Treatment and prevention of travellers' diarrhoea

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Diarrhoea affects millions of international travellers each year, disrupting travel plans and in some cases, provoking chronic bowel symptoms. Here, Professor ROY ROBINS-BROWNE explores the risk factors and causes of travellers' diarrhoea, and the strategies used to prevent and treat this condition. Advice from well-informed healthcare providers can reduce the incidence and severity of travellers' diarrhoea, and enhance their clients' travel experience.

THE United Nations World Tourism Organisation has estimated that more than 35 million travellers from industrialised countries visit less-developed countries each year. Between 20-50 per cent of these travellers will experience diarrhoea as a consequence of consuming faecally contaminated food or water.

Travellers' diarrhoea is defined as the passage of three or more unformed stools over 24 hours, with symptoms starting during or shortly after travel.[1] Other clinical features that may accompany diarrhoea are nausea, vomiting, abdominal pain, fever and blood or mucus in the faeces. Although mostly benign, travellers' diarrhoea often disrupts travel plans and some sufferers may develop chronic diarrhoea, irritable bowel syndrome or even inflammatory bowel disease, such as ulcerative colitis. Travellers' diarrhoea is also a common problem among military personnel deployed to areas where they are exposed to contaminated food and water.

Risk factors

The greatest risk factor for travellers' diarrhoea is destination. High-risk zones where the likelihood of acquiring diarrhoea exceeds 20 per cent and can average as much as 50 per cent,[2] include the Middle East, South and South-East Asia, Central and South America, and the poorer countries of Africa. Intermediate-risk destinations (15-20 per cent) include the countries of Southern and Eastern Europe, Russia, Israel, South Africa, China and the Caribbean Islands.

Other risk factors for acquiring travellers' diarrhoea include the time of year (greatest during summer); how and where one travels (higher in backpackers, adventure travellers and passengers on cruise ships); what one eats and drinks (raw foods, including salads and unpeeled fruit, untreated water and foods procured from street vendors, carry the highest risk).

Host factors that influence the likelihood of acquiring gastrointestinal infections include immunosuppressive disorders, such as AIDS, and treatment with steroids and drugs which elevate the pH of the stomach, such as H_2-blockers and proton pump inhibitors.[3]

Aetiology

Travellers' diarrhoea is almost always the result of an infection, but the specific cause is identified in only about half the cases. In about 85 per cent of these, the cause is bacterial. Interestingly, most patients in whom no pathogen is identified respond to antibiotics, suggesting that these cases are also caused by bacteria.

The single most common cause of travellers' diarrhoea worldwide is *Escherichia (E.) coli*. This *E. coli* is the same species which inhabits the gastrointestinal tracts of healthy humans, but the strains of *E. coli* that cause travellers' diarrhoea differ from the harmless commensals in that they carry specific virulence factors which allow them to cause disease symptoms.[4] The pathogenic varieties of *E. coli* which cause travellers' diarrhoea include enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* and enteroinvasive *E. coli*. Each of these varieties of *E. coli* differ from each other and from commensal *E. coli* in terms of the specific virulence factors they carry.[4]

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Collectively, these varieties of *E. coli* account for more than 50 per cent of cases of travellers' diarrhoea in which a cause is identified. For several destinations, including Central America, East Africa and the Middle East, ETEC alone accounts for approximately half the cases of travellers' diarrhoea.

Other bacterial causes of travellers' diarrhoea include *Campylobacter*, *Salmonella*, *Shigella*, *Aeromonas*, *Plesiomomas*, and *Vibrio* species.[1] The relative importance of these bacteria differs from place to place, year to year and at different times of the year. Viruses most frequently associated with travellers' diarrhoea are noroviruses (formerly called Norwalk-like agents) and rotaviruses. The protozoal parasites which cause travellers' diarrhoea include *Giardia lamblia* (also known as *Giardia intestinalis*), *Cryptosporidium parvum* and *Entamoeba histolytica* (the cause of amoebic dysentery). As with the other aetiological agents, the relative importance of these parasites varies in different locations.

The mechanisms by which most agents cause travellers' diarrhoea are not entirely known. In the case of ETEC, however, we know that the bacteria require two essential, but independent, varieties of virulence determinant to cause disease: these are (1) colonisation factors, which allow the bacteria to occupy regions of the intestine, in particular the small intestine, where *E. coli* are not normally found; and (2) secreted protein enterotoxins which interfere with water and electrolyte transport across the intestinal epithelium (Figure One).

In the case of ETEC strains that infect humans, at least 23 antigenetically distinct colonisation factors, known as colonisation factor antigens or coli surface (CS) antigens, have been identified.[5] The enterotoxins produced by ETEC are known as heat-stable enterotoxin (ST) and heat-labile enterotoxin (LT). ETEC isolated from patients with travellers' diarrhoea may produce one or other or both of these toxins. ST is a low molecular weight, weakly antigenic peptide, whereas LT is a relatively high molecular weight protein, which resembles the enterotoxin of *Vibrio cholerae* and is strongly antigenic.

Both toxins act in a similar fashion to block the uptake of sodium and chloride ions by intestinal absorptive cells and enhance the secretion of chloride ions by intestinal secretory cells. Together, these effects lead to an accumulation of electrolytes in the intestinal lumen, resulting in an osmotic gradient, which not only interferes with the uptake of water by intestinal cells, but may even draw water out from the tissues into the intestinal tract. The consequences of this are watery diarrhoea and dehydration.

Treatment

Because travellers' diarrhoea typically is self-limiting, specific treatment is generally not needed. However, empirical self-treatment may be warranted for moderate-to-severe cases.[6] The main objective of treatment is to prevent dehydration. This can be achieved by drinking oral rehydration fluids or even (in the case of adults) drinking sweetened soft drinks with salt crackers. Formal oral rehydration therapy is required for young children and the elderly.

Regarding specific treatment, there is evidence that children respond better to oral rehydration solutions with reduced sodium (~60 mmol/l) and a total osmolarity of ~250 mmol/l compared to standard WHO oral rehydration solution which contains 90 mmol/l sodium and has a total osmolarity of 311 mmol/l.[7] If diarrhoea is severe, patients may need to temporarily stop their other medications, (for example diuretics and antihypertensive agents). Particular caution is advised with patients undergoing treatment with ACE inhibitors or angiotensin-2 receptor agonists, because of their effect on aldosterone synthesis.

Antimotility and antisecretory drugs do not cure diarrhoea. However, they may offer symptomatic relief by reducing the number of stools passed by between one and two-thirds. Loperamide has both antimotility and antisecretory properties and is the antimotility drug of choice.[1] Loperamide is contraindicated in children younger than two years because of their susceptibility to its narcotic properties. Loperamide also commonly causes post-diarrhoea constipation, and, very occasionally, may aggravate the clinical course of diarrhoea caused by invasive pathogens such as salmonellae and shigellae.

Treatment with appropriate antimicrobial agents can also reduce the severity and duration of travellers' diarrhoea. A recent Cochrane meta-analysis of six studies showed that 84 per cent of 391 patients were free of symptoms 72 hours after starting antimicrobial treatment, compared with 50 per cent of 306 who took placebo.[8] Fluoroquinolones, such as ciprofloxacin, are among the most effective agents, and have a long half-life allowing for once-or-twice daily dosing. A single large dose may be as effective as three days' treatment.[9] Although ciprofloxacin is believed to be safe for use in children, in the USA it is not approved for patients younger than 18 years. Resistance to fluoroquinolones is emerging in *Campylobacter* species, and is likely to become more common with increasing usage.

Azithromycin is a suitable alternative to ciprofloxacin. It appears to be as effective as the latter, is licensed for use in children and has fewer drug interactions. Rifamixin is a semisynthetic derivative of rifamycin. When taken by mouth, it is virtually non-absorbable. In several clinical trials to date it has been found to be as effective as ciprofloxacin in shortening the duration of diarrhoea,[10] but it is not yet approved for Australia.

Treatments which are not effective for travellers' diarrhoea include kaolin-pectin preparations, activated charcoal, anticholinergics, and *Lactobacillus* preparations. Regardless of the treatment, patients who do not respond after 24 hours should seek medical advice. Other indications for medical intervention include evidence of dehydration, frequent vomiting that prevents the oral intake of adequate amounts of fluid, significant gastrointestinal bleeding, and diarrhoea lasting more than three days.

Prevention

The risk of acquiring travellers' diarrhoea can be reduced by (1)

avoidance, (2) appropriate immunisations and (3) treatment with antimicrobials and other agents. Avoidance centres mainly on the prudent choice of food and drink. Standard advice to travellers is to avoid drinking local water, including still bottled water and ice cubes. Travellers should also avoid salads and other uncooked foods, including unpeeled fruit. A commonly quoted rule is 'boil it, cook it, peel it, or forget it', but this dictum may be hard to follow. A study of travellers to Asia and Africa revealed that only 2 per cent of those surveyed adhered to all of the recommendations concerning avoidance.[11]

Vaccination against cholera and typhoid fever may be indicated for travellers to some endemic countries, but does little to reduce the incidence of travellers' diarrhoea, which rarely is attributable to cholera or typhoid fever. An oral cholera vaccine comprising inactivated whole cholera bacilli and a fragment of cholera toxin may reduce the severity of infection with LT-producing strains of ETEC due to antigenic cross-reactivity between cholera toxin and LT.[12] However, this vaccine is not registered for use against ETEC in most countries, including Australia. Vaccines based on colonisation antigens of ETEC are being developed for use in humans, but the large number of colonisation factor antigens makes this a challenging task.[13]

Immunisation against ETEC with vaccines containing pig-specific colonisation factors is highly effective in preventing diarrhoea in piglets, which are susceptible to pig-specific strains of ETEC from birth. These vaccines are administered to sows, which then transfer immunity to their offspring via antibodies in colostrum, the early milk that is produced after birth. The antibodies in colostrum bind to the surface of the ETEC strain and prevent it from adhering to intestinal cells, thus providing high-level protection to ETEC strains that carry the same antigens as those in the vaccine.[14]

The demonstrated efficacy of colostral antibodies in animals has prompted investigations of the use of hyperimmune colostrum from cattle (a rich source of antibodies) as a means to prevent travellers' diarrhoea in humans. For these studies, cows are hyperimmunised with various bacteria or antigens associated with travellers' diarrhoea. In one such study, volunteers given colostrum from cows immunised with an ETEC strain were completely protected against all manifestations of travellers' diarrhoea (including diarrhoea, anorexia, malaise, cramps, vomiting and fever) compared with volunteers given control, non-immune colostrum.[15]

An Australian-based company, Anadis Ltd, has prepared a multivalent colostrum preparation from cows immunised with the most common varieties of ETEC. This antibody preparation is marketed as Travelan, a non-prescription caplet, which afforded high levels of protection against ETEC in volunteer studies. Because it contains antibodies to a wide variety of antigens of *E. coli*, it may also be expected to offer some protection against other agents of travellers' diarrhoea, such as enteroaggregative strains of *E. coli*, which are important emerging pathogens.[16]

Bismuth subsalicylate (Peptobismol) is another non-antibiotic measure that has been shown to be effective in preventing travellers' diarrhoea. Although it has some anti-secretory, anti-bacterial and anti-inflammatory properties, these are insufficient to allow its use for treatment. Bismuth subsalicylate causes blackening of the tongue and stools, which, although harmless, may reduce compliance.[10]

Numerous studies over a period of more than 40 years have shown that prophylaxis with antimicrobial agents can prevent diarrhoea in up to 90 per cent of travellers. However, this form of prophylaxis is not recommended due to the risk of side-effects (including diarrhoea), the potential to select for resistant microorganisms while promoting a false sense of security, and the risk of masking more serious infections such as malaria or typhoid fever resulting from partial treatment.[17]

Occasionally, antimicrobial prophylaxis, in conjunction with other preventative measures, may be warranted for travellers at high risk, such as, those with achlorhydria, and those who cannot afford a brief illness, such as politicians and international athletes. ■

Conflict of interest statement:
The author is a non-executive director of Anadis Ltd and is a member of Anadis' Scientific Advisory Committee. He also indirectly owns shares in Anadis.

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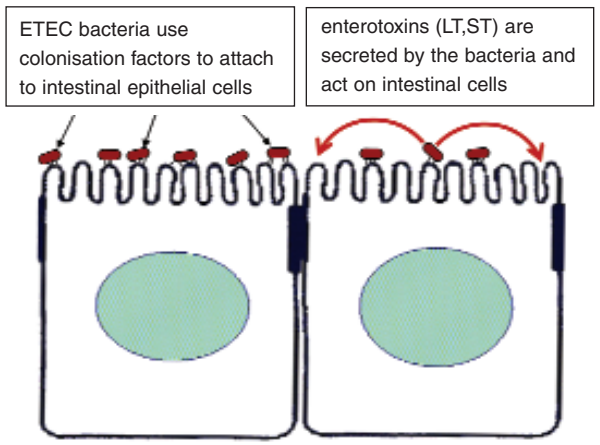
Figure One: Diagrammatic representation of enterotoxigenic *E. coli* (ETEC) adhering to small intestinal epithelial cells via colonisation factors, and secreting enterotoxins, LT and ST, which interfere with water and electrolyte transport across the intestinal mucosa.



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For each of the following questions:
Choose (a), if A, B and C are correct;
Choose (b), if A and C are correct;
Choose (c), if B and D are correct;
Choose (d), if only D is correct;
Choose (e), if all are correct.

Q.1 Travellers' diarrhoea:
(a) Is most commonly caused by pathogenic varieties of *E. coli*
(b) May be caused by protozoa, such as *Giardia and Cryptosporidium* species
(c) May be caused by viruses, including norovirus and rotavirus
(d) Does not usually result from an infection
(e) All above statements are correct.

Q.2 Common vehicles of the agents of travellers' diarrhoea include:
(a) Recently boiled water
(b) Freshly prepared salads
(c) Carbonated soft drinks
(d) Ice cubes
(e) All above statements are correct.

Q.3 Reducing the risk of travellers' diarrhoea involves:
(a) Being cautious about what can one eats and drinks
(b) Taking systematically-active antibiotics
(c) Taking clinically proven, non-antimicrobial compounds, such as Travelan or bismuth subsalicylate
(d) Being immunised against hepatitis A, cholera and typhoid fever
(e) All above statements are correct.

Q.4 Individuals at increased risk of acquiring travellers' diarrhoea include:
(a) Patients taking proton pump inhibitors
(b) Backpackers
(c) Patients with HIV/AIDS
(d) International athletes
(e) All above statements are correct.

Q.5 Regarding the treatment of travellers' diarrhoea:
(a) The most important consideration is to maintain hydration
(b) Treatment with fluoroquinolones or azithromycin may shorten the duration of diarrhoea in up to 80 per cent of patients
(c) Young children often require formal oral rehydration treatment
(d) Loperamide should not be given to children under two years
(e) All above statements are correct.