Management of the returning traveler with diarrhea

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***Abstract*:** Traveler's diarrhea (TD) strikes 20–60% of travelers visiting developing countries. It occurs shortly after the return and can be distinguished into two categories: acute and persistent TD. Acute TD, mostly caused by bacterial and viral pathogens, is usually mild and self-limited, and deserves empirical symptomatic and/or antibiotic therapy in selected cases. Fluoroquinolones are progressively superseded in this indication by azithromycin, a well tolerated macrolide active against most bacteria responsible for TD, including the quinolone-resistant species of *Campylobacter jejuni* that are now pervasive, especially in Southeast Asia and India. Persistent TD in the returning traveler is much rarer than its acute counterpart and may be associated with three types of causes. Persistent infections, among which *Giardia* and possibly *Entamoeba* predominate, account for a significant proportion of cases. Postinfectious processes represent a second cause and comprise temporary lactose malabsorption and postinfectious irritable bowel syndrome, now considered a major cause of persistent TD. Finally, apparently unrelated chronic diseases causing diarrhea are occasionally unmasked by TD and represent a third type of persistent TD, among which the well established case of incident inflammatory bowel disease poses intriguing pathogenesis questions. This review discusses recent advances in the field and provides practical recommendations for the management of TD in adult, immunocompetent returning travelers.

***Keywords*:** *Campylobacter* infections, colonic diseases, diarrhea, dysentery, functional, inflammatory bowel diseases, travel

Introduction

Travelers visiting developing countries frequently experience acute infectious diarrhea, with an incidence rate for a 2-week stay in the order of 20–60% [Steffen *et al.* 2004; Hill, 2000; Von Sonnenburg *et al.* 2000]. The problem of diarrhea in a returning traveler encompasses two different clinical pictures. In its common acute form, it is merely a case of traveler's diarrhea (TD) that occurs towards the end of the trip or shortly after the return. A less frequent form, persistent diarrhea of the returning traveler, differs markedly from the former in terms of etiology and management, and will be discussed separately. This article deals with the practical aspects of managing diarrhea in the immunocompetent, adult returning traveler, and will leave aside the topic of prophylaxis.

Acute diarrhea in the returning traveler

Epidemiology and clinical features

The incidence of TD varies among various destinations, and the risk is inversely related to the socioeconomic status of the visited countries [Greenwood *et al.* 2008]. The relative risks are higher for southern Asia and India, followed by sub-Saharan Africa and South America. In a broad survey of TD, the standardized incidence rate for a 2-week stay ranged from below 40% (Brazil, Caribbean) to more than 60% (India, Kenya) [Steffen *et al.* 2004].

On the average, TD typically occurs around the fourth or fifth day of stay abroad [Steffen *et al.* 2004]. 'Classical TD' is defined as the voiding of at least three unformed stools per 24 h, with at

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least one accompanying symptom (nausea, vomiting, abdominal cramps or pain, fever, blood in the stool) [Von Sonnenburg *et al.* 2000]. Classical TD is the most frequent form (40–58%) but milder forms are also taken into account in studies.

Although it may cause considerable incapacitation, since approximately one third of patients are unable to pursue planned activities [Steffen, 2005], TD is rarely severe. Slightly fewer than one in four patients voids more than six unformed stools per day, no more than 8.4% has more than ten movements per day, and between 1% and 7% have subjective fever and/or blood in their stool [Steffen *et al.* 2004]. The self-reported mean duration of symptoms is between 61–106 hours. Objective information about the duration of TD may be derived from the placebo arms of randomized controlled trials: in a representative historic study of antibiotics for the treatment of TD, 100% of patients allocated to the placebo arm were in remission after 5 days [Salam *et al.* 1994]. In a survey of 73,630 short-term travelers, 14 were hospitalized and no fatalities were reported [Steffen *et al.* 2004].

Etiology and diagnosis

Global data regarding the etiology of TD [Svenungsson *et al.* 2000; Von Sonnenburg *et al.* 2000; Ansdell and Ericsson, 1999] may be schematically summarized as follows: bacteria predominate clearly, with both types of *Escherichia coli* [entero-hemorragic (EHEC), entero-toxigenic (ETEC)] remaining the most frequently associated pathogens [Jiang *et al.* 2002; Adachi *et al.* 2001]. A third type of *Escherichia coli*, diffusely adherent *E. coli* (DAEC) has been associated with 9% of cases of TD [Vargas *et al.* 1998]. *Campylobacter jejuni*, *Salmonella*, *Shigella* and *Plesiomonas* come next in frequency as bacterial pathogens responsible for TD. Viruses account for up to one-third of cases with noroviruses being the most frequently reported organisms [Chapin *et al.* 2005; Ko *et al.* 2005; Jones *et al.* 2004], and parasitic infections (mostly *Giardia lamblia* and *Entamoeba histolytica*) are less frequent but well-established causes. A significant regional particularity is that of Southeast Asia and India, where the frequency of *Campylobacter* is higher and accounts for up to 64% of cases [Tribble *et al.* 2007].

In about 60% of cases of TD, no infectious pathogens can be isolated from stool using standard methods. Many such cases are probably bacterial, as has been suggested by the results of placebo-controlled therapeutic trials and by the presence of pathogenic ETEC and DAEC genes using PCR in 29% of culture-negative stools from patients with TD acquired in Central America and India [Meraz *et al.* 2008].

The self-limited nature of TD makes it unnecessary to document a specific pathogen in most cases, so that systematic stool cultures are not recommended. Stool cultures may be considered, however, in patients with fever or colitis symptoms, in patients with comorbidities that increase the risk of complications, and in patients with coexisting inflammatory bowel disease. A promising development in the field of microbiologic diagnosis is the possibility to identify specific pathogens using the detection of bacterial or viral DNA in stool samples [Grimes *et al.* 2008; Zlateva *et al.* 2005]. Such methods are still reserved for research purposes but may be adopted in the clinical setting in following years.

Treatment options

Symptomatic therapy. Loperamide, a synthetic opioid, has been approved by the American FDA for use in adults and children older than 2 years, and is the antimotility agent of choice. It appears to be safe in most types of diarrhea, although its use is not recommended when there is gross blood in the stool or a temperature >38.5°C [Hill *et al.* 2006]. In patients with TD, the efficacy of loperamide alone or as an adjunct to antibiotherapy [Riddle *et al.* 2008] is well established. The recommended dosages are a loading dose of 4 mg orally, and then 2 mg after each loose stool, until a maximum of 16 mg per day is reached in adults. The use of loperamide is not recommended in pregnant or lactating women (pregnancy risk category C, risk cannot be ruled out). Loperamide is generally well tolerated but may cause constipation, sometimes with abdominal distension and discomfort.

Antibiotics. Antibiotics have clearly demonstrated effectiveness in reducing the duration and severity of TD, at the price of side effects [Unauthored 2008; De Bruyn *et al.* 2000; Hill *et al.* 2006]. The recommended agents and dosages are summarized in Table 1. The need to balance the advantages and drawbacks of antibiotic treatment when choosing patients who will really benefit from therapy has been stressed by some commentators, who advocate avoiding

Table 1. Recommended antibiotics for the treatment of traveler's diarrhea. Modified from Hill *et al.* [2006].

Agent	Dosage
Fluoroquinolones	
Norfloxacin	400 mg p.o. b.i.d.
Ciprofloxacin	500 mg p.o. b.i.d.
Ofloxacin	200 mg p.o. b.i.d.
Levofloxacin	500 mg p.o. q.d.
Azithromycin	1000 mg p.o. o.d.
Rifaximin	200 mg p.o. t.i.d.

unnecessary exposure to antibiotics in patients whose disease would spontaneously resolve anyway [Genton and D'Acremont, 2007].

Fluoroquinolones are predictably active for empirical therapy in most parts of the world and remain the drugs of first choice. However, important levels of fluoroquinolone resistance progressively develop worldwide over time, reaching 58% for the 1999–2003 period [Ruiz *et al.* 2007], with the edge of quinolone resistance progressing in Southeast Asia, where 93% of *Campylobacter* isolates were found to be ciprofloxacin-resistant [Tribble *et al.* 2007]. Fluoroquinolones are not recommended in pregnant or lactating women (pregnancy risk category C, risk cannot be ruled out) and in children <18 years of age. Their most frequent side effects are gastrointestinal (anorexia, nausea, vomiting and abdominal discomfort), followed in frequency by central nervous system reactions (mild headache, dizziness, insomnia and alterations of mood). Tendinitis, QT prolongation and increases in transaminases may rarely occur.

Azithromycin, a macrolide effective against *Campylobacter* species as well as against most bacterial pathogens that cause TD worldwide, is recommended as a drug of choice for the treatment of TD from any part of the world [Hill *et al.* 2006]. Azithromycin is safe for use in children and pregnant women (pregnancy risk category B, no evidence of risk in humans). Its most frequent side effects are gastrointestinal (chiefly mild nausea), followed by pruritus, rash and an increased risk of vaginitis.

Rifaximin, an oral nonabsorbed antibiotic derived from rifampin, has been approved for the treatment of TD caused by noninvasive *E. coli* in travelers >12 years old. In clinical studies, its efficacy has been similar to that of ciprofloxacin, with less unwanted effects [Dupont *et al.* 2007]. However, rifaximin must not be used for TD associated with fever of blood in the stool, or in TD likely to be caused by *Campylocater jejuni*. Rifaximin must not be used during pregnancy (pregnancy risk category C, risk cannot be ruled out) and in lactating women. Rifaximin has virtually no unwanted effects.

Conduct of therapy

Clinical features are poor predictors of the infective organism [Svenungsson *et al.* 2000], and obtaining stool cultures is unnecessary in most cases, so that therapy must usually be chosen empirically. Considering the benign course of TD, therapeutic abstention or symptomatic treatment may be chosen for mild cases. Fluid replacement with alternating salt and sugar solutions or oral rehydration solutions is, however, indicated in most cases. Antimicrobials can be reserved for more severe cases of classical TD, particularly when fever or bloody stools are present [Al-Abri *et al.* 2005]. In several head-to-head comparisons, single-dose therapy has been shown to have an efficacy equivalent to that of the more classical 3-day course of antibiotics [Ericsson *et al.* 2001, 1997, 1990]. In the absence of firm data on the subject, it is reasonable to choose a single-dose course of antibiotics in patients with moderate symptoms and no fever or blood in the stool, and to reserve 3-day therapy regimens for more severe cases. No specific treatment option has been tested for virus-associated cases of TD.

Persistent diarrhea in the returning traveler

Persistence of diarrhea after acute TD is infrequent: in two large studies of TD, less than 2% of patients with TD went on to chronic diarrhea lasting more than a month [Addiss *et al.* 1990; Steffen *et al.* 1987]. Whereas persistent TD was traditionally considered as pertaining to infectious causes [Dupont and Capsuto, 1996], two other disease categories account for a growing number of recognized cases: postinfectious processes, and unveiling of an underlying chronic condition.

Intestinal infections

The principal infectious causes of persistent TD are mentioned in Table 2. Cases of persistent diarrhea have been described in association with most bacteria responsible for TD (*Escherichia coli, Shigella, Campylobacter, Aeromonas hydrophila*). In current practice however, bacteria rarely account for diarrhea lasting for more than 2 weeks, with the notable exception of

Table 2. Principal enteric pathogens associated with infectious causes of persistent traveler's diarrhea. In each column, names are printed in decreasing order of frequency.

Bacteria	Protozoa	Helminths
Clostridium difficile	*Giardia lamblia*	*Ascaris lumbricoides*
Camplylobacter jejuni	*Entamoeba histolytica*	*Enterobius vermicularis*
Salmonella spp	*Cryptosporidium parvum*	*Strongyloides stercoralis*
Shigella spp	*Cyclospora cayetanensis*	
Aeromonas hydrophila	*Histoplasma capsulatum*	
Mycobacteria	*Leishmania donovani*	

postantibiotic *Clostridium difficile* colitis, which may follow a common case of antibiotic-treated TD [Norman *et al.* 2008] and persist for several weeks.

The most frequent infectious causes of persistent TD are represented by protozoa infections [Goodgame, 2003; Okhuysen, 2001], mostly *Giardia lamblia, Cryptosporidium parvum*, and an 'emerging' protozoa, *Cyclospora cayetanensis* [Herwaldt, 2000; Ortega *et al.* 1993]. *Isospora belli* and *Cryptosporidium parvum* have been occasionally reported but are rare in immunocompetent patients.

The diagnosis of intestinal giardiasis traditionally relied on the stool 'ova and parasites' (O&P) microscopic examination; that is, the direct observation of cysts or trophozoites in three separate fresh stool samples. However, this method tends to be superseded by various immunoassays, some of which are enzyme-linked, that compare favorably with the stool O&P examination in terms of sensitivity and specificity [Aziz *et al.* 2001]. The diagnosis of giardiasis by detection of trophozoites and cysts in duodenal biopsies is more invasive, and unnecessary in many cases. Small bowel biopsies of patients with giardiasis can reveal a range of pathologic findings, but usually no histopathologic abnormalities are identified [Oberhuber *et al.* 1997]. The recommended treatment for giardiasis is oral metronidazole 250 p.o. t.i.d. for 5 days, or tinidazole 2 g in a unique dose [Gardner and Hill, 2001].

Amoebae (*Entamoeba histolytica*) are a classical cause of long-lasting colitis acquired in tropical areas, typically associated with a dysenteric syndrome (voiding of mucus and blood with little or no stool, abdominal pain, rectal syndrome). However, the general medical judgment regarding intestinal amebiasis has markedly changed since newer diagnostic tests have allowed to distinguish easily truly pathogenic amoebae (*Entamoeba histolytica*) from nonpathogenic amoebae (*Entamoeba dispar* and *Entamoeba moshkovskii*), which are undistinguishable by visual microscopy. Whereas the reality of 'true' amoebic colitis is undisputed, it is likely that many cases of unrelated digestive symptoms have been falsely attributed to amebiasis in the past, on the basis of nonpathogenic amoebae having been found in the stool. Commentators have seriously challenged the notion that any clinical picture of nondysenteric colitis could really be attributed to amebiasis at all [Anand *et al.* 1997]. It is likely that the true frequency of amebiasis as an etiology for persistent TD has been overestimated.

Direct examination of stool has a relatively poor sensitivity for the diagnosis of intestinal amebiasis and does not allow for distinction between pathogenic and nonpathogenic amoebae. Antigen stool test has demonstrated a good sensitivity for the presence of amoebae and allows to tell apart the various types [Haque *et al.* 1998]. Although probably less sensitive than stool antigen testing, serology may be useful for diagnosing of amebiasis. Infection with *Entamoeba histolytica* results in the development of antibodies, while digestive colonization by *Entamoeba dispar* infection does not. Antibodies will usually be detectable within 5–7 days of acute infection and may persist for years. The treatment of invasive amoebic colitis relies on metronidazole (500–750 mg p.o. t.i.d. for 7–10 days), which offers a cure rate of approximately 90% [Li and Stanley, 1996].

Intestinal helminths (chiefly *Ascaris*, *Enterobius* and *Strongyloides*) are rare causes of diarrhea [MacPherson, 1999]. Rare cases of persistent TD have been described in association with intestinal tuberculosis, atypical mycobacteria, leischmaniasis and intestinal histoplasmosis [Goulet *et al.* 2005]. Tropical sprue, a condition of uncertain origin associated with diarrhea, malabsorption and variable duodenal villous atrophy [Lo *et al.* 2007; Walker, 2003], is usually

observed in residents of tropical areas but has been rarely described in returning travelers [Macaigne *et al.* 2004].

Postinfectious processes

These follow an episode of infectious diarrhea but are not caused by the persistence of microbiologic agents in the digestive system. Temporary lactose malabsorption directly results from damage to the intestinal mucosa and is a frequent consequence of bacterial or viral gastroenteritis. The ingestion of lactose in subjects without lactase activity may cause abdominal bloating and, less frequently, diarrhea [Beyerlein *et al.* 2008]. However, the problem should not last more than a few days after resolution of the initial diarrhea. When evaluating patients with suspected symptomatic lactose malabsorption, clinicians should carefully review the relationship between the alleged symptoms and the amounts of ingested lactose. Indeed, the physiologic threshold of ingestion for the appearance of lactose-related symptoms is over 240 ml of cow's milk (or 12 g of lactose – cow's milk contains 5% lactose) in subjects with complete alactasia, as has been demonstrated in a blinded, crossover study [Suarez *et al.* 1995]. Thus, in otherwise normal adults (i.e. without gastrectomy or conditions associated with shortening of the bowel), symptoms appearing after the ingestion of smaller amounts of milk are probably unrelated to lactose malabsorption.

Post-infectious irritable bowel syndrome (PI-IBS). The fact that functional bowel disorder occasionally supervenes on an episode of acute, infectious diarrhea has been known for decades [Chaudhary and Truelove, 1962] and has received substantial documentation in recent years [Dupont, 2008; Thabane *et al.* 2007]. The data collected so far suggest that PI-IBS is relatively common, and probably accounts for most cases of persistent diarrhea in the returning traveler [Connor, 2005]. The reported incidence of PI-IBS following an enteric infection is 4–32%, with typical irritable bowel syndrome according to the Rome III criteria being the predominant observed form. PI-IBS may follow acute diarrhea caused by bacteria as well as viruses [Marshall *et al.* 2007], protozoa [Dizdar *et al.* 2007] and helminths [Soyturk *et al.* 2007], and has been reported after TD [Stermer *et al.* 2006; Okhuysen *et al.* 2004; Ilnyckyj *et al.* 2003]. Risk factors for the appearance of PI-IBS have been recently reviewed [Spiller and Garsed, 2009] and include the duration of the initial illness, tobacco smoking, female sex, depression, hypochondriasis and adverse life events in the preceding 3 months. No clear-cut risk factor pertaining to the infectious agent has been consistently found. In one retrospective study, the risk of PI-IBS after *Campylobacter jejuni* infections was significantly higher than that associated with *Salmonella* spp. [Neal *et al.* 1997]. Standard biologic, endoscopic and histologic studies are normal in patients with PI-IBS, as they are in patients with IBS. However, the pathogenesis PI-IBS may involve a 'micro-inflammatory' process, since several subtle inflammatory abnormalities have been demonstrated in the digestive mucosa of patients with PI-IBS, namely an increased number of lymphocytes and serotonin-producing enterochromaffin cells [Dunlop *et al.* 2003; Spiller *et al.* 2000], IL-1β [Gwee *et al.* 2003] and an increased intestinal permeability [Marshall *et al.* 2004]. Furthermore, visceral hypersensitivity and abnormalities of serotonin metabolism have been demonstrated in animal model of PI-IBS [Keating *et al.* 2008; Bercik *et al.* 2004]. So far, no specific prevention and therapy for PI-IBS are available and its management is similar to that of 'sporadic' IBS [Dalrymple and Bullock, 2008; Spiller *et al.* 2007]. Of particular interest is the efficacy of probiotics to treat symptoms of sporadic IBS, as has been recently demonstrated in two well-designed randomized controlled trials of *Bifidobacterium infantis 35624* [Brenner *et al.* 2009; Whorwell *et al.* 2006; O'Mahony *et al.* 2005].

Unveiling of a chronic condition

Not infrequently, an apparently unrelated chronic condition causing diarrhea appears in the aftermath of an acute gastroenteritis, a typical example of which is the discovery of celiac disease during the work-up of a case of persistent TD [Landzberg *et al.* 2005]. Whether true causality or mere coincidence is at work in such cases is uncertain. In most cases, the true nature of the association between the two diseases pertains to the common medical circumstance that preclinical, silent diseases often become apparent after the affected organ is submitted to some kind of stress. The management of unexplained, persistent diarrhea in a returning traveler should include a basic diagnostic work-up directed at the causes of chronic diarrhea, a matter that has been extensively reviewed elsewhere [Schiller, 2004]. A special mention, however, is deserved by the case of inflammatory bowel disease (IBD).

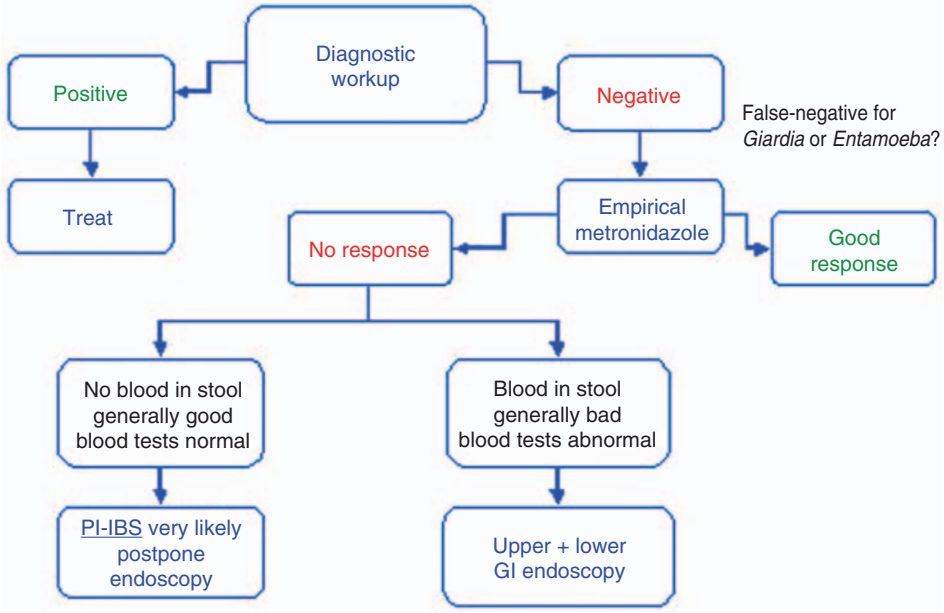

Figure 1. Basic management algorithm for patients with persistent traveler's diarrhea. See text for the details of the diagnostic work-up. PI-IBS, post-infectious irritable bowel syndrome.

Indeed, the finding of overt IBD supervening on a case of acute, infectious diarrhea is classical, and this phenomenon has been substantiated in retrospective studies [Porter *et al.* 2008; Garcia Rodriguez *et al.* 2006]. The existence and potential nature of a causal relationship between the acute infection and the IBD in such cases is uncertain [Irving and Gibson, 2008]. Finally, rare occurrences of factitious digestive parasitosis linked to psychiatric conditions, such as the Munchhausen syndrome, have been described in returning travelers [Gill and Hamer, 2002].

Practical approach

In addition to a detailed history and physical examination, patients with persistent TD should receive a basic diagnostic work-up comprising blood tests and a stool examination. The blood tests should explore the possibility of anemia, eosinophilia, systemic inflammation, basic nutritional deficiencies, hyperthyroidism, and the presence IgA antibodies directed against tissue transglutaminase (which are diagnostic of celiac disease) [De Saussure *et al.* 2005]. The stool tests should assess the presence of classical bacterial pathogens and *Clostridium difficile* toxin A, and should include O&P on three separate fresh stool samples. If available locally, immunologic testing for *Giardia lamblia* and *Entamoeba histolytica* antigens in a stool sample is advisable.

A proposed management algorithm is presented in Figure 1. If the initial diagnostic work-up is negative, a false-negative test for *Giardia* or *Entamoeba* cannot be excluded, and a course of metronidazole is recommended (500 mg p.o. t.i.d. for 7 days). If symptoms persist in a generally well patient who had no visible blood in the stool and devoid of any significant laboratory abnormality, the diagnosis of PI-IBS is very likely and further diagnostic studies may be postponed. On the contrary, the next diagnostic step should comprise upper and lower digestive endoscopic studies with biopsies of all the explored segments.

Conclusion

The high attack rate and incapacitation potential of acute TD are in sharp contrast with its almost universally benign course. Antibiotherapy is chosen empirically and is highly effective, but the magnitude of its clinical benefit is disputed, and its use should be restricted to the more severe forms of acute TD. Persistent diarrhea in the returning traveler represents a challenging situation, in which the clinician must identify patients suffering from various persistent infections or unrelated chronic diarrheal diseases, among a majority of subjects presenting with postinfectious functional bowel disorders.

Conflict of interest statement

None declared.

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