Acute Infectious Diarrhoea in Children – The Role of Drug Treatment

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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 subsalicyiate 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. Racecadotril and diosmectite 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

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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 chlorine 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[8] or by inhibiting the Na+/glucose co-transporter (SGLT1).[9]

Hypersecretion of chlorine is the result of enterotoxin activity both on the enterocyte itself and on the enteric nervous system.[6] Enterotoxins open one of two chlorine 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

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 chlorine channel regulated by the cystic fibrosis transmembrane conductance regulator (CFTR).[4,12,13] Cholera toxin, in addition, provokes the release of neurotransmitters from enteric neurons, mast cells and enterochromaffin cells, which further increases chlorine secretion.[14] A separate chlorine channel, the calcium-activated chlorine channel (CaCC), is opened by the rotavirus NSP4 enterotoxin[14,15] and *Vibrio parahaemolyticus* TDH toxin[16] by inducing an increase in cytosolic calcium concentration. A transmural electric potential difference that results from the excess of secreted chlorine drives sodium movement through the intercellular space into the lumen.[4] This excess of chlorine, 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.[17,18] A shallow ulceration of the mucosa is formed, exposing a denudated submucosa that is prone to bleeding.[17] A typical exudate of mucus containing white blood cells and streaks of blood is formed and subsequently discharged in the stools. *Shigella*, *Campylobacter*, *Salmonella*, enteroinvasive *E. coli*, *Yersinia enterocolitica* and *V. parahaemolyticus* are among the infectious agents that can cause bloody inflammatory diarrhoea.

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.[19] However, if there is progression to more copious diarrhoea, drinking an oral glucose–electrolyte solution containing sodium, potassium and a base would be necessary.[21] Oral rehydration efficacy is based on the fact that sodium and glucose are co-transported through the SGLT1, the protein carrier located in the brush border of enterocytes; this transporting system is preserved undamaged during most intestinal infections.[4] 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.[22]

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.[23] The negative impact on nutritional status is directly proportional to the duration of diarrhoea, especially in infants.[24–26] Oral rehydration solutions (ORS) do not reduce diarrhoea severity, and can even increase stool purging and diarrhoea duration.[27] Some malabsorption of the glucose contained in the ORS is expected in viral gastroenteritis where the Na+/glucose co-transporter (SGLT1) is impaired.[4] This may be the reason for the incremental stool purging and the need for unscheduled intravenous therapy for treatment failure seen in some children rehydrated with the standard ORS.[28,29]

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.[30,31] Instead, ineffective and sometimes harmful antidiarrhoeal drugs and antimicrobials are widely used, whether by prescription or bought over the counter.[32–35]

In a household survey conducted in peri-urban Mexico City,[32] 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.[32] Those on self-medication had an even higher risk of using the wrong drug or an inadequate individual or total dose.[32] 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.[33] 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.[34] 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.[35]

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.[36] 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.[36,37] However, these educational programmes should consider that changing an individual's understanding of diarrhoea and its management is inherently difficult.[38]

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 diarrhoea and dehydration.[35] 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 diarrhoea and dehydration.[40] 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;[41] 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%.[42] 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.[43]

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.[45] 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 trial[44] furazolidone was almost as effective as tetracycline, while in in the second trial[45] 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.[46] 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.[47]

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,[15,49] secondary sepsis with other luminal Gram-negative bacteria,[50,51] toxic megacolon with perforation,[52] haemolytic–uraemic syndrome[53–55] and encephalopathy with seizures.[56,57] Loss of serum proteins in the intestinal lumen has been documented during *Shigella* infection,[58] which, in addition to appetite loss and poor food intake, contributes to malnutrition and growth retardation in children.[59] Shigella is among the pathogens that can induce the development of post-infectious irritable bowel syndrome, the risk being higher if the initial infection lasts longer.[60,61] 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;[62] ampicillin, chloramphenicol, tetracycline, trimethoprim/sulphamethoxazole and nalidixic acid are no longer recommended due to the global emergence of *Shigella* drug resistance to these antimicrobials.[46,63–66]

Table 1: Antidiarrhoeal Drugs According to Their Main Mechanism of Action

Intestinal Transit Inhibitors (Opiate Agonists)
Loperamide
Diphenoxylate
Intraluminal Agents (Bulk-forming Agents, Clays and Other Binding Resins)
Silicates (kaolin, attapulgite, diosmectite)
Cholestyramine
Antisecretory Agents
Enkephalinase inhibitors (racecadotril)
Bismuth subsalicylate
Somatostatin analogues (octreotide, lanreotide)
Serotonin (5-HT) antagonists (ondansetron, ketanserin)
Calcium–calmodulin antagonists (chlorpromazine, zaldaride)
Clonidine
Indomethacin
CFTR chlorine channel blockers (glibenclamide, thiazolidinone, SP-303)

CTFR = cystic fibrosis transmembrane regulator.

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.[67–69] 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.[70,71]

Non-antimicrobial antidiarrhoeal drugs can be divided into three groups according to their main mechanism of action (see *Table 1*). 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.[72,73] Loperamide is well known, available over the counter and widely used for treatment of diarrhoea. *In vivo*[74] and *in vitro*[75] 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

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

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

CNS = central nervous system
Modified from Edelman et al., 1985[13]

duration of diarrhoea by 0.8 days and a lower stool count at 24 hours compared with patients who received placebo.[76] 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 antidiarrhoeals 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.[87] It is thus possible that cholestyramine and ORS cannot be used at the same time because cholestyramine may exchange its chlorine 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 hyperchloraemic metabolic acidosis when treated with cholestyramine.[91,92]

Diosmectite is a naturally occurring multilamellar clay silicate with strong binding properties.[93] *In vitro* or *in vivo* experiments have shown that, unlike other clay bulk-forming agents that mainly bind water, diosmectite can also bind viruses[93] and bacterial toxins[93–96] and suppresses cytokine-induced intestinal inflammation.[97] The clinical efficacy of diosmectite to reduce diarrhoea duration has been proved in several clinical trials.[98–101] 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.[102]

Octreotide, 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 diarrhoea in children.[45] Zaldaride, 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.[102–105] Novel antisecretory agents in current development, such as CFTR chlorine channel blockers, are reviewed extensively elsewhere.[71,106] Bismuth subsalicylate (BSS) is a long-established over-the-counter antidiarrhoeal drug with antimicrobial and antisecretory actions.[107,108] Three clinical trials[109–111] 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[110] and Bangladesh[111] 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 Reye's syndrome,[112] BSS is not recommended for routine treatment of diarrhoea in children. Racecadotril, formerly called acetorphan, is an antisecretory drug that does not affect intestinal motility[113–117] and has no CNS effects.[114] 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 δ-receptors in the gut, thus reducing cytosolic c-AMP activity[117] and thereby controlling electrolyte secretion.[118] However, endogenous enkephalins are rapidly degraded by the action of enkephalinase, an endopeptidase that abounds in the gut.[119] Racecadotril works by inhibiting enkephalinase, thus preserving the antisecretory activity of endogenous enkephalins.[119,120] 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[121] and France.[122] Both studies found that racecadotril significantly reduced the mean 48-hour stool output: by 46% in Peru[121] and by 50% in France.[122] 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.[121] 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 antidiarrhoeal agents, cholestyramine, loperamide and bismuth subsalicylate do not add a worthwhile effect over the clinical course of the disease and are not free from potentially serious side effects when used in children. Racecadotril and diosmectite 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 antidiarrhoeal 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. ■

1. Parashar UD, Holman RC, Bresee JS, et al., Epidemiology of diarrheal disease among children enrolled in four West Coast health maintenance organizations, *Pediatr Infect Dis J*, 1998;17:605–11.
2. Forster J, Guarino A, Parez N, et al., Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis among European children younger than 5 years of age, *Pediatrics*, 2009;123:e393–400.
3. Ehrenkranz P, Lanata CF, Penny ME, et al., Rotavirus diarrhea disease burden in Peru: the need for a rotavirus vaccine and its potential cost savings, *Rev Panam Salud Publica*, 2001;10:240–8.
4. Nguyen VM, Nguyen VT, Huynh PL, et al., The epidemiology and disease burden of rotavirus in Vietnam: sentinel surveillance at 6 hospitals, *J Infect Dis*, 2001;183:1707–12.
5. Ochoa TJ, Salazar-Lindo E, Cleary TG, Management of children with infection-associated persistent diarrhea, *Semin Pediatr Infect Dis*, 2004;15:229–36.
6. Field M, Intestinal ion transport and the pathophysiology of diarrhea, *J Clin Invest*, 2003;111:931–43.
7. Davidson GP, Gall DG, Petric M, et al., Human rotavirus enteritis induced in conventional piglets. Intestinal structure and transport, *J Clin Invest*, 1977;60:1402–9.
8. Jourdan N, Brunet JP, Sapin C, et al., Rotavirus infection reduces sucrase-isomaltase expression in human intestinal epithelial cells by perturbing protein targeting and organization of microvillar cytoskeleton, *J Virol*, 1998;72:7228–36.
9. Halaihel N, Lievin V, Alvarado F, Vasseur M, Rotavirus infection impairs intestinal brush-border membrane Na(+)-solute cotransport activities in young rabbits, *Am J Physiol Gastrointest Liver Physiol*, 2000;279:G587–95.
10. Barrett KE, New insights into the pathogenesis of intestinal dysfunction: secretory diarrhea and cystic fibrosis, *World J Gastroenterol*, 2000;6:470–4.
11. Jentsch TJ, Stein V, Weinreich F, Zdebik AA, Molecular structure and physiological function of chloride channels, *Physiol Rev*, 2002;82:503–8.
12. Giannella RA, Escherichia coli heat-stable enterotoxins, guanylins, and their receptors: what are they and what do they do?, *J Lab Clin Med*, 1995;125:173–81.
13. Ménard LP, Dubreuil JD, Enteroaggregative Escherichia coli heat-stable enterotoxin 1 (EAST1): a new toxin with an old twist, *Crit Rev Microbiol*, 2002;28:43–60.
14. Estes MK, Morris AP, A viral enterotoxin. A new mechanism of virus-induced pathogenesis, *Adv Exp Med Biol*, 1999;473:73–82.
15. Lundgren O, Svensson L, Pathogenesis of rotavirus diarrhea, *Microbes Infect*, 2001;3:1145–56.
16. Takahashi A, Kenjyo N, Imura K, et al., Cl-secretion in colonic epithelial cells induced by the Vibrio parahaemolyticus hemolytic toxin related to thermostable direct hemolysin, *Infect Immun*, 2000;68:5435–8.
17. Sansonetti P, Microbes and microbial toxins: paradigms for microbial-mucosal interactions III. Shigellosis: from symptoms to molecular pathogenesis, *Am J Physiol Gastrointest Liver Physiol*, 2001;280:G319–23.
18. Schroeder GN, Hilbi H, Molecular pathogenesis of Shigella spp.: controlling host cell signaling, invasion, and death by type III secretion, *Clin Microbiol Rev*, 2008;21:134–56.
19. Khurco MS, Mahajan R, Zargar SA, et al., The colon in shigellosis: serial colonoscopic appearances in Shigella dysenteriae I, *Endoscopy*, 1990;22:35–8.
20. Huffman SL, Combest C, Role of breast-feeding in the prevention and treatment of diarrhea, *J Diarrhoeal Dis Res*, 1990;8:68–81.
21. King CK, Glass RI, 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.
22. Boschi-Pinto C, Velebit L, Shibuya K, Estimating child mortality due to diarrhoea in developing countries, *Bull World Health Organ*, 2008;86:710–7.
23. Bhattacharya MK, Manna B, Dutta D, et al., Risk factors for development of dehydration in young children with acute watery diarrhoea: a case-control study, *Acta Paediatr*, 1995;84:160–4.
24. Lima AA, Moore SR, Barboza MS Jr, et al., Persistent diarrhea signals a critical period of increased diarrhea burdens and nutritional shortfalls: a prospective cohort study among children in northeastern Brazil, *J Infect Dis*, 2000;181:1643–51.
25. Checkley W, Epstein LD, Gilman RH, et al., Effects of acute diarrhea on linear growth in Peruvian children, *Am J Epidemiol*, 2003;157:166–75.
26. Assis AMO, Barreto ML, Santos LMP, et al., Growth faltering in childhood related to diarrhea: a longitudinal community based study, *Eur J Clin Nutr*, 2005;59:1317–23.
27. El-Mougi M, El-Akkad N, Hendawi A, et al., Is a low-osmolarity ORS solution more efficacious than standard WHO ORS solution?, *J Pediatr Gastroenterol Nutr*, 1994;19:83–6.
28. Multicentre evaluation of reduced-osmolarity oral rehydration salts solution. International Study Group on Reduced-osmolarity ORS solutions, *Lancet*, 1995;345:282–5.
29. CHOICE Study Group, Multicenter, randomized, double-blind clinical trial to evaluate the efficacy and safety of a reduced osmolarity oral rehydration salts solution in children with acute watery diarrhea, *Pediatrics*, 2001;107:613–8.
30. Desjeux D, Favre I, Simongiovanni J, et al., Why is oral therapy associated with drugs in the treatment of diarrhea?, *J Pediatr Gastroenterol Nutr*, 1996;22:112–4.
31. Nizami SQ, Khan IA, Bhutta ZA, Self-reported concepts about oral rehydration solution, drug prescribing and reasons for prescribing antidiarrhoeals for acute watery diarrhoea in children, *Trop Doct*, 1996;26:180–3.
32. Bojalil R, Calva JJ, Antibiotic misuse in diarrhea. A household survey in a Mexican community, *J Clin Epidemiol*, 1994;47:147–56.
33. Jousilahti P, Madkour SM, Lambrechts T, Sherwin E, Diarrhoeal disease morbidity and home treatment practices in Egypt, *Public Health*, 1997;111:5–10.
34. Nizami SQ, Khan IA, Bhutta ZA, Drug prescribing practices of general practitioners and paediatricians for childhood diarrhoea in Karachi, Pakistan, *Soc Sci Med*, 1996;42:1133–9.
35. Szajewska H, Hoekstra JH, Sandhu B, The Working Group on Acute Diarrhoea of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, Management of acute gastroenteritis in Europe and the impact of the new recommendations: a multicenter study, *J Pediatr Gastroenterol Nutr*, 2000;30:522–7.
36. Salazar-Lindo E, Chea-Woo E, Kohatsu J, Miranda PR, Evaluation of clinical management training programme for diarrhea, *J Diarrhoeal Dis Res*, 1991;9:227–34.
37. Bhattacharya R, Kaur P, Reddy DC, Impact of education in the knowledge and practices of rural mothers and key family members on diarrhoea and its treatment at home, *J Diarrhoeal Dis Res*, 1998;6:15–20.
38. Hudelson PM, ORS and the treatment of childhood diarrhea in Managua, Nicaragua, *Soc Sci Med*, 1993;37:97–109.
39. Centers for Disease Control and Prevention (CDC), Rotavirus surveillance-worldwide, 2001–2003, *MMWR Morb Mortal Wkly Rep*, 2008;57:1255–7.
40. Atmar RL, Estes MK, The epidemiologic and clinical importance of norovirus infection, *Gastroenterol Clin N Am*, 2006;35:275–90.
41. Rodriguez WJ, Kim HW, Arrobio JO, et al., Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children, *J Pediatr*, 1977;91:188–93.
42. Staat MA, Azimi PH, Berke T, et al., Clinical presentations of rotavirus infection among hospitalized children, *Pediatr Infect*

Dis J, 2002;21:221–7.
43. Phavichitr N, Catto-Smith AG, Acute gastroenteritis in children: What role for antibacterials?, *Pediatr Drugs*, 2003;5:279–90.
44. Pierce NF, Banwell JG, Mitra RC, et al., Controlled comparison of tetracycline and furazolidone in cholera, *Br Med J*, 1968;3(5613):277–80.
45. Rabbani GH, Islam MR, Butler T, et al., Single-dose treatment of cholera with furazolidone or tetracycline in a double-blind randomized trial, *Antimicrob Agents Chemother*, 1989;33:1447–50.
46. Hoge CW, Gambel JM, Srijan A, et al., Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years, *Clin Infect Dis*, 1998;26:341–5.
47. Sack DA, Sack RB, Nair GB, Siddique AK, Cholera, *Lancet*, 2004;363:223–33.
48. Struelens MJ, Patte D, Kabir I, et al., Shigella septicemia: prevalence, presentation, risk factors and outcome, *J Infect Dis*, 1985;152:784–90.
49. Saraswathi K, De A, Jog A, Gogate A, Shigella septicemia, *Indian Pediatr*, 2002;39:777–9.
50. Hallalin KC, Nelson JD, Coliform septicemia complicating shigellosis in children, *JAMA*, 1965;192:441–3.
51. Neglia TG, Marr TJ, Davis AT, Shigella dysentery with secondary Klebsiella sepsis, *J Pediatr*, 1976;89:253–4.
52. Wilson AP, Ridgway GL, Sarner M, et al., Toxic dilatation of the colon in shigellosis, *BMJ*, 1990;301:1325–6.
53. Koster F, Levin J, Walker L, et al., Hemolytic-uremic syndrome after shigellosis. Relation to endotoxemia and circulating immune complexes, *N Engl J Med*, 1978;298:927–33.
54. Bhimma R, Rollins NC, Coovadia HM, Adhikari M, Post-dysenteric hemolytic uremic syndrome in children during an epidemic of Shigella dysentery in Kwazulu/Natal, *Pediatr Nephrol*, 1997;11:560–4.
55. Houdouin V, Doit C, Mariani P, et al., A pediatric cluster of Shigella dysenteriae serotype 1 diarrhea with hemolytic uremic syndrome in 2 families from France, *Clin Infect Dis*, 2004;38:e96–9.
56. Ashkenazi S, Dinari C, Zevulunov A, Nitzan M, Convulsions in childhood shigellosis. Clinical and laboratory features in 153 children, *Am J Dis Child*, 1987;141:208–10.
57. Khan WA, Dhar U, Salam MA, et al., Central nervous system manifestations of childhood shigellosis: prevalence, risk factors, and outcome, *Pediatrics*, 1999;103:e18.
58. Bennish ML, Salam MA, Wahed MA, Enteric protein loss during shigellosis, *Am J Gastroenterol*, 1993;88:53–7.
59. Black RE, Brown KH, Becker S, Effects of diarrhea associated with specific enteropathogens on the growth of children in rural Bangladesh, *Pediatrics*, 1984;73:799–805.
60. Wang LH, Fang XC, Pan GZ, Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis, *Gut*, 2004;53:1096–101.
61. Ji S, Park H, Lee D, et al., Post-infectious irritable bowel syndrome in patients with Shigella infection, *J Gastroenterol Hepatol*, 2005;20:381–6.
62. Guidelines for the control of shigellosis, including epidemics due to Shigella dysenteriae type 1, World Health Organization, 2005. Available at: www.who.int/child_adolescent_health/documents/9241592330/en/index.html.
63. Martin LJ, Flint J, Ravel A, et al., Antimicrobial resistance among Salmonella and Shigella isolates in five Canadian provinces (1997 to 2000), *Can J Infect Dis Med Microbiol*, 2006;17:243–50.
64. Sivapalasingam S, Nelson JM, Joyce K, Het al., High prevalence of antimicrobial resistance among Shigella isolates in the United States tested by the National Antimicrobial Resistance Monitoring System from 1999 to 2002, *Antimicrob Agents Chemother*, 2006;50:49–54.
65. Kuo CY, Su LH, Perera J, et al., Antimicrobial susceptibility of Shigella isolates in eight Asian countries, 2001–2004, *J Microbiol Immunol Infect*, 2008;41:107–11.
66. Kosek M, Yori PP, Pan WK, et al., Epidemiology of highly endemic multiply antibiotic-resistant shigellosis in children in the Peruvian Amazon, *Pediatrics*, 2008;122:e541–9.
67. Fedorak RN, Field M, Antidiarrheal therapy: Prospects for new agents, *Dig Dis Sci*, 1987;32:195–205.
68. Schiller R, Review article: anti-diarrhoeal pharmacology and therapeutics, *Aliment Pharmacol Ther*, 1995;9:87–106.
69. Farthing MJ, Antisecretory drugs for diarrheal disease, *Dig Dis*, 2006;24:47–58.
70. Costello AM, Bhutta TI, Antidiarrhoeal drugs for acute diarrhoea in children, *BMJ*, 1992;304:1–2.
71. Farthing MJ, Novel agents for the control of secretory diarrhoea, *Expert Opin Investig Drugs*, 2004;13:777–85.
72. Schiller LR, Santa Ana CA, Morawski SG, Fordtran JS, Mechanism of the antidiarrheal effect of loperamide, *Gastroenterology*, 1984;86:1475–80.
73. Harford WV, Krejs GJ, Santa Ana CA, Fordtran JS, Acute effect of diphenoxylate with atropine (Lomotil) in patients with chronic diarrhea and fecal incontinence, *Gastroenterology*, 1980;78:440–3.
74. Hughes S, Higgs NB, Turnberg LA, Loperamide has antisecretory activity in the human jejunum *in vivo*, *Gut*, 1984;25:931–5.
75. Burleigh DE, Loperamide but not morphine has anti-secretory effects in human colon, in vitro, *Eur J Pharmacol*, 1991;202:277–80.
76. Li ST, Grossman DC, Cummings P, Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis, *PLoS Med*, 2007;4:e98.
77. Chow CB, Li SH, Leung NK, Loperamide associated necrotising enterocolitis, *Acta Paediatr Scand*, 1986;75:1034–6.
78. Bhutta TI, Tahir KI, Loperamide poisoning in children, *Lancet*, 1990;335:363.
79. Olm M, Gonzalez FJ, Garcia-Valdecasas, et al., Necrotising colitis with perforation in diarrhoeic patients treated with loperamide, *Eur J Clin Pharmacol*, 1991;40:415–6.
80. Gussin RZ, Withdrawal of loperamide drops, *Lancet*, 1990;335:1603–4.
81. DuPont HL, Hornick RB, Adverse effect of lomotil therapy in shigellosis, *JAMA*, 1973,226:1525–8.
82. Portney BL, DuPont HL, Pruitt D, et al., Antidiarrheal agents in the treatment of acute diarrhea in children, *JAMA*, 1976,236:844–6.
83. Thompson WG, Cholestyramine, *Can Med Assoc J*, 1971;104:305–9.
84. Mullan NA, Burgess MN, Bywater RJ, Newsome FM, The ability of cholestyramine resin and other adsorbents to bind Escherichia coli enterotoxins, *J Med Microbiol*, 1979;12:487–96.
85. Brouillard MY, Rateau JG, Cholestyramine adsorbs Escherichia coli and Vibrio cholerae toxins by way of ion exchange mechanism, *Ann Gastroenterol Hepatol (Paris)*, 1990;26:27–30.
86. Duffau G, Emilfork M, Prenzel I, et al., Cholestyramine in the treatment of acute bacterial diarrhea in infants, *Bol Med Hosp Infant Mex*, 1979;36:735–42.
87. Vesikari T, Isolauri E, Maki M, Efficacy of cholestyramine in acute infantile diarrhoea: placebo-controlled double-blind trial in hospitalized children and in outpatients, *J Diarrhoeal Dis Res*, 1984:151–8.
88. Vesikari T, Isolauri E, A comparative trial of cholestyramine and loperamide for acute diarrhoea in infants treated as outpatients, *Acta Paediatr Scand*, 1985;74:650–4.
89. Isolauri E, Vesikari T, Oral rehydration, rapid feeding, and cholestyramine for treatment of acute diarrhea, *J Pediatr Gastroenterol Nutr*, 1985;4:366–7.
90. Isolauri E, Vähäsarja V, Vesikari T, Effect of cholestyramine on acute diarrhoea in children receiving rapid oral rehydration and full feedings, *Ann Clin Res*, 1986;18:99–102.
91. Scheel PJ Jr, Whelton A, Rossiter K, Watson A, Cholestyramine-induced hyperchloremic metabolic acidosis, *J Clin Pharmacol*, 1992;32:536–8.
92. Fan FS, Chow KM, Szeto CC, Li PK, Hyperchloraemic metabolic acidosis, Emerg Med J, 2008,25:613.
93. Dupont C, Vernisse B, Anti-diarrheal effects of diosmectite in the treatment of acute diarrhea in children: a review, *Pediatr Drugs*, 2009,11:89–99.
94. Clark KJ, Sarr AB, Grant PG, et al., *In vitro* studies on the use of clay, clay minerals and charcoal to adsorb bovine rotavirus and bovine coronavirus, *Vet Microbiol*, 1998;63:137–46.
95. Fioramonti J, Droy-Lefaix MT, Bueno L, Changes in gastro-intestinal motility induced by cholera toxin and experimental osmotic diarrhoea in dogs: effects of treatment with an argillaceous compound, *Digestion*, 1987;36:230–7.
96. Weese JS, Cote NM, deGannes RV, Evaluation of *in vitro* properties of di-tri-octahedral smectite on clostridial toxins and growth, *Equine Vet J*, 2003;35:638–41.
97. Mahraoui L, Heyman M, Plique O, et al., Apical effect of diosmectite on damage to the intestinal barrier induced by basal tumour necrosis factor-a, *Gut*, 1997;40:339–43.
98. Guarino A, Bisceglia M, Castellucci G, et al., Smectite in the treatment of acute diarrhea: a nationwide randomized controlled study of the Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP) in collaboration with primary care pediatricians. SIGEP Study Group for Smectite in Acute Diarrhea, *J Pediatr Gastroenterol Nutr*, 2001;32:71–5.
99. Narkeviciute I, Rudzeviciene O, Leviniene G, et al., Management of Lithuanian children's acute diarrhoea with Gastrolit solution and dioctahedral smectite, *Eur J Gastroenterol Hepatol*, 2002;14:419–24.
100. Yen ZS, Lai MS, Best evidence topic report. Smectite for acute diarrhoea in children, *Emerg Med J*, 2006;23:65–6.
101. Szajewska H, Dziechciarz P, Mrukowicz J, Meta-analysis: Smectite in the treatment of acute infectious diarrhoea in children, *Aliment Pharmacol Ther*, 2006;23:217–27.
102. Dupont C, Foo JL, Garnier P, et al., Oral diosmectite reduces stool output and diarrhea duration in children with acute watery diarrhea, *Clin Gastroenterol Hepatol*, 2009;7:456–62.
103. DuPont HL, Ericsson CD, Mathewson JJ, et al., Zaldaride maleate, an intestinal calmodulin inhibitor, in the therapy of travelers' diarrhea, *Gastroenterology*, 1993;104:709–15.
104. Okhuysen PC, DuPont HL, Ericsson CD, et al., Zaldaride maleate (a new calmodulin antagonist) versus loperamide in the treatment of traveler's diarrhea: randomized, placebo-controlled trial, *Clin Infect Dis*, 1995,21:341–4.
105. Silberschmidt G, Schick MT, Steffen R, et al., Treatment of travellers' diarrhoea: zaldaride compared with loperamide and placebo, *Eur J Gastroenterol Hepatol*, 1995;7:871–5.
106. Verkman AS, Lukacs GL, Galietta LJ, CFTR chloride channel drug discovery—inhibitors as antidiarrheals and activators for therapy of cystic fibrosis, *Curr Pharm Des*, 2006;12:2235–47.
107. DuPont HL, Bismuth subsalicylate in the treatment and prevention of diarrheal disease, *Drug Intell Clin Pharm*, 1987;21:687–93.
108. Gorbach SL, Bismuth therapy in gastrointestinal diseases, *Gastroenterology*, 1990;99:863–75.
109. Schiano-Brücher H, Avendano P, O'Ryan M, et al., Bismuth subsalicylate in the treatment of acute diarrhea in children: a clinical study, *Pediatrics*, 1991;87:18–27.
110. Figueroa-Quintanilla D, Salazar-Lindo E, Sack RB, et al., A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease, *N Engl J Med*, 1993;328:1653–8.
111. Chowdhury HR, Yunus M, Zaman K, et al., The efficacy of bismuth subsalicylate in the treatment of acute diarrhoea and the prevention of persistent diarrhoea, *Acta Paediatr*, 2001;90:605–10.
112. Food and Drug Administration, HSS, Labeling for oral and rectal over-the-counter drug products containing aspirin and nonaspirin salicylates, Reye's Syndrome warning. Final rule, *Fed Regist*, 2003;68:18861–9.
113. Marçais-Collado H, Uchida G, Costentin J, et al., Naloxone-reversible antidiarrheal effects of enkephalinase inhibitors, *Eur J Pharmacol*, 1987;144:125–32.
114. Baumer P, Danquechin-Dorval E, Bertrand J, et al., Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhea, *Gut*, 1992;33:753–8.
115. Bergmann JF, Chaussade S, Couturier D, et al., Effects of acetorphan, an antidiarrhoeal enkephalinase inhibitor, on oro-caecal and colonic transit times in healthy volunteers, *Aliment Pharmacol Ther*, 1992,6:305–13.
116. Duval-Iflah Y, Berard H, Baumer P, et al., Effects of racecadotril and loperamide on bacterial proliferation and on the central nervous system of the newborn gnotobiotic piglet, *Aliment Pharmacol Ther*, 1999,13(Suppl. 6):9–14.
117. Rachmilewitz D, Karmeli F, ChorevM, Selinger Z, Effect of opiates on human colonic adenylate cyclase activity, *Eur J Pharmacol*, 1983;93:169–73.
118. Kachur JF, Miller RJ, Filed M, Control of guinea pig intestinal electrolyte secretion by a delta-opiate receptor, *Proc Natl Acad Sci U S A*, 1980;77:2753–6.
119. Primi MP, Bueno L, Baumer P, et al., Racecadotril demonstrates intestinal antisecretory activity *in vivo*, *Aliment Pharmacol Ther*, 1999;13(Suppl. 6):3–7.
120. Turvill J, Farthing M, Enkephalins and enkephalinase inhibitors in intestinal fluid and electrolyte transport, *Eur J Gastroenterol Hepatol*, 1997;9:877–80.
121. Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, Gutierrez M, Racecedotril in the treatment of acute watery diarrhoea in children, *N Engl J Med*, 2000;343:463–77.
122. Cézard JP, Duhamel JF, Meyer M, et al., Efficacy and tolerability of racecadotril in acute diarrhea in children, *Gastroenterology*, 2001;120:799–805.
123. Edelman R, Prevention and treatment of infectious diarrhea: Speculations on the next 10 years, *Am J Med*, 1985;78:99–106.