Persistent Diarrhea in Travelers

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Most patients with traveler's diarrhea can be efficiently treated with available pharmacological agents. A more difficult problem is the persistent diarrhea (lasting ≥14 days) that occurs in ~3% of travelers who have acute diarrhea. In the initial evaluation of these patients, ideally three stool samples should be obtained for examination for pathogens. If an agent is not identified or the patient has not responded to specific therapy, he or she may be empirically treated with an antimicrobial drug directed toward common bacterial enteropathogens, if such treatment has not already been administered. For those patients whose conditions do not respond, antiprotozoal therapy may be employed empirically. If diarrhea continues, then an endoscopic evaluation is indicated, and specific treatment can be given if an agent or condition is identified. A proportion of patients will continue to have diarrhea following empirical therapy and a gastroenterologic workup. These individuals are best given symptomatic treatment and reassured that the prognosis is good.

More than 300 million people cross international boundaries each year, and at least 16 million of them are travelers from industrialized countries to developing tropical countries [1]. About one-third of these travelers from industrialized countries experience a bout of acute diarrhea. Diarrhea is the most common medical affliction among such travelers. Traveler's diarrhea is also a major cause of morbidity among longer-term residents to these areas, including expatriates, Peace Corps volunteers, and military personnel [2, 3]. While most cases of traveler's diarrhea clinically last <1 week, a percentage persist for months and as long as a year [4-6]. Physicians who see travelers returning from developing tropical regions are aware of the importance of chronic diarrhea. Many who suffer from it are exposed unnecessarily to recurrent courses of antimicrobial drugs. In this review we consider the frequency of this complication as well as its potential etiology, and then we present a perspective for workup and treatment. The term persistent diarrhea is used for diarrhea lasting ≥14 days [7].

Incidence

Limited data are available to determine the frequency of persistent diarrhea in travelers. In table 1, three studies are identified wherein a cohort of travelers was followed sufficiently long to allow an assessment of risk of prolonged illness. In the first study, by Steffen et al. [8], the occurrence of diarrhea among a large number of Swiss international travelers (remaining outside their country for ≤3 months) was evaluated. Among the returning vacationers the reported frequency of diarrhea lasting >30 days was 0.9% (73 of the 7,886 persons).

In a second study [2], the incidence of diarrhea lasting at least 1 month was determined among 4,607 Peace Corps volunteers from the United States who were stationed in high-risk regions for a 2-year period. Seventy-eight (1.7%) experienced diarrhea lasting ≥1 month. In the third study [9], among a group of 35 students who had traveled in several Latin American cities during a 1-month period, one (2.9%) developed persistent diarrhea.

It is reasonable to assume that the three studies are representative of the larger problem, in view of the large sample sizes for two of the studies and because of the similarity of the results. The frequency of development of persistent diarrhea among international travelers to high-risk areas is therefore ~3%; diarrhea lasting for ≥30 days occurs in ~1%-2%. A slightly higher rate can be expected among persons living in high-risk areas for a longer period and under less-hygienic conditions (e.g., Peace Corps volunteers and adventure travelers). The diarrheal illness may last for 6-12 months or even longer [1, 6]. It is invariably worrisome to the patients, and it leads to a forced change in lifestyle. The condition may lead to hospitalization [10], recurrent courses of unnecessary antimicrobials [6], and an inability to carry out normal activities [8].

In one large study [8], persistent diarrhea ranked second among health impairments acquired during international travel that led to an inability to work.

Two of the studies looking at large numbers of persons who had temporarily relocated to developing countries provided evidence to suggest that the frequency of occurrence of prolonged diarrhea varies according to the region visited. Steffen et al. [8] found the highest rates among Swiss tourists visiting West Africa and regions of the Far East. This study included persons traveling to all major world regions. Addiss et al. [2], studying more than 4,000 Peace Corps volunteers, found that the highest rates of chronic diarrhea occurred among those stationed in Haiti, Central and West Africa, and Nepal.

Etiology

Published studies of the etiology of persistent traveler's diarrhea are incomplete in that select groups (often seen in a hospi-
Table 1. Prospective population-based studies of the occurrence of persistent (>14 d) diarrhea in travelers.

<table>
<thead>
<tr>
<th>Subjects' country of origin/region visited [reference]</th>
<th>No. of subjects followed</th>
<th>No. (%) of subjects having persistent diarrhea ≥14 d</th>
<th>≥30 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland/worldwide [8]</td>
<td>7,886</td>
<td>...</td>
<td>73 (9%)</td>
</tr>
<tr>
<td>United States/Haiti, Central and West Africa, Nepal [2]</td>
<td>4,607</td>
<td>...</td>
<td>78 (1.7%)</td>
</tr>
<tr>
<td>United States/Latin America [9]</td>
<td>35</td>
<td>...</td>
<td>1 (2.9%)</td>
</tr>
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</table>

* This was a study of Peace Corps volunteers living in 21 countries.
† The subjects were on a 1-month tour of 12 Latin American cities.

tional clinic) have been evaluated for a limited number of pathogens. In most studies the full range of pathogens was not sought, and many reports describe single cases of defined etiology. Furthermore, limitations in study design do not allow a determination of relative frequency of the pathogens. The studies do indicate, however, that a number of agents should be considered in the workup of travelers with prolonged diarrhea. While the parasites are not important causes of acute traveler’s diarrhea, these agents appear to be more important in the syndrome of persistent diarrhea. *Giardia lamblia* has been repeatedly identified as a major cause of the syndrome. A well recognized cause of the prolonged diarrhea of travelers is *Cryptosporidium parvum*, while *Isospora belli* is a less common cause. Soave and Ma [11] reported that two of eight individuals traveling to Africa (an infant and an adult) experienced clinical cryptosporidiosis lasting for 21 days and 14 days, respectively. Jokipii and Jokipii [12] looked at Finnish travelers who had acquired traveler’s diarrhea while in Leningrad (now St. Petersburg). The study included 68 otherwise healthy people, for whom the mean duration of illness was 12.2 days (range, 2–26 days).

Like *Cryptosporidium* species, *I. belli* can cause chronic diarrhea in travelers. In one study of persistent diarrhea [13], *I. belli* was identified in one (1.4%) of 70 servicemen studied. Another parasite that has been recently discovered to cause prolonged diarrhea is variably identified as a cyanobacterium-like, coccidia-like, and—more recently—*Cyclospora* organism. The organism has been identified in both immunocompromised and immunocompetent patients [14]. Travelers and expatriates with persistent diarrhea have acquired infection by this newly recognized pathogen during stays in Nepal [15, 16]. In one report, 55 adults were characterized as having prolonged watery diarrhea, anorexia, fatigue, and weight loss [15]. The mean duration of illness was 43 days (range, 4–107 days), and 45 of the adults were ill for ≥14 days. Malabsorption of d-xylene in these patients was shown to occur [15], and in a follow-up study [16] they were found to have small-bowel injury, including mucosal inflammation, villous atrophy, and crypt hyperplasia. A large number of other parasitic agents may on occasion cause prolonged diarrhea in the international traveler or expatriate from an industrialized region; these organisms include *Entamoeba histolytica*, *Dientamoeba fragilis*, *Strongyloides stercoralis*, *Capillaria philippinensis*, *Fasciolopsis buski*, *Trichuris trichiura*, *Schistosoma* species, and *Sarcocystis* species.

Bacterial agents are important as causes of the protracted illness of travelers. The organisms identified in patients previously studied include enteropathogenic *Escherichia coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli*, *Shigella* species, *Campylobacter jejuni*, and *Aeromonas* species. It has been known that EPEC [17] and HEp-2 cell–adherent *E. coli* [18–20] can cause chronic diarrhea in endemic settings. In all probability, these adherent bacteria will be shown to be important causes of persistent diarrhea in travelers.

In one study, four of six children requiring hospitalization due to chronic diarrhea were infected with EPEC [10]. The children had traveled from the United Kingdom to the Indian subcontinent or Morocco. In a second study [21], three children, also from the United Kingdom, who had recently traveled to the Indian subcontinent had chronic diarrhea and were shown to be infected with EPEC.

In Nepal, Taylor et al. [22] found in a clinic serving expatriates that seven (19%) of 37 patients with persistent diarrhea who were studied were infected by ETEC. *Shigella* species organisms were identified as a cause of prolonged diarrhea in two studies [10, 22]; they were detected in one (17%) of the six children in one study and in two (5%) of 37 in the second. *C. jejuni* was identified in six (16%) of the 37 patients who had diarrhea for ≥14 days [22].

*Aeromonas* species have also been implicated as a cause of chronic and persistent diarrhea in travelers, as reported by Gracey et al. [23]. Four adults infected by a strain of *Aeromonas hydrophila* had chronic diarrhea lasting from 2 to 12 months. One person had aeromonas diarrhea following travel to Italy. The diarrhea became recurrent and was associated with passage of blood and mucus in stool and with abdominal cramps, all of 2 months’ duration. The other three patients with aeromonas diarrhea became ill during travel in Southeast Asia, and the diarrhea lasted for 4–12 months after their return to their home country. The illnesses of three of the four persons were successfully treated with a course of trimethoprim-sulfamethoxazole (TMP-SMZ). The fourth person’s illness was self-limiting. Although largely unexplored to date, *Clostridium difficile* should be considered as a cause of traveler’s diarrhea that persists, particularly in those who have received an antimicrobial agent for treatment or prophylaxis. Other bacterial agents may rarely be identified in cases of persistent traveler’s diarrhea, including *Salmonella* species, *Plesiomonas shigelloides*, and dysgonic fermenter 3.

Despite complete evaluations for conventional etiologic agents, the majority of cases of persistent traveler’s diarrhea...
are of undetermined etiology. A group of miscellaneous causes should be considered and sought in selected cases. Small-bowel bacterial overgrowth can be found in some of the cases [13, 24]. Bacterial overgrowth appears to be produced by a nonspecific inhibition of small-bowel motility patterns and intestinal stasis, probably produced by an initial enteric infection, resulting in luminal colonization by aerobic and anaerobic flora and diarrhea. Preexistent HIV infection may be responsible for the resultant diarrhea. Lactase deficiency may be induced by a small-bowel pathogen causing lactose malabsorption. Diet history can provide an important clue leading to this diagnosis.

Tropical sprue with a chronic malabsorption syndrome is seen in persons living for longer periods of time (from 1 month to 1 or more years) in certain high-risk regions, including Puerto Rico, the Dominican Republic, Haiti, Cuba, the West Indies, India, Burma, Southeast Asia, and the Philippines. The patient typically experiences a bout of acute watery diarrhea with abdominal pain, cramps, and excessive intestinal gas, followed by temporary diminishment of the symptoms before the disease progresses to clinical malabsorption. The etiology of sprue in this setting is unknown. It is possible that a sprue-like syndrome may occur when there has been severe or recurrent damage to the small-bowel mucosa, leading to histologic alteration and malabsorption. There are undoubtedly numerous causes of the syndrome.

Some of the cases of persistent traveler’s diarrhea of uncertain etiology appear to resemble Brainerd diarrhea. The condition was first described when an outbreak of chronic diarrheal illness in Brainerd, Minnesota, occurred. The illness persisted for at least 18 months and was caused by consumption of raw milk [25]. A similar if not identical form of chronic diarrhea has been seen following consumption of untreated water [26]. In some cases of persistent diarrhea, an ordinarily self-limiting episode of traveler’s diarrhea may unmask an underlying chronic gastrointestinal tract disease such as irritable bowel syndrome, inflammatory bowel disease, diverticulitis, colorectal carcinoma, or Whipple’s disease [27]. In addition, a number of drugs can cause diarrhea, including laxatives and magnesium-containing preparations, methylpapa, thyroid hormone replacements, local herbal medications, and alcohol.

**Evaluation and Treatment of Patients With Persistent Diarrhea**

A suggested workup for persistent diarrhea is given in Figure 1. The approach is based on limited data. With the availability of additional data, the approach will be modified accordingly. The evaluation of a person with persistent diarrhea should start with a complete history and physical examination. All patients with persistent diarrhea should have at least one fecal sample examined for conventional etiologic agents. Ideally, three samples should be obtained. The samples are examined for bacterial and parasitic enteropathogens. While recovery of a potential enteropathogen is not proof of an etiologic role, it is usually advisable to initiate appropriate antimicrobial therapy directed against the agent when a specific pathogen is identified. For shigella, aeromonas, or ETEC infection, antibacterial therapy is given (as described below for empirical treatment of unproven diarrhea). If *C. jejuni* is identified, erythromycin is given; the dosage for adults is 250 mg four times a day for 5 days (that for children is given below, in the discussion of empirical treatment).

If the patient is known to be immunocompromised, *C. parvum* or *I. belli* should be suspected and vigorously sought. Optimal treatment of cryptosporidiosis in the HIV-infected adult is with paromomycin (500 mg four times a day for 2 weeks) [28]. Administration of the drug may need to be continued thereafter (at a reduced dosage) to prevent relapse. For isosporiasis in HIV-infected adults, the drug to administer is TMP-SMZ (160/800 mg four times a day for 10 days, followed by 160/800 mg three times a week on a chronic basis) [29]. A shorter course of therapy can be given to immunocompetent persons [30]. In light of the findings of recent studies, it is also important to examine the stool for organisms of the genus *Cyclospora*. It appears that for cyclospora infection, TMP-SMZ given for 7 days may be useful [31]. For treatment of other parasitic pathogens that may be identified, other sources should be reviewed [32].

An etiologic diagnosis often will not be made in cases of persistent traveler’s diarrhea, even after thorough examination of multiple stool samples. In these cases many physicians would initiate a course of antibacterial or antigiardial therapy if one or both have not already been given. However, in many—
not most—of these patients, the intestinal pathological process may be a result of an earlier infection, and antimicrobial therapy thus cannot be expected to be helpful. If empirical therapy is to be used, a 5-day regimen of an antibacterial drug is recommended, although for most cases of acute traveler’s diarrhea, single-dose treatment (for milder illness) or a 3-day therapeutic regimen (for more serious illness) is recommended [33]. The suggested drug for treatment of adults is a fluoroquinolone, unless their travel was to an area where resistance to trimethoprim is rare among enteric bacterial pathogens.

We have provided data suggesting that in one region of Mexico (Guadalajara), during the summertime, bacterial pathogens have remained susceptible over the past decade [34]; thus, TMP-SMZ is the preferred therapy during travel to this area. During the dry wintertime in this area, C. jejuni becomes an important pathogen and ETEC largely disappears [35]. The same seasonal pattern of pathogenicity (ETEC in the summer and C. jejuni in the autumn and winter) has also been seen among Finnish travelers to Morocco [36].

The drug and dosage to use should include one of the following: norfloxacin, 400 mg twice a day [37]; ciprofloxacin, 500 mg twice a day [38]; ofloxacin, 300 mg twice a day [39]; or fleroxacin, 400 mg once a day [40] (all for 3–5 days). When TMP-SMZ is used to treat adults with diarrhea, it is given at a dosage of 160/800 mg twice a day for 5 days [41]. For children there are two reasonable approaches to empirical antibacterial therapy, with dosages based on body weight. The first is to give TMP-SMZ (10/5 mg/[kg·d]), in two divided doses) plus erythromycin (at doses based on body weight: 11–18 kg, 375 mg/d; 18.5–25 kg, 500 mg/d; 25.5–36 kg, 750 mg/d; and >36 kg, 1,000 mg/d, all as four divided doses per day) for 5 days. The second approach would be to administer furazolidone as a single drug [42] (7.5 mg/[kg·d], in four divided doses) for 5 days.

If the subject’s condition fails to improve as a result of antibiotic therapy, or if on clinical grounds the physician caring for the patient suspects that a parasitic agent is involved, then antiparasitic treatment may be given, although the benefit of this approach as applied to a general population remains unproven. A nitroimidazole derivative may be effective against Giardia species and small-bowel bacterial overgrowth. If available, a longer-acting drug such as tinidazole may be given to children there are two reasonable approaches to empirical antimicrobial therapy and for which no cause has been identified after a complete gastrointestinal evaluation usually should be treated with nonspecific antidiarrheal preparations (e.g., loperamide). An alternative approach is to treat the patient as if he or she has irritable bowel syndrome, with a lactose-free diet, fiber (e.g., Metamucil), and antispasmodics. The patients should not receive recurrent doses of antimicrobial drugs, including antiparasitic agents such as metronidazole. This is all too frequently done, leading to a cycle of partial clinical response followed by recurrence of symptoms. Although unproven, it is possible that the intermittent dosing of the antimicrobial drug serves to worsen the problem through profound alteration of intestinal flora. These patients should be reassured that the outlook is good; most chronic diarrhea is self-limiting, although it may last as long as a year [5, 6].

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