

Diarrhoea and The High Risk Traveller

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Travellers' diarrhoea is the most likely event to affect world travellers whether they travel for commerce or pleasure. The gastro-intestinal disorder can be a nuisance, or debilitate, disable and ruin a business trip, or vacation. It can incapacitate those enjoying deluxe hotel accommodation and devastate the economy-driven back-packer. It decimates the health of tour groups and expeditions and returning patients bring infection home. Its onset may be preventable and the impact ameliorated by travellers who follow good pretravel advice and take dietary and hygienic precautions. Realistically, short pre-travel health consultations militate against counselling every potential traveller. Those at highest risk and people who would be most inconvenienced by a severe attack should be identified and targeted.

Travellers' diarrhoea (TD) is defined as passage of at least 3 unformed stools over 24 hours and at least one sign or symptom of enteric infection eg. Abdominal cramps¹. The disorder can be a mere nuisance to the traveller or a threat to life in the vulnerable. Global travellers are six times more likely to experience diarrhoea than if they had stayed at home² and some return to infect family and colleagues. Gastro-intestinal illness, results from eating contaminated food, drinking contaminated untreated water and water containing glacial sediment or, with different physical characteristics from the traveller's home supply. Surveillance of air travellers of all ages returning to Scotland from abroad revealed alimentary symptoms accounting for 76% of symptoms reported^{3,4}.

Symptoms

Diarrhoea frequently starts within two to three days after exposure to infection, or a new environment. Untreated, the condition lasts about four days, with 10% suffering for a week and 1-2% of the affected suffering symptoms for a month⁵. In a very few, diarrhoea lingers for months and some cases develop into dysentery, that is diarrhoea containing blood, usually caused by *shigella dysenteriae*, or *entamoeba histolytica* -an important management distinction⁵.

Prevalence

The most frequent travel health affliction to affect the international tourist, prevalence rates vary from 8% to 55% depending on country visited^{1,2}. Estimates suggest 30-50% of travellers will develop traveller's diarrhoea during a 1 to 2 week stay in high-risk areas⁵. Many older travellers return home with the infection and seek treatment from family doctors⁶. To keep this in perspective, acute non-travel related diarrhoea (NTD) of presumed infective origin affects 20% of England's population annually. About 6% of adults report an acute occurrence of diarrhoea in a preceding two week period, with 1 in 6 seeking general practitioner treatment⁶. Travel to South Asia carries the highest risk followed by sub-Saharan Africa and South America.

Higher risk travellers include:

- Those living in the local community in an area of poor hygiene,
- Elderly and very young travellers, who will also be
- more adversely affected if they become dehydrated
- and suffer electrolyte balance^{7,8,9},
- Gap year travellers, backpackers, expeditioners, expatriates⁵,
- Those on medication to decrease gastric acid secretion, e.g. proton pump inhibitors⁵, People with pre-existing disease such as type 1 diabetes and AIDS⁵.

High risk groups.

Elderly travellers. Ageing changes make it more likely that older travellers are vulnerable to TD. The increased incidence of achlorhydria caused by atrophic gastritis associated with ageing may permit ingested bacteria to survive transit through the stomach. Shortening and broadening of the villi in the small bowel and atrophy of mucosa causes toxins to take longer to pass through the intestine. In the very old, associated dehydration and loss of body salts may endanger life. Altered immunity and ageing changes render elderly travellers more likely to succumb to infection and suffer more deleterious effects⁹.

Very young travellers less aware of risk and dietary and hygienic precautions, may also have lower immunity and be subject to dehydration and metabolic and electrolyte disturbance.

Gap year students resist dietary and hygiene advice and sleep in insalubrious locations⁵.

Expeditioners and those working on voluntary service overseas (VSOs) enter areas of poor hygiene with high exposure to contaminated food and water⁵.

Expatriates remain at high risk of diarrhoea for the first 2 years of residence in developing countries¹⁰.

Effect of Destination on Risk of Travellers' Diarrhoea

Several local factors markedly increase the level of risk. These are the country and the location in the country, the length of stay, the itinerary in the country, and the season. Younger age, female sex, dining in restaurants, and recent arrival in country are also risk factors for diarrhea^{11,12}. Risk areas can be categorised as:

Lowest rates (<4%) occur in travellers moving around low risk regions, namely North America, Western Europe, Japan, Australia and New Zealand.

Intermediate risk incidence rates occur in the Caribbean, Southern Europe, Israel and South Africa ,

High rates between 20 and 55% occur in developing parts of the world. such as The Middle East, South East Asia (though not Singapore,) north and central Africa, South America^{12,13}.

In travel from a low risk to a high risk region the risk is about 40%, to an intermediate risk country 10% and to another low risk country 2-5%⁵.

The Microbial Causes of Diarrhoea.

Travellers' diarrhoea is largely caused by detectable and undetected microbial enteropathogens.

Bacteria

- Enterotoxigenic *E. coli* (ETEC)
- Enterocaggregative *E. coli* (EAEC)
- *Campylobacter jejuni*
- *Salmonella* spp. Enterotoxigenic *Bacteroides fragilis* is a recently identified pathogen

Parasites:

- *Giardia lamblia*
- *Cryptosporidium parvum*
- *Cyclospora cayentensis*
- *Entamoeba histolytica*

Viruses

- Rotavirus
- Norovirus^{15,16,17,18}

In up to 80% of cases the infection is caused by *E. coli* with strains of *Campylobacter jejuni* causing many cases in southern Asia. Most important pathogens are enterotoxigenic *E. coli* (ETEC) enterocaggregative *E. coli* (EAEC). and probably diffusely adherent *E. coli* (DAEC). While DAEC cause a majority of cases in high-risk regions, invasive enteropathogens including *Campylobacter jejuni*, *Shigella* spp. and *Salmonella* spp. are more commonly encountered in south Asia than in Africa and Latin America. Some 20-40% of cases of TD remain unexplained after comprehensive micro-biological evaluation, but most probably are due to undetected bacterial infections^{13,14,15}. Enteric viral infections such as Noroviruses or rotavirus are the most commonly implicated non-bacterial cause of TD, responsible for 10% of cases. Parasites can be found in only 2-10% of acute cases¹¹.

A review of 52 published studies examined the incidence, aetiology, and impact of diarrhoea in travellers away from home for more than 2 weeks. It included studies undertaken on military personnel and confirmed that aetiology varied by region, with Southeast Asia having a relatively lower prevalence of enterotoxigenic *E. coli* (13% of cases) and a relatively higher prevalence of *Campylobacter* (24%) and *Salmonella* (11%). Overall, pathogens were identified in 55% of cases. ETEC was the commonest pathogen in Latin America and the Caribbean (28%) and the Middle East (29%). ETEC (17%) and *Shigella* (9%) were the commonest pathogens isolated in sub-Saharan Africa¹⁰.

Prophylaxis and Treatment

Clinical management of acute episodic diarrhoea varies greatly and doctors and nurses often delay therapeutic intervention, or limit prescription of medication. Inappropriate, or delayed, treatment and failure to prescribe appropriate anti-diarrhoeal agents can mean the illness is unnecessarily prolonged. Mortality due to traveller's diarrhoea is uncommon but, 1% of people are ill enough to require hospital admission^{15,16}. Affected people who consult a doctor are likely to be older, in poor health and taking regular medication. Low levels of sanitation at travel destination and eating establishments, are strong predictors for acquisition of travellers' diarrhoea and women are more susceptible than men¹⁹.

Precautions to minimize the risk of developing travellers' diarrhoea emphasise avoidance of potentially contaminated food or drink and prophylactic measures including non-pharmacological and antimicrobial strategies^{20,21}. Adherence to pretravel instructions is universally poor however²². Where food and water are concerned, 'boil, cook, peel or avoid it,' remains good advice. In high risk regions hands should be regarded as "unclean" and washed rigorously in uncontaminated water and dried hygienically after toilet and food handling. Focus on food and water hygiene should remain a health management educational objective for potential travellers. Pre-travel advice regarding traveller's diarrhoea can however help reduce duration of illness^{23,24}.

Probiotics and Prebiotics.

Preferred options to TD management are to either pre-vent infection through chemoprophylactic measures or, treat symptoms rapidly as they occur. Prebiotics and probiotics have attracted interest with their ability to affect the colonic microbiota composition positively, thus increasing resistance to infection and diarrhoeal disease.²⁶ Galacto-oligosaccharides (GOS) stimulate growth of bifidobacteria. A comparative study using a second generation prebiotic GOS mix-ture (B-GOS) showed significant increase in beneficial bifidobacteria and decrease in less beneficial colonic cells, increase of phagocytosis and natural killer cell activity and production of anti-inflammatory cytokynin interleukin. This may result in positive effects on both microflora composition and immune response. One small blind placebo controlled study of a daily sachet of galacto-oligosaccharide mixture found a significant reduction (36%) in TD. The second generation prebiotic food supplement B-GOS, taken immediately prior to and during travel, may be of value in preventing or diminishing the impact of travel related diarrhoea. Older travellers in particular may benefit from a 7 day pretravel and vacation dietary complement of B-GOS.^{28, 35}

Anti-motility Agents

Anti-motility agents available as public pharmacy products, are used widely by many travellers without adverse effect³⁶. They reduce the number of unformed stools and shorten duration of symptoms and relieve acute intestinal spasm, abdominal pain and distension. Placebo studies show them to be fast acting and clinically effective in mild to moderate, non-invasive diarrhoea and safe and effective when used in non-dysenteric diarrhoea. There was no prolongation of illness or complication if administered in cases of diarrhoea. Where invasive organisms were identified, and treated with antimicrobials, they do not prolong fever or delay pathogen excretion in stools. Loperamide is useful for travellers' diarrhoea. It is a peripherally acting opiate without abuse potential, which does not cross the blood-brain barrier and has little impact on the systemic circulation. A 4mg. dose of loperamide in a healthy adult does not slow oro-caecal transit and in diarrhoea states will normalise transit of intestinal content. Loperamide may mask dehydration and depletion of electrolytes and dehydration may increase the variability of drug response. Delay in loperamide intervention is difficult to justify. A combination of an antibiotic and an anti-motility agent is often prescribed^{37'38'39'40'41,42}.

Prophylactic Antibiotics

Chemoprophylaxis with antibiotics is effective and reduces incidence of TD by 58% to 100%. Randomised control trials have shown that, doxycycline, ciprofloxacin, and trimethoprim-sulfamethoxazole are useful prophylactic antibiotics. The Cochrane data-base review of options for treating diarrhoea confirmed that fluoroquinolones are popular choices for empiric treatment, with azithromycin as an alternative where contraindications or resistance preclude fluoroquinolone use. Rifaximin is an alternative with fewer side effects but is inactive for *Campylobacter* infection and the effect against *Shigella* is uncertain^{43'44}. Their use needs to be balanced against risk of adverse events from systemically absorbed antibiotics, drug resistance and *Clostridium difficile* associated diarrhoea.

Prophylactic antibiotics should be considered for people who are at high risk of travellers' diarrhoea and who have:

- increased susceptibility to infection or are immuno-compromised e.g. people receiving chemotherapy or immunosuppressive drugs.

- a high risk of complications if they were to develop TD, e.g. chronic gastrointestinal disease (such as Crohn's disease, ulcerative colitis).
- an ileostomy or colostomy.
- type 1 diabetes mellitus, renal disease and congestive heart failure in whom diarrhoeal

illness might severely impact on their health. • a critical trip where a diarrhoea episode would have high social impact, such as back-packers and expeditioners, gap year students and VSO workers in rural areas of developing countries and businessmen involved in crucial negotiations.

For people who are travelling to high-risk locations where access to medical assistance is poor or not available, such as mountaineers in the Himalayas or Andes, antibiotic prophylaxis is not the preferred choice^{54,55}.

Also people taking acid-suppressive drugs e.g. proton pump inhibitors, should not be routinely offered antibiotic prophylaxis.

Antibiotic Therapy for Attacks of TD

Given the frequency of diarrhoea and its often suboptimal management in developing countries, self-treatment should be considered. High risk travellers should be educated on the importance and techniques of oral rehydration and that antibiotics be reserved for severe attacks, with anti-motility agents avoided in the presence of fever or signs of invasive disease. There is often reluctance in health professionals to prescribe anti-diarrhoeal medication. The belief that anti-motility drugs should not be used in acute diarrhoea where fever may indicate invasive pathogen infection has been widely held. Over half the GPs and nurses questioned, in one study agreed with the statements "anti-diarrhoeals" keep toxins or pathogens inside the intestine where they do more damage to the gut", and "anti-diarrhoeals" prolong illness by delaying excretion of the pathogen" a premise not supported by research based evidence. In management of an adult presenting with diarrhoea, a third of family doctors would take no action for 24 hours, with 12% delaying for 48 hours in the case of TD. Many advise the patient to avoid solid food over this time, although starvation as treatment has no scientific basis and may encourage fluid loss³⁶. No significant adverse events were associated with the antibiotic treatment of diarrhoea in 1,045 clinical visits^{45,47,48,49,50,51}.

Antibiotic therapy is recommended either with or without loperamide for travellers with moderate to severe diarrhoea (three or more unformed stools during an 8-hour period,) particularly if associated with nausea, vomiting, abdominal cramping, fever, or bloody stools. Antimicrobials reduce diarrhoea duration, as well as reducing related symptoms such as abdominal cramping and time spent incapacitated and are effective against enteropathogens.

Trimethoprim/sulfamethoxazole-effective and widely used in the past, resistance is however wide-spread.

Ciprofloxacin is often employed empirically with single dose therapy effective in most cases⁴⁸. Problems with the fluoroquinolones have emerged relating to tendinitis and tendon rupture. Fluoroquinolones may deplete colonic flora and predispose persons treated with these drugs to *Clostridium difficile* colitis⁴⁹. *Campylobacter* strains from diverse regions have shown an increased resistance to the fluoroquinolone class of drugs⁵⁰.

Rifamycin is a non-systemic antibiotic, with very little drug passing through the gastrointestinal wall into the circulation. It has been compared with placebo and ciprofloxacin for treatment of travellers' diarrhoea in randomized, double-blind clinical trials and is highly effective, with few side effects and low risk of developing antibiotic resistance. It is not effective against *Campylobacter jejuni*, and there is no evidence of efficacy against *Shigella* or *Salmonella* species. Oral rifaximin is a safe and effective treatment of travellers' diarrhoea caused by non-invasive pathogens and can be used with loperamide⁵¹.

Oral replacement therapy (ORT) must be considered for the frail elderly and the very young as they are at higher risk from dehydration and where the patient is debilitated⁵².

Summary

High risk travellers should be targeted and given pre-travel advice regarding traveller's diarrhoea. This is educative and can potentially help reduce duration of the illness.

High risk groups travellers should be encouraged to carry OTC medications eg. loperamide and self-treat simple acute episodes of TD.

Use of an anti-motility agent and an antibacterial brings fastest relief. See Table 1, page 11.

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Table 1. Medications for travellers' diarrhoea

Loperamide effective but best avoided in the presence of fever or signs of invasive disease.

Ciprofloxacin potential side effects (tendonitis and rupture, Clostridium difficile colitis, Campylobacter strains often resistant)

Rifamycin not effective against campylobacter jejuni and invasive forms of TD, such as shigella but has a good safety profile

Azithromycin short lasting nausea, effective against bacterial forms and febrile, dysenteric TD

Oral replacement therapy must be considered for the frail elderly as they are at higher risk from dehydration.