Acute Infectious Diarrhoea in Children – The Role of Drug Treatment

Eduardo Salazar-Lindo

Director, GastroLab

Abstract

Acute infectious diarrhoea is a common problem with a wide spectrum of clinical severity in children. Replacing the fluid and electrolytes lost, preferably by using an oral rehydration solution, and continuing to feed the child with age-appropriate foods is the basis for the treatment of this disease. This article reviews the role of antimicrobials and non-antimicrobial antidiarrhoeal drugs in the treatment of children with acute infectious diarrhoea. With the exception of cholera, routine use of antimicrobials to treat watery diarrhoea cases is neither necessary nor appropriate. Antimicrobials are indicated in invasive diarrhoeas when Shigella infection is suspected. Among the non-antimicrobial antidiarrhoeal agents, cholestyramine, loperamide and bismuth subsalicylate do not have a worthwhile additive effect over the clinical course of the disease and are not free from potentially serious side effects when used in children. Racea, diosmectite and racecadotril are two effective and safe antidiarrhoeal agents that can be used in children, in addition to oral rehydration, to shorten diarrhoea duration and to reduce its volume – two clinical outcomes that physicians and parents expect in the treatment of this disease. New antidiarrhoeal agents are in development, pending testing in clinical trials.

Keywords

Diarrhoea, oral rehydration, antidiarrhoeals, ciprofloxacin, cholestyramine, loperamide, bismuth subsalicylate, diosmectite, racecadotril, cholera, shigella, rotavirus

Acute infectious diarrhoea is a very common disorder in children, and has a wide spectrum of clinical severity. Sometimes it takes the form of a mild episode that recedes after a few hours; however, at other times it may quickly lead to dehydration, acidosis and potassium depletion or to sepsis, or it may persist for several days, causing nutritional wasting. Because of its abrupt onset and frequent association with alarming symptoms such as fever and vomiting, an episode of diarrhoea carries great concern among family members, even in mild cases. For instance, it has been estimated that in North America and Europe, 4–8% of all emergency room visits among children under five years of age are for a case of acute diarrhoea.1,2 In developing countries, the disease burden is further increased by a high rate of hospital admissions and deaths from early or late complications of the disease.3,4 Consequently, prompt, effective and safe treatment of children with acute diarrhoea is essential to their wellbeing. This article aims to discuss the role of both antimicrobial and non-antimicrobial drugs in the treatment of children with acute infectious diarrhoea within the context of using oral rehydration as the mainstay of appropriate clinical management.

Clinical Syndromes

Diarrhoea is usually recognised as the passage of stools that are looser and more frequent than normal. Clinically, diarrhoeic stools can appear with or without mucus and blood. The term ‘watery diarrhoea’ is generally used when no blood or mucus is present in the stools; ‘dysentery’ or ‘bloody diarrhoea’ is used otherwise. Acute diarrhoea is generally a self-limiting disease lasting from one to two to five to seven days. However, occasionally diarrhoea may continue regardless of the treatment provided; the term ‘persistent diarrhoea’ is used to refer to an episode of diarrhoea that lasts for 14 days or more. In some cases diarrhoea persists because the infectious agent has the ability to stay in the gut for a long time; in other cases it is because the host is too young or malnourished and unable to mount a rapid and effective healing response to the initial infectious insult.5

Mechanisms of Infectious Diarrhoea

In essence, watery diarrhoea occurs because an excess of water flowing from the small bowel reaches the large intestine, affecting its capacity to reabsorb water. The excess of water in the small bowel may be the result of osmotic forces present in the gut’s lumen from unabsorbed solutes or from hypersecretion of chloride and accompanying ions.6 It has been hypothesised that mature enterocytes destroyed by an infectious organism such as rotavirus are replaced by immature cells migrating from the intestinal crypts causing a temporary loss of effective absorption of ingested nutrients.7 More recent studies with animal models have shown that rotavirus infection may induce carbohydrate malabsorption without enterocyte damage by directly decreasing intestinal disaccharidase activity or by inhibiting the Na+/glucose co-transporter (SGLT1).8 Hypersecretion of chloride is the result of enterotoxin activity both on the enterocyte itself and on the enteric nervous system.9 Enterotoxins open one of two chloride channels located at the brush border of the enterocyte in the proximal jejunum.10,11 Vibrio cholerae toxin and Escherichia coli LT1, LT2, STa and EAST1 toxins are able to...
Motility Disorders  

Diarrhoea

elicit an increase of cyclic adenosine monophosphate (c-AMP) or cyclic guanosine monophosphate (c-GMP) concentration within the enterocyte, which in turn triggers the opening of the chloride channel regulated by the cyclic fibrosis transmembrane conductance regulator (CFTR).\(^6\)\(^{-8}\) Cholera toxin, in addition, provokes the release of neurotransmitters from enteroendocrine cells, mast cells and enterochromaffin cells, which further increases chloride secretion.\(^9\) A separate chloride channel, the calcium-activated chloride channel (CaCC), is opened by the rotavirus NSP4 enterotoxin\(^1\)\(^{-4}\) and Vibrio parahaemolyticus TDH toxin\(^6\) by inducing an increase in intracellular calcium concentration. A transmural electric potential difference that results from the excess of secreted chloride drives sodium movement through the intercellular space into the lumen.\(^5\) This excess of chloride, sodium, other ions and unabsorbed nutrients present in the lumen and the water attracted to compensate for the high osmolarity make up the watery diarrhoea.

Bloody inflammatory diarrhoea, on the other hand, is mainly a large bowel event caused by infectious agents with the capacity to invade the intestinal wall. The invading organism triggers a cascade of inflammatory events, including the release of pro-inflammatory cytokines that attract white blood cells from the bloodstream to the subepithelial space, transmigration of these white blood cells into the lumen through the paracellular pathway, intercellular spread of the invading organism and, ultimately, necrosis of contiguous epithelial cells.\(^6\)\(^{-8}\) A shallow ulceration of the mucosa is formed, exposing a denuded submucosa that is prone to bleeding.\(^6\) A typical exudate of mucus containing white blood cells and streaks of blood is formed and subsequently discharged in the stools.

**Oral Rehydration**

The basis of acute diarrhoea treatment, regardless of its clinical type, the age of the patient or the severity of the disease, is the replacement of lost water and electrolytes. The objective is to correct or prevent dehydration, the main reason why a patient could die or sustain permanent damage from diarrhoea. In most cases water and electrolyte replacement can be achieved using the oral route. Early on in the illness, or in mild cases, drinking plain water after each diarrhoeic stool and continuing normal feeding – including breast milk in breastfed infants – could be sufficient.\(^2\)\(^{-6}\) However, if there is progression to more copious diarrhoea, drinking an oral glucose-electrolyte solution containing sodium, potassium and a base would be necessary.\(^7\) Oral rehydration efficacy is based on the fact that sodium and glucose are co-transported through the SGLT1, the protein located in the brush border of enterocytes; this transporting system is preserved undamaged during most intestinal infections.\(^7\) The small intestine is able to absorb water due to the driving force created by the movement of sodium and glucose from the lumen into the cell and then into the bloodstream. Potassium and a base (citrate or bicarbonate) are also well absorbed. Many lives have been saved across the world thanks to this simple, effective and inexpensive therapy.\(^7\)

**Existing Practices for the Treatment of Acute Diarrhoea with Drugs**

Reducing the severity of clinical diarrhoea, i.e. stool volume and duration, is as important and necessary as treating or preventing dehydration, acidosis and potassium depletion. Dehydration is more likely to occur in a shorter period of time if stool purging is large and frequent and replacement of fluids is insufficient.\(^2\)\(^{-6}\) The negative impact on nutritional status is directly proportional to the duration of diarrhoea, especially in infants.\(^2\)\(^{-6}\) Oral rehydration solutions (ORS) do not reduce diarrhoea severity, and can even increase stool purging and diarrhoea duration.\(^2\) Some malabsorption of the glucose contained in the ORS is expected in viral gastroenteritis where the Na+/glucose co-transporter (SGLT1) is impaired.\(^6\) This may be the reason for the incremental stool purging and the need for unscheduled intravenous therapy for treatment failure seen in some children hydrated with the standard ORS.\(^2\)\(^{-6}\)

The lack of an effect of ORS on the severity of the disease is perceived as one of several significant barriers to widespread and consistent use of oral rehydration alone in the treatment of diarrhoea.\(^2\)\(^{-6}\) Instead, ineffective and sometimes harmful antimicrobial drugs and antimicrobials are widely used, whether by prescription or bought over the counter.\(^2\)\(^{-6}\)

In a household survey conducted in peri-urban Mexico City,\(^2\)\(^{-6}\) 37% of 287 individuals who had diarrhoea within the past two weeks responded that they were using an antibiotic; only 5% of them reported visible blood in the stools, a criterion that would indicate the potential need for an antibiotic. Furthermore, subjects with diarrhoea in this Mexican study who had consulted a physician were six times more likely to be on an antibiotic than those who had not.\(^2\)\(^{-6}\) Those on self-medication had an even higher risk of using the wrong drug or an inadequate individual or total dose.\(^2\) A study in Egypt interviewing 9,711 mothers of children who had diarrhoea in the previous 24 hours found that 54.2% of all children with diarrhoea were given at least one drug, half of them two drugs and only 22.6% ORS.\(^2\) In an observational study performed in Karachi, Pakistan, of 996 encounters between physicians (28 paediatricians and 62 general practitioners) and children with diarrhoea, it was observed that ORS were prescribed in 52 and 51%, antibacterials in 41 and 36%, anti-amoebics in 26 and 22% and antidiarrhoeals in 48 and 29% of encounters with general practitioners and paediatricians, respectively.\(^2\) In a survey conducted between October 1998 and March 1999 among 2,997 primary care physicians and hospital-based paediatricians from 29 European countries who were presented with a hypothetical case of a six-month-old infant with acute watery diarrhoea and dehydration, 84% of the respondents said that they would use oral rehydration to rehydrate this patient, 22% would use an antidiarrhoeal and 44% would recommend an antimicrobial drug.\(^2\)

Clearly, there is a perceived need for effective and safe drugs to treat diarrhoea as an adjunct to oral rehydration. Both physicians and patients expect that diarrhoea will stop immediately.\(^2\)\(^{-6}\) Better training of health professionals in clinical management and sustained health education programmes for parents on appropriate home management of diarrhoea cases would help in reducing the use of harmful and unnecessary drugs for children with diarrhoea.\(^2\)\(^{-6}\) However, these educational programmes should consider that changing an individual’s understanding of diarrhoea and its management is inherently difficult.\(^2\)

**The Role of Antimicrobial Drugs in the Treatment of Acute Diarrhoea**

Routine empirical use of antimicrobials in the treatment of acute watery diarrhoea is neither necessary nor appropriate. A viral agent
against which antimicrobials have no effect is the cause of a large portion of cases. Hospital-based surveillance networks with sites around the world reported that rotavirus infection was responsible for no fewer than 40% of admissions of children below five years of age with diarrhea and dehydration.49 Norovirus, which was initially believed to cause mainly sporadic outbreaks in special settings such as cruise ships or recreational areas, is now considered to be second to rotavirus as a cause of hospitalisation of infants with diarrhea and dehydration.50 The clinical presentation of rotavirus gastroenteritis is distinctive: the patient is usually an infant, vomiting is a prominent and early symptom, diarrhoea is watery without mucus or blood and fever is mild;51 furthermore, if vomiting, watery diarrhoea and fever combined are present in one child, the chances of rotavirus being the causative agent could be around 56%.52 However, in a clinical situation it may not always be feasible to differentiate whether a virus or a bacterium is the cause of an episode of acute watery diarrhoea. If a bacterial cause is suspected, issues such as disease severity, likely response of the bacteria to the selected antibacterial, cost, adverse drug reactions and development of antimicrobial resistance should be considered before prescribing an antimicrobial.44

Antimicrobials should be used only for specific enteric pathogens and a given clinical severity; this approach involves a thoughtful clinical evaluation of each case. Cholera and shigellosis are among the few gastrointestinal infections in which a specific antimicrobial could meaningfully shorten the disease severity, decrease the risk of complications and reduce its transmission.

In an early placebo-controlled clinical trial, Pierce et al.44 found that administering 500mg of oral tetracycline every six hours for two days to adults with severe cholera had the following results: the mean total stool volume was reduced from 13.5 litres on placebo to 3.9 litres on tetracycline, a 71.1% reduction, mean duration of diarrhoea was reduced from 75.5 hours in the placebo group to 31.6 hours in the tetracycline group and mean duration of vibrio excretion in the stools was reduced from 71.5 hours in the placebo group to 14.5 hours in the tetracycline group. In a trial conducted about 20 years later in the same population, Rabbani et al.53 showed that administering a single oral dose of 1g of tetracycline to adults with severe cholera also significantly reduced the total stool volume, duration of diarrhoea and excretion of the organism compared with placebo. In both trials, the clinical efficacy of furazolidone against cholera was also assessed; in the early trial54 furazolidone was almost as effective as tetracycline, while in the second trial55 furazolidone fared similarly to the placebo group, highlighting the ability of the cholera vibrio, as occurs with many other bacterial enteropathogens, to develop resistance to certain antimicrobials over time.56 Current standard treatment of a suspected or confirmed case of cholera includes, in addition to prompt and vigorous rehydration, the use of an antimicrobial to which the cholera agent is sensitive in that area.57

Shigella infection is generally regarded as a harmful condition that, without prompt and effective antimicrobial treatment, can result in prolonged disease with serious nutritional impairment and, eventually, death. Death from shigellosis does not necessarily result from dehydration as in cholera, but rather from local or systemic complications such as shigellemia, secondary sepsis with other luminal Gram-negative bacteria,58–60 toxic megacolon with perforation,58 haemolytic-uraemic syndrome61,62 and encephalopathy with seizures.58,63 Loss of serum proteins in the intestinal lumen has been documented during Shigella infection,59 which, in addition to appetite loss and poor food intake, contributes to malnutrition and growth retardation in children.64 Shigella is among the pathogens that can induce the development of post-infectious irritative bowel syndrome, the risk being higher if the initial infection lasts longer.64,65 The World Health Organization (WHO) recommends treatment with an antimicrobial whenever shigellosis is suspected.62 This approach takes into consideration the damage Shigella could cause if not treated promptly and effectively, as described above. However, in practical terms this recommendation may involve treating most cases as shigellosis since it is not always possible to distinguish it from other causes of bloody diarrhoea. Ciprofloxacin is the antimicrobial of first choice,64 ampicillin, chloramphenicol, tetracycline, trimethoprim/sulphamethoxazole and nalidixic acid are no longer recommended due to the global emergence of Shigella drug resistance to these antimicrobials.66–68

<table>
<thead>
<tr>
<th>Table 1: Antidiarrhoeal Drugs According to Their Main Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intestinal Transit Inhibitors (Opiate Agonists)</strong></td>
</tr>
<tr>
<td>Loperamide</td>
</tr>
<tr>
<td>Diphenoxylate</td>
</tr>
<tr>
<td><strong>Intraluminal Agents (bulk-forming Agents, Clays and Other Binding Resins)</strong></td>
</tr>
<tr>
<td>Silicates (kaolin, attapulgite, diosmectite)</td>
</tr>
<tr>
<td>Cholestyramine</td>
</tr>
<tr>
<td><strong>Antisecretory Agents</strong></td>
</tr>
<tr>
<td>Enkephalinase inhibitors (racecadotril)</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
</tr>
<tr>
<td>Somatostatin analogues (octreotide, lanreotide)</td>
</tr>
<tr>
<td>Serotonin (5-HT) antagonists (ondansetron, ketanserin)</td>
</tr>
<tr>
<td>Calcium-calmodulin antagonists (chlorpromazine, zoladane)</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
<tr>
<td>CPTF = cyclic fibrosis transmembrane regulator.</td>
</tr>
</tbody>
</table>

**The Role of Non-antimicrobial Antidiarrhoeal Agents**

The search for an effective and safe antidiarrhoeal drug is a long-term effort in medicine that is progressing in tandem with a better understanding of the mechanisms of diarrhoea production.69–71 Several promising candidate antidiarrhoeal drugs that were effective at reducing intestinal secretion in vitro or in animal models had to be discarded either because the reduction in stool volume was found to be modest or because of severe side effects that outweighed its potential clinical value when tested under clinical conditions.72–74 Non-antimicrobial antidiarrhoeal drugs can be divided into three groups according to their main mechanism of action (see Table 7). Loperamide and diphenoxylate hydrochloride are synthetic opiate agonists that alter intestinal motility. They work by slowing intestinal transit, which temporarily pools fluid in the intestinal lumen and thereby increases the time available for absorption, or simply delays the stool purging.71,74 Loperamide is well known, available over the counter and widely used for treatment of diarrhoea. In vivo75 and in vitro76 studies have shown that loperamide may also have some antisecretory activity. There are more than 300 published clinical trials reporting studies of loperamide treatment of infectious diarrhoea. A meta-analysis of 13 trials that compared loperamide against placebo in children under 12 years of age with infectious diarrhoea found that those on loperamide had shorter...
Motility Disorders  Diarrhoea

Table 2: Attributes of an Ideal Antidiarrhoeal and Comparative Characteristics of Some of the Currently Available Antidiarrhoeal Drugs

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Parameters</th>
<th>Loperamide</th>
<th>Bismuth Subsalicylate</th>
<th>Diosmectite</th>
<th>Racecadotril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear-cut mechanism of action that fits within the current knowledge of infectious diarrhoea pathogenesis</td>
<td>• Reduces hypersecretion</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>• Prevents the infectious organism from deploying its virulence factors</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>High therapeutic index regardless of the infectious agent involved</td>
<td>• Significantly reduces stool output compared with oral rehydration alone</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>• Reduces to 50% the number of patients who are without diarrhoea after 24–30 hours of treatment compared with oral rehydration alone</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fast-acting</td>
<td>Recovery from diarrhoea is clearly perceivable from the first doses, as can be shown in a recovery rate curve compared with oral rehydration alone by the log-rank test</td>
<td>Not tested</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High safety profile (no local or systemic side effects such as constipation or CNS involvement)</td>
<td>• Constipation as a side effect of antimotility properties of the gut</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>• Systemic side effects as a result of pharmacological activity in other tissues</td>
<td>Yes</td>
<td>Potentially</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Does not interfere with oral rehydration</td>
<td>Clinical signs of dehydration disappear and feeding can be resumed within 4–6 hours after oral rehydration is initiated</td>
<td>Not tested</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CNS = central nervous system.
Modified from Edelman et al., 1985. 123

duration of diarrhoea by 0.8 days and a lower stool count at 24 hours compared with patients who received placebo. 128 Eight children out of 927 in the loperamide group, all under three years of age, and none of 764 in the placebo group developed a serious adverse event (ileus, lethargy or death). The occurrence of necrotising enterocolitis, 77 intestinal obstruction 78 and bowel perforation 79 in infants after taking loperamide as treatment for diarrhoea has been reported. Clearly, the risk of severe side effects, including possible fatalities, with loperamide outweighs its modest antidiarrhoeal effect. Currently, the paediatric formulation of loperamide in drops is unregistered and has been withdrawn in most parts of the world. 80 Diphenoxylate has also been linked to side effects related to the pharmacologically created intestinal stasis and is thus contraindicated in invasive diarrhoeas. 81 Diphenoxylate is well absorbed, crosses the blood–brain barrier and may cause central nervous system (CNS) side effects and, potentially, addiction. Diphenoxylate requires prescription and should preferably not be used in children.

Intraluminal bulk-forming agents such as kaolin–pectin mixture and attapulgite are generally considered not very effective antidiarrhoelas because they merely strengthen the consistency of stools without actually reducing their water content. 82 Although these agents are regarded as innocuous, they can potentially cause some harm when the apparent improvement of stool consistency induces delayed replacement of the fluid lost. Adsorbent agents such as the anion-exchange resin cholestyramine, which exchanges its chloride anions with bile acids in the intestinal lumen and binds them in the resin matrix, are primarily used to treat hypercholesterolaemia and to relieve the pruritus associated with liver failure. 83 This strong binding property of cholestyramine was shown in cell culture and animal models to also work by binding bacterial enterotoxins such as E. coli ST, LT toxins 84 and cholera toxin, 85 suggesting that cholestyramine may have antidiarrhoeal properties. Controlled clinical trials conducted in children with acute diarrhoea in Chile 86 and Finland 87–90 have shown that cholestyramine shortens the duration of diarrhoea and is generally well tolerated.

However, in one of the Finnish studies it was found that metabolic acidosis, which is primarily caused by diarrhoea and dehydration, could be worsened or prolonged if cholestyramine is given before dehydration is fully corrected. 88 It is thus possible that cholestyramine and ORS cannot be used at the same time because cholestyramine may exchange its chloride with the ORS bicarbonate, interfering with the correction of acidosis. It should also be noted that patients who are volume-depleted or have any other condition that involves a decreased renal blood flow can develop hyperchloremic metabolic acidosis when treated with cholestyramine. 89

Diosmectite is a naturally occurring multilamellar clay silicate with strong binding properties. 90 In vitro or in vivo experiments have shown that, unlike other clay bulk-forming agents that mainly bind water, diosmectite can also bind viruses 91 and bacterial toxins 92,93 and suppresses cytokine-induced intestinal inflammation. 94 The clinical efficacy of diosmectite to reduce diarrhoea duration has been proved in several clinical trials. 95 More recently, two multicentre, double-blind, placebo-controlled trials involving 602 children with acute diarrhoea and dehydration in Peru and Malaysia have shown that diosmectite significantly reduces both duration of diarrhoea and stool volume, and has been found to be safe and well tolerated. 96

Octracetate, lanreotide, ketanserin, chlorpromazine, clonidine and indomethacin, some of the drugs with antisecretory properties,
will not be reviewed here. They are primarily used to treat severe refractory chronic diarrhoeas. Their frequent association with severe side effects makes them impractical for treating acute watery diarrhea in children. Zaldarriaga, a calcium–calmodulin antagonist with antisecretory properties, has been tested in clinical trials, mainly in traveller’s diarrhoea, and proved no superior to placebo or loperamide. Novel antisecretory agents in current development, such as CFTR chloride channel blockers, are reviewed extensively elsewhere. Bismuth subsalicylate (BSS) is a long-established over-the-counter diarrhoeal drug with antimicrobial and antisecretory actions. Three clinical trials conducted in children with acute diarrhoea have shown that BSS had a modest but significant effect in reducing total stool volume and duration of diarrhoea. The studies in Peru and Bangladesh showed that the effect of BSS on stopping diarrhoea occurred rather late in the course of the disease, suggesting a non-antisecretory mechanism of action. Because of this modest clinical performance, plus the potential association of salicylates with Reyes’s syndrome, BSS is not recommended for routine treatment of diarrhoea in children. Racecadotril, formerly called acetophenon, is an analgesic that does not appear to have any CNS effects. Racecadotril was developed through an understanding of the role of endogenous opioids (enkephalins) in controlling intestinal secretion. Enkephalins, which are putative neurotransmitters, bind to and activate the receptors in the gut, thereby reducing cysolic c-AMP activity and thereby controlling electrolyte secretion. However, endogenous enkephalins are rapidly degraded by the action of enkephalidase, an endopeptidase that abounds in the gut. Racecadotril works by inhibiting enkephalidase, thus preserving the antisecretory activity of endogenous enkephalins. Two randomised, double-blind, placebo-controlled trials have assessed the efficacy and tolerability of racecadotril in infants and children with acute watery diarrhoea who were treated with oral rehydration in Peru and France. Both studies found that racecadotril significantly reduced the mean 48-hour stool output: by 46% in Peru and by 50% in France. The effect was similar whether rotavirus was found in the stools or not. In the study in Peru it was also shown that the median duration of diarrhoea was significantly shorter in those who received racecadotril. Both studies reported that the drug was well tolerated.

Summary
Acute infectious diarrhoea is a common problem with a wide spectrum of clinical severity in children. The combination of replacing the fluid and electrolytes lost, preferably by using an ORS, and continuing to feed the child with age-appropriate foods is the basis for the treatment of this disease. With the exception of cholera, routine use of antimicrobials to treat watery diarrhoea is neither necessary nor appropriate. Antimicrobials are indicated only in invasive diarrhoeas when Shigella infection is suspected. Among the non-antimicrobial diarrhoeal agents, cholestyramine, loperamide and bismuth subsalicylate do not affect the course of the disease and are not free from potentially serious side effects when used in children. Racecadotril and dismecosate are two agents with good safety profiles that are currently available for use in addition to oral rehydration to shorten the duration of the diarrhoea and to decrease its volume – two clinical outcomes that physicians and parents expect to obtain from the treatment of this disease. New diarrhoeal agents are in development, pending testing in clinical trials. Antidiarrhoeal drugs should incorporate certain characteristics (see Table 2) in order to be considered safe and effective options for the treatment of children with infectious watery diarrhoea.
Motility Disorders

Diarrhea