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Management of Travellers' Diarrhoea

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Abstract

The most common health problem encountered in international travellers to tropical and subtropical areas is diarrhoea. Even though it is not a life-threatening condition, it may influence deeply the quality of a vacation or the success of a business trip. The majority of cases of travellers' diarrhoea are due to bacterial pathogens, but viruses and parasites have also been implicated in a minority of patients.

It is advocated that travellers with diarrhoea provide themselves with sources of salt (crackers or soup) and mineral water, to prevent and treat dehydration. Otherwise, treatment recommendations follow illness severity. For mild cases, symptomatic relief alone can be recommended. Loperamide is an effective agent improving diarrhoea and associated symptoms. For moderate diarrhoea (requiring a forced change in itinerary) combination therapy is advised using a fluoroquinolone together with loperamide. Severe diarrhoea [fever >38°C, dysentery (bloody stools) or incapacitating symptoms] should prompt the voyager to take an antibiotic alone for 3 to 5 days. Loperamide is relatively contraindicated in these cases.

For the minority of patients receiving chemoprophylaxis to prevent travellers' diarrhoea, fluoroquinolones taken once a day while in the area at risk produce the highest protection rate (up to 95%). However, most authorities do not recommend routine prophylaxis for travellers.

1. Definition

In 1993 there were 500 million international tourist arrivals, which was equal to 8% of the world population.[1] Each year approximately 5.3% of the journeys are from industrialised countries to developing tropical and subtropical areas and approximately 40% of these people experience diarrhoea.[2] Using these estimates, we can say that approximately 26.5 million travellers venture annually into high risk regions from developing countries, resulting in 6.4 million individuals experiencing diarrhoea. Characteristically, the disease is manifested within the first week after arrival in the region of high risk, but it may occur at any time during the trip, and even after returning home.[3]

Most treatment studies define travellers' diarrhoea as the passing of ≥3 loose stools in a 24-hour period, in association with at least 1 symptom of enteric disease such as nausea, malaise, vomiting, abdominal cramps, fever, tenesmus or the passage of bloody, mucoid stools.[3,4] Although typically a mild affliction, it can profoundly influence the quality of a vacation or the success of a business trip or even a military operation.[5]

Everyone from developed countries travelling into the high risk, tropical and subtropical areas of the developing world must be ready to treat acute diarrhoea, should it develop during their stay. In the following, current recommendations for the management of travellers' diarrhoea are reviewed.

2. Aetiology and Epidemiology

The most important risk factor for acquiring travellers' diarrhoea is the destination. Destination can be divided into high risk areas with an incidence of diarrhoea of 20 to 50% (Latin America, Africa, certain parts of the Middle East, the Dominican Republic or Haiti, and Asia); intermediate risk areas with an incidence of 8 to 20% (Southern Europe, Israel, South Africa and a number of the Caribbean islands); and low risk areas with an incidence of 7% or less (Canada, the US, Northern Europe, Japan, Australia, New Zealand and a few Caribbean islands).[6]

Numerous studies performed around the world have shown that enterotoxigenic *Escherichia coli* (ETEC) is the most common causative organism in travellers' diarrhoea. However, a number of other agents can also cause the disease. Table I compares the frequency of the most common organisms causing travellers' diarrhoea from 2 different periods, before 1987 and from 1987 to 1997, and also compares the prevalence of the most common agents in Latin America, Asia and Africa. A diversity of other pathogens have been implicated, including *Shigella* spp., *Salmonella* spp., enteroadherent and enteroinvasive *E. coli*, noncholera *Vibrios*, *Aeromonas* and *Plesiomonas*. *Campylobacter jejuni*

Table I. Aetiology of travellers' diarrhoea. Figures given as percentages [median (range)]

Pathogen	1974-1987[a]			1988-1997		
	Latin America	Asia	Africa	Latin America[b]	Asia[c]	Africa[d]
Enterotoxigenic *Escherichia coli*	42 (26-72)	16 (0-37)	36 (33-71)	18 (11-32)	17 (6-32)	31 (25-57)
Shigella spp.	8 (0-30)	0 (0-13)	0 (0-15)	8 (2-30)	5 (4-19)	2 (0-9)
Salmonella spp.	1 (0-16)	4 (0-33)	0	2 (0.6-4)	10 (2-18)	3 (2-22)
Campylobacter jejuni	ND	12 (1-17)	ND	3 (0.6-5)	21 (0.5-58)	1.4 (0-21)
Rotavirus	4 (0-36)	0	0	3 (0-6)	1.5 (0-7)	2 (0-8)
No agents	48 (22-82)	68 (43-94)	53 (29-64)	48 (37-60)	50 (19-66)	47 (37-57)

a Black,[6] Echeverria et al.,[7] Taylor et al.[8,9]

b Ericsson et al.,[10,11,14] DuPont et al.,[12] Bourgeois et al.[13]

c Adkins & Merrell,[15] Hyams et al.,[16] Petrucelli et al.,[17] Kuschner et al.[18]

d Bourgeois et al.,[13] Taylor et al.,[19] Haberberger et al.,[20] Haberberger & Scott,[21] Mattila et al.,[22] Gascon et al.,[23] Steffen et al.[24]

ND = not determined.

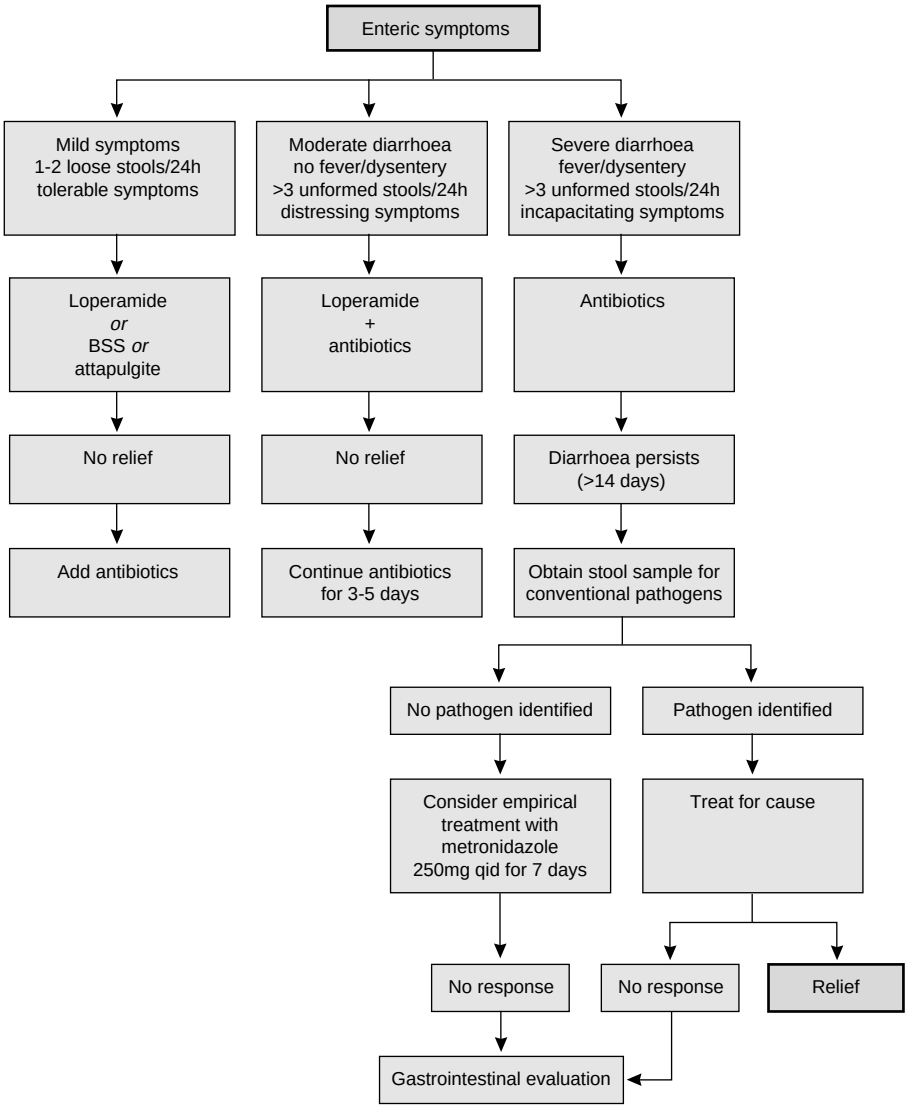

Fig. 1. Suggested approach to the empirical treatment of traveller's diarrhoea. See table II for drug selection and dosage. **BSS** = bismuth salicylate (bismuth subsalicylate); **qid** = 4 times daily.

occurs more frequently in Thailand and during winter time in Mexico and Morocco. Viral enteropathogens such as rotavirus and less often Norwalk-like virus have been associated with acute disease and may be responsible for as much as 10% of the cases of gastroenteritis seen in international travellers.[13]

Parasites can also cause travellers' diarrhoea, but most commonly they are associated with persistent diarrhoea.[25] *Giardia lamblia* or *Cyclospora* should be considered in visitors returning from Nepal, while *Giardia* and *Cryptosporidium* are common causes of diarrhoea during travel to St Petersburg, in Russia. Overall, no organisms are

identified in approximately 50% of the patients with acute travellers' diarrhoea. However, a good number of these cases respond to empirical antibacterial therapy, providing indirect evidence that bacterial pathogens are responsible for the illness.

3. Treatment

Travellers' diarrhoea *per se* is not a severe or life-threatening disease; thus, the reason for employing a treatment regimen such as an antibiotic is to attenuate the severity and duration of diarrhoea, and to minimise the time lost due to the affliction.

Self-treatment for travellers' diarrhoea has become a very effective option for most patients. Before departure, travellers to high risk areas should be provided with an antibiotic (normally a quinolone) for 3 to 5 days of treatment, loperamide for up to 2 days, and possibly a thermometer. Prepacked oral rehydration solutions are advisable for tourists visiting high risk unpopulated areas without a known 'safe' water supply, or for infants, pregnant women and frail elderly people. If diarrhoea develops, the patient should be able to evaluate the severity of the illness using a clinical algorithm (fig. 1).

Guidelines for therapy may follow the clinical severity of the illness. Symptomatic relief for mild disease (no change in itinerary required) can be accomplished with the use of loperamide, attapulgite or bismuth salicylate (bismuth subsalicylate); however, loperamide is probably the most effective nonspecific agent available.[26] Zaldaride (zaldaride maleate), an intestinal calmodulin inhibitor, not yet licensed, has been shown to be as effective as loperamide in improving diarrhoea.[27] If conditions do not improve with loperamide treatment, patients should be encouraged to take an antimicrobial.

Combination therapy using a single dose of an antimicrobial agent together with loperamide has proven more efficacious than either agent alone in the treatment of moderate diarrhoea (as defined in

Table II. Drugs for the treatment of travellers' diarrhoea

Drug	Dose (mg)	Comments
Quinolones		Safety in children and pregnant women not established
ciprofloxacin	750 SD *or* 500 PO bid × 3 days	
ofloxacin	400 SD *or* 200 PO bid × 3 days	
norfloxacin	800 SD *or* 400 PO bid × 3 days	
fleroxacin	400 SD *or* 200 PO od × 3 days	
Cotrimoxazole (trimethoprim/sulfamethoxazole)	2 double strength tablets SD (320 TMP/1600 SMX) *or* 1 double strength tablet bid × 3 days (160 TMP/800 SMX) Children: 5 TMP/kg + 25 SMX/kg bid × 3 days	Use is limited because of widespread drug resistance and lack of coverage for *Campylobacter*
Azithromycin	500 PO od × 3 days	Alternative to quinolones in areas where quinolone-resistant *Campylobacter* spp. are prevalent (e.g. Thailand)
Loperamide	4mg initially, then 2mg after each unformed stool, not to exceed 8 mg/day; to be used < 48 hrs	Should not normally be employed in febrile dysenteric disease
Bismuth salicylate (bismuth subsalicylate)	524mg (2 tablets, or 30ml of 262mg/15ml liquid) PO every 30 min × 8 doses; to be used <48h	Stains tongue and stools black, contraindicated in patients with aspirin (acetylsalicylic acid) allergy
Attapulgite	3g initially, then 3g after each unformed stool *or* every 2h (whichever comes first) for a total of 9 g/day; to be used <48h	Nonabsorbed, well tolerated during pregnancy
Zaldaride (zaldaride maleate)	2 × 20 initially, then 3 doses of 20 on the first day and 4 doses of 20 on the second day	Not currently licensed

bid = twice daily; **od** = once daily; **PO** = oral; **SD** = single dose; **SMX** = sulfamethoxazole; **TMP** = trimethoprim.

fig. 1). Antibiotics have thus become important tools in the management of travellers' diarrhoea. Patients with a temperature of >38.5°C, or when they are passing bloody stools, should not receive antimotility agents to prevent the rare potentiation of illness by an invasive pathogen. A previous study has demonstrated clinical worsening of illness in shigellosis when an antimotility agent, diphenoxylate, was employed.[28] In another study of patients infected with *Salmonella* and *Shigella*, loperamide, when combined with ciprofloxacin, did not worsen the diarrhoea, suggesting that the potentiation of invasive diarrhoea by antimotility agents might not occur when an effective antimicrobial is also given.[19]

Table II lists drugs, doses and suggestions for the therapy of travellers' diarrhoea. Quinolones are now the drugs of choice for the empirical treatment of this entity. Ciprofloxacin has been shown to decrease the duration of diarrhoea to approximately 1 episode per day, relieve associated symptoms (abdominal cramps) and minimise the number of liquid stools passed.[29] In areas where quinolone-resistant *C. jejuni* has been found, such as Thailand, azithromycin may be an effective option for therapy with which microbiological eradication and clinical response may be seen.[18] Patients who are still passing unformed stools on day 2 after a single large dose of an antimicrobial should continue to take the same drug in its usual dose for 3 to 5 days. A minority of individuals will not improve with 3 to 5 days of adequate empirical treatment. Drug resistance or a nonbacterial illness (caused by parasites or viruses) should be considered in these cases.

3.1 Fluids and Electrolytes

The majority of patients with acute travellers' diarrhoea do not become dehydrated. Carbonated flavoured beverages (containing sugar), hot drinks and dietary sources of salt (such as crackers or soups) are enough for fluid and electrolyte replacement. However, infants, pregnant women and the frail elderly are at higher risk of dehydration. For these groups, oral rehydration solutions should be provided before travelling.

4. Special Situations

4.1 Management of Persistent Diarrhoea

Close to 3% of travellers to developing countries will acquire persistent diarrhoea (diarrhoea lasting ≥14 days) and 1 to 2% will have diarrhoea for ≥30 days.[25] There are numerous potential aetiologies of persistent diarrhoea and the investigation may be complex. It is pertinent to consider parasites, since these pathogens frequently cause persistent illness. Among them, *G. lamblia*, *C. parvum*, *Isospora belli* and *Cyclospora* have been found to produce prolonged diarrhoea. Table III shows a list of possible infectious and noninfec-

Table III. Causes of persistent diarrhoea

Infectious causes	Miscellaneous causes
Parasites	Small bowel bacterial overgrowth
Most common	Lactase deficiency
Giardia lamblia	Tropical sprue
Cryptosporidium parvum	Brainerd diarrhoea
Isospora belli	**Undiagnosed gastrointestinal diseases**
Cyclospora cayetanensis	Diverticulitis
Less common	Irritable bowel syndrome
Entamoeba histolytica	Inflammatory bowel disease
Dientamoeba fragilis	Colorectal carcinoma
Strongyloides stercoralis	Whipple's disease
Capillaria philippinensis	**Drugs**
Fasciolopsis buski	Laxatives
Trichuris trichiura	Methyldopa
Schistosoma spp.	Thyroid hormones
Sarcocystis spp.	Local herbal medications
Balantidium coli	Alcohol (ethanol)
Bacterial pathogens	
Escherichia coli	
enterotoxigenic (ETEC)	
enteropathogenic (EPEC)	
enterohaemorrhagic (EHEC)	
Shigella spp.	
Aeromonas spp.	
Campylobacter jejuni	
Clostridium difficile	
Salmonella spp.	
Plesiomonas shigelloides	

Table IV. Recommended treatment of parasitic infections associated with persistent diarrhoea

Parasite	Recommended treatment
Most common	
Giardia lamblia	Metronidazole 250mg PO tid for 7 days *or* tinidazole 1.5-2g PO SD, *or* quinacrine hydrochloride 100mg tid after meals × 7 days (not available in US), or furazolidone 5 mg/kg/day in 4 doses/day × 7 days (for children)
Cryptosporidium parvum	No effective agent available
Isospora belli	Cotrimoxazole (trimethoprim/sulfamethoxazole) 1 double strength tablet (160/800mg) qid PO× 10 days, then bid × 3wk
Cyclospora cayetanensis	Cotrimoxazole 1 double strength tablet (160/800mg) PO bid × 7 days
Less common	
Entamoeba histolytica	Paromomycin 500mg PO tid × 7 days *or* di-iodohydroxyquinolone (iodoquinol) 650mg PO tid × 20 days plus metronidazole 750mg tid × 5 days
Dientamoeba fragilis	Iodoquinol 650mg PO tid × 20 days *or* tetracycline 500mg PO qid × 10 days
Strongyloides stercoralis	Albendazole 400mg PO × 3 days *or* thiabendazole 25mg/kg PO bid × 2 days *or* ivermectin 200μg/kg/day × 2 days
Trichuris trichiura	Albendazole 400mg po SD

bid = twice daily; **PO** = oral; **qid** = 4 times daily; **SD** = single dose; **tid** = 3 times daily.

tious causes of persistent diarrhoea. As shown in the algorithm (fig. 1), a stool sample for conventional pathogens should be obtained and the patient should receive specific treatment depending upon the results of culture. Empirical antimicrobial therapy is indicated in all those with moderate or severe diarrhoea. If a stool sample does not reveal an organism or if the patient cannot find medical assistance, and clinical response to the antibacterial drug is not seen, a trial of empirical metronidazole could be an option. Patients who continue with diarrhoea despite metronidazole treatment will need a gastrointestinal evaluation.

Table IV shows recommended antiparasitic regimens depending upon the organism identified.

5. HIV and Travel

The 1997 US Public Health Service/Infectious Diseases Society of America (USPHS/IDSA) guidelines for prevention of opportunistic infections in individuals with HIV states that antimicrobial prophylaxis for travellers' diarrhoea is not routinely advocated for HIV-positive patients travelling to high risk areas.[30] All HIV-infected travellers to developing countries should carry a supply of an antimicrobial agent to be taken empirically should diarrhoea occur, e.g. ciprofloxacin 500mg twice daily for 3 to 5 days. The same recommendation regarding food and water handling applies to HIV-positive and HIV-negative individuals. Care must be taken with food and beverages consumed. HIV/AIDS patients may have unusual manifestations of common enteric diseases (e.g. a higher incidence of bacteraemia with *Salmonella* or *Campylobacter*).

6. Pregnancy and Travel

Unnecessary travel to high risk territories for pregnant women should be discouraged. Diarrhoea may be a serious problem to a pregnant woman; therefore, there is a need to be extremely prudent with beverage and food consumption practices. If diarrhoea commences, the patient should maintain good hydration preferably with the use of oral rehydration therapy. The only antidiarrhoeal agents permitted during pregnancy are the nonabsorbed drugs such as attapulgite.[31] Sulphonamides, trimethoprim and quinolones, as well as bismuth salicylate, are contraindicated during pregnancy.[32]

7. Prevention

Education is an important step in preventing the disease. Pretravel advice should be given to the voyager. The old adage 'boil it, cook it, peel it or

forget it' still remains applicable. In one Swiss study, the incidence of diarrhoea was significantly dependent on the number of dietary mistakes made.[33] Here, 17 possible mistakes were identified among the travellers, including consumption of uncooked food, fruits which could not be peeled and unbottled cold drinks. The incidence of travellers' diarrhoea associated with 1 or 2 mistakes was about 15% and with >10 mistakes the rate of illness was 25%. An unresolved issue is how to motivate travellers to follow these strict dietary restrictions. Simple, prudent instructions include food served steaming hot [160°F (>65°C)], dry items such as bread, foods with high sugar content (syrups, jellies), citrus fruits (low pH), and carbonated or steamy hot beverages.

8. Antimicrobial Prophylaxis

The use of antimicrobial agents for prophylaxis may merit consideration in individuals with an underlying medical condition such as active inflammatory bowel disease, type 1 (insulin-dependent) diabetes, heart failure in the elderly, and achlorhydric states. Prophylaxis should also be contemplated in travellers unwilling to lose 6 to 10 hours during an important short term trip due to illness, and some would use prophylaxis in tourists requesting it although that is controversial.

The benefits of prophylaxis must be weighed against the advantages of empirical therapy begun early in the course of diarrhoea. Prophylactic antibiotics may give travellers a false sense of protection from the hazards associated with eating particular local foods and beverages. Prophylaxis probably should not be used when the period of risk exceeds 3 weeks. Known problems associated with antimicrobial prophylaxis include: occurrence of candida vaginitis or *Clostridium difficile*–associated diarrhoea, emergence of resistance by body flora or the development of photosensitivity reactions, rashes and severe reactions such as Stevens-Johnson syndrome or anaphylaxis.

When antimicrobials are used in prophylaxis, they are taken daily as a single dose while in the area at risk, and for a day or two after leaving the region, in half the therapeutic dosage. Protection rates with ciprofloxacin given at a dosage of 500mg once daily have reached as high as 95%.[34] Table V shows the dosage of different preventive regimens.

Table V. Prophylactic regimens for the treatment of travellers' diarrhoea

Drug	Dosage	Protection rate (%)
Lactobacillus GC	1 capsule daily	47
Cotrimoxazole (trimethoprim/ sulfamethoxazole	1 double strength tablet daily	70-80
Fluoroquinolones		90
norfloxacin	400 mg/day	
ciprofloxacin	500 mg/day	
ofloxacin	300 mg/day	
Bismuth salicylate (bismuth subsalicylate)	2 × 262mg tablets, chewed with meals and at bed time (8 tablets/day)	62

9. Future Directions

9.1 Vaccines

Bacterial pathogens, mainly ETEC, are still a major source of travellers' diarrhoea. Immunoprevention for the most frequent organism could significantly decrease the number of cases of illness. A vaccine against ETEC is entering phase III trials. The vaccine is a killed whole-cell ETEC containing the colonisation fimbriae of prevalent organisms plus the binding subunit of closely related cholera toxin. It is taken as 2 oral doses at least 1 week before travel.[35,36]

9.2 Medications

Nonabsorbed agents are highly successful in treating travellers' diarrhoea. They are favoured because of their better adverse effect profile and their tolerability in children and pregnancy.

Aztreonam[11] and bicozamycin[37] have been shown to be effective in the treatment of travellers' diarrhoea, but they are not available for use. Rifaximin is being tested in clinical trials.[38]

Novel antisecretory drugs such as zaldaride are being developed for symptomatic treatment of travellers' diarrhoea.[39] This agent was effective, well tolerated and did not produce detectable post-treatment constipation.

10. Conclusion

Developing countries still interested in tourism will need to improve food hygiene and the quality of local water in order to entice people to visit those regions without the fear of the development of diarrhoea or other illnesses. An excellent and inexpensive reference for physicians caring for patients with travellers' diarrhoea and other travellers-related problems is available through the internet from the CDC website (http://www.cdc.gov).

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