Journal of Gastroenterology and Hepatology (2004) **19,** 610–618

REVIEW

Traveler's diarrhea

ANNA C CASBURN-JONES* AND MICHAEL JG FARTHING†

**Department of Medicine, Gardiner Institute, Western Infirmary and †Faculty of Medicine, Wolfson Medical School Building, University of Glasgow, Glasgow, UK*

INTRODUCTION

Diarrheal illness is a major health problem associated with international travel in terms of frequency and economic impact. Traveler's diarrhea refers to an enteric illness acquired when a person travels from a developed to a developing country, but can include any travel-associated diarrheal disease. Today, over 50 million people travel each year from developed countries to developing countries and 20–50% of these travelers report having diarrhea during the first 2 weeks of their stay. The chances of acquiring this condition depend on well-known risk factors, such as origin and destination of travel, travel season, and various host factors.[1-3] Traveler's diarrhea is an important factor in tourism because the threat of illness may deter travelers from a high-risk area, and is also an important economic factor for the host country due to the influence on foreign investment and business ventures. There has been no significant decline in the incidence of traveler's diarrhea since the 1970s, despite efforts made by the tourism industry to improve local infrastructure (e.g. water treatment, sanitation and healthcare).[2,3]

DEFINITION

Traveler's diarrhea is defined as the passage of three or more unformed stools in 24 h during or shortly after travel, or any number of loose stools if accompanied by fever, cramping, abdominal pain or vomiting.[4,5] This definition has allowed standardization for research but many travelers experience milder symptoms that do not fit this definition; 25% of tourists in one study reported a change in stool consistency but passed only 1–2 motions per day.[6] The definition can be widened to include more trivial bowel disturbances that are sufficient enough to disrupt a business commitment or travel plans. Dysentery in travelers is defined as any number of loose stools accompanied by blood.

EPIDEMIOLOGY

Risk factors for traveler's diarrhea

Geographical destination is the most important determinant of risk; the geographical variation in prevalence rates of diarrhea will depend on local water quality, sewage disposal, asymptomatic carriage of enteropathogens by the local population (especially food handlers), catering standards in hotels and restaurants or other food outlets. Geographicaql destination can be classified according to the degree of risk of acquiring diarrhea.[7] High-risk destinations include Latin America, Africa, the Middle East and Asia (attack rates are 20–50%); intermediate-risk places include southern Europe, China, Russia, and the Caribbean (attack rates are 0–15%); while low risk destinations include Canada, USA, northern Europe, Australia, New Zealand and Japan (attack rates are 2–4%). Seasonality can be an important factor; the risk appears to be higher for *Escherichia coli*-induced traveler's diarrhea in the rainy season and summer time in some regions, but not for *Campylobacter jejuni*.[8] Mode of travel influences exposure to enteropathogens. For example, the risk is increased for back-packers and soldiers, possibly due to greater ingestion of potentially contaminated food and water, and a more adventurous lifestyle.[9]

Host factors

Extremes of age increase the risk of traveler's diarrhea because of decreased immunity and greater fecal/oral contamination. Immunodeficiency states (persons with AIDS, IgA deficiency) increase the risk. Gastric acid is an important barrier to the transfer of orally acquired enteropathogens in the small intestine and consequently patients with hypo or achlorhydria, including those with gastric atrophy, pernicious anemia or post gastrectomy are potentially at increased risk of infection. It is now

Correspondence: Dr Anna C Casburn-Jones, Honorary Clinical Research Fellow, Department of Medicine, Gardiner Institute, Western Infirmary, University of Glasgow G11 6NT, UK. Email: acj2q@clinmed.gla.ac.uk

Accepted for publication 3 June 2003.

evident that users of H2 receptor antagonists and proton pump inhibitors are at increased risk of intestinal bacterial infections, especially those over 65 years of age.[10] Patients with chronic gastrointestinal disorders may have an increased risk due to reduced mucosal defences. Host genetics may be important: patients with blood group O more frequently experience shigellosis and have more severe cholera. Previous travel to a high risk area during the preceding 6 months does confer some protection against traveler's diarrhea, although this is not long-lasting.[11]

Transmission

Traveler's diarrhea is acquired through the ingestion of fecally contaminated food and less commonly water. High-risk foods include raw or poorly cooked seafood or meat, salads and raw vegetables, dairy products in areas with no refrigeration, cold buffets, food from street traders, fruits that cannot be peeled, ice-cream, ice, and local tap water. Some microorganisms can survive in food heated to 50°C (too hot to touch) and multiply as the temperature decreases.[12] Several enteropathogens can survive freezing in ice cubes and multiply in soft and alcoholic drinks, even whiskey or tequila cannot reliably 'sterilize' ice.[13,14] Person to person spread is relatively unimportant for travelers, although some viruses such as the Norwalk virus and other small round structured viruses (SRSV) may be spread by aerosol, which might contribute to the high secondary attack rates that occur in families and on cruise ships.[15] Some enteropathogens, mainly bacteria and protozoa, are spread during sexual activity, particularly during intimate oro-anal contact. Risk factors for sexually transmitted intestinal infections include sexual promiscuity, sexual practices allowing fecal-oral transmission, and the carriage of enteric pathogens by asymptomatic homosexual men.

Swimming pools and seawater contaminated with sewage and/or fecal microorganisms are sources of infection, particularly protozoa, and are risk factors for traveler's diarrhea. Swimming pool water can be contaminated by the feces of young children and cysts of certain parasites. *Cryptosporidium parvum* and *Giardia intestinalis* are able to survive in chlorinated water for extended periods. Freshwater lakes are not routinely monitored and many that have been tested in the UK have been contaminated with cyanobacterial toxins, thought to arise from nitrate and phosphate fertilizers and hot weather. Viral diarrhea can be acquired through water and possibly aerosol transmission.

CAUSATIVE ORGANISMS

Epidemiological studies during the last 20 years have shown that the vast majority of episodes of traveler's diarrhea are due to intestinal infection; traveler's diarrhea is caused by a specific organism in approximately 80% of cases (Table 1).[7,16] Prior to this, diarrhea in travelers was attributed to a 'change in the water' or possibly 'traveler's nerves' as a result of stress or overindulgence in local food or wine. The majority of cases are secondary to bacteria; enterotoxigenic *Escherichia coli* (ETEC) is the most frequently isolated in all parts of the world but the highest isolation rates are generally in Africa and Central America. *Shigella* spp. is also common in these regions, whereas *Campylobacter jejuni* is more common in travelers to Asia. Despite the importance of cholera as a cause of diarrhea in the Indian subcontinent and in Central and South America, it rarely affects travelers. Protozoa, viruses and helminths are

Table 1 Common causes of traveler's diarrhea

Enteropathogen	Isolation percentage	Areas of highest incidence
Bacteria	50–80	
Escherichia coli		
Enterotoxigenic (ETEC)	20–50	Worldwide, especially Africa, Central America
Enteroadhesive (EAEC)		
Enteroinvasive	5–15	Latin America, Asia
Shigella spp.	5–15	Mexico, Africa
Campylobacter jejuni	10–15	Asia
Salmonella spp.	5–25	Southern Europe
Aeromonas, *Pleisomonas*	5	Thailand
Vibrio	5	Southern Asia
Viruses	0–20	
Adenovirus (types 40, 41)		
Rotavirus		Mexico
Small round structured viruses		
Protozoa	<5	
Giardia intestinalis	0–5	Russia, Eastern Europe
Entamoeba Histolytica	0–5	Unusual in short-term traveller
Cryptosporidium parvum		Russia
Cyclospora spp.		Nepal, Haiti, Mexico

also implicated but only contribute to 10–15% of the causes of traveler's diarrhea. Certain destinations are renowned for infection with specific enteropathogens, for example giardiasis in parts of eastern Europe. Although viruses are a major cause of diarrhea in children, they are much less common as the cause of traveler's diarrhea in adults.

PATHOPHYSIOLOGY

Enterotoxigenic *Escherichia coli* produces two major toxins: the heat labile toxin (LT) and the heat stable toxin (STa). The LT closely resembles the cholera toxin and consists of one A subunit (A1 and A2 linked by a disulfide bond) and five B subunits. The LT binds to a receptor on the enterocyte microvillous membrane, the GM1 ganglioside, which induces configurational changes in the membrane allowing entry of the enzymically active A1 subunit. The A1 subunit is an ADP-ribosyl transferase and is transported through the cytoplasm and then covalently links ADP ribose to Gs, the stimulatory component of adenylate cyclase (an enzyme located on the basolateral cell membrane), resulting in enzyme activation and increased intracellular concentrations of cyclic adenosine monophosphate (cAMP). This activates a secretory cascade involving protein kinase C, protein phosphorylation and the opening of chloride channels in the apical membrane of the enterocyte, predominantly in the crypts. As the interior of the cell is electronegative relative to the outside, an electrical driving force for chloride extrusion occurs. The STa is a much smaller molecule and acts through an apical receptor, which is directly linked to membrane-bound guanylate cyclase. The ST toxins are also ADP-ribosylating toxins but activate guanylate cyclase to increase intracellular cyclic guanylate monophosphate (cGMP). Like cAMP, cGMP causes activation of cyclic nucleotide dependent protein kinases, protein phosphorylation and the opening of chloride channels. In addition to the effects of LT and ST on chloride ion secretion, both enterotoxins also inhibit sodium and chloride absorption. Although these intracellular mechanisms have been well characterized, there is increasing evidence that both LT and STa can promote intestinal secretion through neural reflexes in the enteric nervous system.[17]

Small round structured viruses and rotavirus enter the villus epithelial cells and produce cytopathic changes, which eventually result in enterocyte loss. There is therefore an acute villous atrophy during the first 24–48 h of infection following which there is proliferation of crypt cells and subsequent recovery in villus morphology. Loss of enterocytes accounts for the decrease in disaccharidase activity, and hence transient lactose intolerance that can be associated with these infections.

The microbial pathogens that produce dysentery express virulence factors that either allow direct invasion of the epithelial cell and/or liberate cytotoxins which produce cell death. *Shigella* spp., *Salmonella* spp., and EIEC all express invasion plasmid antigens (Ipa) on their surface which subvert the cytoskeleton of the epithelial cell allowing formation of endocytotic vesicles which transport the organism into the host cytoplasm. Cell lysis, organism multiplication occurs with liberation of cytotoxin intracellularly. The invasin and cytotoxin virulence factors are only part of a cascade of events that produces inflammation in the distal ileum and colon. *Entamoeba histolytica*, an important cause of dysentery, is not strictly an invasive organism. Following lectin-mediated adherence to the epithelial cell it liberates a variety of cytotoxic compounds, which rapidly produce cell death. Amoebapore is a pore-forming protein which creates high conductance ion channels in the cell membrane, allowing rapid influx of calcium and other ions leading to disequilibrium and cell death. *E. histolytica* then phagocytoses the dead cell and moves on to penetrate further into the mucosa. Protozoal enteropathogens such as *G intestinalis*, *C parvum* and *Cyclospora* spp., are all associated with varying degrees of villus architectural abnormality and an inflammatory response in the mucosa, but how they cause persistent diarrhea is not completely understood. Diarrhea can occur in the absence of morphological changes, suggesting other mechanisms must also be operating.

CLINICAL FEATURES

Traveler's diarrhea may occur anytime during travel or within 10 days of return, but typically occurs on the third day after arrival, with a second episode starting approximately a week after arrival.[7] Most individuals pass 3–5 loose or watery stools a day, but 20% pass >6 watery stools a day. It is typically mild and self-limiting; the mean duration of diarrhea is 4 days with a median of 2 days, 10% last more than 1 week, 2% will persist for a month, and 1% for more than 3 months.[2,18] Symptoms usually resolve for those individuals with months of diarrheal symptoms following travel to high-risk areas, but a few may be ill for up to a year.[18] Up to 90% complain of abdominal cramps and 10% complain of fever and/or vomiting. Approximately 20% of persons are confined to bed for 1–2 days and[16] about 20% have dysentery syndrome with fever and bloody diarrhea. Other common symptoms are fecal urgency, tenesmus, nausea, malaise, weakness, headache and myalgia. Low-grade fever is frequent but is more common in cases with an identified pathogen. Vomiting is a major symptom of food poisoning, usually due to a preformed bacterial toxin. *Staphylococcus aureus* and *Bacillus cereus* are illnesses associated with bacterial toxins. These infections generally have short incubation times, 1–12 h, and a much shorter duration of illness, usually a few hours. This contrasts with the typical illness of traveler's diarrhea, which usually lasts for a few days.

Traveler's diarrhea can be classified into three clinical categories according to symptoms: (i) acute watery diarrhea; (ii) dysentery; and (iii) persistent diarrhea with or without intestinal malabsorption (Table 2).

Acute watery diarrhea

Most episodes of acute watery diarrhea are mild and transient but can be severe with large volume stools.

Table 2 Spectrum of enteropathogens causing acute watery diarrhea and dysentery

Enteropathogen	Acute watery diarrhea	Dysentery
Bacteria		
Escherichia coli	+	–
Enterotoxigenic (ETEC)	+	–
Enteropathogenic (EPEC)	+	–
Enteroaggregative (EAggEC)	+	–
Enteroinavsive (EIEC)	+	+
Enterohaemorraghic (EHEC)	+	+
Shigella spp.	+	+
Salmonella spp.	+	+
Campylobacter spp.	+	+
Yersinia spp.	+	+
Vibrio cholera and other vibrios		
Protozoa		
Giardia intestinalis	+	–
Cryptosporidium parvum	+	–
Microsporidia	+	–
Isospora belli	+	–
Cyclospora cayetanensis	+	–
Entamoeba histolytica	+	+
Viruses		
Adenovirus (types 40,41)	+	–
Rotavirus	+	–
Small round structured viruses	+	–
Helminths		
Strongyloides stercoralis	–	–
Schistosoma spp.	–	+

Dehydration is rarely significant and systemic symptoms are mild or absent. In neonates, children and the elderly dehydration may be more profound with acidosis. Fever is unusual, but if present is low-grade. Other symptoms such as anorexia, nausea, vomiting, abdominal cramps, flatulence and bloating may be present but are generally not prominent.

Dysentery

Dysentery commonly presents with loose small volume stools with blood and mucus. The onset may start as watery diarrhea but classic dysenteric symptoms usually rapidly supervene. Dysentery is a consequence of inflammation of the colon and distal ileum due to invasive enteropathogens. Prodromal symptoms are common and include headache, myalgia and general malaise. Abdominal pain and cramps, which can be severe, occur in the lower abdomen usually during predefecation. Pain, tenesmus and fever frequently accompany the diarrhea. The illness is normally self-limiting but can be prolonged. In fulminant cases, fortunately rare for travelers, toxic megacolon, colonic perforation, peritonitis, and septicemia can occur.

Table 3 Causes of persistent diarrhea in travelers

Enteropathogen
Bacteria
Salmonella spp.
Campylobacter spp.
Intestinal tuberculosis
Protozoa
Giardia intestinalis
Cryptosporidium parvum
Cyclospora cayetanensis
Helminths
Strongyloides
Colonic schistosomiasis
Miscellaneous
Inflammatory bowel disease
Tropical sprue
Post-infectious irritable bowel

Persistent diarrhea

Less than 1% of travelers suffer from persistent diarrhea (Table 3). The diarrhea may have the features of steatorrhea accompanied by marked weight loss. Other systemic symptoms may be present such as nausea, anorexia, dyspepsia, malaise and low-grade fever. Persistent infections in the small intestine can produce a disaccharidase deficiency, which may manifest as lactose intolerance.

There is good evidence to indicate that intestinal infection may initiate a functional bowel disorder such as irritable bowel syndrome (IBS). Some patients with so-called postinfective IBS have a mild but significant increase in mucosal inflammatory cells and an increase in 5-HT containing enterochromaffin cells, both of which are thought to contribute to symptom production.

COMPLICATIONS

Reiter's syndrome (arthritis, urethritis, conjunctivitis with muco-cutaneous lesions) can complicate acute diarrheal infections, notably *Campylobacter jejuni*, *Salmonella* spp., *Shigella* spp. and *Yersinia enterocolitica*. Not all individuals manifest all features of the syndrome. There is a close association with HLA haplotype B27. Guillain–Barré syndrome is associated with *Campylobacter jejuni* infection, which now appears to be the most common cause of the syndrome in the developed world. Neurological symptoms have been documented to occur between 1 and 21 days after the onset of bowel symptoms, predominantly affecting motor neuropathy, and generally carries a poor prognosis.[19] Hemolytic uremic syndrome (HUS) is a rare complication of *Shigella dysenteriae* type 1 infection and enterohaemorraghic *Escherichia coli* (EHEC) infection. This serious complication is secondary to the effects of the shiga toxin and shiga-like toxins 1 and 2, the latter

being produced by EHEC. Salmonellosis may disseminate widely from the gut and affect many other organs, causing complications such as acute endocarditis, aortitis, septic arthritis and osteomyelitis, and occasionally infections of the urogenital and tract and lungs. Protozoal infections such as *E. Histolytica* may be complicated by amebic hepatitis and amebic abscesses.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Diagnosis of acute watery diarrhea is evident from the history and the need to make a specific etiological diagnosis is rarely necessary. The most common organism to cause traveler's diarrhea is ETEC, but as this is not identified routinely in the laboratory a specific diagnosis is never made. Vomiting with limited diarrhea is usually due to a virus or preformed toxin.

However, it is important to identify patients with potentially dangerous diarrhea or dysentery: large volume diarrhea, bloody and mucoid stools or high-grade fever. Pathogen identification is important in aiding treatment for those at-risk patients with stool microscopy and culture as the first line of investigation. A fresh stool specimen should be prepared as a saline wet mount and examined microscopically; three stool samples should be examined under the light microscope for parasites by an experienced observer, and then cultured for bacterial enteropathogens.

Persistent diarrhea should be more intensively investigated. Common causes are bacillary or amebic dysentery, giardiasis, cryptosporidiosis and cyclospora. High quality fecal microscopy by an experienced parasitologist using special stains is the standard approach for detecting *G. intestinalis, Cryptosporidium parvum, Cyclospora cayetanensis, Entamoeba histolytica and* the Microsporida. The sensitivity of examining a single stool specimen for *Giardia* spp. infection is only 70% and improves to 85-90% with examination of three separate stool specimens. Newer antigen detection assays have been developed that increase the sensitivity of the examination. Enzyme-linked immunoassay (EIA) and direct immunofluorescence (DFA) staining have both been developed for *Giardia* spp., and for *Cryptosporidium* spp., with increased sensitivity. The modified acid-fast stain is used to visualize *Cryptosporidium*, *Cyclospora* and *Isospora* spp., as well as by immunoassays and examination of multiple specimens. In stool-culture negative diarrhea when protozoal infection is strongly suspected, mucosal biopsy from the distal duodenum via upper gastrointestinal endoscopy/enteroscopy may be useful. Protracted but stool-culture negative (three negative stools collected on three separate days) diarrhea should be investigated for continuing infection, a first presentation of inflammatory bowel disease, or for a rarer presentation such as celiac disease, tropical sprue, HIV enteropathy or colorectal malignancies. Referral to a gastroenterologist is advisable at this stage.

PREVENTION

There are several approaches to the prevention of traveler's diarrhea. The first is to decrease exposure by environmental and educational approaches. Improving the public health infrastructure of developing countries is an important but long-term goal, so caution in what one eats and drinks remains the cornerstone of prevention. 'Boil it, cook it, peel it or forget it' encompasses the message and will reduce risk.[20] Travelers' compliance with dietary precautionary measures is poor. Only 2% of Swiss travelers going to Africa and Asia were able to adhere to dietary guidelines.[21] Food should be heated to >65°C, bottled or boiled water (at least 10 min boiling is required), or the use of water purification tablets, and avoidance of high-risk foods are advocated. Pre-travel advice should also include education about high-risk leisure activities such as swimming in unsafe and unclean waters. However, the impact of pre-travel health advice on the incidence of traveler's diarrhea remains unsatisfactory, mostly because there are problems with motivating the traveler to take precautions, especially regarding what to eat and drink.

Chemoprophylaxis is another approach. Routine administration of antibiotic prophylaxis is currently not recommended despite the excellent protection rates provided by antibiotics. This is because of potential adverse reactions; there is a risk of antimicrobial resistance, a potential for antibiotic side-effects, and a false sense of security may be assumed by the traveler. Of the various antibiotics that have been investigated, 4-fluoroquinolones are considered to be the first choice worldwide, however, quinolone-resistant pathogens are increasingly being isolated. The increasing resistance and emergence of *in vivo* resistance of *C. jejuni* to quinolones has been reported from Thailand and South-east Asia and is a serious concern.[22] Isolation of quinolone-resistant *E. coli* strains remained rare until 1990, since when quinolones have been used for treatment on a widespread scale.

Fluoroquinolones achieve a protective efficacy of >90%, have an excellent safety profile and wide spectrum of cover. Ciprofloxacin 500 mg daily is started on the day of arrival and continued for 2 days after return, but should not be taken for more than 3 weeks.[23] Norfloxacin, fleroxacin, ofloxacin and levofloxacin are as effective.[16] Ciprofloxacin, when taken daily in a single low dose (e.g. 400 mg norfloxacin or[24] 250 mg ciprofloxacin per day)[25] increases protection against traveler's diarrhea by up to 90%, providing that the enteropathogens present in the region of study are susceptible to the agent. However, side-effects have been observed, such as skin rash, vaginal candidiasis, central nervous system reactions, phototoxicity, gastrointestinal complaints and rarely, more severe events, including anaphylaxis. Quinolones are not approved for prophylaxis in children and pregnant women. Alternative antibiotics have lower protective rates or have a higher incidence of side-effects. These include sulfonamides, cotrimoxazole, neomycin, doxycyline and mecillinam. Newer prophylactic agents (bicozamycin, aztreonam and azithromycin) show promise.[26–28]

The decision to use antibiotic prophylaxis should be made on a case by case basis and may be considered in those most at risk. (i) Travelers with underlying disease increasing the risk or severity of diarrhea such as patients with immunodeficiency, pre-existing bowel disease, gastric hypochlorydia, insulin-dependent diabetes mellitus, cardiac disease, or chronic renal failure. (ii) Travelers on an important itinerary such as official visits or military operations. (iii) Short-stay travelers: days lost through illness would decrease the success of the visit.

There is interest in the development of a novel prophylactic agent, an antimicrobial agent that is minimally absorbed from the gut, allowing high intestinal concentration and avoiding serious although rare toxicity. In recent studies, rifaximin, a rifamycin derivative with broad-spectrum antibacterial activity,[29] has shown promising results with regards to safety and efficacy for the treatment of patients with infectious bacterial diarrhea who traveled to Mexico, Guatemala or Kenya.[30] This agent, which is presently used in Italy to treat enteric bacterial infection, could be considered a potential candidate for prophylaxis.[31]

Non-antimicrobial agents such as bismuth subsalicylate offer protection rates of 65%, the optimal dose is 524 mg (two tablets) four times a day. It has fewer but less traveler-friendly side-effects such as temporary blackening of the tongue and stools, and tinnitus. It is inconvenient to take because of the four times daily regimen and has lower protection rates with poor compliance. Bismuth subsalicylate is not a recommended option for prophylaxis in Europe, where it is not widely available.

Immunoprophylaxis is another preventative option. There are no widely available vaccines for acute diarrheal disease. An oral live cholera vaccine is available but only produces 52% protection against ETEC; protection is short-lived but may be adequate for short-term travelers.[32] Other vaccines against rotavirus, ETEC, *Shigella* spp. and *Salmonella* spp. are under development. The etiology of traveler's diarrhea is extremely variable, and it would be difficult for even a 'broad-spectrum vaccine' to sufficiently cover a great variety of the enteropathogens that are responsible for traveler's diarrhea. The chances that a vaccine will be effective are limited.

Another alternative approach to prevention are probiotics. A probiotic is defined as a live microbial food ingredient beneficial to health.[33] Protective mechanisms that may play a role in the action of these medications include the production of acids, hydrogen peroxide or antimicrobial substances, as well as the competition for nutrients or adhesion receptors, antitoxin action and stimulation of the immune system.[34] The principal concept of protection mediated by non-pathogenic bacteria remains appealing as probiotics have low toxicity and interaction difficulties. However, currently they have been shown to be poor prophylactic agents. To date, no probiotic has been able to demonstrate clinically relevant protection worldwide. Oksanen *et al.*[35] reported that *Lactobacillus* GG prophylaxis given to tourists traveling to Turkey led to a 12% reduction in traveller's diarrhea; however, the effect was significant only for one destination. In another double-blind, randomized, controlled trial, the risk of traveler's diarrhea was 4% in American travelers who received *Lactobacillus* GG and 7% in the control group, which indicates that there was minimal, although significant, protection.[36] No protective effect was evident in studies of other lactobacilli, such as *Lactobacillus fermentum* and *Lactobacillus acidophilus,* because various strains seem to differ in their potential for colonization of the intestine.[35,37] A mild but significant and dose-dependent (250 mg and 1000 mg) protection against traveler's diarrhea, with a variable regional effect, was reported for travelers to North Africa and Turkey who were taking *Saccharomyces boulardii.*[38] However, probiotics have been shown to be effective in reducing antibiotic-associated diarrhea.[39]

Prebiotics such as administration of oligofructose may be an alternative option. The concept of 'feeding' preferred bacterial substances such as oligofructose may increase the number of 'protective' organisms such as bifidobacteria. Further evidence is required to confirm whether this approach has any clinical benefit.

At present there is no satisfactory prophylactic option for traveler's diarrhea, and worldwide monitoring of antimicrobial susceptibility patterns and the search for novel antimicrobial agents, such as nonabsorbed antibiotics and nonantibiotic medications should continue.

MANAGEMENT

Self-therapy is the mainstay of treatment because most cases are mild and self-limiting. Many travelers now carry oral rehydration salts, antidiarrheal agents and antibiotics. Any pre-travel advice should include fluid and dietary advice, what and when to use antidiarrheals and when to seek medical advice.

Approaches to treatment

Replacement of fluid and electrolyte losses is usually sufficient with oral rehydration. Fruit juices, tea, bottled drinks and salty soups or Bovril (sodium and potassium replacement) are recommended. Avoidance of solid food is advised until the stools are formed, followed by introduction of carbohydrates (bread, crackers, potatoes, rice, pasta) beneficial in the promotion of glucose-sodium cotransport. Commercially available preparations of glucose and electrolyte solutions, oral rehydration solutions (ORS), reconstituted with 'clean' or boiled water are useful for those at particular risk of dehydration, including infants, young children, the elderly or those with severe symptoms. One 'homemade' ORS recipe is 6 level teaspoons of sugar, 1 level teaspoon of salt and 1 L of water. Fruit juices can be added for improved taste and potassium supplementation, however, high sucrose/glucose containing soft drinks should be avoided because of concerns about monosaccharide intolerance with associated osmotic diarrhea.

Symptomatic relief with antidiarrheals such as loperamide and diphenoxylate/atropine combinations are beneficial. These agents act by increasing intestinal

transit time (antimotility) and enhancing the potential for reabsorption of fluid and electrolytes. They have a modest effect on reducing fecal losses. Loperamide reduces stool frequency by up to 80%. Adult dosage is 4 mg (two capsules) with 2 mg after each unformed stool, and the maximum dose is 16 mg in a 24-h period. In general, antimotility agents are safe and moderately effective in decreasing stool frequency, although their most profound effects in modifying the duration and severity of the illness occur when combined with an antimicrobial agent.[40,41] These agents are usually not recommended in patients with dysentery because of the risk of colonic dilatation associated with infective colitis. However, there is limited clinical evidence for this concern.[42] Antimotility agents have also been thought to increase the fecal carriage of gut enteropathogens, but there is little evidence that this is the case. Loperamide has been shown to be safe in the treatment of bacillary dysentery if used in conjunction with an antibiotic.[41] Loperamide may have some antisecretory activity, but this contribution to its clinical efficacy is probably marginal. These agents are not recommended in children under the age of 2 years because of occasional reports of central nervous system depression.[43] Other antimotility agents (e.g. codeine) are as effective but have the potential to cause central toxicity. Water-absorbing antidiarrheal agents are the least effective (e.g. attapulgite), but can be given to young children and pregnant women.

Bismuth subsalicylate is an effective antidiarrheal and is useful in the treatment of traveler's diarrhea,[16] reducing the number of unformed stools by approximately 50%. This is attributed to the antisecretory action of its salicylate moiety, however, it is also thought to have antibacterial and anti-inflammatory properties.[44] As previously stated, it is not a popular drug of choice because a large number of tablets must be taken (8 tablets), it has a delayed onset of action (up to 4 h), it can interfere with the absorption of other medications (e.g. doxycyline) and has some unpleasant side-effects (tinnitus, black tongue).

There is an ongoing search for the ideal antisecretory agent that will directly inhibit secretory processes within the enterocyte. Intracellular signaling mechanisms were an initial pharmacological target, especially those related to calcium and the calcium binding protein, calmodulin. Zaldaride maleate, a calmodulin inhibitor, has been evaluated in phase III randomized controlled trials but future development was discontinued because of no additional benefit compared with standard antidiarrheal agents.[45,46] Recent attention has focused on the enteric nervous system (ENS). It is now well established that the ENS is involved in the promotion of intestinal secretion.[47] A number of neurotransmitters have been identified in the ENS, many are thought to be involved in intestinal secretion and are therefore potential pharmacological targets for the treatment of watery diarrhea.[48] 5-hydroxytryptamine has been implicated in the secretory state induced by the cholera toxin and there is evidence that 5-HT2 and 5-HT3 receptor antagonists can inhibit secretion both in animal models and in the human model of cholera secretion.[48,49] Another approach has been to use inhibitors of the enzyme enkephalinase, such as acetorphan, which enhances the activity of endogenous opioids in the intestine. The enkephalins act as neurotransmitters in the gastrointestinal tract by activating opiate receptors and thus reducing the level of cAMP. This produces a reduction in water and electrolyte secretion without any detectable effect on intestinal motility. Racecadotril has antisecretory and antidiarrheal actions and is effective in *in vivo* model systems[50] as well as humans. In a study in Peru in the treatment of acute watery diarrhea in hospitalized children, racecadotril was shown to be effective and safe.[51] The racecadotril group had a clinically consistent and significant reduction in 48 h stool output, total stool output before recovery, total intake of oral rehydration solution, and duration of diarrhea. Racecadotril can reduce both the severity and duration of diarrhea and the duration of hospitalization when used as an adjunct to oral rehydration therapy.

Antimicrobial agents

Antibiotics should be considered in moderate to severe watery diarrhea (>6 stools/24 h) and dysentery. There is now unequivocal evidence that broad spectrum antibiotics given for 3–5 days can significantly reduce the duration and severity of traveler's diarrhea.[16,32] Stool frequency is reduced by 50% and the duration of illness limited to 12–24 h. 4-fuoroquinolones have the highest efficacy with the fewest side-effects: recent studies of single dose or 1–2 day regimens have shown that fluoroquinolones have similar therapeutic benefits.[52–54]

Self-treatment with antibiotics is controversial. It is reasonable for certain travelers to carry antibiotics for self-therapy, providing clear instructions are given.[55] The financial responsibility of the cost of self-treatment, including travel vaccines and antimalarials, belongs to the traveler. There are continuing concerns about the emergence of drug resistance with indiscriminate use but, like other mild non-fatal infections such as chest and urinary infections, occasional use is unlikely to have a major impact on world resistance patterns. The ultra short course regimens of antibiotics used for traveler's diarrhea may be less likely to produce resistance, although this has not been studied extensively in a clinical setting.[56]

Antibiotics are recommended for the treatment of dysentery caused by most organisms. Mild dysenteric illnesses can resolve spontaneously but travelers need to seek medical advice if bleeding is severe and/or there are other prominent systemic symptoms such as fever, malaise or abdominal pain. Specific antimicrobial treatment is indicated in cases of dysenteric shigellosis, amoebiasis and *Campylobacter jejuni* infections. In campylobacter infection there is good evidence that antibiotics do not alter the natural course of the illness if antibiotics are started >4 days after the onset of symptoms. Metronidazole 400 mg 3 times daily for 5 days, is prescribed in the developing world for acute diarrhea because it treats amebiasis and giardiasis. If severe, EIEC infection with evidence of systemic involvement can be treated with the same antibiotics recommended for dysenteric shigellosis, but a role for routine use has not been established. Antimicrobial therapy in EHEC

infection remains controversial for two reasons: (i) antibiotics do not significantly improve outcome, especially if started well after infection is established;[57] and (ii) there is anecdotal evidence that antibiotics can promote the development of HUS, due to the increased lysis of organisms and release of shiga-like toxins and endotoxin leading to HUS.[58,59]

Infants and young children

Travelers with young children or babies are advised to carry a supply of oral rehydration preparations. Therapy is fluid and electrolyte replacement and continued feeding, especially breast-feeding. Medical advice should be sought if a child has fever for more than 24 h or has moderate/severe dehydration. Ciprofloxacin cannot be given to children in view of the potential damage to growing cartilage and antibiotics are generally avoided.

POST-TRAVEL MANAGEMENT

If diarrhea persists beyond 14 days, appropriate medical advice should be sought with a view to further investigation. Most of the enteropathogens are treatable with antimicrobial therapy. If no infective cause is found, additional investigation is required to exclude underlying bowel pathology, such as tropical sprue or inflammatory bowel disease. Persistent symptoms may reflect the development of postinfective IBS.

CONCLUSION

Traveler's diarrhea is usually a mild self-limiting illness. Antibiotic prophylaxis has a limited role in certain groups of travelers. Oral rehydration solutions are useful for fast fluid and salt replacement and antibiotic treatment is indicated in moderate to severe watery diarrhea and dysentery. Enhanced worldwide surveillance systems of antimicrobial susceptibility/resistance would enable accurate treatment recommendations. Rates of diarrhea in the developing world have not declined in four decades and continued public pressure to improve public health hygiene is imperative, not only for the traveler but also for the indigenous population.

REFERENCES

1 World Health Organisation. World Health Report 1996. *J. Commun. Dis.* 1996; **28**: 215–9.
2 Steffen R, van der Linde F, Gyr K, Schar M. Epidemiology of diarrhea in travelers. *JAMA* 1983; **249**: 1176–80.
3 Steffen R, Collard F, Tornieporth N *et al.* Epidemiology, etiology, and impact of traveler's diarrhea in Jamaica. *Jama* 1999; **281**: 811–7.
4 Merson MH, Morris GK, Sack DA, Wells JG, Feeley JC, Sack RB *et al.* Travelers' diarrhea in Mexico. A prospective study of physicians and family members attending a congress. *N. Engl. J. Med.* 1976; **294**: 1299–305.
5 Sack DA, Kaminsky DC, Sack RB *et al.* Prophylactic doxycycline for travelers' diarrhea. Results of a prospective double-blind study of Peace Corps volunteers in Kenya. *N. Engl. J. Med.* 1978; **298**: 758–63.
6 MacDonald KL, Cohen ML. Epidemiology of travelers' diarrhea: current perspectives. *Rev. Infect. Dis.* 1986; **8** (Suppl. 2): S117–21.
7 Steffen R, Boppart I. Travellers' diarrhea. *Baillieres Clin. Gastroenterol.* 1987; **1**: 361–76.
8 Ericsson CD, DuPont HL. Travelers' diarrhea: approaches to prevention and treatment. *Clin. Infect. Dis.* 1993; **16**: 616–24.
9 Kollaritsch H. Traveller's diarrhea among Austrian tourists in warm climate countries. I. Epidemiology. *Eur J. Epidemiol.* 1989; **5**: 74–81.
10 Neal KR, Scott HM, Slack RC, Logan RF. Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study. *BMJ* 1996; **312**: 414–5.
11 Dupont HL, Haynes GA, Pickering LK, Tjoa W, Sullivan P, Olarte J. Diarrhea of travelers to Mexico. Relative susceptibility of United States and Latin American students attending a Mexican University. *Am. J. Epidemiol.* 1977; **105**: 37–41.
12 Bandres JC, Mathewson JJ, DuPont HL. Heat susceptibility of bacterial enteropathogens. Implications for the prevention of travelers' diarrhea. *Arch. Intern. Med.* 1988; **148**: 2261–3.
13 Sheth NK, Wisniewski TR, Franson TR. Survival of enteric pathogens in common beverages: an *in vitro* study. *Am. J. Gastroenterol.* 1988; **83**: 658–60.
14 Dickens DL, DuPont HL, Johnson PC. Survival of bacterial enteropathogens in the ice of popular drinks. *JAMA* 1985; **253**: 3141–3.
15 Reid JA, Caul EO, White DG, Palmer SR. Role of infected food handler in hotel outbreak of Norwalk-like viral gastroenteritis: implications for control. *Lancet* 1988; **2** (8606): 321–3.
16 DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. *N. Engl. J. Med.* 1993; **328**: 1821–7.
17 Farthing MJ. Enterotoxins and the enteric nervous system – a fatal attraction. *Int. J. Med. Microbiol.* 2000; **290**: 491–6.
18 DuPont HL, Capsuto EG. Persistent diarrhea in travelers. *Clin. Infect. Dis.* 1996; **22**: 124–8.
19 Rees JH, Soudain SE, Gregson NA, Hughes RA. Campylobacter jejuni infection and Guillain–Barre syndrome. *N. Engl. J. Med.* 1995; **333**: 1374–9.
20 Kozicki M, Steffen R, Schar M. 'Boil it, cook it, peel it or forget it': does this rule prevent travellers' diarrhea? *Int. J. Epidemiol.* 1985; **14**: 169–72.
21 Steffen R. Epidemiology of travellers' diarrhea. *Scand. J. Gastroenterol. Suppl* 1983; **84**: 5–17.
22 Hoge CW, Gambel JM, Srijan A, Pitarangsi C, Echeverria P. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. *Clin. Infect. Dis.* 1998; **26**: 341–5.
23 Rademaker CM, Hoepelman IM, Wolfhagen MJ, Beumer H, Rozenberg-Arska M, Verhoef J. Results of a double-blind placebo-controlled study using ciprofloxacin for prevention of travelers' diarrhea. *Eur J. Clin. Microbiol. Infect. Dis.* 1989; **8**: 690–4.
24 Johnson PC, Ericsson CD, Morgan DR, Dupont HL, Cabada FJ. Lack of emergence of resistant fecal flora dur-

ing successful prophylaxis of traveler's diarrhea with norfloxacin. *Antimicrob. Agents Chemother.* 1986; **30**: 671–4.
25 Parry H, Howard AJ, Galpin OP, Hassan SP. The prophylaxis of travellers' diarrhea; a double blind placebo controlled trial of ciprofloxacin during a Himalayan expedition. *J. Infect.* 1994; **28**: 337–8.
26 DuPont HL, Ericsson CD, Mathewson JJ, de la Cabada FJ, Conrad DA. Oral aztreonam, a poorly absorbed yet effective therapy for bacterial diarrhea in US travelers to Mexico. *JAMA* 1992; **267**: 1932–5.
27 Shanks GD, Ragama OB, Aleman GM, Andersen SL, Gordon DM. Azithromycin prophylaxis prevents epidemic dysentery. *Trans. R. Soc. Trop. Med. Hyg.* 1996; **90**: 316.
28 Ericsson CD, DuPont HL, Galindo E *et al.* Efficacy of bicozamycin in preventing traveler's diarrhea. *Gastroenterology* 1985; **88**: 473–7.
29 Hoover WW, Gerlach EH, Hoban DJ, Eliopoulos GM, Pfaller MA, Jones RN. Antimicrobial activity and spectrum of rifaximin, a new topical rifamycin derivative. *Diag. Microbiol. Infect. Dis.* 1993; **16**: 111–8.
30 DuPont HL, Ericsson CD, Mathewson JJ *et al.* Rifaximin: a nonabsorbed antimicrobial in the therapy of travelers' diarrhea. *Digestion* 1998; **59**: 708–14.
31 Rendi-Wagner P, Kollaritsch H. Drug prophylaxis for travelers' diarrhea. *Clin. Infect. Dis.* 2002; **34**: 628–33.
32 Caeiro JP, DuPont HL. Management of travellers' diarrhea. *Drugs* 1998; **56**: 73–81.
33 Isolauri E. Probiotics for infectious diarrhea. *Gut* 2003; **5**: 436–7.
34 Marteau PR, de Vrese M, Cellier CJ, Schrezenmeir J. Protection from gastrointestinal diseases with the use of probiotics. *Am. J. Clin. Nutr.* 2001; **73** (Suppl. 2): 430S–436S.
35 Oksanen PJ, Salminen S, Saxelin M *et al.* Prevention of travellers' diarrhea by Lactobacillus GG. *Ann. Med.* 1990; **22**: 53–6.
36 Hilton E, Kolakowski P, Singer C, Smith M. Efficacy of Lactobacillus GG as a diarrheal preventive in travelers. *J. Travel Med.* 1997; **4**: 41–3.
37 Katelaris PH, Salam I, Farthing MJ. Lactobacilli to prevent traveler's diarrhea? *N. Engl. J. Med.* 1995; **333**: 1360–1.
38 Kollaritsch H, Holst H, Grobara P, Wiedermann G. [Prevention of traveler's diarrhea with Saccharomyces boulardii. Results of a placebo controlled double-blind study]. *Fortschr. Med.* 1993; **111**: 152–6 (in German).
39 Cremonini F, Di Caro S, Nista EC *et al.* Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhea. *Aliment Pharmacol. Ther.* 2002; **16**: 1461–7.
40 Ericsson CD, Nicholls-Vasquez I, DuPont HL, Mathewson JJ. Optimal dosing of trimethoprim-sulfamethoxazole when used with loperamide to treat traveler's diarrhea. *Antimicrob. Agents Chemother.* 1992; **36**: 2821–4.
41 Murphy GS, Bodhidatta L, Echeverria P *et al.* Ciprofloxacin and loperamide in the treatment of bacillary dysentery. *Ann. Intern. Med.* 1993; **118**: 582–6.
42 DuPont HL, Hornick RB. Adverse effect of lomotil therapy in shigellosis. *JAMA* 1973; **226**: 1525–8.
43 Motala C, Hill ID, Mann MD, Bowie MD. Effect of loperamide on stool output and duration of acute infectious diarrhea in infants. *J. Pediatr.* 1990; **117**: 467–71.
44 Gorbach SL. Bismuth therapy in gastrointestinal diseases. *Gastroenterology* 1990; **99**: 863–75.
45 DuPont HL, Ericsson CD, Mathewson JJ, Marani S, Knellwolf-Cousin AL, Martinez-Sandoval FG. Zaldaride maleate, an intestinal calmodulin inhibitor, in the therapy of travelers' diarrhea. *Gastroenterology* 1993; **104**: 709–15.
46 Silberschmidt G, Schick MT, Steffen R *et al.* Treatment of travellers' diarrhea: zaldaride compared with loperamide and placebo. *Eur. J. Gastroenterol. Hepatol.* 1995; **7**: 871–5.
47 Hubel KA. Intestinal nerves and ion transport: stimuli, reflexes, and responses. *Am. J. Physiol.* 1985; **248** (Part 1): G261–71.
48 Farthing MJ. Novel targets for the control of secretory diarrhea. *Gut* 2002; **50** (Suppl. 3): III15–8.
49 Farthing MJ. 5-Hydroxytryptamine and 5-hydroxytryptamine-3 receptor antagonists. *Scand. J. Gastroenterol. Suppl.* 1991; **188**: 92–100.
50 Turvill J, Farthing M. Enkephalins and enkephalinase inhibitors in intestinal fluid and electrolyte transport. *Eur. J. Gastroenterol. Hepatol.* 1997; **9**: 877–80.
51 Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, Gutierrez M. Racecadotril in the treatment of acute watery diarrhea in children. *N. Engl. J. Med.* 2000; **343**: 463–7.
52 Salam I, Katelaris P, Leigh-Smith S, Farthing MJ. Randomised trial of single-dose ciprofloxacin for travellers' diarrhea. *Lancet* 1994; **344**: 1537–9.
53 Ericsson CD, DuPont HL, Mathewson JJ. Single dose ofloxacin plus loperamide compared with single dose or three days of ofloxacin in the treatment of traveler's diarrhea. *J. Travel Med.* 1997; **4**: 3–7.
54 Steffen R, Jori J, DuPont HL, Mathewson JJ, Sturchler D. Treatment of travellers' diarrhea with fleroxacin: a case study. *J. Antimicrob. Chemother.* 1993; **31**: 767–76.
55 Casburn-Jones AC, Sabin C, Maybin S, Zuckerman JN. Retrospective longitudinal study on gastrointestinal morbidity in VSO volunteers working abroad. *Gut* 2003; **52** (Suppl. 1): A371.
56 Wistrom J, Gentry LO, Palmgren AC *et al.* Ecological effects of short-term ciprofloxacin treatment of travellers' diarrhea. *J. Antimicrob. Chemother.* 1992; **30**: 693–706.
57 Proulx F, Turgeon JP, Delage G, Lafleur L, Chicoine L. Randomized, controlled trial of antibiotic therapy for *Escherichia coli* O157: H7 enteritis. *J. Pediatr.* 1992; **121**: 299–303.
58 Carter AO, Borczyk AA, Carlson JA *et al.* A severe outbreak of *Escherichia coli* O157: H7–associated hemorrhagic colitis in a nursing home. *N Engl. J Med.* 1987; **317**: 1496–500.
59 Pavia AT, Nichols CR, Green DP *et al.* Hemolytic–uremic syndrome during an outbreak of *Escherichia coli* O157: H7 infections in institutions for mentally retarded persons: clinical and epidemiologic observations. *J. Pediatr.* 1990; **116**: 544–51.