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Leading article – Tropical infection of the gastrointestinal tract and liver series

Travellers' diarrhoea

International travel features in the lives of more than 300 million people each year, 30 million of whom travel from an industrialised to a developing country. Depending on the geographical location, 20–50% can expect to experience an episode of acute diarrhoea.[1 2] Most of these episodes are self limiting and the person concerned comes to no serious harm. The illness can substantially interfere with holiday plans, however, or disrupt a professional or business trip. There are considerable economic implications for the host country, as the threat of such an illness may make some travellers disinclined to visit some parts of the world and thus reduce potential income from tourism. Health risks may also be a negative factor in influencing decisions regarding foreign investment and business ventures in these locations.

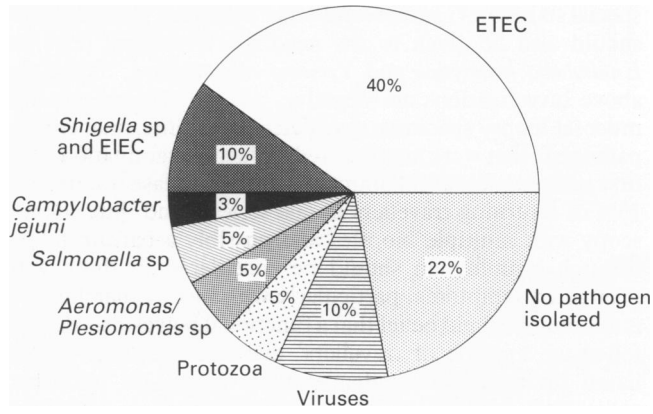

Figure 1: Spectrum and approximate prevalence of enteropathogens in travellers' diarrhoea. ETEC=enterotoxigenic E coli, *EIEC=enteroinvasive* E coli.

Aetiology

In at least 80% of cases of travellers' diarrhoea, the illness is due to an infectious agent (Fig 1). There is nothing particularly remarkable about the spectrum of enteropathogens involved, they merely represent the repertoire of agents contaminating the environment or carried by the population of the host country.[1 3] Indeed it is the same enteropathogens that produce the high diarrhoeal disease attack rates in infants and young children and that are responsible for the continuing high mortality of diarrhoeal disease in the developing world. The visitor from the industrialised country, however, has generally not met such an array of organisms and thus, unlike the indigenous population, host defence is low and thus disease susceptibility high. Enterotoxigenic *Escherichia coli* (ETEC) continues to be the most commonly isolated enteropathogen in travellers' diarrhoea but other bacteria, viruses including rotavirus and the Norwalk family of viruses, and intestinal protozoan parasites such as *Giardia lamblia*, *Cryptosporidium parvum*, and *Entamoeba histolytica*, are also important although their major impact is often limited to specific geographical locations. New enteropathogens continue to be discovered. A new coccidian parasite, which invades small intestinal epithelial cells has been found in travellers from Asia and provisionally named, *Cyclospora cayetanensis*.[4 5]

Transmission

Food is the most important vehicle for acquisition of these infections although consumption of contaminated water is also important. Enteropathogens survive in ice[6] and swimming pools,[7 8] and these are now recognised routes for the acquisition of intestinal infection. The protozoan parasites in particular can survive as cysts even in apparently adequately chlorinated water. Seawater surrounding beaches in the United Kingdom and some locations in southern Europe can be heavily contaminated with sewage and faecal microorganisms and is yet another source of intestinal infection.[9 10] Viral diarrhoeas are usually short lived and are acquired through water and possibly aerosol. Several major outbreaks of Norwalk virus have been reported on cruise ships; these outbreaks are often associated with a high secondary attack rate, which suggests person to person spread.

Clinical features

The symptoms of travellers' diarrhoea in tourists commonly start on the third day of the stay abroad, which if untreated lasts for a mean of four days but with a median of just two days.[3] Symptoms, however, may persist for more than one month in 1–2% of travellers. In most, travellers' diarrhoea is a mild illness with bowel frequency of less than six times daily although associated symptoms of nausea, vomiting, and severe cramping abdominal pain may produce substantial morbidity. About 20% of patients will have fever or blood in their stools, or both suggesting invasive disease.

This is the first of a series of leading articles concerning tropical infection of the gastrointestinal tract and liver. The editorial committee is most grateful to Dr Gordon Cook, the series editor, and his contributors for their timely contributions to the journal.

Diagnosis

There is generally no need to make a specific diagnosis in most cases of travellers' diarrhoea. Although clinical features may guide the type of organism involved, watery diarrhoea being probably a result of ETEC, *Cryptosporidium parvum* or a viral enteropathogen and dysentery a result of an invasive organism such as *Shigella* sp, *Salmonella* sp or *Campylobacter jejuni*, clinical diagnosis is imprecise. As the illness resolves within a few days and treatment is supportive and not specifically directed towards the enteropathogen, management remains empirical. When symptoms persist beyond seven days, however, stool examination is advised as specific treatment for bacterial or amoebic dysentery and other infections such as giardiasis would hasten recovery.

In the small number of protracted cases that reach the gastroenterologist, three questions immediately come to the forefront: (a) is there evidence of persistent infection? (b) is this the first presentation of non-specific inflammatory bowel disease?, and (c) is this a postinfective functional bowel disorder? Infection must be excluded by thorough examination of at least three stool specimens taken on separate days; this should include concentration techniques for cysts and special stains for *C parvum* and other parasites. Consideration should also be given to the need for serological tests for *Entamoeba histolytica* and *Yersinia enterocolitica*, and if the above investigations are negative, a duodenal aspirate and mucosal biopsy specimen may detect small intestinal enteropathogens that were not detected by faecal examination. The first presentation of inflammatory bowel disease occurred in 15% of returning travellers in one series,[11] and thus colonoscopy with multiple biopsies and possibly a barium follow through examination should be considered in those with protracted symptoms, particularly with bloody diarrhoea. It is a commonly held belief that a functional bowel disorder can follow an episode of travellers' diarrhoea. This is largely based on anecdotal evidence, there being no published controlled studies on the relation between travellers' diarrhoea and the onset of the irritable bowel syndrome. Although most gastroenterologists will have seen patients whose irritable bowel symptoms apparently began after an episode of travellers' diarrhoea or food poisoning, every effort should be made to exclude infection and non-specific inflammatory bowel disease before such a conclusion is reached.

Risk factors

The main goal for clinicians, public health workers, and indeed travellers themselves is the prevention of acute infective diarrhoea. Identification of risk factors goes part of the way to achieving this objective. The major risk factor for the acquisition of diarrhoeal illness by travellers is the high prevalence of infective enteropathogens in tropical and subtropical destinations. Geographical locations can be classified according to risk. Low risk areas where attack rates are generally <8% include North America, Northern and Central Europe, Australia, and New Zealand. Intermediate risk areas include the Caribbean, the Northern Mediterranean, Israel, Japan, and South Africa. High risk areas with diarrhoea rates of 20–50% are found in Latin America, Africa, and Asia. It should be remembered, however, that acute diarrhoea also occurs in travellers from Europe to the USA with a background prevalence of travellers diarrhoea of about 4%. Host factors are also thought to determine susceptibility to the development of travellers' diarrhoea and to its severity. These include age <6 years, reduced gastric acidity, immunodeficiency disorders, and possibly chronic gastrointestinal disorders predisposing to diarrhoea.[1-3]

TABLE I *Prevention of travellers' diarrhoea*

Approach	*Specific measures*	*Reduction in attack rate (approximate percentage)*
Minimise entry of enteropathogens	Avoid uncooked/unpeeled food, ice cubes, tap water, etc. Avoid reheated food left at room temperature. Food should be >65°C. Beware swimming pools, lakes and seawater	Unknown
Antimicrobial chemoprophylaxis*	Sulphonamides	50
	Neomycin	30
	Doxycycline	75
	Cotrimoxazole	85
	Trimethoprim	60
	4-Fluoroquinolones (for example, Ciprofloxacin, Norfloxacin, Ofloxacin)	>85
Non-antibiotic	Bismuth subsalicylate*	60
	Lactobacillus species	Unknown
	Vaccines	Unknown

*For details of clinical trials see references [1 2 15 16]

Prevention

The most satisfactory way of preventing travellers' diarrhoea is to avoid ingestion of the infective agents (Table I). Mode of travel is important in that those staying in five star hotels are less likely to encounter diarrhoeal disease than the 'adventure traveller' living close to local residents with recurrent exposure to food and water in unhygienic surroundings. Despite reiteration of traditional advice of avoiding uncooked or unpeeled food, and drinking only boiled or bottled water, these simple measures for preventing travellers' diarrhoea almost always fail. Formal evaluation of Swiss travellers visiting Africa and Asia showed that only 2% could consistently adhere to the strict dietary advice given.[12] Even when travellers are careful, they can be often caught out. Bacterial enteropathogens can survive in food that is too hot to touch (50°C)[13] and bacterial enteropathogens in ice cubes can be recovered from alcoholic drinks containing tequila, whiskey, and other spirits for substantial periods after the ice cube had been placed in the drink.[6 14]

For professionals and business travellers it is often impossible and indeed unsociable not to eat with local residents and thus, other measures for the prevention of travellers' diarrhoea have been sought. Since the early 1960s it has been clear that antimicrobial chemotherapy taken during the period at risk can substantially reduce the diarrhoea attack rates.[1 15] Early studies with sulphonamides and neomycin have been superseded by agents such as doxycyline, cotrimoxazole, trimethoprim, erythromycin, mecillinan, bicozamycin, and the newer 4-fluoroquinolone drugs (Table I). Many of these agents can be expected to reduce attack rates by 80–95%. These agents, however, have not been widely recommended for all travellers because of their adverse effects. Skin rashes and vaginal candiasis occur in about 3% of subjects and photosensitivity reactions, bone marrow suppression, antibiotic associated colitis, and more severe reactions such as the Stevens-Johnson syndrome, may occur in as many 1 in 10000 exposed subjects.[2] Thus, travellers who choose antimicrobial chemoprophylaxis place themselves at risk of a potentially fatal adverse drug effect, while attempting to prevent what is usually a mild to moderate, self limiting illness. There are also concerns that increasing use of antibiotics for mild, non-fatal disorders would hasten the development of antibiotic resistance, thereby reducing the treatment options for infections in which antibiotics are essential.[1 2] Nevertheless antimicrobial prophylaxis may be appropriate in a small number of subjects who have a serious health problem, which would be adversely affected by an episode of travellers' diarrhoea, these who cannot follow dietary restrictions, and those for whom any change in their itinerary might have important deleterious impact on the purpose of travel (Fig 2).

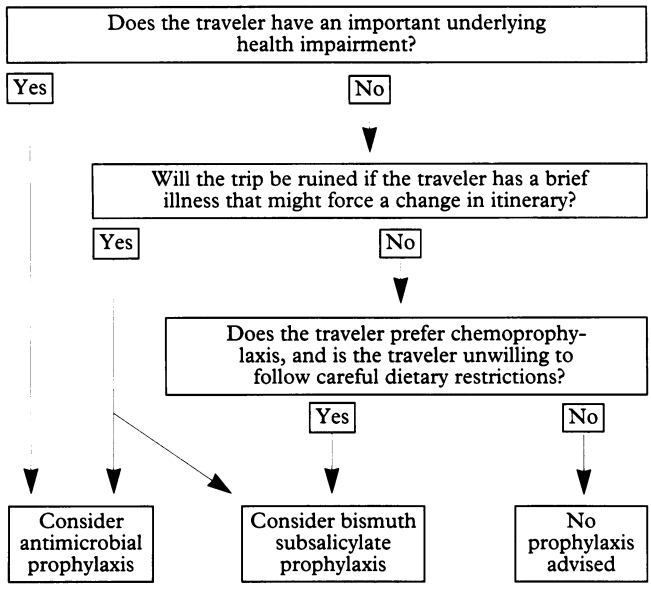

Figure 2: Determining the advisability of prophylaxis against travellers' diarrhoea during a stay of less than three weeks in a high risk area of Latin America, Africa or Southern Asia.
From Du Pont and Ericsson[2] (with permission), which was adapted from Farthing et al.[1]

Non-antibiotic approaches to chemoprophylaxis are also available in the form of bismuth subsalicylate[16] and other bismuth preparations but these drugs are less effective than antibiotics. The use of probiotics such as *Lactobacilli* sp has been proposed as an approach to prophylaxis,[17] although therapeutic efficacy has not been clearly established.[18] Vaccines appropriate for use in travellers' diarrhoea are under development but as yet not freely available.

Treatment

The most important aspect of treatment for travellers' diarrhoea is the replacement of fluid and electrolyte losses, either by formal oral rehydration therapy with glucose-electrolyte solutions, or informally by encouraging a high fluid intake, particularly of salty soups and fruit juices (sodium and potassium replacement) combined with complex carbohydrate such as rice, potato or bread to promote active glucose-sodium cotransport[1 15] (Table II). In infants and young children and possibly the elderly, this is most safely achieved by using prepackaged oral rehydration salts that can be reconstituted in clean water. Anti-diarrhoeal preparations should be avoided in infants and young children and in all patients with dysentery but can provide symptomatic relief in people with watery diarrhoea by reducing stool frequency. As most episodes of travellers' diarrhoea are secretory diarrhoeas as a result of *E coli* enterotoxins, small intestinal anti-secretory agents would presumably reduce faecal losses and the duration of the illness. No agent is currently available although the calmodulin antagonist, zaldaride maleate has recently been shown to improve symptoms in people with travellers' diarrhoea.[19] 5-HT_3 and 5-HT_2 receptor antagonists may also find a role in the treatment of secretory diarrhoea as these drugs have been shown to reduce intestinal secretion in enterotoxin models of diarrhoea.[20 21]

Antimicrobial agents are effective in the treatment of travellers' diarrhoea although their widespread use for self treatment continues to be controversial.[1 2 15] Antimicrobial agents are, however, required for the treatment of typhoid fever, dysenteric shigellosis, and amoebiasis and are useful in the treatment of cholera, giardiasis, and in ETEC and *Campylobacter* sp infections. Their use in non-bacteraemic salmonellosis, yersinosis, *Aeromonas*, and *Plesiomonas* sp infection and cryptosporidiosis remains controversial. A variety of agents, however, such as cotrimoxazole, doxycyline, and a 4-fluoroquinolone antibiotics taken for three to five days or even less, can reduce the duration and severity of the illness.[1 2 15] These antibiotics can turn a three to five day illness into one that can last only 12–24 hours (Table II). As these therapeutic benefits may be obtainable after one or two doses of antibiotic it is difficult to justify withholding treatment providing the small but nevertheless real risks of antibiotic treatment are acknowledged. It would seem appropriate that travellers should, with the help of their doctor, develop self treatment strategies, which should include early introduction of fluid and electrolyte replacement, the appropriate use of anti-diarrhoeal preparations, and a short course of an antibiotic. Travellers should be advised, however, to seek medical advice for severe diarrhoea and dehydration that does not respond rapidly to rehydration and medical treatment, for dysentery, and for mild or moderate diarrhoea that persists for longer than seven days.

TABLE II *Treatment options for travellers' diarrhoea*

Treatment	*Specific intervention*	*Impact on illness*
Restoration and maintenance of water and electrolyte balance	Oral glucose-electrolyte solution	No effect on duration but reduces morbidity and mortality
Antimicrobial chemotherapy*	Cotrimoxazole Bicozamycin Furazolidone Doxycycline Pivmecillinam 4-Fluoroquinolones	Reduced average duration from 4·5 to 1·5 days
Non-antibiotic therapy*	Bismuth subsalicylate Anti-diarrhoeal agents	Reduces stool frequency No effect on duration of illness

*For details of clinical trials see references[1 2 15 16].

Ultimately, the diarrhoeal fate of travellers should not lie in the development of complex rituals to escape a contaminated environment nor should it depend on the continuing development of new antibiotics to combat drug resistance. The future lies in the investment in safe water supplies, effective sanitation, and high quality food handling in all countries of the world.

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