drinks poorly or not able to drink -Skin fold goes back very slowly.	-Drowsy, limp, cold, sweaty; comatose or not -Very sunken -Dry -Absent tears		
Characteristics of the studies¶ (Children's age/number and context of studies)	1 month to 5 years/7 studies (5 in LMIC)	1 month to 3 years/8 studies (4 in HIC)	1 month to 5 years/5 studies (2 in HIC)	1 month to 5 years/4 studies (2 in HIC)

CDS, clinical dehydration scale; *HIC*, high-income countries; *LMIC*, low- and middle-income countries; *WHO*, World Health Organization

*≥ 2 clinical signs, moderate dehydration, ≥ 5%; ≥ 3 clinical signs, severe dehydration, ≥ 10%

† ≥ 3 clinical signs, moderate dehydration, ≥ 5%; ≥ 7 clinical signs, severe dehydration, ≥ 10%

¶ Characteristics of the studies in which the scale has been evaluated. Information extracted and modified from Falszewska et al. [30]

The clinical interrogation should focus on determining level of stool output and the hydration status (asking about urine output, number of stools and vomiting episodes, and the amount of liquid and food intake), the characteristics of diarrhea (i.e., watery, mucus or bloody stools), the duration of symptoms, history of travel to endemic areas, past medical history (immunosuppression or comorbidities), immunizations (i.e., RV), ingestion of drugs (e.g., antibiotics, or laxatives), history of family members with similar manifestations, and on documenting the pre-illness weight [24, 25].

Physical examination should focus on the evaluation of the hydration status. The gold standard for determining the degree of dehydration is the child's weight loss. Since, in most cases, the precise pre-illness child's weight is unknown, we must rely on the evaluation of the dehydration signs. When analyzed individually, the best three dehydration signs are altered capillary refill time, abnormal skin turgor, and abnormal respiratory pattern [26]. However, since one single sign is not enough for detecting dehydration appropriately, dehydration scales combining two or more signs are to be used. There are three commonly used scales: the clinical dehydration scale (CDS) [27], Gorelick [28], and WHO scales [4]. Table 1 provides a comparison of the three scales and the signs used for their classification. In HIC, it may be more frequent the use of CDS or Gorelick scale, while in LMIC, the WHO scale is the preferred one. However, these scales' accuracy has been found suboptimal [29]. The evidence from children in HIC suggests that WHO and Gorelick scales are not useful for assessing dehydration, and the CDS scale, although still not very accurate, it might be the best of the three to predict the degree of dehydration [30]. Further research on the development of new tools for assessing the severity of dehydration should be encouraged.

Laboratory Evaluation

Laboratory studies are not routinely required. Serum electrolytes, renal function, and acid-base status (bicarbonate levels) are only helpful when markedly abnormal, therefore, should only be ordered in cases of severe dehydration or when there is a strong suspicion of electrolytes imbalance (e.g., seizures, or arrhythmias) [24, 26, 31].

Since most diarrheal episodes are considered self-limited and, the identification of an enteropathogen does not affect the management and natural history of the disease in most of the cases, determining the specific etiology is not a priority. However, in some cases, identifying the cause could have the potential of decreasing the indiscriminate use of antibiotics, and therefore, of preventing the development of bacterial resistance and dysregulation of the microbiome [32].

Viral identification can be achieved using traditional enzyme immunoassays for rotavirus and adenovirus, which are widely available [23]. Identification of other viruses (e.g., calicivirus) can be obtained with the nucleic acid amplification test. However, viral identification is not routinely recommended. Specific bacteria detection can be performed with bacterial cultures or rapid molecular tests by rapid polymerase chain reaction (PCR). Stool cultures are costly, cover few microorganisms, and do not provide rapid results. Therefore, they are not routinely recommended [23, 33]. Yet, they should be ordered in cases of toxic appearance, sepsis, high fever (> 39 °C/102 °F), dysentery, immunosuppression, diarrhea > 7 days, or history of travel to bacterial infection high-risk areas [33–35].

Regarding rapid molecular tests, several commercial multiplex assays are available for bacterial identification [36]. They can identify 8 to 22 pathogens in a matter of minutes or hours, which makes them very useful for decision-making. However, these tests are expensive and not widely available, which make them not feasible in LMIC. Some guidelines recommend them in cases of clinical suspicion of enteric fever (*Salmonella typhi*) and bacteremia/sepsis [23]. Recent studies have found that introducing rapid tests in LMIC contexts may have an impact on targeting antibiotic therapies in children [37]. Nevertheless, there is still not enough evidence for using them routinely.

Stool microbiological examination is only indicated in cases of strong suspicion of parasitic infections, such as diarrhea > 7 days or history of travel to endemic areas [35]. *Clostridium difficile* toxin test should be considered when there is a history of recent antibiotic treatment (previous 8–12 weeks) to rule out AAD [38]. Tests for other anaerobic bacteria, such as *B. fragilis* toxin detection, are not routinely recommended [12]. Blood cultures should be obtained in infants younger than 3 months of age, suspicion of sepsis or enteric fever, and when there is a history of hemolytic anemia or immunosuppression [23]. It should be noted that a proper clinical interpretation should accompany any microbiological test because the presence of a microorganism does not necessarily mean it is the cause of the disease.

Fluids Management

The mainstay of the management of the diarrhea is the fluid replacement. The WHO defines three different management plans according to the hydration status: plans A, B, and C [4]. Plan A aims to prevent dehydration and malnutrition, and it includes giving the child more fluids than usual. Suitable fluids for this purpose are those that contain appropriate amounts of salt and glucose, such as oral rehydrated solutions (ORS), salted drinks, and vegetable or chicken soups [4]. Commercial electrolyte solutions (CES) might be an alternative as well. Inappropriate and potentially dangerous fluids are carbonated beverages, commercial fruit juices or any sweetened beverages, and beverages with laxative or stimulant

effects (coffee or some teas) [4]. A general rule is to give suitable fluids after each loose stool 50–100 mL in younger than 2 years old, and 100–200 mL in older children [4].

Plan B is the recommended treatment for patients with some (mild-to-moderate) dehydration [4, 5, 23, 24]. Plan B is based on the oral rehydration therapy (ORT). Three systematic reviews have concluded that there are no significant differences between ORT and intravenous rehydration in non-severe dehydration, in terms of treatment failure, dysnatremia, total of fluid intake, and weight gain [39–41]. Moreover, ORT (and also nasogastric rehydration) showed a reduction of 1.2 days in the total hospital stay in comparison with intravenous therapy. ORT is not only safer and faster to initiate, but also cheaper than the intravenous therapy [42–44]. Therefore, ORT should always be the first line of treatment reserving intravenous for cases in which the former fails.

In plan B, fluid replacement is based on the calculated percentage of dehydration. WHO recommends 75 mL/kg orally with ORS, administered continuously until dehydration signs are lost (around 2–4 h). The recommended ORS for ORT is the low osmolarity oral rehydration solution (L-ORS). In comparison with a standard oral rehydration solution (S-ORS) (sodium, 90 mEq/L; osmolarity, 311 mOsm/L), the L-ORS (sodium, 90 mEq/L; osmolarity, 245 mOsm/L) significantly reduces the stool output and vomiting, without causing more hyponatremia [45]. There is not enough evidence to support other types of ORS (e.g., polymer-based ORS) for plan B [46].

Some evidence from children in HIC shows that half-strength apple juice might be an alternative to L-ORS for ORT in children with mild dehydration. Freedman et al. compared a half-strength apple juice (sodium, 0 mEq/L; osmolarity, 365 mOsm/L) with a CES (sodium, 45 mEq/L; osmolarity, 250 mOsm/L), finding that the former resulted in fewer treatment failures [47]. The rationale of these results relies on the salty taste, which makes many children with no dehydration or very mild to refuse S-ORS, L-ORS, and CES, and thus, a tastier solution might be helpful in these children. However, these results might not be applicable to other contexts (e.g., LMIC, or children with high sodium losses or very high fecal output), because fluid replacement with a solution without sodium may predispose the child to potentially dangerous hyponatremia. More evidence is required to support, or to discard, this alternative.

Plan C is the recommended approach for patients with severe dehydration, shock, or when there are contraindications for ORT (i.e., persistent vomiting, ileus, severe abdominal distension, unconsciousness or worsening dehydration despite ORT) [4, 5, 24, 25]. This plan requires a rapid intravenous rehydration (6 h for infants and 3 h for older children) [4]. The best solution for achieving this goal is not known. Although WHO and AAP recommend Ringer's lactate [4, 48], other guidelines recommend 0.9% saline [24, 35]. A registered Cochrane review title is aiming to compare the effectiveness of 0.9% saline with balanced solutions (i.e., solutions with less chloride, with additional cations, such as potassium, calcium, or magnesium, and anions, such as lactate, acetate, or gluconate, which are metabolized to bicarbonate) and it will help to elucidate what is the best fluid for intravenous rehydration [49]. The use of 0.9% saline for resuscitation in comparison with balanced solutions (RL and Plasma-Lyte®) has been associated with metabolic acidosis and hyperchloremia in different conditions [50]. Until new evidence emerges, 0.9% saline should only be reserved for bolus therapy in cases of hypovolemic shock.

The length of the rehydration therapy has also been a matter of research hypovolemic shock, and when no other solution is available. Two major approaches have been used: rapid (fluid replacement in 3 to 6 h) vs. standard (fluid replacement in 12 to 24 h). Two systematic reviews that evaluated both approaches found similar results in terms of the success of rehydration, the time to discharge from the emergency department (ED), the ED re-visiting, readmission, and the correction of the electrolyte disturbances [51, 52]. Hence, rapid rehydration is the most frequently recommended approach for plan C in either LMIC [24] or HIC [4].

Hypodermoclysis or subcutaneous route has been studied as an alternative to intravenous rehydration. Two single-arm studies found that recombinant human hyaluronidase-facilitated subcutaneous (rHFSC) rehydration may be an acceptable alternative in children with difficult venous access [53, 54]. However, these studies were industry-sponsored, they lacked a control group and they had very small sample sizes. The only available RCT in children with non-severe dehydration concluded that the rHFSC was non-inferior to intravenous rehydration and was easy to use [55]. More evidence is needed before recommendations are drawn upon their use. One systematic review is currently ongoing [56].

Dietary Management

At least as important as the fluid management, is the dietary management. According to the WHO, infants and children should always continue feeding to prevent nutritional damage [4]. If the infant is breastfed, except in cases of severe dehydration, breastfeeding should always continue (even during plan B). Older children, should continue usual feeding for their age at home. Offering the child food frequently is recommended. Frequent, small portions are tolerated better than less frequent, large ones. For decades, he best time to restart feeding after rehydration was a topic of discussion. A systematic review found no differences in the need for intravenous rehydration, vomiting episodes, or the development of persistent diarrhea, when restarting feeding early after rehydration (within 12 h) in comparison with delayed

feeding (after 12 h) [57]. Hence, after rehydration, all children should restart their feeding as early as possible.

Perhaps the most common area of controversy on dietary management has been the use lactose-free milk formula. An early review found a small beneficial effect on the duration of diarrhea and reduction of treatment failure with lactose-free in comparison with regular feeding (lactose-containing formula) [58]. More recent systematic reviews show a reduction in the duration of the diarrhea between 12 and 17 h. However, the quality of the evidence was low, and some subgroup analyses have suggested that the effect might be significant in children in HIC but not in children from LMIC [59, 60]. Moreover, there is evidence suggesting that feeding children with diluted milk is not only ineffective but could also be harmful [60]. Therefore, considering the low quality of evidence, the small effect and the uncertainty around its effect, there is no evidence to routinely give lactose-free milk of formula, and there is enough evidence to avoid the use of diluted milk.

Antidiarrheals

For decades, there has been a search for interventions that may reduce the stool volume and the duration of diarrhea. Different alternatives have been studied even though many guidelines do not recommend their use [4, 35]. Among the most studied interventions are the probiotics, which are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [61]. Evidence has shown that probiotics do have a beneficial effect in reducing the duration of the diarrhea [62]. However, most of the synthesized evidence has several limitations (high risk of bias in studies and substantial heterogeneity), which reduces the certainty of the results. The challenge with probiotics might be related to a large variety of probiotics, i.e., different strains, combinations, and doses. Some probiotics strains might be useful, but others might not. The most studied strains for the treatment of diarrhea are *Sacharomyces boulardii*, *Lactobacillus* GG (*casei* strain, also called: LGG), and *Lactobacillus reuteri*. All of them have shown some effect in reducing diarrhea duration by 15–24 h in comparison with placebo [63–65]. Other strains have no effect or have not been appropriately studied to be recommended.

Smectite is a medicinal clay commonly prescribed to reduce the stool output. Although the evidence is also of low quality, smectite seems to reduce the diarrhea duration by approximately 24 h [66, 67]. Racecadotril is an antisecretory drug that inhibits intestinal enkephalinase without slowing intestinal transit [68]. Although commonly used in some countries, the evidence behind this drug is more limited. Early systematic reviews found a significant effect on the diarrhea duration [69, 70]. However, recent studies showed that racecadotril was no different from placebo [71, 72].

Zinc is a micronutrient essential for many metabolic processes in the body. Zinc deficiency is a public health problem as it has been associated with poor growth and increase in morbidity and mortality [73]. Moderate to high quality evidence shows that zinc reduces the duration of the diarrheal episode and the risk of having another episode in the following 3 months [74, 75]. Nonetheless, the vast majority of its evidence comes from LMIC (in which is widely recommended), and very few reports on its effectiveness in HIC are available [76].

Loperamide, a popular intervention for the treatment of diarrhea in adults, is an opioid receptor agonist that acts by binding to opiate receptors in the gut [77]. A systematic review by Li et al. found that is effective in reducing the diarrhea on average, 19 h in comparison with placebo [78]. However, there are serious concerns on its use in children. Several cases of severe abdominal distension, respiratory depression, serious cardiac adverse reactions, and deaths have been described with the use of loperamide in children [22]. Loperamide is contraindicated in children younger than 2 years old.

Gelatin tannate is a compound based on tannic acid suspension in a gelatin solution. Its specific mechanism of action is unknown but it seems to have astringent, anti-inflammatory, and antibacterial properties [79]. Although it is used in several European countries in adults and children, a recent systematic review concluded that its effect is no different from placebo in children [79]. Additional interventions that have been studied and have either a very small effect (lactose-free milk and yogurt), or no effect at all "(multiple micronutrients without zinc, vitamin A, prebiotics, gelatine tannate, and kaolin pectin) on the duration of the diarrhea, are not indicated [60, 79].

To summarize, most of the interventions have shown some effect in reducing the diarrhea duration. However, the evidence of differences among them (trials comparing them against each other are scarce). In a recent network meta-analysis, our group analyzed all the evidence available to determine the relative differences among the interventions. We found that in general, probiotics (LGG, *S. boulardii*, and *L. reuteri*), smectite, zinc, racecadotril, and symbiotics provide a very similar effect: a reduction between 18 and 30 h in duration, and there were no significant differences in the effect among them [60]. Nevertheless, the quality of the evidence that supports the evidence was low to very low in all the cases, except for symbiotics and zinc [60]. These two interventions seem to be, among all, the ones that, with more certainty, produce a significant reduction on the duration of the diarrhea. The evidence of symbiotics comes almost exclusively from HIC, while the evidence of zinc is almost exclusively coming from LMIC. The evidence that supports the effect of smectite, probiotics, and racecadotril has very low certainty to be routinely recommended. Table 2 summarizes the effect of all the interventions mentioned above based on the certainty of the evidence that supports them, for reducing the diarrhea.

Table 2 Summary of the effectiveness of the best interventions for reducing the diarrhea and controlling vomiting

Outcome of interest	Summary of effectiveness	Certainty of the evidence[†]	Interventions	Details of the effect	Comments/remarks
Reduction in the duration of the diarrhea	Effective	High certainty on the results	Zinc	Reduces 18 h the duration of the diarrhea	Effect seems to be larger in inpatients and in children in LMIC Not effective in younger than 6 months
			Symbiotics (prebiotics + probiotics)	Reduces 26 h the duration of the diarrhea	Studied mostly in patients in HIC. Effect only applies to following mixtures: (1) *L. acidophilus*, *L. rhamnosus*, *B. bifidum*, *B. longum*, *E. faecium* + FOS (2) *L. paracasei* B21060 + ABG and XOS (3) *S. thermophilus*, *L. rhamnosus*, *L. acidophilus*, *B. infantis*, *B. lactis* + FOS (4) *L. casei*, *L. rhamnosus*, *L. plantarum*, *B. lactis* + FOS and GOS and polydextrose and thiamine (5) *B. lactis* B94 + inulin
			Loperamide	Reduces 17 h the duration of the diarrhea	Studied in both HIC and LMIC. Although effective, is the most unsafe intervention: associated with ileus, somnolence, and abdominal distension
		Low certainty on the results	Smectite	Reduces 23 h the duration of the diarrhea	It has been studied in both HIC and LMIC. Low quality of evidence due to high RoB of studies and inconsistency
			Racecadotril	Reduces 78 h the duration of the diarrhea	It has been studied in both HIC and LMIC. Conflicting evidence. Low quality of evidence due to high RoB of studies and inconsistency
			Probiotics	Reduces 17–23 h the duration of the diarrhea	Low quality of evidence due to high RoB of studies and inconsistency Differences in effects among the strains. The most studied and effective are *S. boulardii*, *LGG*, and *L. reuteri*. Many available strains have not enough evidence or no evidence at all.
			Lactose-free milk	Reduces 12 h the duration of the diarrhea	Evidence only for < 12–24 months and mostly in non-breastfed infants Very low quality of the evidence due to high RoB and inconsistency
			Yogurt	Reduces 16 h the duration of the diarrhea	Includes yogurt with and without probiotics. Very low quality of the evidence due to high RoB and inconsistency
	Not effective	High certainty on the results	Prebiotics	Not different from placebo	Studies in HIC, not in LMIC
		Low certainty on the results	Vitamin A	Not different from placebo	Mostly studied in LMIC
			Micronutrients without zinc	Not different from placebo	Mostly studied in LMIC
			Gelatin tannate	Not different from placebo	Mostly studied in HIC
			Kaolin pectin	Not different from placebo	Mostly studied in HIC
Cessation of vomiting and preventing hospitalizations	Effective	High certainty on the results	Ondansetron	Increases the likelihood of achieving cessation of vomiting (OR 3.57, 95% CI 2.17 to 6.25)	Recommended dose is 0.15 mg/kg (single dose in the emergency department, orally or intravenously).

Table 2 (continued)

Outcome of interest	Summary of effectiveness	Certainty of the evidence[†]	Interventions	Details of the effect	Comments/remarks
				Reduction in hospitalization rates (OR 0.34, 95% CI 0.16 to 0.69)	
	Not effective	Low certainty on the results	Metoclopramide	Not different from placebo	It has been associated with significant neurological adverse events
			Domperidone	Not different from placebo	Studies in both HIC and LMIC.
			Dexamethasone	Not different from placebo	Only one study in a HIC (USA)
			Granisetron	Not different from placebo	Only one study in a HIC (Saudi Arabia)
			Dimenhydrinate	Not different from placebo	Produces more adverse events than placebo (somnolence)

95% CI, 95% confidence interval; *ABG*, arabinogalactan; *FOS*, fructooligosaccharides; *GOS*, galactooligosaccharides; *HIC*, high-income countries; *LMIC*, low- and middle-income countries; *OR*, odds ratio; *RoB*, risk of bias; *XOS*, xilooligosaccharides

Table developed by authors supported on the information from selected references [44, 60, 87]

[†] Certainty of the evidence is supported on the GRADE methodology. High certainty on the results means that the evidence that supports the effect was judged as moderate to high quality. Therefore, it can be interpreted as evidence of enough quality to be confident in that the effect found is very close to the truth. Low certainty on the results means that the evidence was judged as of low to very low quality. Meaning that there is a lot of uncertainty on the effect

Finally, when deciding what adjuvant treatment to use, cost-effectiveness should also be considered. For instance, treatment with zinc has been found not only effective but also cost-effective in some LMIC [80–83]. The cost-effectiveness of the other interventions has not been extensively studied.

Antiemetics

When present, vomiting might range from one single episode to repeated, and sometimes persistent, which affects fluid intake at home and the rehydration therapy at the hospital. When vomiting is not severe, it can be easily controlled by giving fluids or L-ORS slowly in small amounts. If vomiting persists, it threatens the success of the ORT. In these cases, antiemetics are indicated. Two systematic reviews found that ondansetron is the only effective intervention for the cessation of vomiting, reducing hospitalizations, and the need for intravenous rehydration, but it may increase the diarrheal episodes [84, 85]. As a result, some guidelines recommend ondansetron in children with persistent vomiting [23, 24, 86]. In a recent network metanalysis from our group, we analyzed seven antiemetics (dexamethasone, dimenhydrinate, domperidone, granisetron, metoclopramide, and ondansetron) and concluded that ondansetron is the only intervention superior to placebo [87]. Table 2 displays the details of the effect of the studied antiemetics.

Antimicrobials

Antimicrobials are not routinely recommended. Their use is associated with the hemolytic-uremic syndrome, relapses, and persistent diarrhea [87, 88]. They are only indicated when there is a risk of serious invasive disease or complications, and there is evidence that the treatment will improve clinical outcomes, or when there is a need for stopping a microorganism spread [87].

Thus, antibiotics are always indicated in infections by *Shigella* and *V. cholerae*, and in selected cases of infections by non-typhoidal *Salmonella* (younger than 3 months of age or immunocompromised children), *Campylobacter* (in severe infections) [89], and *Cryptosporidium* (immunocompromised children) [90–92]. Quinolones (i.e., ciprofloxacin) and macrolides (i.e., azithromycin) are the best choices for empirical treatment for these microorganisms, but it will largely depend on local microbiological susceptibility [9, 93]. It should be noted that although they are the first choice for this microorganisms, quinolones should be used with caution considering that they increase the risk of arthropathy [94]. Empirical treatment for cases of bacteremia or sepsis includes third-generation cephalosporins (i.e., ceftriaxone) until cultures' results are obtained [23]. Table 3 summarizes the

Table 3 Summary of antimicrobial treatment according to identified microorganisms

Clinical syndrome	Etiology[†]	Antimicrobials and doses[¶]	Comments/remarks
Traveler's diarrhea	ETEC or viruses	Azithromycin 12 mg/kg/day once daily dose for 3 days or ciprofloxacin 20–30 mg/kg/day bid for 3–5 days	Treatment is recommended only in life-threatening infections or to prevent transmission
Acute bloody diarrhea (dysentery)	*Shigella*	Ciprofloxacin 20–30 mg/kg/day bid for 3 days (PO or IV) or azithromycin 20 mg/kg/day once daily dose for 3 days	Treatment is recommended for all patients For IV therapy, ceftriaxone is the preferred agent: 50 mg/kg/day once-daily dose for 3–5 days
	Salmonella	Ciprofloxacin 20–30 mg/kg/day bid for 5 days (PO or IV) or ceftriaxone 50 mg/kg/day once-daily dose for 3–5 days (IV) Note: if antimicrobial susceptibility available and sensitivity is documented, ampicillin or TMP/SMX could be used.	No need for antibiotic treatment except in patients with typhoid fever, under 3 months of age, sepsis, immunodepression, malnutrition, or bacteremia. In these cases, IV ceftriaxone is preferred.
	Campylobacter jejuni	Ciprofloxacin 20–30 mg/kg/day bid for 5 days or azithromycin 12 mg/kg/day once daily dose for 3 days	*C. jejuni* is related with foodborne diarrhea disease and international travel
	STEC EIEC	N/A	No need for routine treatment
	E. histolytica	Metronidazole 35–50 mg/kg tid for 5–7 days or tinidazole 40 mg/kg bid for 5 days	It should be treated with antimicrobials in all the cases
Acute watery diarrhea	Viruses (rotavirus, norovirus, adenovirus, astrovirus)	N/A	No antibiotic treatment indicated
	Salmonella	Ciprofloxacin 20–30 mg/kg/day bid for 3 days or azithromycin 20 mg/kg/day once daily dose for 3 days	No need for routine treatment except in the following cases: immunocompromised children, < 3 mo, sepsis, or malnutrition
	Campylobacter jejuni	Azithromycin 20 mg/kg/day once daily dose for 3 days or ciprofloxacin 20–30 mg/kg/day bid for 3 days	No need for routine antibiotic treatment except in cases of sepsis or malnutrition. Ciprofloxacin can be used as alternative but not widely recommended
	V. cholerae	Azithromycin 20 mg/kg once-daily dose or ciprofloxacin 20–30 mg/kg/day bid for 3 days	Treatment indicated in all the cases. Azithromycin is preferred in areas with high resistance rates to ciprofloxacin
	Cryptosporidium	Nitazoxanide (according to the age): 1–3 years, 100 mg bid; 4–11 years, 200 mg bid; > 12 years, 500 mg bid, for 3 days.	Treatment indicated only in immunosuppressed patients especially HIV infection and malnourished children. In HIV children, duration of treatment may range from 3 to14 days
	Giardia	Metronidazole 30–50 mg/kg/day for 5 days or albendazole 400 mg/day for 3–5 days	Treatment indicated in all the cases
	Blastocystis hominis	Metronidazole 35–50 mg/kg tid for 5–7 days or nitazoxanide 100–200 mg bid for 3 days	Treatment indications are not well established. *B. hominis* should be treated only when no other etiology can explain the clinical manifestations.

bid, *bis in die (*twice a day); *EIEC*, eneteroinvasive *E. coli*; *ETEC*, enterotoxigenic *E. coli*; *HIV*, human immunodeficiency virus; *IV*, intravenous; *mo*, months; *N/A*, not applicable; *PO*, per os (by mouth); *STEC*, Shiga toxin *E. coli*; *tid*, *ter in die* (three times per day)

Table developed by authors supported on the information from selected references [9, 20, 97, 98]

[†] Only main microorganisms are mentioned

[¶] Recommended and alternative treatments are provided in most of the cases. Unless otherwise stated all doses and regimes are specified for oral administration

antimicrobial treatments according to the most commonly identified microorganisms in diarrhea in children.

Prevention

The best strategy to prevent diarrhea has been the implementation of safe drinking water, adequate sanitation and hygiene, and handwashing with soap. The second most important preventive intervention is the RV [16]. The introduction of the RV in the national immunization programs has reduced from 54 to 20% of the attributable incidence of rotavirus infections in Africa [10]. In general, the decline of rotavirus disease ranged from 25 to 55% [10, 17]. It is widely recommended that all infants without known contraindication should receive rotavirus immunization [23]. Additional available vaccines are not routinely recommended. Cholera and typhoid vaccines are only recommended in high-risk populations (travels to high-endemic areas, intimate exposure, or microbiologists) [23]. Combined ETEC + *Shigella* vaccines are under evaluation but their effectiveness is yet to be established [95].

Conclusion

Diarrhea is one of the most common diseases in childhood. Unfortunately, it is still a cause of death in LMIC and a frequent cause of visits to the emergency department in HIC. We have reviewed the main aspects of the disease and provided a summary of the most current evidence that may be helpful to clinicians that deal with children with diarrhea in any setting.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet. 2003;361(9376):2226–34.
2. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430–40.
3. Schnadower D, Finkelstein Y, Freedman SB. Ondansetron and probiotics in the management of pediatric acute gastroenteritis in developed countries. Curr Opin Gastroenterol. 2015;31(1):1–6. https://doi.org/10.1097/mog.0000000000000132.
4. World Health Organization, editor. The treatment of diarrhoea: a manual for physicians and other senior health workers. In: World Health Organization. Geneva; 2005.
5. American Academy of Pediatrics A. Practice parameter: the management of acute gastroenteritis in young children. Pediatrics. 1996;97(3):424–35.
6. Guerrant RL, Hughes JM, Lima NL, Crane J. Diarrhea in developed and developing countries: magnitude, special settings, and etiologies. Rev Infect Dis. 1990;12(Supplement 1):S41–50. https://doi.org/10.1093/clinids/12.Supplement_1.S41.
7. Giannattasio A, Guarino A, Lo VA. Management of children with prolonged diarrhea. F1000Res. 2016;5:F1000 Faculty Rev-206. https://doi.org/10.12688/f1000research.7469.1.
8. Bányai K, Estes MK, Martella V, Parashar UD. Viral gastroenteritis. Lancet. 2018;392(10142):175–86.
9. Cherry JD, Harrison GJ, Kaplan SL, Hotez PJ, Steinbach WJ. Feigin and Cherry's textbook of pediatric infectious diseases: Elsevier; 2018.
10. Operario DJ, Platts-Mills JA, Nadan S, Page N, Seheri M, Mphahlele J, et al. Etiology of severe acute watery diarrhea in children in the global rotavirus surveillance network using quantitative polymerase chain reaction. J Infect Dis. 2017;216(2):220–7.
11. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001–2006. Pediatrics. 2008;122(6):1266–70. https://doi.org/10.1542/peds.2008-0469.
12. Akhi MT, Seifi SJ, Asgharzadeh M, Rezaee MA, Oskuei SA, Pirzadeh T, et al. Role of enterotoxigenic *Bacteroides fragilis* in children less than 5 years of age with diarrhea in Tabriz, Iran. Jundishapur J Microbiol. 2016;9(6):e32163.
13. Ramamurthy D, Pazhani GP, Sarkar A, Nandy RK, Rajendran K, Sur D, et al. Case-control study on the role of enterotoxigenic Bacteroides fragilis as a cause of diarrhea among children in Kolkata. India PloS One. 2013;8(4):e60622. https://doi.org/10.1371/journal.pone.0060622.
14. Riera-Montes M, O'ryan M, Verstraeten T. Norovirus and rotavirus disease severity in children: systematic review and meta-analysis. Pediatr Infect Dis J. 2018;37(6):501–5.
15. Das JK, Duggan C, Bhutta ZA. Persistent diarrhea in children in developing countries. In: Textbook of pediatric gastroenterology, hepatology and nutrition: Springer; 2016. p. 195–202.
16. Riera-Montes M, Cattaert T, Verstraeten T. Rotavirus vaccination may reduce acute gastroenteritis rates across all age groups in England. Value Health. 2017;20(9):A780.
17. Aliabadi N, Antoni S, Mwenda JM, Weldegebriel G, Biey JN, Cheikh D, et al. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008–16: findings from the Global Rotavirus Surveillance Network. Lancet Glob Health. 2019;7(7):e893–903.
18. Hassan E, Baldridge MT. Norovirus encounters in the gut: multifaceted interactions and disease outcomes. Mucosal Immunol. 2019:1–9.
19. Kliegman R, Stanton B, St. Geme JW, Schor NF, Behrman RE, Nelson WE. Nelson textbook of pediatrics. 2020.
20. Long SS, Brady MT, Jackson MA, Kimberlin DW. Red book 2018: report of the committee on infectious diseases: American Academy of Pediatrics; 2018.
21. Thiagarajah JR, Donowitz M, Verkman AS. Secretory diarrhoea: mechanisms and emerging therapies. Nat Rev Gastroenterol Hepatol. 2015;12(8):446–57.
22. Bresee JS, Duggan C, Glass RI, King CK. Managing acute gastroenteritis among children; oral rehydration, maintenance, and nutritional therapy. 2003.
23. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis 2017;65(12):e45-e80.
24. Guarino A, Ashkenazi S, Gendrel D, Vecchio AL, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology,

Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr. 2014;59(1):132–52.
25. Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. Pediatrics. 2004;114(2):507.
26. Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? Jama. 2004;291(22):2746–54.
27. Friedman JN, Goldman RD, Srivastava R, Parkin PC. Development of a clinical dehydration scale for use in children between 1 and 36 months of age. J Pediatr. 2004;145(2):201–7. https://doi.org/10.1016/j.jpeds.2004.05.035.
28. Gorelick MH, Shaw KN, Murphy KO. Validity and reliability of clinical signs in the diagnosis of dehydration in children. Pediatrics. 1997;99(5):e6-e.
29. Freedman SB, Vandermeer B, Milne A, Hartling L, Johnson D, Black K, et al. Diagnosing clinically significant dehydration in children with acute gastroenteritis using noninvasive methods: a meta-analysis. J Pediatr. 2015;166(4):908–16 e6.
30. Falszewska A, Szajewska H, Dziechciarz P. Diagnostic accuracy of three clinical dehydration scales: a systematic review. Arch Dis Child. 2018;103(4):383–8. https://doi.org/10.1136/archdischild-2017-313762.
31. Pruvost I, Dubos F, Aurel M, Hue V, Martinot A. Valeur des données anamnestiques, cliniques et biologiques pour le diagnostic de déshydratation par diarrhée aiguë chez l'enfant de moins de 5 ans. Presse Med. 2008;37(4):600–9.
32. Lynch SV, Ng SC, Shanahan F, Tilg H. Translating the gut microbiome: ready for the clinic? Nat Rev Gastroenterol Hepatol. 2019:1–6.
33. Churgay CA, Aftab Z. Gastroenteritis in children: Part II. Prevention and management. Am Fam Physician. 2012;85(11):1066–70.
34. Lo Vecchio A, Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, et al. An international consensus report on a new algorithm for the management of infant diarrhoea. Acta Paediatr. 2016;105(8):e384–e9.
35. Women's NCCf, Health Cs. Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years. 2009.
36. Binnicker MJ. Multiplex molecular panels for diagnosis of gastrointestinal infection: performance, result interpretation, and cost-effectiveness. J Clin Microbiol. 2015;53(12):3723–8.
37. Pernica JM, Steenhoff AP, Mokomane M, Moorad B, Lechiile K, Smieja M, et al. Rapid enteric testing to permit targeted antimicrobial therapy, with and without Lactobacillus reuteri probiotics, for paediatric acute diarrhoeal disease in Botswana: a pilot, randomized, factorial, controlled trial. PLoS One. 2017;12(10):e0185177. https://doi.org/10.1371/journal.pone.0185177.
38. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):e1–e48.
39. Hartling L, Bellemare S, Wiebe N, Russell KF, Klassen TP, Craig WR. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. Cochrane Database Syst Rev. 2006;3.
40. 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 randomised controlled trials. BMC Med. 2004;2(1):11.
41. 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):483–90.
42. Mejía A, Atehortua SC, Sierra JM, Mejía ME, Ramírez C, Florez ID. Costs of oral and nasogastric rehydration compared to intravenous rehydration in children under 5 years of age with diarrhea in Colombia. Rev Salud Publica (Bogota). 2017;19(1):17–23.
43. Pershad J. A systematic data review of the cost of rehydration therapy. Appl Health Econ Health Policy. 2010;8(3):203–14. https://doi.org/10.2165/11534500-000000000-00000.
44. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
45. Hahn S, Kim Y, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. Cochrane Database Syst Rev. 2002;1:CD002847. https://doi.org/10.1002/14651858.CD002847.
46. Gregorio GV, Gonzales MLM, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. Cochrane Database Syst Rev. 2016;12:CD006519. https://doi.org/10.1002/14651858.CD006519.pub3.
47. Freedman SB, Willan AR, Boutis K, Schuh S. Effect of dilute apple juice and preferred fluids vs electrolyte maintenance solution on treatment failure among children with mild gastroenteritis: a randomized clinical trial. JAMA. 2016;315(18):1966–74. https://doi.org/10.1001/jama.2016.5352.
48. American Academy of Pediatrics. Practice parameter: the management of acute gastroenteritis in young children. American Academy of Pediatrics. Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Pediatrics. 1996;97(3):424–35.
49. Florez ID. Balanced solutions vs. 0.9% saline for children with acute diarrhoea and severe dehydration [title]. In: Cochrane Infectious Diseases Group. 2019. https://www.cochrane.org/title/balanced-solutions-vs-09-saline-children-acute-diarrhoea-and-severe-dehydration.
50. Antequera Martín AM, Barea Mendoza JA, Muriel A, Sáez I, Chico-Fernández M, Estrada-Lorenzo JM, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. Cochrane Database Syst Rev. 2019;(7). https://doi.org/10.1002/14651858.CD012247.pub2.
51. Toaimah FHS, Mohammad HMF. Rapid intravenous rehydration therapy in children with acute gastroenteritis: a systematic review. Pediatr Emerg Care. 2016;32(2):131–5.
52. Iro M, 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.
53. Allen CH, Etzwiler LS, Miller MK, Maher G, Mace S, Hostetler MA, et al. Recombinant human hyaluronidase-enabled subcutaneous pediatric rehydration. Pediatrics. 2009;124(5):e858–e67.
54. Zubairi H, Nelson BD, Tulshian P, Fredricks K, Altawil Z, Mireles S, et al. Hyaluronidase-assisted resuscitation in Kenya for severely dehydrated children. Pediatr Emerg Care. 2019;35(10):692–5.
55. Spandorfer PR. Subcutaneous rehydration: updating a traditional technique. Pediatr Emerg Care. 2011;27(3):230–6.
56. Saganski GF, de Souza Freire MH. Safety and effectiveness of hypodermoclysis compared to intravenous fluid infusion for rehydrating children with mild to moderate dehydration: a systematic review protocol. JBI Database System Rev Implement Rep. 2019;17(7):1270–6.
57. Gregorio GV, Dans LF, Silvestre MA. Early versus delayed refeeding for children with acute diarrhoea. Cochrane Database Syst Rev. 2011;7.
58. Gaffey MF, Wazny K, Bassani DG, Bhutta ZA. Dietary management of childhood diarrhea in low-and middle-income countries: a systematic review. BMC Public Health. 2013;13(S3):S17.
59. MacGillivray S, Fahey T, McGuire W. Lactose avoidance for young children with acute diarrhoea. Cochrane Database Syst Rev. 2013;10.

60. Florez ID, Veroniki A-A, Al Khalifah R, Yepes-Nuñez JJ, Sierra JM, Vernooij RW, et al. Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: a systematic review and network meta-analysis. PLoS One. 2018;13(12):e0207701.
61. Cremon C, Barbaro MR, Ventura M, Barbara G. Pre- and probiotic overview. Curr Opin Pharmacol. 2018;43:87–92. https://doi.org/10.1016/j.coph.2018.08.010.
62. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010;11.
63. Feizizadeh S, Salehi-Abargouei A, Akbari V. Efficacy and safety of Saccharomyces boulardii for acute diarrhea. Pediatrics. 2014;134(1):e176–e91.
64. Dinleyici EC, Eren M, Ozen M, Yargic ZA, Vandenplas Y. Effectiveness and safety of Saccharomyces boulardii for acute infectious diarrhea. Expert Opin Biol Ther. 2012;12(4):395–410. https://doi.org/10.1517/14712598.2012.664129.
65. Urbańska M, Gieruszczak-Białek D, Szajewska H. Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for diarrhoeal diseases in children. Aliment Pharmacol Ther. 2016;43(10):1025–34.
66. Pérez-Gaxiola G, Cuello-García CA, Florez ID, Pérez-Pico VM. Smectite for acute infectious diarrhoea in children. Cochrane Database Syst Rev. 2018;4.
67. Das RR, Sankar J, Naik SS. Efficacy and safety of diosmectite in acute childhood diarrhoea: a meta-analysis. Arch Dis Child. 2015;100(7):704–12. https://doi.org/10.1136/archdischild-2014-307632.
68. Tormo R, Polanco I, Salazar-Lindo E, Goulet O. Acute infectious diarrhoea in children: new insights in antisecretory treatment with racecadotril. Acta Paediatr. 2008;97(8):1008–15.
69. Szajewska H, Ruszczyński M, Chmielewska A, Wieczorek J. Systematic review: racecadotril in the treatment of acute diarrhoea in children. Aliment Pharmacol Ther. 2007;26(6):807–13.
70. Lehert P, Chéron G, Calatayud GA, Cézard J-P, Castrellón PG, Garcia J-MM, et al. Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. Dig Liver Dis. 2011;43(9):707–13.
71. Gharial J, Laving A, Were F. Racecadotril for the treatment of severe acute watery diarrhoea in children admitted to a tertiary hospital in Kenya. BMJ Open Gastroenterol. 2017;4(1):e000124.
72. Kang G, Thuppal SV, Srinivasan R, Sarkar R, Subashini B, Venugopal S, et al. Racecadotril in the management of rotavirus and non-rotavirus diarrhea in under-five children: two randomized, double-blind, placebo-controlled trials. Indian Pediatr. 2016;53(7):595–600.
73. Penny ME. Zinc supplementation in public health. Ann Nutr Metab. 2013;62(Suppl. 1):31–42.
74. Lazzerini M, Wanzira H. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2016;12.
75. Alam DS, Yunus M, El Arifeen S, Chowdury HR, Larson CP, Sack DA, et al. Zinc treatment for 5 or 10 days is equally efficacious in preventing diarrhea in the subsequent 3 months among Bangladeshi children. J Nutr. 2010;141(2):312–5.
76. Crisinel PA, Verga M-E, Kouame KSA, Pittet A, Rey-Bellet CG, Fontaine O, et al. Demonstration of the effectiveness of zinc in diarrhoea of children living in Switzerland. Eur J Pediatr. 2015;174(8):1061–7.
77. Awouters F, Niemegeers C, Janssen P. Pharmacology of antidiarrheal drugs. Annu Rev Pharmacol Toxicol. 1983;23(1):279–301.
78. Li S-TT, Grossman DC, Cummings P. Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis. PLoS Med. 2007;4(3):e98.
79. Florez ID, Sierra JM, Niño-Serna LF. Gelatin tannate for acute diarrhoea and gastroenteritis in children: a systematic review and meta-analysis. Arch Dis Child. 2019. https://doi.org/10.1136/archdischild-2018-316385.
80. Gregorio GV, Dans LF, Cordero CP, Panelo CA. Zinc supplementation reduced cost and duration of acute diarrhea in children. J Clin Epidemiol. 2007;60(6):560–6.
81. Patel AB, Dhande LA, Rawat MS. Economic evaluation of zinc and copper use in treating acute diarrhea in children: a randomized controlled trial. Cost Eff Resour Alloc. 2003;1(1):7.
82. Robberstad B, Strand T, Black RE, Sommerfelt H. Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. Bull World Health Organ. 2004;82:523–31.
83. Mejía A, Atehortúa S, Flórez ID, Sierra JM, Mejia ME, Ramírez C. Cost-effectiveness analysis of zinc supplementation for treatment of acute diarrhea in children younger than 5 years in Colombia. J Pediatr Gastroenterol Nutr. 2015;60(4):515–20.
84. Fedorowicz Z, Jagannath VA, Carter B. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Cochrane Database Syst Rev. 2011;9.
85. Carter B, Fedorowicz Z. Antiemetic treatment for acute gastroenteritis in children: an updated Cochrane systematic review with meta-analysis and mixed treatment comparison in a Bayesian framework. BMJ Open. 2012;2(4):e000622.
86. Cheng A. Emergency department use of oral ondansetron for acute gastroenteritis-related vomiting in infants and children. Paediatr Child Health. 2011;16(3):177–9.
87. Niño-Serna L, Acosta-Reyes J, Veroniki AA, Florez ID. Antiemetics in Children with Acute Gastroenteritis: A Meta-Analysis. Pediatrics 2020; forthcoming
88. Brandt KG, de Castro Antunes MM, da Silva GAP. Acute diarrhea: evidence-based management. J Pediatr (Versão em Português). 2015;91(6):S36–43.
89. Kliegman R, Stanton B, Behrman RE, St. Geme JW, Schor NF, Nelson WE. Nelson textbook of pediatrics. 2016.
90. Endtz HP. 50 - Campylobacter Infections. In: Ryan ET, Hill DR, Solomon T, Aronson NE, Endy TP, editors. Hunter's tropical medicine and emerging infectious diseases (Tenth Edition). London: Content Repository Only! 2020. p. 507–11.
91. Das JK, Salam RA, Bhutta ZA. Global burden of childhood diarrhea and interventions. Curr Opin Infect Dis. 2014;27(5):451–8.
92. Abubakar I, Aliyu SH, Arumugam C, Usman NK, Hunter PR. Treatment of cryptosporidiosis in immunocompromised individuals: systematic review and meta-analysis. Br J Clin Pharmacol. 2007;63(4):387–93. https://doi.org/10.1111/j.1365-2125.2007.02873.x.
93. Das JK, Ali A, Salam RA, Bhutta ZA. Antibiotics for the treatment of Cholera, Shigella and Cryptosporidiumin children. BMC Public Health. 2013;13(3):S10. https://doi.org/10.1186/1471-2458-13-s3-s10.
94. O'Ryan GM, Ashkenazi-Hoffnung L, O'Ryan-Soriano MA, Ashkenazi S. Management of acute infectious diarrhea for children living in resource-limited settings. Expert Rev Anti-Infect Ther. 2014;12(5):621–32.
95. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child. 2011;96(9):874–80. https://doi.org/10.1136/adc.2010.208843.
96. Walker R. New possibilities for the development of a combined vaccine against ETEC and Shigella. BMJ Glob Health. 2017;2(Suppl 2):A11–A2.
97. Cohen R, Raymond J, Gendrel D. Antimicrobial treatment of diarrhea/acute gastroenteritis in children. Archives de Pédiatrie. 2017;24(12 Supplement):S26–S9. https://doi.org/10.1016/S0929-693X(17)30515-8.
98. Ashkenazi S, Schwartz E, O'Ryan M. Travelers' diarrhea in children: what have we learnt? Pediatr Infect Dis J. 2016;35(6):698–700.