Leading Article

Travellers' diarrhoea: slow but steady progress*

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Travellers' diarrhoea (TD) is one of the world's most common disease entities; only very rarely is it associated with mortality (usually in the already debilitated, or at the extremes of life), but the significant morbidity with which it is associated not infrequently interferes with a crowded schedule or with a leisure or sporting activity.^{1–5} Numerous titles have been applied to this clinical syndrome, including 'tourista', 'Montezuma's revenge', 'Hong Kong dog' and 'Delhi belly'.¹ One estimate is that 12 million individuals travel annually from an industrialized ('western') country to one in the tropics or subtropics;⁶ the incidence of TD varies in this group from around 20 to 50%. There is a very significant geographical variation in prevalence. High-risk areas include:⁷ north Africa, sub-Saharan Africa, the Indian subcontinent, southeast Asia, southern America, Mexico and the Middle East; intermediate risk areas include: the north Mediterranean, Canary Islands and the Caribbean islands; and low-risk areas include: North America, western Europe⁸ and Australia. In a retrospective study carried out in Switzerland, a large group of travellers was given a questionnaire following foreign travel;⁷ incidence of the disease varied greatly, the highest figure (50%) being associated with travel to Tunisia. There is no detailed study of TD acquired in a European country.⁸

The disease tends to become less common with advancing years; it is unclear whether this is due to the fact that older travellers (≥ 60 years) have a more discerning lifestyle, or whether relative immunity ensues with increasing age.^{3,7} There is limited evidence that individuals who have lived for long periods of time in areas where TD is common, tend to experience TD less frequently than those who have not previously been exposed to it.^{3,4}

Clinical features

TD is invariably contracted by ingestion of contaminated water/food and is characterized by an acute onset of watery diarrhoea (usually of small-intestinal origin); when colorectal involvement exists, diarrhoea may be bloody. Abdominal colic, nausea and vomiting may also be present;^{1–4} fever is an unusual sequel, being recorded in 1–10% of infected individuals. Prostration and resultant dehydration (with electrolyte imbalance) can cause major problems in a severe case. Rarely, symptoms become chronic, and it seems likely that a small proportion of cases of TD predispose to tropical sprue.⁹ This disease has clear geographic predilections and it seems possible that this is resultant upon the pathogenicity of one or more of the predominant environmental microorganisms in that geographical location. Unfortunately for the investigator, by the time sprue has become clinically overt, the initiating infection(s) has invariably been cleared from the gastrointestinal tract. Chronic diarrhoea of lesser severity is a relatively common problem following recovery from the acute disease and this can usually be attributed to: (i) tropical enteropathy (in which there is minor derangement of enterocyte structure and function), and/or (ii) the irritable bowel syndrome.

On clinical grounds, an important differential diagnosis of TD is inflammatory bowel disease presenting for the first time during tropical exposure.^{10,11} In a retrospective review of UK residents presenting to the Hospital for Tropical Diseases, London, with acute 'bloody diarrhoea' in relation to a visit to the tropics the majority had inflammatory bowel disease (usually ulcerative colitis), a number which exceeded those for shigellosis and amoebic colitis.¹⁰

Acute disease can proceed along an especially 'virulent' course in certain high-risk groups:^{3,4,7} individuals suffering from achlorhydria (*Salmonella* sp. and *Vibrio* sp. infections are also known to be significantly more common in this group), patients suffering from known inflammatory bowel disease, those who have experienced gastrointestinal tract surgery or suffer from a malignancy of the gastrointestinal tract, those suffering from

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acquired or congenital immunodeficiency, others receiving immunosuppressive therapy, and HIV/AIDS patients. In addition, those receiving diuretics, in whom maintenance of electrolyte balance is precarious, and those at the extremes of life also fall within the high-risk group. It is particularly important to take these factors into account when advising on chemoprophylaxis (see below).⁷

Aetiology

Twenty-five years ago the aetiology of TD was undetermined. In 1970, Rowe *et al.*¹² recorded results of a study involving British soldiers newly arrived at Aden. In 19 (54.3%) out of 33 cases in which a known pathogen could not be isolated, a new serotype of *Escherichia coli* was isolated in the acute phase of TD; in a further 14 (40%), a number of different *E. coli* serotypes were also isolated. (B.H. Kean had suggested in the 1950s (on circumstantial evidence) that bacterial pathogens were implicated.^{3,4,12}) Sack *et al.*¹³ have recently recorded the identity of *E. coli* serotypes isolated from US Peace Corps volunteers serving in various countries. In Kenya, 06:H16, 06:H⁻, 027:H7, 0159:H4 and 0159:H34 were present, whilst in Morocco they isolated 06:H16, 0128:H12, 027:H20 and 0169:H⁻; in Honduras, however, the following were recorded: 08:H9, 015:H49, 015:H⁻ and 027:H20. Therefore, many common enterotoxigenic *E. coli* (ETEC)¹⁴ are involved in TD. There is, however, no doubt that many other microorganisms can also be involved.^{4-6,8} *Salmonella* sp., *Shigella* sp., *Campylobacter jejuni*, enteroadherent *E. coli*⁵ and *Vibrio* sp. (bacterial); rota- and Norwalk (viruses), and *Giardia lamblia*, *Coccidia* sp. and *Entamoeba histolytica* (protozoan parasites). Other bacteria which have been implicated include: *Aeromonas hydrophila*, *Plesiomonas shigelloides*,⁶ and *Yersinia enterocolitica*. There is clear evidence that the likely causative agent varies significantly in different geographical locations; for example, the causative organisms in an affected individual in Asia, Central America and Africa are different on probability grounds, although this is not relevant to a specific case.^{4,6,7} Furthermore, more than one organism is frequently present.⁴ In a study involving US Peace Corps workers in Thailand, 33% of infected individuals had 2–4 different pathogens present. Although protozoan parasites are usually incorporated in the list of aetiological agents of TD, the incubation period is usually somewhat longer than is usual for this clinical syndrome, and this applies especially to *G. lamblia*. When the colorectum is predominantly involved, *Shigella* sp., enteroinvasive *E. coli* and enterohaemorrhagic *E. coli* may be responsible, and in addition *Entamoeba his-*

tolytica. Rarely, *Herpes simplex* and *Chlamydia trachomatis* have been implicated. It is, of course, likely that new pathogens will emerge in future years.

Pathophysiology

The pathophysiology of TD varies and depends on the site of the gastrointestinal tract involved. Whereas in the small-intestine toxigenic diarrhoeas predominate, in the colorectum invasive disease is more common. In the context of chemoprophylaxis, it is essential to appreciate that the range of responsible organisms is very broad, ranging from bacteria and viruses (see above) to protozoan parasites, including *Cryptosporidium* sp., *Isospora belli* and *Blastocystis hominis*.

ETEC are characterized by both toxin production and mucosal adherence via specific fimbriae,¹⁵ the latter property is necessary for disease production because toxin-producing non-adherent mutants fail to trigger disease. Enteropathogenic *E. coli* adhere to intestinal mucosal cells, and although they do not invade them, destroy their microvilli; they are probably not a major cause of TD. Enteroadherent *E. coli* (detected in 15% of patients suffering from TD in one study¹⁵) do not belong to classical serotypes of enteropathogenic *E. coli*, but adhere to Hep 2 cells in culture; they neither produce a toxin nor invade. Enteroinvasive *E. coli* behave in a manner similar to *Shigella* sp. and account for up to 5% of TD cases. Their main site of action is the colorectum and the major clinical manifestation is therefore dysentery resulting from epithelial cell invasion, intracellular multiplication, and with resultant mucosal inflammation and ulceration.¹⁵ Enterohaemorrhagic *E. coli* produce disease via verotoxin production; they are an uncommon cause of TD.

Prophylaxis

In prophylaxis, every traveller should take maximal care to avoid ingestion of water/food which is likely to be contaminated; common sense is of paramount importance! Use of prophylactic agents is controversial.¹⁻⁵ Wiström and Norrby⁷ have summarized several studies involving chemoprophylaxis; different trials involved several different geographical locations. Doxycycline, co-trimoxazole, trimethoprim, mecillinam, bicazamycin and the fluoroquinolone compounds (norfloxacin and ciprofloxacin) have all been used. High protection rates ($\geq 90\%$) have been claimed for co-trimoxazole and the fluoroquinolones; for trimethoprim a rate of around 50% has been recorded. These studies therefore clearly confirm

that on statistical grounds the greatest number of cases of TD have a bacterial aetiology as their basis. The major problem with antibiotic chemoprophylaxis, however, is the risk of significant side effects, which are dominated by dermatological reactions, including the Stevens–Johnson syndrome⁷ and pseudomembranous colitis; with cotrimoxazole a rate of 20% of significant skin reactions has been recorded, necessitating discontinuation of prophylaxis. Also, the acquisition of resistant faecal *E. coli* during chemoprophylaxis has been recorded in several studies;⁷ although data are frequently incomplete, an increase from 21% to 100% has been recorded using doxycycline in Kenya, and one of 3% to 100%, using cotrimoxazole in Mexico.⁷ If chemoprophylaxis is to be used, either norfloxacin or ciprofloxacin seem to be the best agents, although *C. jejuni* strains rapidly acquire resistance.⁸ In one recent study carried out in Egypt, only two out of 105 individuals who took norfloxacin developed TD, compared with 30 (26%) out of 117 given a placebo.¹⁶ Ciprofloxacin should be avoided in children due to experimental evidence that damage to cartilage can occur in young experimental animals; however, there is no current evidence for this in *Homo sapiens*.

Should chemoprophylaxis be widely recommended therefore in what is essentially a benign clinical syndrome? In addition to the objections so far outlined, there is the possibility of producing a false sense of security – leading to an increase in exposure to other infections, for example, viral hepatitis.¹⁵ It is the view of the writer of this review that the following groups should be seriously considered for chemoprophylaxis (but never for more than 3 weeks): travellers with a bad 'track record' of TD,¹⁵ those in whom hypochlorhydria is a reality (or possibility), patients suffering from inflammatory bowel disease, HIV-infected individuals, patients in whom electrolyte balance is precarious (for example, those receiving diuretic therapy) and others with chronic renal failure, the 'elderly' (not easily defined!), and a nebulous group in whom a bout of TD is professionally embarrassing (for example, the armed services, airline pilots, athletes, politicians, businessmen and other professionals on tight schedules, etc).

The role of anti-peristaltic agents used prophylactically is also controversial. Their action is unphysiological, and it has been suggested that they can mask a more serious infection, for example *S. typhi*, although diarrhoea is an unusual presenting symptom in this disease. By delaying excretion of a pathogen(s) it is also possible that they prolong clinical disease. Furthermore, in children, paralytic ileus is a major complication, and this has occasionally given rise to mortality.¹⁷

What is the role of bismuth subsalicylate? The bismuth moiety has antimicrobial activity, whereas

salicylate possesses antisecretory properties.⁴ Early studies in Mexico by DuPont and colleagues³ clearly showed that when given as a suspension (the sheer bulk required precluded its use by travellers with baggage-weight restrictions) this agent significantly reduced the likelihood of TD. In more recent studies, the same group, also working in Mexico, has demonstrated that when given in tablet form (two four-times daily for up to 3 weeks, that is, 2.1 g daily), a 65% protection rate can be achieved.¹⁸ However, at half that dose, efficacy was greatly reduced. The number of cases of pathogen-positive TD in a group of patients treated with bismuth subsalicylate was seven out of 29, compared with 35 out of 59, in a placebo group; ETEC was present in three and 22, respectively, and *Shigella* sp. in two and eight, respectively.¹⁸

What is the status of vaccine development as a protective against TD? A B-subunit/whole-cell cholera vaccine has recently been shown to produce relative protection.¹⁹ In a study involving Finnish tourists to Morocco, this vaccine induced a 52% protection rate against diarrhoea caused by ETEC, 65% protection when the infection was mixed, 71% when the aetiology consisted of a combination of ETEC and another pathogen, and 82% when ETEC and *Salmonella enterica* were present concurrently. Sack has concluded that 'any advances in prevention and treatment of diarrhea in travelers will be directly applicable to the worldwide problem of diarrhea in children, which is far more important on a global scale'.¹³ Clearly, however, this statement does not apply to the present B subunit/whole cell cholera vaccine because protection only lasts for about 3 months. A further approach which is under consideration consists of the oral administration of colostrum-derived antibodies against ETEC.⁴

A recent experimental investigation has indicated that lactobacilli which have the ability to adhere to the intestinal mucosa can prevent *E. coli* colonization. In a limited study, one such preparation, *Lactobacillus* GG, has been shown to reduce the prevalence of TD by up to 40%;⁴ clearly much further work remains to be done!

Chemotherapy?

Treatment of TD depends first and foremost on oral rehydration; all travellers should carry oral rehydration sachets with them. When properly constituted, 'Dioralyte' (Rhône-Poulenc Rorer) solution contains: glucose 90, Na⁺ 60, K⁺ 25, Cl⁻ 45 and citrate 20 mmol/l. Corresponding concentrations for another proprietary preparation 'Rapolyte' (Janssen) are: 111, 60, 20, 50 and 10 mmol/l. The WHO/UNICEF rehydration fluid contains glucose 111, Na⁺ 90, K⁺ 20, Cl⁻ 80 and

citrate 10 mmol/l. However, in a mild case adequate rehydration can usually be achieved using ordinary mineral water. There is not a consensus view regarding the role of chemotherapy in established TD. It is the opinion of the writer of this review that short-course chemotherapy can only be justified in severe cases; this applies particularly at the extremes of life and in high-risk groups (see above), especially HIV-infected individuals.⁵ Early work carried out in Mexico by DuPont and colleagues clearly showed that both co-trimoxazole and trimethoprim reduced the length of symptoms derived from TD.^{4,18} Recent trials, using most of the antibiotics which have been given at various times for chemoprophylaxis (see above), have also indicated that the length of symptoms can be shortened. One of the most recent, also from Mexico, demonstrated that ofloxacin (600 mg daily for 3 days) produced a cure in 77 (95%) out of 81, compared with 56 (71%) out of 79 patients who received a placebo ($P = 0.0001$).²⁰

The future

Recent reports in the lay press have indicated that London's water supplies are heavily contaminated

with microorganisms.²¹ Is the population of London (and perhaps that of other major British cities), therefore, likely to suffer from a higher prevalence of TD in the future? One can perhaps take comfort, for in November 1834 Sidney Smith wrote as follows: 'He who drinks a tumbler of London water has literally in his stomach more animated beings than there are men, women, and children on the face of the globe'. The present situation seems to be considerably better than it was in those days!²²

Although vaccines to combat ETEC will probably become widely available in the future,^{8,19} it seems inconceivable that either a vaccine or any other method to counteract the very broad range of microorganisms accounting for TD will be forthcoming. Therefore, although the traveller should in the future be statistically less likely to experience 'Montezuma's revenge' he/she will never be immune to this clinical syndrome which will continue to be a persisting menace to the more adventurous members of our species.

References

1. Cook, G.C. *Tropical Gastroenterology*. Oxford University Press, Oxford, 1980. pp. 228–229.
2. Farthing, M.J.G. & Keusch, G.T. Global impact and patterns of intestinal infection. In: Farthing, M.J.G. & Keusch, G.T. (eds) *Enteric Infection: Mechanisms, Manifestations and Management*. Chapman & Hall, London, 1989, pp. 3–12.
3. DuPont, H.L. Travelers' diarrhea. In: Gracey, M. (ed.) *Diarrhea*. CRC Press, Boca Raton, 1991, pp. 115–126.
4. Gorbach, S.L. Traveler's diarrhea. In: Gorbach, S.L., Bartlett, J.G. & Blacklow, N.R. (eds) *Infectious Diseases*. W.B. Saunders Co, Philadelphia, London, 1992, pp. 622–628.
5. Okhuysen, P.C. & Ericsson, C.D. Traveler's diarrhea. *Curr Opin Gastroenterol* 1992, **8**: 110–114.
6. Black, R.E. Epidemiology of travelers' diarrhea and relative importance of various pathogens. *Rev Infect Dis* 1990, **12** (Suppl. 1): S73–S79.
7. Wiström, J. & Norrby, R. Antibiotic prophylaxis of travellers' diarrhoea. *Scand J Infect Dis* 1990, Suppl. **70**: 111–129.
8. Ljungh, Å.H. Travellers' diarrhoea and the European tourist. *Eur J Gastroenterol Hepatol* 1992, **4**: 764–770.
9. Cook, G.C. The small intestine and its role in chronic diarrheal disease in the tropics. In: Gracey, M. (ed.) *Diarrhea*. CRC Press, Boca Raton, 1991, pp. 127–162.
10. Harries, A.D., Myers, B. & Cook, G.C. Inflammatory bowel disease: a common cause of bloody diarrhoea in visitors to the tropics. *Br Med J* 1985, **291**: 1686–1687.
11. Schumacher, G., Kollberg, B. & Ljungh, Å. Inflammatory bowel disease presenting as travellers' diarrhoea. *Lancet* 1993, **341**: 241–242.
12. Rowe, B., Taylor, J. & Bettelheim, K.A. An investigation of travellers' diarrhoea. *Lancet* 1970, **i**: 1–5.
13. Sack, R.B. Travelers' diarrhea: microbiologic bases for prevention and treatment. *Rev Infect Dis* 1990, **12** (Suppl. 1): S59–S63.
14. Doyle, M.P. Pathogenic *Escherichia coli*, *Yersinia enterocolitica*, and *Vibrio parahaemolyticus*. In: Waites, W.M. & Arbutnot, J.P. (eds) *Foodborne Illness*. Edward Arnold, London, 1991, pp. 77–85.
15. Tellier, R. & Keystone, J.S. Prevention of traveler's diarrhea. In: Gardner, P. (ed.) *Infectious Disease Clinics of North America: Health Issues of International Travelers*. W.B. Saunders Co, Philadelphia, London, 1992, Vol. 6 (no. 2), pp. 333–354.
16. Scott, D.A., Haberberger, R.L., Thornton, S.A. & Hyams, K.C. Norfloxacin for the prophylaxis of travellers' diarrhea in US military personnel. *Am J Trop Med Hyg* 1990, **42**: 160–164.
17. Bhutta, T.I. & Tahir, K.I. Loperamide poisoning in children. *Lancet* 1990, **335**: 363.
18. DuPont, H.L., Ericsson, C.D., Johnson, P.C. & Cabada, F.J. de la. Use of bismuth subsalicylate for the prevention of travelers' diarrhea. *Rev Infect Dis* 1990, **12** (Suppl. 1): S64–S67.
19. Peltola, H., Siitonen, A., Kyrönseppä, H. *et al.* Prevention of travellers' diarrhoea by oral B-subunit/whole cell cholera vaccine. *Lancet* 1991, **338**: 1285–1289.
20. DuPont, H.L., Ericsson, C.D., Mathewson, J.J. & DuPont, M.W. Five versus three days of ofloxacin therapy for traveler's diarrhea: a placebo-controlled study. *Antimicrob Agents Chemother* 1992, **36**: 87–91.
21. London water: shock report. *Evening Standard (London)*. 1992, 29 July, p. 1.
22. Cook, G.C. Preventive strategies for the avoidance of infectious diarrhoea. In: Gracey, M. & Bouchier, I.A.D. (eds) *Infectious Diarrhoea*. Baillière Tindall, London, 1993 (in press).