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Diarrhoea: a significant worldwide problem

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Abstract

Diarrhoea is a problem, not only of the developing world, but also of the Western world. However, the economic implications of diarrhoeal diseases are particularly evident in the poorer countries. The most common worldwide cause of diarrhoea is intestinal infection and infants, pre-school children, the elderly, and those with congenital or acquired immunodeficiency run a high risk of contracting such infections. Diarrhoeal disease can be classified into three major clinical syndromes: acute watery diarrhoea, bloody diarrhoea, and persistent diarrhoea. A number of different micro-organisms can cause infectious diarrhoea, depending on the clinical setting. The development of oral rehydration solution has provided a simple approach to rehydration and maintenance of hydration in patients with acute watery diarrhoea, and has been implemented worldwide under the auspices of the World Health Organization. However, rehydration does not treat the diarrhoea itself, which will persist until the infection resolves. Since the drugs currently used for the treatment of diarrhoea, such as the opiate agents and antibiotics, have limitations, the search continues for a drug that acts predominantly on secretory pathways without affecting gastrointestinal motility. Novel therapeutic approaches include 5-HT_2 and 5-HT_3 receptor antagonists, calcium–calmodulin antagonists, and σ-receptor agonists. Another approach has concentrated on the antisecretory role of the neurotransmitter, enkephalin, and has resulted in the development of the enkephalinase inhibitor, racecadotril. This drug has true antisecretory activity, and has demonstrated good efficacy and tolerability in clinical trials.

Keywords: Antisecretory agents; Diarrhoeal diseases; Enteropathogens; Oral rehydration solution

1. Introduction

Intestinal infection is the most common cause of diarrhoea worldwide and is responsible for the deaths of 3–4 million individuals each year, the majority of whom are pre-school children [1,2]. In some countries in the developing world children may suffer many attacks of acute diarrhoea every year, each of which contributes to the infection-malnutrition cycle and consequent impaired growth and development. The seventh cholera pandemic continues to produce high morbidity and mortality in many parts of the developing world including the Indian subcontinent, sub-saharan Africa, and some parts of Central and South America. Most of the deaths from acute infectious diarrhoea result from excessive fluid and electrolyte losses, which result in dehydration and acidosis [3,4]. Thus, the majority of these deaths are avoidable providing fluid and electrolyte losses are replaced promptly.

The major burden of infectious diarrhoea falls upon individuals, particularly infants and young children, who live in the developing world. However, despite industrialization, wealth, and public health interventions to ensure water quality and sewage disposal, acute intestinal infections are increasing in the Western world. This is particularly due to foodborne infections such as *Salmonella* spp., *Campylobacter jejuni*, and enterohaemorrhagic *Escherichia coli* O157:H7 [5]. Waterborne infection is also important in the developed world, particularly as a result of contamination of domestic water supplies with the cysts of *Giardia intestinalis* and *Cryptosporidium parvum* [6]. Other factors contributing to the rise in acute infectious diarrhoea in

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the industrialized world include the widespread use of broad-spectrum antibiotics, impaired host immunity due to HIV infection, anti-cancer chemotherapy, and the increase in foreign travel from Western countries to the developing world.

2. Global impact of infectious diarrhoea

It has been estimated that there may be as many as 4 billion cases of acute diarrhoea each year worldwide. In the economically deprived parts of the world such as the Indian subcontinent, Africa, and Latin America, children may experience between three and ten episodes of diarrhoea each year [2]. Even in the wealthy industrialized world acute diarrhoea in children has a significant morbidity and mortality. In the USA it has been estimated that there are up to 8 million consultations for acute diarrhoea each year resulting in 250 000 hospital admissions and more than 500 deaths. The economic implications of diarrhoeal disease are self-evident, but are particularly damaging to poor countries where the case management of acute diarrhoeal disease in a child may result in the consumption of a significant proportion of the total healthcare budget for that individual. HIV-related diarrhoea emphasizes this point; of the 22 million individuals predicted to be infected with HIV by the year 2000, 10 million will reside in Africa, 9 million in Asia, and 2 million in Latin America with only 1 million in Europe. Thus, the most economically vulnerable communities in the world will face a major pressure on their already compromised healthcare budgets.

Table 1
Groups at special risk of infectious diarrhoea

Risk factors	Groups at risk
Age	Infants and young children The elderly
Non-immune host defence — gastric acid	The elderly Hypo- and achlorhydria Recipients of acid inhibitory drugs
Immunodeficiency	Congenital immunodeficiency (common variable immune deficiency) HIV/AIDS Cancer and cancer chemotherapy
Increased exposure to enteropathogens	Travellers Food- and waterborne disease
Antibiotics	Recipients of antibiotics The elderly and cancer patients are at increased risk

3. Who is at risk?

Several groups of individuals are at increased risk of intestinal infections (Table 1). Infants, pre-school children, and the elderly are particularly susceptible. During the first few months of life the breastfed infant is relatively protected from intestinal infection, but exposure to enteropathogens increases during the weaning period as the protective benefits of maternal milk are lost. As the infant and young child develops, acquired immunity to the common enteropathogens increases such that the age-specific prevalence of many intestinal infections decreases during adolescence and early adult life. The elderly appear to have increased susceptibility to infection partly due to declining immune function and possibly also to decreased gastric acid secretion. This is especially evident in those with pernicious anaemia and with gastric atrophy as a result of chronic infection with *Helicobacter pylori*.

Congenital and acquired immunodeficiency is recognized as a major risk factor for intestinal infection. Common variable immune deficiency is classically associated with protozoal infections, particularly giardiasis and cryptosporidiosis. HIV infection has underscored the importance of cellular immunity in the host defence against enteric infection; in this setting, intracellular protozoa such as *C. parvum*, *Microsporidium* spp., *Isospora belli*, and *Cyclospora cayetanensis* predominate [6]. Anti-cancer chemotherapy is also associated with opportunistic intestinal infection including that due to cytomegalovirus and *Clostridium difficile*. The widespread use of broad-spectrum antibiotics in cancer patients and in many other groups of hospitalized and ambulant individuals has demonstrated the clinical relevance of antibiotic-associated diarrhoea, much of which is attributable to opportunistic infection with *C. difficile* although other organisms are also involved.

The importance of gastric acid as a physical barrier to intestinal infection has been re-emphasized by the widespread use of acid inhibitory drugs such as the H_2-receptor antagonists and the proton pump inhibitors [7,8]. There is evidence that these agents significantly increase the risk of acquiring an intestinal bacterial infection, particularly in the elderly.

4. What are the clinical patterns of infection?

Infective diarrhoeal disease can be classified into three major clinical syndromes: acute watery diarrhoea, bloody diarrhoea, and persistent diarrhoea. Acute watery diarrhoea produces rapid loss of fluid and electrolytes, and can produce profound dehydration with alteration in consciousness and vascular col-

Table 2
Enteropathogens responsible for infectious diarrhoea[a]

Enteropathogen	Acute watery diarrhoea	Dysentery	Persistent diarrhoea
Viruses			
Rotavirus	+	−	−
Adenovirus (types 40, 41)	+	−	−
Small round structured viruses	+	−	−
Cytomegalovirus	+	+	+
Bacteria			
V. cholerae and other vibrios	+	−	−
ETEC	+	−	−
EIEC	+	+	−
EHEC	+	+	+
Shigella spp.	+	+	+
Salmonella spp.	+	+	+
Campylobacter jejuni	+	+	+
Yersinia enterocolitica	+	+	+
Clostridium difficile	+	+	+
M. tuberculosis	−	+	+
Protozoa			
Giardia intestinalis	+	−	+
Cryptosporidium parvum	+	−	+
Microsporidium spp.	+	−	+
Isospora belli	+	−	+
Cyclospora cayetanensis	+	−	+
Entamoeba histolytica	+	+	+
Helminths			
Strongyloides stercoralis	−	−	+
Schistosoma spp.	−	+	+

[a] ETEC, enterotoxigenic *E. coli*; EIEC, enteroinvasive *E. coli*; EHEC, enterohaemorrhagic *E. coli*.

lapse in infants and young children. In children, watery diarrhoea is usually due to rotavirus or to enteric adenoviruses, whereas enterotoxigenic *E. coli* and *Vibrio cholerae* are more common in adults.

Bloody diarrhoea is usually due to invasive enteropathogens such as *Shigella* spp., *Salmonella* spp., and *Campylobacter jejuni*. These organisms predominantly infect the distal ileum and colon. Enterohaemorrhagic *E. coli* has emerged as an important dysenteric organism in the industrialized world and, like the other invasive pathogens, may be complicated by the haemolytic-uraemic syndrome and thrombotic thrombocytopenic purpura [5]. In addition, these infections may be complicated by reactive arthritis or a complete Reiter's syndrome (arthritis, uveitis, and conjunctivitis). Recently it has become evident that infection with *Campylobacter jejuni* is an important cause of the polyneuropathy known as the Guillain-Barré syndrome.

Persistent diarrhoea can be due to continuing infections with many of the organisms cited above, although the intracellular protozoa (*C. parvum*, *Cyclospora cayetanensis*, *Microsporidium* spp.) have emerged as important causes of HIV-related persistent diarrhoea [6]. In children, enteropathogenic and enteroaggregative *E. coli* are also important.

5. What is the cause?

The microbial enteropathogens responsible for acute watery diarrhoea, dysentery, and persistent diarrhoea are shown in Table 2. However, the spectrum of organisms varies depending on the clinical setting. The range of organisms commonly encountered in HIV-related diarrhoea (Table 3) differs from those organisms commonly isolated from travellers (Table 4) [9,10]. Similarly, a number of organisms are predominantly responsible for water- and foodborne infections. Some

Table 3
Enteropathogens responsible for HIV-related diarrhoea

Protozoa	*Cryptosporidium parvum*
	Microsporidium spp.
	Giardia intestinalis
	Isospora belli
	Cyclospora cayetanensis
Bacteria	*Salmonella* spp.
	Shigella spp.
	Campylobacter spp.
	Vibrio parahaemolyticus
	Clostridium difficile
	Mycobacterium avium complex
Viruses	Cytomegalovirus

Table 4
Prevalence of microbial enteropathogens in travellers' diarrhoea[a]

Enteropathogen	Reported isolation rates (%)
Bacteria	
ETEC	20–75
Salmonella spp.	0–16
Shigella spp.	0–30
Campylobacter jejuni	1–11
Aeromonas and Plesiomonas spp.	1–57
Vibrio parahaemolyticus	1–16
EIEC	5–7
Protozoa	
Giardia lamblia	0–9
Entamoeba histolytica	0–9
Cryptosporidium parvum	1–10
Microsporidium, *Cyclospora*	?
Viruses	
Rotavirus	0–36
Multiple pathogens	9–22
No pathogen isolated	15–55

[a] ETEC, enterotoxigenic *E. coli*; EIEC, enteroinvasive *E. coli*.

Table 5
Microbial pathogens responsible for food- and waterborne disease

Source	Organism
Water	*Giardia intestinalis*
	Cryptosporidium parvum
Food	
Preformed toxin	*Staphylococcus aureus*
	Bacillus cereus
	Clostridium botulinum
Intestinal colonization	*Salmonella* spp.
	Campylobacter jejuni
	Enterohaemorrhagic *E. coli*
	Yersinia enterocolitica
	Vibrio parahaemolyticus
	Clostridium perfringens

organisms that cause food poisoning colonize and proliferate within the intestine, whereas others produce preformed toxins in the food which are then available to act immediately on the intestine and produce diarrhoea and often vomiting (Table 5).

6. How should we treat diarrhoea?

A major advance during the second half of this century was the development of glucose-electrolyte solutions for the oral rehydration of infants and young children with acute watery diarrhoea [3,4]. Because of its simplicity this therapeutic approach has been implemented worldwide under the auspices of the World Health Organization and is estimated to have saved millions of lives. However, despite its efficacy in rehydrating and maintaining hydration in individuals with watery diarrhoea, stool volumes do not decrease and sometimes paradoxically increase, thereby raising doubts in the mind of a child's carer as to whether the treatment is actually working. Reducing the osmolality of standard glucose-electrolyte solutions either by reducing the sodium and glucose content or by using a polymer such as rice starch has been shown to reduce stool volume in some circumstances [11]; however, the diarrhoea will still continue until the infection resolves.

Antidiarrhoeal medications such as loperamide, diphenoxylate, or codeine phosphate are widely used by adults with acute diarrhoea, but are contraindicated in infants and young children because of concerns about the possible central effects of opiate or opioid antidiarrhoeal agents and the fact that administration of these drugs to a child might detract from the importance of giving the life-saving intervention, namely oral rehydration therapy.

Antimicrobial chemotherapeutic agents are indicated for the treatment of infectious diarrhoea in a number of situations [10,12,13]. Tetracycline and a variety of other agents are effective in reducing the duration and severity of cholera and other acute watery diarrhoeas such as that due to enterotoxigenic *E. coli*, which is common in travellers. Antibiotics are also indicated for dysenteric shigellosis, typhoid, and other dysenteric pathogens when dictated by the clinical severity of the infection. The use of antibiotics for the treatment of enterohaemorrhagic *E. coli* remains controversial as there is some evidence that antibiotics may increase the risks of an individual developing haemolytic-uraemic syndrome.

Some of the enteropathogens that cause persistent diarrhoea such as *Giardia intestinalis*, *Isospora belli*, *Cyclospora cayetanensis*, and one of the *Microsporidium* spp. — *Encephalitozoon intestinalis*, are amenable to antimicrobial chemotherapy although *Cryptosporidium parvum* continues to be relatively unresponsive to most agents tested to date. Recent studies with the newer macrolide antibiotics (azithromycin and roxithromycin), nitazoxanide, and albendazole suggest that the situation may change in the future.

7. Novel therapeutic targets

There is, however, a continuing search for an agent that will reduce fluid and electrolyte losses during infectious diarrhoea, and that acts predominantly on secretory pathways without having a profound effect on intestinal motility [14]. The drive towards the development of an intestinal antisecretory agent has required basic research into basal and stimulated secretory processes in the intestine, and it has become clear that a variety of neural and neurohumoral mechanisms are involved in intestinal secretory processes.

There is now compelling evidence that cholera toxin and the enterotoxins of *E. coli* are able to activate neural reflex arcs within the intestine that involve a sensory afferent neurone and a secretory efferent neurone [15]. Putative neurotransmitters include substance P and vasoactive intestinal polypeptide (VIP). It is also evident that cholera toxin is able to release the endogenous intestinal secretagogue, 5-hydroxytryptamine (5-HT), which is thought to act via 5-HT_3 receptors located on intestinal neurones to activate the secretory reflex arc. 5-HT may also increase synthesis of the secretagogue prostaglandin E_2 via 5-HT_2 receptors [16]. The use of 5-HT_2 and 5-HT_3 receptor antagonists both in experimental and human models of secretory diarrhoea indicates that this might be a useful therapeutic approach to controlling secretory diarrhoea [17]. There is also preliminary evidence that the calcium–calmodulin antagonist, zaldaride maleate, and the σ-receptor agonist, igmesine, may also have antisecretory activity.

An alternative therapeutic approach to the control of secretory diarrhoea is to take advantage of endogenous absorbagogues such as enkephalin. Enkephalin is a neurotransmitter in the enteric nervous system that acts on opioid δ-receptors, which are thought to be located on the basolateral membrane of enterocytes [18]. Activation of these receptors inhibits the action of adenylate cyclase and inhibits the secretory process. The effects of endogenous enkephalin can be potentiated by inhibiting the enzyme, enkephalinase, which is responsible for its degradation. Such an agent has now been developed: it was originally known as acetorphan and has now been renamed racecadotril (INN). This agent has true antisecretory activity, and clinical studies in diarrhoeal states indicate that it has a place in the management of secretory diarrhoea [19,20].

8. Conclusions

Infective diarrhoea continues to be a major problem worldwide, both in the developing and developed world. Although, ultimately, the provision of high-quality drinking water and appropriate controls on the transmission of micro-organisms through food may be achieved by public health interventions, interim strategies are required to manage the many millions of attacks of infective diarrhoea that take place throughout the world each year. Oral rehydration therapy continues to be the cornerstone of management for acute watery diarrhoea, and antimicrobial chemotherapeutic agents have a place in the treatment of some infections. The development of antisecretory agents as an adjunct to rehydration therapy should reduce fluid requirements by decreasing faecal losses, and will thus provide both symptomatic and physiological benefits to the sufferer.

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