Advising travellers about management of travellers’ diarrhoea

Background
Travellers’ diarrhoea (TD) affects a large proportion of international travellers. These people will often present to general practice for advice before they travel.

Objective
This article will review the current concepts and practical issues for advising people planning to travel about their risks of TD and how to manage symptoms if they develop during the trip.

Discussion
Avoidance, immunisation, non-antibiotic interventions and antibiotic prophylaxis are all methods for preventing TD. However, advice regarding self-management through rehydration, antibiotic treatment and appropriate seeking of medical advice are most important.

Keywords
travel; diarrhea; antidiarrheals; prophylaxis; vaccination

Background
Travellers’ diarrhoea (TD) affects a large proportion of international travellers. This prevalence has not changed over many decades. High-risk areas include developing tropical and semi-tropical regions of South-East Asia, Sub-Saharan Africa and Latin America, whereas moderate-risk areas include South-East Asia, the Middle East, Oceania and the Caribbean. Travellers at high risk of developing TD or at high risk of complications include those with insulin-dependent diabetes mellitus, congestive heart failure, advanced cancer, human immunodeficiency virus (HIV) infection, inflammatory bowel disease or other bowel abnormalities, reactive arthritis, reduced gastric acidity, or those who are HLA-B27-positive.

How is TD defined?
Classic, severe TD is usually defined as at least three unformed bowel movements occurring within a 24-hour period, often accompanied by cramps, nausea, vomiting, fever and/or blood in the stools. Moderate TD is defined as one or two unformed bowel movements and other symptoms occurring every 24 hours or as three or more unformed bowel movements without additional symptoms. Mild TD is defined as one or two unformed bowel movements without any additional symptoms and without interference with daily activities. TD generally resolves spontaneously, usually after 3–4 days, but, in the interim, frequently leads to disruption of planned activities.

What are the causes of TD?
Approximately 50–80% of TD is caused by bacterial infections; enterotoxigenic Escherichia coli (ETEC) is the most common cause overall. Other bacterial causes include enteroinvasive E. coli (EIEC), enteroaggregative E. coli (EAEC), Shigella, Campylobacter and Salmonella species. The exact breakdown of organisms varies according to destination, season and other factors. Noroviruses cause 10–20% of TD cases. Protozoal parasites should be considered particularly in those with persistent diarrhoea (illness lasting ≥14 days) or when antibacterial therapy fails to shorten illness.
How can TD be prevented?
Methods for preventing TD include avoidance, immunisation, non-antibiotic interventions or antibiotic prophylaxis.11

What avoidance measures are generally recommended and do they work?
Avoidance of TD has traditionally relied on recommendations regarding careful food and drink choices (avoiding untreated/unboiled tap water, including ice and water used for brushing teeth, and raw foods such as salads, uncooked vegetables or fruits that cannot be peeled). This underpins the saying ‘Boil it, cook it, peel it or forget it…. easy to remember, impossible to do’. Additional standard advice is that undercooked or raw meat, fish and shellfish are high-risk foods. However, whether deliberately or inadvertently, most people find it very difficult to adhere to dietary restrictions13 and over 95% of people disobey the rules of ‘safe’ eating and drinking within a few days of leaving home. Additionally, there is minimal evidence for a correlation between adherence to dietary precautions and a reduced risk of TD,13 although common sense nevertheless supports care with food selection.4

Where people eat may be more important than what people eat. Risks associated, in descending order, with street vendors, restaurants and private homes. Use of antibacterial handwash before eating is also recommended.14

Which vaccines can be considered?
Immunisation has little practical role in the prevention of TD and the only potentially relevant vaccines are those against rotavirus (infants only) and the oral cholera vaccine.

The cholera vaccine has >90% efficacy for prevention of *Vibrio cholera* but travellers are rarely at risk of infection with this pathogen.1 The vaccine contains a recombinant B subunit of the cholera toxin that is antigenically similar to the heat-labile toxin of ETEC; therefore, the cholera vaccine may also reduce ETEC TD. However, it is not licensed for TD prevention in Australia and, although initially thought to offer a 15–20% short-term (3 months) reduction in TD, a recent Cochrane review showed no statistically significant effects on ETEC diarrhoea or all-cause diarrhoea.15 Overall, there is, therefore, insufficient evidence to support general use of the cholera vaccine for TD protection, but it may still be considered for individuals with increased risk of severe or complicated TD (eg immunosuppressed or underlying inflammatory bowel disease).

Other vaccines directed against organisms spread by the faecal–oral route are the vaccines for typhoid, hepatitis A and polio, but infection with these organisms rarely causes TD.15

Do non-antibiotic interventions work?
Several probiotic agents have been studied for treatment and prevention of TD, including *Lactobacillus* and *Saccharomyces* preparations. However, their effectiveness for TD prevention has been limited,11,16,17 and a consensus group has recommended against their use.4 Other over-the-counter agents are also available (eg travelan, which contains bovine colostrum harvested from cows immunised with an ETEC vaccine) but data regarding overall efficacy of reducing all-cause TD are currently lacking.

Should antibiotic prophylaxis against TD be given?
Quinolone antibiotics are highly effective (80–95%) in preventing TD, but antibiotic prophylaxis is rarely indicated.4 It may result in a false sense of security and hence less caution in dietary choices, it poses risks of side effects, diarrhoea associated with *Clostridium difficile*, and, more importantly, would lead to a vast amount of antibiotic use, thus predisposing to more rapid development of antibiotic resistance globally.11 Therefore non-antibiotic options for prevention and a focus instead on empirical self-treatment if needed according to symptoms are the mainstay of management, aligning with the antimicrobial stewardship perspective of minimisation of antimicrobial overuse and reducing promotion of antimicrobial resistance.

In rare circumstances, it may be reasonable to consider short courses of antibiotic prophylaxis in individuals at very high risk of infection (eg severely immunocompromised).11 Globally, one of the most commonly used agents in this regard is rifaximin, a non-absorbed semisynthetic rifamycin derivative, which has been shown to be effective and is approved for use for TD prevention in some countries, but it is not approved for this indication in Australia. Other options include the antibiotics discussed below for TD self-treatment.

How should self-treatment of TD be managed?
Because of the limitations of TD prevention measures, the pre-travel consultation should be viewed as an opportunity to ‘arm’ travellers with the knowledge and medication needed to appropriately self-treat, should TD occur during their trip.

The first goal of therapy is the prevention and treatment of dehydration, which is of particular concern for young children, pregnant women and the elderly. Commercial packets of oral rehydration salts are readily available in pharmacies and should be purchased before travel. The other element of TD self-treatment is to recommend travellers bring an antimitoty agent plus an antibiotic with them. Loperamide is preferred over the diphenoxylate/atropine combination, as the latter agent is generally less effective and associated with a greater potential for adverse effects.

When should loperamide alone versus loperamide plus an antibiotic be taken?
For mild symptoms of watery diarrhoea, self-treatment with oral rehydration plus loperamide is recommended. Loperamide therapy alone has no untoward effects in mild TD18 but if symptoms worsen, or do not improve after 24 hours, antibiotics should be added. If TD is moderate or severe at onset, then combination therapy with loperamide plus antibiotics should be started immediately, as this optimises the clinical benefit of self-treatment by providing more rapid relief and shortening the symptom duration.10,19
The recommended dose of loperamide is two tablets (4 mg) stat, then one tablet after each bowel motion to a maximum of eight per 24-hour period until the TD has resolved. Despite warnings regarding the safety of antidiarrhoeal agents with bloody diarrhoea or diarrhoea accompanied by fever, the combination with antibiotics is likely to be safe in the setting of mild febrile dysentery, and a number of studies have shown the combination to be more efficacious than use of either agent alone. Rapid institution of effective treatment shortens symptoms to 30 hours or less in most people. For example, the duration of diarrhoea was significantly shorter following treatment with azithromycin plus loperamide (11 h) than with azithromycin alone (34 h).

**Which antibiotic should be recommended for empirical self-treatment of TD?**

The most commonly used antibiotics for empirical TD therapy are fluoroquinolones (either norfloxacin or ciprofloxacin) or azithromycin (Table 1). Cotrimoxazole has been used but is no longer recommended because of widespread resistance. For TD caused by ETEC, the fluoroquinolones and azithromycin have similar efficacy; however, in Asia (particularly South and South-East Asia), Campylobacter is a common cause of TD and strains occurring in this part of the world show a high degree of resistance to fluoroquinolones. Therefore, azithromycin is preferred for travellers to this region. Azithromycin remains generally efficacious despite emerging resistance, and is also the preferred treatment for diarrhoea with complications of dysentery or high fever, and for use in pregnant women or children under the age of 8 years, in whom avoidance of quinolones is preferred. Moreover, the 24-hour dosing of azithromycin may be preferable to the 12-hourly dosing schedule required with fluoroquinolones.

**What is the optimal dosing schedule?**

The fluoroquinolones and azithromycin have been administered as a single dose or for 3 days (Table 1). Usually a single dose is adequate and there is no apparent clinically important difference in efficacy with either dosing schedule for TD. However, for bacteria such as Campylobacter and Shigella dysenteriae, single-dose therapy may be inadequate. It is reasonable, therefore, to give travellers a 3-day supply of antibiotics and tell them to continue taking the therapy (either 12- or 24-hourly, depending on which antibiotic is prescribed) only if their TD symptoms persist. If the TD has resolved, no further antibiotics need to be taken and any remaining antibiotic doses can be kept in case of a second bout of TD. It is prudent to specifically highlight that this advice differs from the usual instructions on which antibiotic is prescribed (either 12- or 24-hourly, depending on which antibiotic is prescribed) only if their TD symptoms persist. If the TD has resolved, no further antibiotics need to be taken and any remaining antibiotic doses can be kept in case of a second bout of TD. It is prudent to specifically highlight that this advice differs from the usual instructions on which antibiotic is prescribed.

**What is the optimal empirical TD management in children?**

There are few data on empirical treatment of TD in children and limited options for therapy. The mainstay of therapy is oral rehydration solution, particularly for children <6 years of age. Antimotility agents are contraindicated for children because of the increased risk of adverse effects, especially paralytic ileus, toxic megacolon and drowsiness (narcotic effect) with loperamide. The lower age limit recommended for avoiding loperamide varies by location; US guidelines state that loperamide should not be given to infants <2 years of age, the UK <4 years and Australian guidelines state <12 years. However, most Australian practitioners are prepared to use loperamide in children aged 6 years or older, if needed to control symptoms.

A paediatric (powder) formulation of azithromycin is available and is the most commonly recommended agent for children. The usual dose is 10–25 mg/kg for up to 3 days. A practical tip is to ensure that the pharmacy does not reconstitute the powder into a solution, as once dissolved, the solution lasts only for 10 days. Instead, sterile water should be provided along with instructions on how to reconstitute the powder if needed. Fluoroquinolones (ciprofloxacin or norfloxacin 10 mg/kg bd) are an alternative option if there are reasons for avoiding azithromycin, with previous concerns regarding potential effects on cartilage not substantiated in recent studies.

**Does starting antibiotics early prevent the chances of developing prolonged symptoms?**

Although TD symptoms are short-lived in most cases, 8–15% of affected travellers are symptomatic for more than a week and 2% develop chronic diarrhoea lasting a month or more. Episodes of TD have been shown to be associated with a quintuple risk of developing irritable bowel syndrome (IBS), and post-travel IBS occurs in 3–10% of travellers. However, it is unknown whether IBS can be prevented by starting antimicrobial therapy earlier in the course of enteric infection.

**Should tinidazole also be prescribed and, if so, for whom?**

Tinidazole can be prescribed as a second antibiotic for empirical self-treatment as it is effective against the protozoan parasitic entic...
pathogen *Giardia intestinalis*. A dose of 2 g (4 x 500 mg tablets) stat is recommended. However, for most short-term travellers, tinidazole may be unnecessary and the complexity of the additional instructions required may be unwarranted. It is optimally recommended, therefore, for travellers departing on trips of significant duration (>2–3 weeks). If prescribed, the instructions should be to take tinidazole if the TD persists following the 3-day course of antibiotic therapy (fluoroquinolone or azithromycin). This will mean that the TD has lasted for at least 72 hours, thus increasing the likelihood of a parasitic cause.

**When should medical care for acute symptoms be recommended?**

While most episodes of TD are amenable to self-treatment, if there is a risk of dehydration due to intolerance of oral fluids or comorbidities, as well as in the setting of frank blood in the stool or unremitting fevers (>38.5°C for 48 hours), medical therapy should be sought.18

**How should TD be managed after return?**

While a full description of TD management is beyond the scope of this article, for returning travellers with diarrhoea, at least one (preferably three) stool sample(s) should be taken, including specific requests for evaluation of parasites. For patients who are unwell, particularly those with fevers or dysentery, initiation of empirical antibiotic treatment with azithromycin or a quinolone may be needed while awaiting results. For those with prolonged symptoms, tinidazole as empirical therapy for protozoan parasites may be considered. Endoscopic evaluation may also be advisable if no infectious cause is found and symptoms do not resolve.

**Key points**

- Travellers’ diarrhoea continues to affect 20–50% of people undertaking trips to areas with under-developed sanitation and there is minimal evidence for beneficial effects of dietary precautions.
- Evidence for the benefit of cholera vaccine in reducing TD is limited, but it can be considered in people at high risk of infection.
- In 50–80% of TD cases, TD is caused by bacterial infection. Mild diarrhoea can be managed with an antimotility agent (loperamide) alone, but for moderate or severe diarrhoea, early self-treatment with loperamide in conjunction with antibiotics is advised.
- Recommended empirical antibiotics are fluoroquinolones (norfloxacin / ciprofloxacin) or azithromycin for up to 3 days, although in the setting of increasing resistance, the latter is preferred for travellers to South and South-East Asia.

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