Drug Prophylaxis for Travelers’ Diarrhea

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Travelers’ diarrhea is the most common health impairment in persons visiting developing countries, affecting 20% to >50% of tourists. Although it is usually benign, travelers’ diarrhea represents a considerable socioeconomic burden for both the traveler and the host country. The most common enteropathogens are enterotoxigenic and enteroaggregative Escherichia coli. Travelers’ compliance with dietary precautionary measures is poor. Despite the excellent protection rates provided by antibiotics, routine administration of prophylaxis is currently not recommended because of potential adverse reactions. Of the various antibiotics that have been tested, quinolones are considered to be the first choice worldwide; however, quinolone-resistant pathogens are increasingly being isolated. Because it is frequently administered and provides only moderate protection, bismuth subsalicylate is not considered a recommendable option for prophylaxis in Europe, where it is rarely available anyhow. To date, no probiotic has been able to demonstrate clinically relevant protection worldwide. In conclusion, there is no satisfactory prophylactic option, and worldwide monitoring of antimicrobial susceptibility patterns and the search for novel antimicrobial agents, such as nonabsorbed antibiotics, and nonantibiotic medications should continue.

Diarrheal illness is by far the most common health impairment associated with international tourism in terms of frequency and economic impact. Today, >50 million people travel each year from developed countries to developing countries, and 20% to >50% of these travelers report being affected by this distressing condition during the first 2 weeks of their stay, with the likelihood of acquiring this condition depending on well-known risk factors, such as origin and destination of travel, travel season, and various host factors [1–3]. When data since the late 1970s are assessed, no relevant difference—in particular, no decrease in the incidence of travelers’ diarrhea (TD)—can be observed, despite the efforts made by the tourist industry to improve local infrastructure (e.g., water treatment, sanitation, heath care) [2, 3].

Although TD is self-limited (duration, ~3–4 days) and benign in most cases, it causes remarkable discomfort and inconvenience for the traveler, who is consequently unable to pursue planned activities. Moreover, TD represents a considerable socioeconomic burden from the perspective of both the traveler (by incurring costs associated with medication, medical services, canceled activities, and change of itinerary) and the destination country (by causing loss of income from tourism) [3–6].

In most studies, classic TD is defined as passage of ≥3 unformed stools in a 24-h period with ≥1 accompanying symptom of enteric disease, such as nausea, vomiting, abdominal cramps, fever, tenesmus, or bloody stool [6]. The definition of TD should also include episodes of diarrhea that occur during the first 7–10 days after the traveler returns home. Illness lasts >1 week in 8%–15% of patients and >1 month in up to 2% of patients. Approximately 20% of patients with TD are confined to bed for ~1–2 days [2, 7]. Patients who are at special risk, however, such as small children, pregnant women, elderly patients, and patients with preexisting illnesses, are at an increased risk of developing complicated and long-lasting disease [8, 9]. Other complications may include dehydration (particularly in children), reactive arthritis, postinfectious enteropathy, and Campylobacter jejuni–associated Guillain-Barré syndrome [2, 10, 11].

The incidence of TD is not influenced by the patient’s sex. However, teenagers and young adults have been found to be at higher risk, most likely because of the ingestion of larger volumes of potentially contaminated food and an adventurous lifestyle [3, 4, 12]. Several findings suggest that, although strict alimentary hygiene may help minimize the risk of acquiring TD, it will definitely not eliminate that risk, because motiva-
tional problems on the part of the traveler exist despite extensive pretravel counseling [4, 13–15]. Therefore, intensive efforts have been undertaken to find an effective prophylactic medication to prevent TD. Various classes of drugs and means of prophylaxis have been investigated, including nonantimicrobial agents, antibiotics, and, more recently, the administration of immunizations.

ETIOLOGY

TD is usually caused by ingestion of food and beverages that are contaminated with fecal matter. Various infectious agents have been identified, and their prevalences differ remarkably according to season and geographical region [16]. Bacteria are the most common enteropathogens and are responsible for up to 80% of all cases of TD. The most common bacteria are enterotoxigenic Escherichia coli, the recently identified enteroaggregative E. coli, Shigella species, Campylobacter jejuni, Salmonella species, and Aeromonas species [8, 17]. Enteric pathogens other than bacteria (protozoa such as Entamoeba histolytica and Giardia lamblia, or enteroviruses) are generally less important as causes of TD. TD due to Rotavirus and Campylobacter species is found more frequently in areas with dry winters [16]. In a considerable proportion (up to 20%) of cases of TD, however, ≥2 potentially enteropathogenic agents could be isolated in the course of the same episode [3]. Depending on the study, 20%–50% of all cases of TD remain of undetermined etiology, despite excellent experimental accuracy and optimal laboratory evaluation [8, 13]. Most of these cases may be caused by enteropathogenic bacteria or their toxins, because the disease can be suppressed by prophylactic use of antimicrobial agents. Speculations about noninfectious causes of TD, such as changes in normal gastrointestinal flora caused by a different diet or excessive alcohol consumption, are usually unjustified, because the documented benefit of prophylactic antibacterial agents is ~90%, which implies that TD is mainly caused by bacteria or their toxins.

CHEMOPROPHYLAXIS

Although TD is usually mild and self-limiting, there is still a need for safe and effective means of prevention. Because contaminated food or beverages are the most important vehicle of transmission of all pathogens that cause TD, precautions regarding dietary habits (the rule of “boil it, cook it, peel it, or forget it!”) remain the cornerstone of prevention. However, the impact of pretravel health advice on the incidence of TD remains unsatisfactory, mostly because there are problems in motivating the traveler into taking precautions regarding what to eat and drink [4, 13–15, 18].

Since the late 1970s, extensive efforts have been undertaken to find effective and well-tolerated prophylaxis for travel-associated gastrointestinal disorders. Different types of drugs, including nonantibiotic agents and prophylactic antibiotics, can be considered for the prevention of TD.

Antibiotics. Despite the excellent protection rates provided by antibiotics, routine administration of prophylactic antimicrobial agents is currently not recommended to the healthy traveler who would just prefer not to experience TD [19–21]. In 1985, a Consensus Conference at the National Institute of Health confirmed the protective effect of antibiotics for TD prevention, but disclaimed a general recommendation of TD prophylaxis for widespread use because of potential drug-associated adverse reactions [21]. One of the first antibiotics studied was doxycycline (100 mg/d), which demonstrated effectiveness because tetracyclines have a broad spectrum of coverage of TD pathogens. Unfortunately, doxycycline-resistant strains evolved in many targeted tourist destinations, which limited its potential use in TD therapy and prophylaxis [22, 23]. In the early 1980s, other systemic antimicrobials, such as trimethoprim-sulfamethoxazole, were also used successfully [24, 25] until increasing drug resistance limited their application to certain areas and seasons, such as inland Mexico during the summer [26, 27].

In the past 10 years, 4-fluoroquinolones (norfloxacin, ciprofloxacin, fleroxacin, ofloxacin, and levofloxacin) have attracted considerable attention as a result of their excellent safety profile and wide spectrum of coverage of enteropathogenic agents [14, 28–31]. It was shown, when taken daily in a single low dose—for instance, 400 mg of norfloxacin per day [31] or 250 mg of ciprofloxacin per day [29]—the protection against TD pathogens. Unfortunately, doxycycline-resistant strains remained rare E. coli strains remained rare until 1990; starting in 1990, quinolones have been used for treatment on a widespread scale. Unfortunately, the situation is evolving, and resistant strains are increasingly being isolated, particularly in Asia [37].

To date, fluoroquinolones have maintained excellent in vitro activity against most bacterial pathogens associated with TD, although the increasing resistance and in vivo emergence of resistance of C. jejuni to quinolones reported from Thailand and Southeast Asia are a matter for serious concern [34–36]. Isolation of quinolone-resistant E. coli strains remained rare until 1990; starting in 1990, quinolones have been used for treatment on a widespread scale. Unfortunately, the situation is evolving, and resistant strains are increasingly being isolated, particularly in Asia [37].

Thus far, quinolones remain the drugs of choice when chemoprophylaxis is indicated for, for instance, patients with severe baseline disease. However, side effects have been observed, such as skin rash, vaginal candidiasis, CNS reactions, phototoxicity,
and gastrointestinal complaints; and, very rarely, there have been severe events, including anaphylaxis (table 1) [5, 38]. Moreover, confusion might occur with regard to how to manage an illness that occurs despite the patient’s receipt of antibiotic prophylaxis. Quinolones are not approved for prophylaxis in children and pregnant women.

Ampicillin, like most other penicillins, is not useful as a therapeutic or prophylactic agent because of widespread resistance and incomplete coverage of TD-causing pathogens [42]. The spectrum of mecillinam, another penicillin, includes mainly gram-negative aerobic microorganisms, but mecillinam lacks effectiveness against such pathogens as enterococci because it shows selection of resistant pathogens in fecal flora.

The new macrolides, such as clarithromycin, have been noted to significantly impair the oropharyngeal and intestinal microbiota by causing overgrowth of new enterobacteria and to select highly resistant isolates when used for prolonged periods, which makes their application for long-term prophylactic purposes unsuitable [45–48].

Because of the spread in resistance to quinolones, there is great interest in the development of novel antimicrobial agents that are minimally absorbed from the gut, which would thereby attain high intestinal levels and avoid serious (although rare) toxicity of systemic drugs in treatment and prophylaxis. In recent studies, rifaximin, a rifamycin derivative with broad-spectrum antibacterial activity [49], has shown promising results with regard to safety and efficacy for the treatment of patients with bacterial infectious diarrhea who traveled to Mexico, Guatemala, and Kenya [50, 51]. This agent, which is presently used in Italy to treat enteric bacterial infection, should be considered as a potential prophylactic candidate that deserves to be evaluated specifically for the purpose of TD prophylaxis.

**Bismuth subsalicylate.** A number of studies have confirmed that bismuth subsalicylate (BSS) has a protective efficacy of up to 65%. This agent has been shown to have short-term intraluminal antibacterial action in the prevention of TD [43, 44, 52]. Optimal protection rates were reported when the substance was administered as 2 tablets 4 times daily (2.1 g/day) for a maximum period of 3 weeks, because it seems that the optimal antibacterial effect is provided by simultaneous ingestion of contaminated food and BSS [43, 52]. Wine, which is anecdotal reported to have some sort of preventive effect, when compared with BSS, was shown to have an equivalent effect in reducing the number of viable organisms; however, the clinical relevance of these data remains doubtful [53].

The most commonly reported adverse reactions associated with BSS were transient blackening of tongue and stools, constipation, tinitus, and nausea (table 1) [43, 44]. It should be noted that BSS can deplete the absorption of doxycycline, reducing its circulating levels, a fact that may be of importance with regard to malaria prophylaxis with doxycycline [54]. In most European countries, however, BSS preparations are not licensed and are considered an attractive option for neither prophylactic nor therapeutic use. A rather large number of tablets has to be taken per day; the side effects simply make BBS an unattractive option for travelers, and the high level of compliance is rewarded by only moderate protection.

**Probiotics.** Another approach to the prevention of TD is the use of probiotics, which are attractive in view of their lack of toxicity and drug interactions. Protective mechanisms that may play a role in the concept of action of these medications include the production of acids, hydrogen peroxide, or antimicrobial substances, as well as the competition for nutrients or adhesion receptors, antitoxin action, and stimulation of the immune system [55]. Many health-related claims have been made concerning probiotics, especially with regard to their potential to prevent and cure intestinal disturbances; however,

### Table 1. Prophylactic drugs used to prevent travelers’ diarrhea.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protective efficacy, %</th>
<th>Side effects</th>
<th>Geographic factors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lactobacilli GG</td>
<td>0–50</td>
<td>None</td>
<td>Depends on the destination</td>
<td>[39, 40]</td>
</tr>
<tr>
<td>Saccharomyces boulardii</td>
<td>0–60</td>
<td>None</td>
<td>Effective in North Africa and Turkey</td>
<td>[41]</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>80–100</td>
<td>Nausea, gastrointestinal complaints, vaginitis, anaphylaxis, CNS effects</td>
<td>Resistance of Campylobacter species in Thailand and Southeast Asia</td>
<td>[28–31, 34–38, 42]</td>
</tr>
<tr>
<td>TMP-SMZ</td>
<td>79–94</td>
<td>Headache, nausea, vaginitis, anaphylaxis, Stevens-Johnson syndrome</td>
<td>Effective in inland Mexico in summer</td>
<td>[25–27]</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>59–86</td>
<td>Gastrointestinal complaints, vaginitis, photosensitivity, anaphylaxis</td>
<td>Widespread resistance worldwide</td>
<td>[22, 23]</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>40–65</td>
<td>Black tongue and stools, constipation, tinitus, encephalopathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None</td>
<td>[41, 43, 44]</td>
</tr>
</tbody>
</table>

*NOTE:* TMP-SMZ, trimethoprim-sulfamethoxazole.

*<sup>a</sup> Although it is rare, encephalopathy may develop in patients with AIDS after administration of excessive doses.*

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only a few probiotic agents have been shown to be effective in randomized controlled trials (table 1).

Oksanen et al. [39] reported that Lactobacillus GG prophylaxis given to tourists traveling to Turkey led to a 12% reduction of TD; however, the effect was significant only for 1 destination. In another double-blind, randomized, controlled trial, the risk of TD was 4% in American travelers who received Lactobacillus GG (dose, 2 × 10^9) and 7% in the control group, which indicates that there was minimal, although significant, protection [40]. No protective effect, however, was evident in studies of other lactobacilli, such as Lactobacillus fermentum and Lactobacillus acidophilus, because various strains seem to differ in their potential for colonization of the intestine [39, 56, 57].

A mild but significant and dose-dependent (250 mg and 1000 mg) protection against TD with a varying regional effect was reported for travelers to North Africa and Turkey who were taking Saccharomyces boulardii [41]. The evaluation of an “oral vaccine,” which consisted of 10^11 heat-inactivated Enterobacteriaceae (Dodecoral; Serotherapeutisches Institut) did not effectively reduce the incidence of TD [57].

On the basis of these data, the principal concept of protection mediated by nonpathogenic bacteria remains appealing, but until now, no probiotic medication has been demonstrated to provide clinically relevant worldwide protection against TD; therefore, a general recommendation for the use of such preparations cannot be provided. It would be worthwhile to intensify research on probiotics, because these medications are low-priced and have excellent safety profiles and acceptance, making them ideal for tourist self-medication (particularly for persons in high-risk groups, such as children and pregnant women).

GENERAL CONSIDERATIONS

A cost-effectiveness analysis that simply compares the cost of chemoprophylaxis with the cost of treatment of patients with TD shows that prevention of TD in short-term travelers is cost effective. The most important contributor to the mean cost of TD was the cost associated with a day of incapacitation associated with illness [5]. Thus, prophylaxis may be recommended once the risks and benefits are clearly understood by the patient. Prophylaxis would be particularly desirable for management of conditions with severe baseline disease, such as chronic gastrointestinal, immunologic (including HIV), endocrinologic, and hematologic disorders; it would also be attractive for use by travelers who are regularly affected by serious (perhaps genetically based) TD [3]. A person with one of these disorders should definitely be considered a candidate for chemoprophylaxis. In addition, chemoprophylaxis should be considered for persons who request preventive medication for important short-term trips abroad, such as politicians or businesspeople.

However, doctors should be conservative in prescribing chemoprophylaxis to these travelers.

In any case, chemoprophylaxis should not be recommended for long-term travel (duration, >3 weeks) because of increased toxicity and interference with the development of natural immunity to a number of enteric pathogens, especially enterotoxigenic E. coli. Besides, prophylaxis may provoke the false impression of security, leading the traveler to take fewer precautions in food selection and thereby causing a relative increase in the incidence of nonbacterial diarrhea. In making a decision about the use of prophylaxis, the benefits of TD prevention need to be clearly balanced against the advantages of a simple 1- or 2-day, highly effective, self-administered therapy begun early in the course of diarrhea.

The groups that are most seriously affected by TD are small children and pregnant women. For both of these groups, neither quinolone-based prophylaxis nor treatment are approved. This limitation, plus the fact that none of the current options for prophylactic medication are entirely satisfactory for broad use because of discouraging protective efficacy, potential adverse events, and the increasing prevalence of drug resistance, means that alternative options for the prevention of TD are clearly required.

It is possible that immunoprophylaxis will be developed, but the chances that a vaccine will be effective are limited, because the etiology of TD is extremely variable, and it would be difficult for even a “broad-spectrum vaccine” to sufficiently cover a great variety of TD-causing pathogens and to protect travelers in a clinically relevant manner [58–60].

CONCLUSIONS

Although most episodes of TD are benign and self-limiting in healthy adults, considerable morbidity and disruption to travel results. Therefore, effective prophylaxis against infectious diarrhea in travelers is desirable, because travelers put pressure on doctors to provide pretravel health advice. A generally acceptable prophylactic agent should meet the following basic requirements: it should provide protection to at least 75% of travelers, it should have an optimal safety profile for use as self-medication (and should also be suitable for use by children and pregnant women), administration should be simple (preferably a single dose taken daily), there should be no drug resistance problems or drug interactions, and, finally, it should be inexpensive. Rifaximin, which shows considerable pharmacologic and safety advantages over the existing drugs, might prove to be a candidate.

For now, worldwide monitoring of antimicrobial susceptibility patterns and the search for new antimicrobial agents and non-antibiotic options of prophylaxis of TD should be intensified.