

Management of travellers' diarrhoea

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Travellers' diarrhoea is one of the most common illnesses in people who travel internationally, and depending on destination affects 20-60% of the more than 800 million travellers each year. In most cases the diarrhoea occurs in people who travel to areas with poor food and water hygiene.¹ This review examines the approach to the prevention and treatment of diarrhoea in travellers. Much of the evidence base for travellers' diarrhoea has been established over the past 30 years, with a strong body of randomised trials and consensus opinion in support of recommendations. The use of antibiotics for self treatment or chemoprophylaxis, however, remains debatable.

What is travellers' diarrhoea?

Classic travellers' diarrhoea is defined as at least three loose to watery stools in 24 hours with or without one or more symptoms of abdominal cramps, fever, nausea, vomiting, or blood in the stool. Mild to moderate diarrhoea is one or two loose stools in 24 hours with or without another enteric symptom. The median time to onset is six or seven days after arrival. Although the diarrhoea often resolves spontaneously over three or four days, up to a quarter of affected travellers need to alter their plans, interrupting their holiday or business activities.²

What causes travellers' diarrhoea?

The causes of travellers' diarrhoea depend on the destination, setting, and season, although studies have been done in only a limited number of countries (table 1).^{3,4} Enteric bacteria are documented as the most common causes: several types of *Escherichia coli* and *Campylobacter*, *Salmonella*, and *Shigella* spp; *Vibrio cholerae* is rare in travellers. Enterotoxigenic *E coli* that produce a heat labile or heat stable toxin are the most common species of *E coli* implicated, with enteroaggregative *E coli* increasingly recognised.⁵

Enterohaemorrhagic *E coli* (producing shiga toxin or vero cytotoxin) are not typically described in travellers. Enterotoxigenic *E coli* predominates in travellers to Latin America but is also seen globally. Rates of *Campylobacter* infection per traveller are highest in those visiting South Asia and South East Asia,⁶ exceeding those of enterotoxigenic *E coli* in some studies.

Norovirus and rotavirus are the most commonly identified viral causes of travellers' diarrhoea, although these agents have not been uniformly examined.⁷ Norovirus is often associated with outbreaks of diarrhoea in holiday resorts or on cruise ships. Parasites are less common causes of travellers' diarrhoea; of these, the protozoa *Giardia intestinalis* and *Cryptosporidium* are most commonly identified.⁸ *Cyclospora* and *Entamoeba histolytica* are less common causes, and typically associated with long term travel. In 10-15% of cases more than one pathogen is identified, and in up to 50% of studies no pathogen is described.^{4,9} Acute food poisoning—the sudden onset of nausea, vomiting, and diarrhoea after ingestion of a toxin (usually produced by *Staphylococcus aureus*, *Bacillus cereus*, or *Clostridium perfringens*) in food that has not been properly cooked or stored, accounts for up to 5% of cases.

What are the consequences of having travellers' diarrhoea?

As the causes of travellers' diarrhoea are multiple the clinical features vary: from the typical watery stools with cramping and nausea associated with enterotoxigenic *E coli*, to dysentery with *Shigella*, to short lived nausea, vomiting, and diarrhoea associated with acute food poisoning or norovirus. Although most cases resolve without treatment over several days, in about 10% the symptoms persist for more than a week, and in about 2% for more than a month.² About one quarter of travellers alter their plans because of diarrhoea, and about 5% seek medical care.² Illness tends to be more severe in infants and young children, and precautions should be taken to deal with a potentially dehydrating diarrhoeal illness in children when travelling. Serious complications include haemolytic uraemic syndrome with bacteria that produce shiga toxin, Guillain Barré syndrome with *Campylobacter*, and post-infectious arthropathies with any invasive bacteria. Prolonged illness (>10 days), illness that begins after return, and

Sources and selection criteria

We identified articles through an electronic search of PubMed and the Cochrane library using the term "travelers' diarrhea" alone and in combination with "treatment", "etiology", and "prevention". Additional studies were sourced from the retrieved articles. We also reviewed our extensive collection of articles on the subject, as well as current national guidelines in travel medicine.

Table 1 Causes of travellers' diarrhoea

Agent*	Frequency (%)†
Bacteria	50-75
<i>Escherichia coli</i> (enterotoxigenic)	10-45
<i>E coli</i> (enteroaggregative)	5-35
<i>Campylobacter</i>	5-25
<i>Salmonella</i>	0-15
<i>Shigella</i>	0-15
Others	0-5
Viruses	0-20
Noroviruses	0-10
Rotavirus	0-5
Parasites	0-10
<i>Giardia intestinalis</i>	0-5
<i>Cryptosporidium</i> spp	0-5
<i>Cyclospora cayetanensis</i>	<1
<i>Entamoeba histolytica</i>	<1
Acute food poisoning	0-5
No pathogen identified	10-50

*Coinfection with multiple pathogens occurs in 10-15% of cases.

†Frequency varies between travel destination, setting, and season.

illness associated with weight loss are more likely to be caused by protozoan parasites such as *Giardia*.

Irritable bowel syndrome can occur after travellers' diarrhoea. In two prospective observational studies, travellers who had diarrhoea were more likely to have a new diagnosis of irritable bowel syndrome at six months after return.^{10 11}

How can travellers' diarrhoea be prevented?

Food, water, and personal hygiene

Travellers' diarrhoea is acquired through the ingestion of contaminated food and water, therefore strict food, water, and personal hygiene precautions should decrease the risk (see box). Despite an increased understanding of the causes and pathogenesis of travellers' diarrhoea, its incidence has not substantially decreased over the past few decades, and travellers who practise preventive measures do not always have a lower incidence of the condition. The risk of travellers'

diarrhoea increasingly seems related to the sanitation level at the destination rather than the ability to adhere to avoidance measures.¹²⁻¹⁵

Vaccines

No single vaccine prevents travellers' diarrhoea, because of the multiple potential causes. Enteric vaccines prevent rotavirus (being introduced into childhood immunisation programmes), hepatitis A, typhoid, and cholera and such vaccines can be given when indicated after a careful risk assessment based on destination and itinerary.

Some enterotoxigenic *E coli* strains express a heat labile enterotoxin that is similar to cholera toxin produced by *V cholerae*. Consideration has therefore been given to using the oral killed cholera vaccine (Dukoral; Crucell, Leiden), which contains a non-toxic portion of cholera vaccine, to induce cross protective immunity against enterotoxigenic *E coli*. Up to 50% of enterotoxigenic *E coli* strains do not, however, express heat labile enterotoxin, and an analysis of studies suggests that using oral killed cholera vaccine would prevent only 1-7% of people from developing travellers' diarrhoea, depending on destination and frequency of heat labile producing enterotoxigenic *E coli*.¹⁶ In a phase II trial, vaccination of travellers with heat labile enterotoxin using a transcutaneous delivery system showed 75% protective efficacy against all cause moderate to severe diarrhoea (defined as ≥ 4 stools in 24 hours).¹⁷ Although no difference was found in the overall incidence of diarrhoea between the recipients of the vaccine and those of placebo, vaccine recipients had fewer stools and a shorter duration of illness.

Chemoprophylaxis

Chemoprophylaxis comprises two approaches: the use of non-antibiotic products (bismuth subsalicylate and probiotics) and the use of antibiotics. Bismuth subsalicylate (preferably in tablet form) provides about 60% protection against travellers' diarrhoea; however, adverse events may be common at the most effective doses.¹⁸ A meta-analysis suggests that probiotics can lessen the likelihood of travellers' diarrhoea by about 15%.¹⁹

Although several randomised placebo controlled studies in the 1970s and '80s showed antibiotic prophylaxis to be effective in preventing travellers' diarrhoea, it is not currently recommended for most travellers for several reasons: the potential adverse events associated with prophylactic antibiotics, predisposition to other infections such as vaginal candidiasis or *Clostridium difficile* associated disease, development of bacterial resistance, cost, and lack of data on the safety and efficacy of antibiotics given for more than two or three weeks.²⁰ In addition, the highly efficacious nature of early self treatment of travellers' diarrhoea further dampens enthusiasm for chemoprophylaxis with antibiotics.

Expert opinion supports the use of prophylactic antibiotics when a trip is vitally important or the consequences of watery diarrhoea would be difficult to manage (for example, after colostomy or ileostomy). Sulfonamides and tetracyclines should not be used

Diet and personal hygiene measures to prevent travellers' diarrhoea

Foods and beverages to be avoided

- Raw or undercooked meats, fish, and seafood
- Unpasteurised milk, cheese, ice cream, and other dairy products
- Tap water and ice cubes
- Cold sauces and toppings
- Ground grown leafy greens, vegetables, and fruit
- Cooked foods that have stood at room temperature in warm environments
- Food from street vendors, unless freshly prepared and served piping hot

Hygiene measures

Render water potable by either bringing it to a boil or treating it with chlorine or iodine preparations* and filtering with a filter of 1 μ m or less

Wash hands before eating

*Protozoan parasites are relatively resistant to chlorine and iodine. Contact time should be extended for cold or turbid water

Table 2 | Approach to prophylaxis and treatment of travellers' diarrhoea in adults

Agent	Dosage (adult)	Comments
Prophylaxis*		
Non-antibiotic:		
Bismuth subsalicylate (Pepto Bismol; Procter & Gamble, Surrey, UK)	525 mg (30 ml liquid or two tablets of regular strength preparation, chewed) four times a day	Avoid in people taking salicylates long term or warfarin. Can interfere with absorption of doxycycline used for malaria prevention, and causes blackening of tongue and stools
Antibiotics†‡:		
Norflloxacin‡	400 mg by mouth daily	
Ciprofloxacin‡	500 mg by mouth daily	Antibiotic prophylaxis should be reserved for highly selected people
Rifaximin	200 mg once or twice daily	
Treatment§		
Hydration¶:		
Specific oral rehydration salts or potable liquids ad libitum	Until thirst quenched	Hydration should be maintained for all forms of diarrhoea
Symptomatic**:		
Bismuth subsalicylate (Pepto Bismol)	525 mg (30 ml liquid or two tablets of regular strength preparation, chewed) every half an hour for eight doses	Reduces number of loose stools by about 50%
Loperamide	4 mg by mouth, then 2 mg after each loose stool. Not to exceed 16 mg daily	More rapid onset of action compared with bismuth subsalicylate. Should not be used with fever (temperature >38.5°C) or gross blood in stools
Antibiotics††:		
Fluoroquinolones:		
Norflloxacin	800 mg by mouth once or 400 mg by mouth twice daily	
Ciprofloxacin	750 mg by mouth once or 500 mg by mouth twice daily	One dose can be given initially and then response evaluated over following 12-24 hours. If diarrhoea is improved, antibiotic can be discontinued, otherwise it can be continued for up to three days
Ofloxacin	400 mg by mouth once or 200 mg by mouth twice daily	
Levofloxacin	500 mg by mouth once or 500 mg once daily	
Azithromycin	1000 mg by mouth once or 500 mg daily for three days	Has better activity against fluoroquinolone resistant <i>Campylobacter</i> that is an increased risk during travel to South Asia and South East Asia. 1000 mg dose can cause nausea
Rifaximin	200 mg by mouth three times daily	Can be used to treat people aged ≥12 years with travellers' diarrhoea caused by non-invasive strains of <i>Escherichia coli</i>

*Chemoprophylaxis is not indicated for most travellers.

†Prophylaxis of travellers' diarrhoea is generally not an approved use of antibiotics.

‡Other fluoroquinolones are likely to be effective but have not been studied for prophylaxis against travellers' diarrhoea.

§Medical care should be sought for dehydration, persistent illness despite treatment, severe abdominal pain, high fever, or bloody stools.

¶In otherwise healthy adults hydration may be achieved by drinking fluids ad libitum, or in young or elderly people or in those with special health needs by drinking oral rehydration solutions.

**Symptomatic therapy alone can be given to people with mild to moderate travellers' diarrhoea (one or two loose stools in 24 hours with or without mild enteric symptoms).

††Antibiotics can be given to people with moderate to severe travellers' diarrhoea (≥3 loose stools in 24 hours plus other enteric symptoms) or diarrhoea that has not responded to symptomatic treatment. In those without blood in stools, combining an antibiotic with loperamide can lead to rapid relief of symptoms.

because of widespread resistance. A fluoroquinolone is the drug of choice when travelling to most areas of the world, and several randomised trials support its efficacy.²⁰ *Campylobacter* spp are often resistant to fluoroquinolones, and when the relative risk is higher, such as in South Asia and South East Asia, azithromycin can be considered. No trials have been published on this agent when used for prophylaxis. Rifaximin, a poorly absorbed derivative of rifamycin, is an alternative choice in regions where *E coli* predominates, such as Latin America and Africa.²¹ Because of

decreased efficacy, it should not be used when potentially invasive pathogens such as *Salmonella*, *Campylobacter*, and *Shigella* are likely.

How can travellers' diarrhoea be treated?

Since behavioural modifications, vaccines, and chemoprophylaxis have limited efficacy on travellers' diarrhoea or may be associated with adverse events, consensus opinion based on randomised placebo controlled and comparative trials supports self treatment (table 2). The goals of treatment are to avoid dehydration, reduce the severity and duration of symptoms, and prevent interruption to planned activities.

Hydration and diet

Hydration is a key intervention that should be done for all forms of diarrhoea and is often all that is necessary in mild illness. Infants and young children, elderly people, and those with chronic debilitating medical conditions can maintain hydration by drinking oral rehydration formulations that combine electrolytes, sugar, and buffer. A randomised trial on healthy adolescents and adults who were taking loperamide for symptomatic

Questions for future research

- What is the cause of travellers' diarrhoea when a pathogen cannot be identified?
- Do avoidance measures prevent illness?
- How often do vero cytotoxin or shiga toxin producing *E coli* and *C difficile* associated disease occur in patients with travellers' diarrhoea?
- What is the frequency of irritable bowel syndrome after an episode of travellers' diarrhoea, and what are the predisposing factors?
- What is the role of rifaximin in the prevention and treatment of travellers' diarrhoea?
- How should vaccines be used in the prevention of travellers' diarrhoea?

Tips for non-specialists

Discuss the likelihood of travellers' diarrhoea with someone who is planning to travel and advise about avoidance measures to decrease the risk of illness: safe foods, beverages, and eating establishments

Avoidance measures are not always sufficient in preventing travellers' diarrhoea, therefore review self management options, including when to use symptomatic measures or take antibiotics, and when to seek medical care

Consider referring travellers who have special health needs (for example, HIV infection, immunocompromised, pregnant) to a specialist travel clinic for advice

Send a stool sample for microscopy and culture in returned travellers who are febrile and have complicated diarrhoea; empirical antibiotic treatment can be considered while awaiting the results of stool cultures

Treat afebrile patients who do not have tenesmus or gross blood in the stool symptomatically and observe. Give empirical antibiotic therapy—a fluoroquinolone or azithromycin—to patients who do present with such symptoms, after obtaining a stool sample

treatment of travellers' diarrhoea, however, showed no additional benefit from specific oral rehydration compared with drinking potable fluids *ad libitum*.²² It is a sensible recommendation during recovery from travellers' diarrhoea to gradually advance the diet from liquids to more complex solids, although this recommendation may not provide additional benefit if the diarrhoea is also being treated with an antibiotic.²³

Symptomatic treatment

The two most common symptomatic treatments for travellers' diarrhoea are bismuth subsalicylate or an antimotility agent. Symptomatic treatment alone can be considered for mild to moderate diarrhoea. In a randomised placebo controlled trial, bismuth subsalicylate reduced the number of loose stools by about 50% and was helpful in reducing nausea.²⁴ Bismuth subsalicylate can be recommended for people with mild diarrhoea, but more effective agents are available for those with moderate or severe diarrhoea. Loperamide has become an antimotility agent of choice because of supporting trials in travellers and its favourable adverse event profile. In a randomised comparative trial with bismuth subsalicylate, loperamide was more effective in controlling diarrhoea and cramping and had a more rapid onset of action, usually within the first four hours.²⁵ Loperamide should not be given to young children, those with diarrhoea and fever (>38.5°C), or when there is gross blood in the stools. Information on probiotics in the treatment of travellers' diarrhoea is insufficient.

Additional educational resources

- Ericsson CD, DuPont HL, Steffen, R, eds. *Travelers' diarrhea*. 2nd ed. Hamilton, Ontario: BC Decker, 2008—reviews all aspects of travellers' diarrhoea
- World Health Organization. International Travel and Health 2008 (www.who.int/ith/en/index.html)—authoritative guidance on travel medicine
- Centers for Disease Control and Prevention. Health Information for International Travel 2008 (www.cdc.gov/travel/default.aspx)—authoritative guidance on travel medicine
- Al-Abri SS, Beeching NJ, Nye FJ. Traveller's diarrhoea. *Lancet Infect Dis* 2005;5:349-60
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Antibiotic treatment

Many randomised placebo controlled and comparative trials done over the past 25 years have shown the efficacy of antibiotics in the treatment of travellers' diarrhoea.²⁶ Most trials indicate that an antibiotic taken as a single dose or for up to three days will improve the condition within 20 to 36 hours. This shortens the duration of diarrhoea by one or two days when compared with controls taking placebo. Adverse events associated with short course therapy are usually mild. The application of this evidence base to clinical practice has differed among clinicians: some advocate prompt self treatment with antibiotics for moderate to severe travellers' diarrhoea, whereas others urge a more cautious approach to what is usually a self limited illness. Clinicians will need to decide in discussion with the traveller they are advising, the most appropriate approach, taking into account the traveller's ability and willingness to tolerate a diarrhoeal illness during his or her trip.

Fluoroquinolones are effective for travellers' diarrhoea acquired in most areas of the world, except when potentially resistant *Campylobacter* is common, such as in South Asia and South East Asia.²⁷ A growing body of evidence documents the effectiveness of azithromycin in treating fluoroquinolone resistant *Campylobacter*,²⁸ as well as other enterics.²⁷ Azithromycin can also be used in the treatment of pregnant women and young children with travellers' diarrhoea; however, the empirical antibiotic treatment of young children should only be used after careful consideration. Rifaximin was not inferior to a fluoroquinolone in a randomised, double blind trial of treatment in Mexico and Jamaica²⁹ where *E coli* associated travellers' diarrhoea was common, but rifaximin is less effective and not recommended when invasive agents, such as *Campylobacter* and *Shigella*, are causative.³⁰

Combination treatment

Combining an antibiotic with loperamide should be considered for people with classic travellers' diarrhoea who need prompt resolution of symptoms. Six randomised controlled trials examined combination treatment (single dose or short course antibiotics plus loperamide) compared with an antibiotic or loperamide alone.^{31,32} The weight of evidence favoured combination treatment when the predominate organisms were sensitive to the antibiotic.^{31,32}

How should returned travellers with diarrhoea be evaluated?

Diarrhoea is one of the most common syndromes in travellers who return ill. In a US cohort of returned travellers, diarrhoea affected 13%,² and in a large multicentre study (travel clinics and tropical disease units) acute or chronic diarrhoea was diagnosed at a rate of 335 cases per 1000 ill returned travellers.³³ Regions associated with the highest relative rates of gastrointestinal infection, as determined by numbers of clinical visits in returned travellers, were South Asia, South America, and sub-Saharan Africa.¹

SUMMARY POINTS

Travellers' diarrhoea affects 20-60% of people travelling primarily to low income regions

Classic travellers' diarrhoea is defined as three or more loose stools in 24 hours with or without at least one symptom of cramps, nausea, fever, or vomiting

Bacteria cause most identified cases; however, viruses and protozoan parasites are also causative

The objectives of self-treatment are to avoid dehydration, reduce the symptoms and duration of illness, and prevent disruption to planned activities

Travellers should maintain hydration, and can use bismuth subsalicylate to treat mild diarrhoea, loperamide to control symptoms when necessary, and a short course of an antibiotic to treat moderate to severe cases

Evaluation and management of returned travellers with diarrhoea includes maintaining hydration during mild illness, bacterial culture of stools and empirical treatment during moderate to severe illness, and, in protracted cases, examination of stools for ova and parasites

Travellers' diarrhoea can be evaluated in a general practice setting with referral to a specialist as needed. If fever, tenesmus, or gross blood in the stool are not present (that is, non-inflammatory diarrhoea) patients can be treated symptomatically and observed. If the patient seems unwell and there are additional symptoms, however, a stool should be cultured for enteropathogens and empirical antibiotic treatment considered using a fluoroquinolone or azithromycin. Unusually, *C difficile* associated disease presents after antibiotic treatment for travellers' diarrhoea.³⁴ In travellers with diarrhoea that has lasted for 10 days to two weeks or longer, stool samples should be evaluated for *Giardia*, *Cryptosporidium*, and other parasites.

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