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CLINICAL REVIEW

Travellers' diarrhoea

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Diarrhoea is a common problem affecting between 20% and 60% of travellers,[1] particularly those visiting low and middle income countries. Travellers' diarrhoea is defined as an increase in frequency of bowel movements to three or more loose stools per day during a trip abroad, usually to a less economically developed region. This is usually an acute, self limiting condition and is rarely life threatening. In mild cases it can affect the enjoyment of a holiday, and in severe cases it can cause dehydration and sepsis. We review the current epidemiology of travellers' diarrhoea, evidence for different management strategies, and the investigation and treatment of persistent diarrhoea after travel.

Who is at risk?

Variation in incidence[1 2] may reflect the degree of risk for different travel destinations and dietary habits while abroad. Destinations can be divided into low, medium, and high risk (see box 1). Rates of diarrhoea are likely to correlate closely with the quality of local sanitation.

Backpackers have roughly double the incidence of diarrhoea compared with business travellers.[4] Travel in cruise ships is associated with large outbreaks of viral and bacterial gastroenteritis.[5] General advice is to avoid eating salads, shellfish, and uncooked meats. There is no strong evidence that specific dietary measures reduce incidence of diarrhoea, but studies examining this are likely to be biased by imperfect recall of what was eaten.[6] Risk factors for travellers' diarrhoea are listed in box 2.

What are the most important causes of travellers' diarrhoea?

Most studies report a failure to identify the causative pathogen in between 40% and 70% of cases.[10] This includes multicentre studies based in high prevalence settings (that is, during travel).[3-12] This low diagnostic yield is partly due to delay in obtaining samples and partly due to the insensitivity of laboratory investigations. Older studies did not consistently attempt to identify enteroaggregative *Escherichia coli* (EAEC), and surveillance studies vary in reporting of other *E coli* species.[3] Where a pathogen is identified, bacteria are the commonest cause of acute travellers' diarrhoea, with the remainder being caused by norovirus, rotavirus, or similar viruses (see table 1⇓). Protozoa such as *Giardia lamblia* can also cause acute diarrhoea, but they are more often associated with persistent diarrhoea, lasting more than two weeks. *Cyclospora catayensis*, another protozoan cause of diarrhoea, was identified in an increased number of symptomatic travellers returning from Mexico to the UK and Canada in 2015.[13]

Table 1⇓ illustrates overall prevalence of causative agents in returning travellers with diarrhoea. However relative importance varies with country of exposure. Rates of enterotoxigenic *E coli* (ETEC) are lower in travellers returning from South East Asia than in those returning from South Asia, sub-Saharan Africa, and Latin America, whereas rates of *Campylobacter jejuni* are higher. Norovirus is a more common cause in travellers to Latin America and sub-Saharan Africa, and *Giardia lamblia* and *Entamoeba histolytica* are more common in travellers to South and South East Asia.[10]

The importance of enterotoxigenic *E coli* as a cause for diarrhoea in travellers returning from Latin America has been decreasing over the past four decades.[10] A large scale analysis of EuroTravNet surveillance data shows increasing incidence of *Campylobacter jejuni* infection in travellers returning from India, Thailand, and Pakistan.[2]

How does travellers' diarrhoea present?

Most episodes of travellers' diarrhoea start during the first week of travel, with the peak incidence on the second or third day after arrival.[8 14]

Typically diarrhoea caused by enterotoxigenic *E coli* ("turista") is watery and profuse, and preceded by abdominal cramps, nausea, and malaise. Symptoms are not a reliable guide to aetiology, but upper gastrointestinal manifestations such as bloating and belching tend to predominate with *Giardia lamblia*, while colitic symptoms such as urgency, bloody diarrhoea, and cramps are seen more often with *Campylobacter jejuni* and *Shigella* spp.

Most episodes will last between one and seven days, with approximately 10% lasting for longer than one week, 5% lasting more than two weeks, and 1% lasting more than 30 days.[8] During the illness, few patients will be severely incapacitated (in one large prospective cohort about 10% of 2800 participants were confined to bed or consulted a physician), but planned activities are often cancelled or postponed.[8]

What you need to know

- Enterotoxic *Escherichia coli* (ETEC) is the most common cause of acute travellers' diarrhoea globally
- Chronic (>14 days) diarrhoea is less likely to be caused by bacterial pathogens
- Prophylactic antibiotic use is only recommended for patients vulnerable to severe sequelae after a short period of diarrhoea, such as those with ileostomies or immune suppression
- A short course (1-3 days) of antibiotics taken at the onset of travellers' diarrhoea reduces the duration of the illness from 3 days to 1.5 days
- Refer patients with chronic diarrhoea and associated symptoms such as weight loss for assessment by either an infectious diseases specialist or gastroenterologist

Methods

We searched PubMed and Cochrane Library databases for "travellers' diarrhoea," and "travel-associated diarrhoea," to identify relevant articles, which were added to personal reference collections and clinical experience. Where available, systematic reviews and randomised controlled trials were preferentially selected.

Box 1: Risk of travellers' diarrhoea according to destination[1 3]

High risk destinations

- South and South East Asia*
- Central America*
- West and North Africa*
- South America
- East Africa

Medium risk

- Russia
- China
- Caribbean
- South Africa

Low risk

- North America
- Western Europe
- Australia and New Zealand

*Regions with particularly high risk of travellers' diarrhoea

Box 2: Factors increasing risk of travellers' diarrhoea[4-9]

By increased dietary exposure

- Backpacking
- Visiting friends and family
- All-inclusive holidays (such as in cruise ships)

By increased susceptibility to an infectious load

- Age <6 years
- Use of H_2 receptor antagonists and proton pump inhibitors
- Altered upper gastrointestinal anatomy
- Genetic factors (blood group O predisposes to shigellosis and severe cholera infection)

How can travellers' diarrhoea be prevented?

Several controlled trials have failed to demonstrate an impact of food and drink hygiene advice on rates of diarrhoea.[15] However, the clear food-related source of most diarrhoeal pathogens means that general consensus among travel physicians is to continue to recommend boiling water, cooking food thoroughly, and peeling fruit and vegetables.[6] Other basic advice includes avoiding ice, shellfish, and condiments on restaurant tables, using a straw to drink from bottles, and avoiding salads and buffets where food may have been unrefrigerated for several hours. Travellers should be advised to drink bottled water where available, including in alcoholic drinks, as alcohol does not sterilise non-bottled water. If bottled water is not available, water can be purified by boiling, filtering, or use of chlorine based tablets.[16] There is some weak evidence that use of alcohol hand gel may reduce diarrhoea rates in travellers,[17] but, based on studies in non-travellers, it is reasonable to strongly encourage travellers to adhere to good hand hygiene measures. Two recent systematic reviews estimated hand washing with soap reduces the risk of diarrhoeal illness by 30-40%.[18 19]

When is antibiotic prophylaxis recommended?

For most travellers antibiotic chemoprophylaxis (that is, daily antibiotics for the duration of the trip) is not recommended. While diarrhoea is annoying and distressing, severe or long term consequences from a short period of diarrhoea are rare, and routine use of chemoprophylaxis would create a large tablet burden and expose users to possible adverse effects of antibiotic therapy such as candidiasis and diarrhoea associated with *Clostridium difficile*.

Chemoprophylaxis should be offered to those with severe immune suppression (such as from chemotherapy for malignancy or after a tissue transplant, or advanced HIV infection), underlying intestinal pathology (inflammatory bowel disease, ileostomies, short bowel syndrome), and other conditions such as sickle cell disease or diabetes where reduced oral intake may be particularly dangerous (table 2⇓).[22] These patient groups may be unable to tolerate the clinical effects and dehydration associated with even mild diarrhoea, or the consequences of more invasive complications such as bacteraemia. For such patients, it is important to discuss the benefits of treatment aimed at preventing diarrhoea and its complications against the risks of antibiotic associated diarrhoea and other side effects. If antibiotics are prescribed then consideration should be given to any possible interactions with other medications that the patient is taking.

A small comparative study in US soldiers showed that malaria prophylaxis with daily doxycycline has the added benefit of reducing rates of travellers' diarrhoea caused by enterotoxigenic *E coli* and *Campylobacter jejuni*.[23]

Do vaccines have a role in prevention of travellers' diarrhoea?

Vaccines have been developed and licensed against *Salmonella typhi*, *Vibrio cholerae*, and rotavirus—all with reasonable efficacy. However, unlike enterotoxigenic *E coli*, none of these is a major cause of travellers' diarrhoea, and only vaccines against *S typhi* are recommended for most travellers to endemic settings. Phase 3 trials of enterotoxigenic *E coli* toxin vaccines have been undertaken but have failed to demonstrate efficacy.[24] Studies suggest vaccines against enterotoxigenic *E coli* would have a major public health impact in high burden countries, and further candidate vaccines are in development.[25]

What are the options for self administered treatment?

Table 3⇓ summarises the options for self treatment.

Anti-motility agents and oral rehydration therapy

For most cases of travellers' diarrhoea, oral rehydration is the mainstay of treatment. This can be achieved with clear fluids such as diluted fruit juice or soups. Young children, elderly people, and those at greater risk from dehydration (that is, those with medical comorbidities) are recommended to use oral rehydration salts (or a mixture of six level teaspoons of sugar and half a teaspoon of salt in a litre of clean water if rehydration salts are unavailable) (see http://rehydrate.org/rehydration/index.html).

Anti-motility agents such as loperamide may be appropriate for mild symptoms, or where rapid cessation of diarrhoea is essential. Case reports of adverse outcomes such as intestinal perforation suggest anti-motility agents should be avoided in the presence of severe abdominal pain or bloody diarrhoea, which can signify invasive colitis.[26] Systematic review of several randomised controlled trials have demonstrated a small benefit from taking bismuth subsalicylate, but this has less efficacy in reducing diarrhoea frequency and severity than loperamide.[27]

Antibiotics

Symptomatic treatment is usually adequate and reduces antibiotic use. However, some travellers will benefit from rapid cessation of diarrhoea, particularly if they are in a remote area with limited access to sanitation facilities or healthcare. Several systematic reviews of studies comparing antibiotics (including quinolones, azithromycin, and rifaximin) against placebo have shown consistent shortening of the duration of diarrhoea to about one and a half days from around three days.[28-30] Short courses (one to three days) of antibiotics are usually sufficient to effect a cure.[30]

For some people travelling to high and moderate risk areas (see box 1) it will be appropriate to provide a short course of a suitable antibiotic, with advice to start treatment as soon as they develop diarrhoea and to keep well hydrated. Choice of antibiotic will depend on allergy history, comorbidities, concomitant medications, and destination. Avoid quinolones for both prophylaxis and treatment of travellers to South East and South Asia as levels of quinolone resistance are high.[31] Azithromycin remains effective in these areas, but resistance rates are likely to increase.

A meta-analysis of nine randomised trials showed that the addition of loperamide to antibiotic treatment (including azithromycin, ciprofloxacin, and rifamixin) resulted in statistically significantly higher rates of cure at 24 and 48 hours compared with antibiotic alone.[32] Travellers can be advised to add loperamide to their antibiotic treatment to reduce the time to symptomatic improvement as long as there are no features of invasive colitis such as severe pain, high fever, or blood visible in the diarrhoea.[30] If any of these symptoms develop, travellers are advised to seek medical advice immediately.

Returned travellers with persistent diarrhoea

Most bacterial causes mentioned do not cause persistent diarrhoea in immune competent adults. Travellers with diarrhoea persisting beyond 14 days may present in primary or secondary care on their return and require assessment for other underlying causes of persistent diarrhoea.

Table 4⇓ lists the important clinical history and symptoms that can point to the underlying cause.

What investigations should be sent?

For diarrhoeal symptoms that persist beyond 14 days following travel (or sooner if there are other concerning features such as fever or dysentery), offer patients blood tests for full blood count, liver and renal function, and inflammatory markers; stool samples for microscopy and culture; and examination for ova, cysts, and parasites. Historically, advice has been to send three stool samples for bacterial culture, but this is unlikely to increase the diagnostic yield. Instead, stool microscopy can be used to distinguish inflammatory from non-inflammatory causes: a small observational study found presence of faecal leucocytes was predictive of a positive bacterial stool culture.[33] Yield from stool culture may be increased by dilution of the faecal sample, and the introduction of molecular tests such as polymerase chain

reaction (PCR) for common gastrointestinal pathogens such as *Campylobacter* spp may decrease turnaround times and increase yield.[34]

Additional tests should be offered according to symptoms and risk (table 4⇓). If the patient has eosinophilia and an appropriate travel history, the possibility of schistosomiasis, strongyloides, and other helminthic infections should be considered. While schistosomiasis can rarely cause diarrhoea in the context of acute infection, serology may be negative in the first few months of the illness.

Imaging is required only if the patient has signs of severe colitis or local tenderness, in which instances toxic megacolon, inflammatory phlegmon, and hepatic collections should be excluded. Patients with severe colitis or proctitis may need joint assessment with gastroenterology and consideration of endoscopy, or laparotomy if perforation has occurred.

Where infectious and non-infectious causes have been appropriately excluded, the most likely diagnosis is post-infectious irritable bowel syndrome, although diarrhoea can also herald underlying bowel pathology and anyone with red flags for malignancy should be referred by the appropriate pathway for assessment. Post-infectious irritable bowel syndrome has an incidence of around 30% after an acute episode of travel associated gastroenteritis.[35 36] It is more commonly a sequela of prolonged episodes of diarrhoea or diarrhoea associated with fever and bloody stools.[36] There is weak evidence from small randomised trials suggesting that exclusion of foods high in fermentable carbohydrates (FODMAP) may be helpful.[37] Exclusion of dietary lactose and use of loperamide, bile acid sequestrants, and probiotics can also be tried, but there is limited evidence for long term benefit.[35-38]

How should giardiasis be managed?

The most common pathogen identified in returning travellers with chronic diarrhoea is *Giardia lamblia,* particularly among people returning from South Asia.[39] Use of *G lamblia* PCR testing has increased detection,[40] which potentially will identify infection in some patients previously labelled as having post-infectious irritable bowel syndrome and in those whose diarrhoea may have been attributed to non-pathogenic protozoa. Most patients respond to 5-nitroimidazoles (a systematic review of a large number of trials has shown similar cure rates with tinidazole 2 g once only or metronidazole 400 mg three times daily for five days[41]), but refractory cases are increasingly common and require investigation, identification of underlying risk factors, and repeated treatment (various antimicrobials have been shown to be effective but may have challenging risk profiles).

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Questions for future research

- What is the justification for using antibiotics to treat a usually self limiting illness, in the wider context of rising levels of global antimicrobial resistance rates? What is the clinical impact of resistant enterobacteriaciae found in stool samples from returning travellers?[42 43]
- To what extent do host genetic factors increase susceptibility to gastrointestinal pathogens, and can this help to identify at risk populations and tailor treatments to individual patients?
- What is the long term efficacy of new pharmacological treatments such as selective serotonin reuptake inhibitors and rifaximin in post-infectious irritable bowel syndrome?

Tips for non-specialists

- Include consideration of chemoprophylaxis for high risk individuals in pre-travel assessment
- Advise all travellers on hygiene measures (such as hand washing and food consumption) and symptom management of diarrhoea
- Avoid quinolones for prophylaxis or treatment in travellers to South East and South Asia
- Where diarrhoea persists beyond 14 days, consider investigations to rule out parasitic and non-infectious causes. The presence of white blood cells on stool microscopy indicates an inflammatory cause

Additional educational resources

Resources for patients

- National Travel Health Network and Centre (NaTHNaC): http://travelhealthpro.org.uk/travellers-diarrhoea/
  Provides pre-travel advice, as well as links to country-specific advice
- Fit for Travel: www.fitfortravel.nhs.uk/advice/disease-prevention-advice/travellers-diarrhoea.aspx
  Provides similar pre-travel advice on hygiene and disease prevention
- Patient.co.uk: http://patient.info/doctor/travellers-diarrhoea-pro
  Has patient leaflets and more detailed information about investigation and management of travellers' diarrhoea

Resources for healthcare professionals

- Centers for Disease Control and Prevention yellow book: http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/travelers-diarrhea
  Provides a guide to pre-travel couselling
- Rehydration Project website: http://rehydrate.org/rehydration/index.html
  Has additional information about non-pharmacological management of diarrhoea

How patients were involved in the creation of the article

No patients were involved in the creation of this review.

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Tables

Table 1| Frequency of pathogens causing travellers' diarrhoea23101112

Pathogen	Prevalence*	Clinical features
Bacterial		
Enterotoxigenic *Escherichia coli* (ETEC)	12-34%	Acute watery diarrhoea, abdominal cramping. Fever less common
Enteroaggregative *E coli* (EAEC)	1-24%	Acute watery diarrhoea
Campylobacter jejuni	8-32%	Acute diarrhoea, abdominal cramps, bloody stools, fever
Salmonella spp	4-9%	Acute diarrhoea, fever, vomiting, abdominal cramps
Shigella spp	2-14%	Acute diarrhoea, abdominal cramps, bloody stools, fever, tenesmus. Features may persist
Aeromonas spp	<5%	Acute watery diarrhoea, fever, abdominal cramps
Plesiomonas spp	<5%	Acute lower abdominal pain, bloody stools, tenesmus, fever
Vibrio cholerae	<1%	Acute profuse watery diarrhoea
Viral		
Norovirus	7-9%	Acute watery diarrhoea, vomiting
Rotavirus	13-17%	Acute watery diarrhoea, abdominal cramps, vomiting, low grade fever
Parasitic		
Giardia lamblia	1-6%	Chronic diarrhoea, may be steatorrhoea, flatus, distension
Cryptosporidium spp	1-3%	Watery diarrhoea, sometimes abdominal cramps, may be prolonged
Entamoeba histolytica	1-4%	Acute lower abdominal pain, bloody stools, tenesmus, fever

*Percentage of all cases of diarrhoea with identified cause in these studies

Table 2| **Antibiotic chemoprophylaxis options for immunosuppressed or other high risk travellers**

Antibiotic	Dose	Percentage protection[6-21]
Ciprofloxacin	500 mg once daily	80-100%
Norfloxacin	400 mg once daily	75-95%
Rifaximin	200 mg once or twice daily	72-77%
Bismuth subsalicylate	2 tablets four times daily	62-65%

Table 3| **Summary of self treatment choices**

Severity of symptoms	Treatment
All cases	Liberal intake of clear fluids. Oral rehydration salts for young children, elderly people, and travellers with medical comorbidities
Mild symptoms (1-2 unformed stools per 24 hours)	Loperamide: 4 mg taken immediately, then 2 mg for each loose stool to a maximum of 16 mg per day
Moderate symptoms:	
South and Central America, Africa	Ciprofloxacin: 500 mg twice daily for three days
South and South East Asia	Azithromycin: 1 g single dose, or 500 mg daily for three days Rifaximin: 200 mg three times daily for three days
High fever, severe abdominal pain, bloody diarrhoea	Seek local medical assistance Avoid loperamide

Table 4| **Assessment of chronic diarrhoea**

Symptoms	Cause
Bloating, nausea, belching	*Giardia lamblia,* microsporidiosis
Fever	*Salmonella typhi* or *S paratyphi,* malaria
Bloody diarrhoea	*Entamoeba histolytica,* inflammatory bowel disease
Arthropathy, uveitis	Inflammatory bowel disease, reactive arthritis after colitis
Greasy, malodorous stools	Malabsorption, *Giardia lamblia,* lactose intolerance
History	
Unprotected sexual intercourse	HIV, *Shigella* spp, *Lymphogranuloma venereum, Giardia lamblia*
Antibiotic use	*Clostridium difficile*
Symptoms before travel	Coeliac disease, inflammatory bowel disease, irritable bowel disease
Autoimmune disease	Hyperthyroidism, coeliac disease