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# Travellers' Diarrhoea: Contemporary Approaches to Therapy and Prevention

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## Contents



## Abstract

Travellers' diarrhoea remains a major public health problem, contributing to significant morbidity and disability. Because bacterial enteropathogens cause a majority of this form of diarrhoea, antibacterial drugs are effective when used in chemoprophylaxis or for empirical treatment.

A review of the MEDLINE listings for travellers' diarrhoea for the past 4 years was conducted; a library of >1000 scientific articles on the topic was also considered in developing this review.

Persons who travel from industrialised countries to developing countries of the tropical and semitropical world are the individuals who experience travellers' diarrhoea. While diarrhoea occurs with reduced frequency among persons travelling to low-risk areas from other low- or other high-risk areas, and there remain areas of intermediate risk, this review looks primarily at the illness occurring in persons from industrialised regions visiting high-risk regions of Latin America, Africa and Southern Asia.

The material reviewed deals with the high frequency of acquiring diarrhoea during international travel to high-risk areas, seen in approximately 40%, and the expected bacterial causes of illness, of which diarrhoeagenic *Escherichia coli* is the most important. The host risk factors associated with increased susceptibility

to diarrhoea include young age, lack of previous travel to high-risk regions in the past 6 months, indiscriminate food and beverage selection patterns, and host genetics.

It appears feasible to decrease the rate of illness among the travelling public by careful food and beverage selection or through chemoprophylaxis with nonabsorbed rifaximin. Chemoprophylaxis with rifaximin should help to reduce the occurrence of travellers' diarrhoea and hopefully prevent post-diarrhoea complications, including irritable bowel syndrome. Early empirical therapy with antibacterial drugs, including rifaximin, a fluoroquinolone or azithromycin, will decrease the duration of illness and return travellers more quickly to their planned activities.

With collaboration between local governments and public health researchers, it may be possible to improve hygiene in areas to be visited, which may translate into reduced rates of illness. More liberal use of rifaximin prophylaxis is likely to reduce the occurrence of illness and complications of disease. Vaccines and immunoprophylactic products may be beneficial for prevention of a subset of individuals otherwise developing diarrhoea.

Approximately 50 million persons cross international boundaries each year, travelling into high-risk areas of the tropical and semi-tropical world. Diarrhoea affects an estimated 20 million of these persons.[1] This review briefly considers the current information about travellers' diarrhoea and focuses on recent studies of chemoprophylaxis and empiric therapy, attempting to answer two major questions.

- How can travellers to high-risk areas reduce the occurrence of diarrhoea using diet restrictions and pharmacological approaches?
- What medication should travellers have with them for self-treatment of diarrhoeal illness while abroad and away from medical attention?

The article also deals with other aspects of travellers' diarrhoea and concludes with future directions of research in this dynamic area of travel medicine.

## 1. Literature Review and Inclusion Criteria

MEDLINE was reviewed for articles published on travellers' diarrhoea for the years 2002–5 to identify the newer material. This was augmented by an extensive file system of >1000 articles on the topic maintained by the author.

The world can be divided into three regions based on the level of hygienic standards present and expected rate of diarrhoea among international visitors.[2] Diarrhoea can occur in persons travelling from one low-risk area (US, Canada, Western Europe, Japan, Australia and New Zealand) to another, or from a high-risk region to one of these low-risk areas; however, the rate of illness is between 2% and 4%. In people travelling from low-risk areas to areas of intermediate risk (such as some islands in the Caribbean, some parts of the northern Mediterranean, the Middle East, China or Russia), diarrhoea occurs in approximately 10–15%. For travel from a low- to a high-risk region (Latin America, Africa and Southern Asia) the diarrhoea rate averages 40%.[1] This review examines the literature on diarrhoea associated with travel to these high-risk areas, and four major areas are discussed.

1. An overview of the topic of travellers' diarrhoea is presented to provide a basis of knowledge in the area with emphasis on incidence, causes and sources, and host risk factors;

2. Studies of disease control are described along with data from a recently conducted trial where the nonabsorbed antibacterial drug rifaximin was used to prevent travellers' diarrhoea;

3. Studies showing the benefit of antibacterial therapy of travellers' diarrhoea are reviewed, along with recommendations for empirical therapy;

4. Future directions in disease reduction, therapy and chemoprophylaxis are considered in the face of growing antibacterial resistance because of wide-

spread use of antibacterial drugs in animals and humans.

## 2. Historical Aspects

In the 1950s and early 1960s, Kean and colleagues[3-6] began studies of travellers' diarrhoea among tourists and students travelling to Mexico. The research team found that antibacterial drugs were effective in reducing the occurrence of illness, providing the first evidence that bacteria were the primary causes of the syndrome. A study carried out in 1957 revealed that more than one-third of tourists to Mexico were taking prophylactic antibacterials in an attempt to prevent diarrhoeal disease during travel.[5] During the 1968 Mexico Olympics, the British team credited prophylactic oral streptomycin-sulfa drugs with keeping them disease free; they also reported that the US and Australian teams were using less effective preventive sulfonamides and were experiencing intestinal illness more frequently.[7]

## 3. Epidemiology

### 3.1 Sources of Illness

The major vehicle for transmission of diarrhoea in high-risk regions is food,[8-10] with water and ice being less common sources of illness.[11,12] Particularly high-risk foods include moist items served at room temperature, such as salads, buffet items and fruits that have not been peeled (e.g. tomatoes and berries). Previously cooked foods are often unsafe. For example, hamburgers are frequently stored at room temperature for some hours after initial cooking, and are therefore frequently unsafe. Low-risk foods include recently cooked meals; coffee or tea with a temperature ≥59°C, which effectively kills bacterial pathogens;[13] dry foods such as bread (without butter or spreads); fruits that can be peeled; items with a low pH, such as citrus fruit; and foods with a high sugar content, such as syrup, honey and jam. All enteric pathogens are dose related and the level of microbial contamination of water is low. For this reason, it should be safe to rinse the mouth and toothbrush with tap water after brushing teeth in most urban areas of the developing world. It is ill advised to drink tap water, even in places where the hotel indicates they have a filter for purifying the water. Carbonated bottled drinks, soft drinks and beer should be considered safe. Bottled water with a discernible seal on twisting the cap can be considered to be safe in nearly all regions of the world.

### 3.2 Host Susceptibility

It is frequently observed, in groups of travellers exposed to the same or very similar food and environmental risks, that some individuals often become ill while others rarely succumb to illness. This suggests that individual susceptibility to enteric disease varies widely.

Doses of a limited number of enteric pathogens required to produce enteric infection and disease have been determined in volunteers challenged with single large doses of enteropathogens. Volunteer studies have provided evidence that neutralisation of gastric acid at the time of challenge increases susceptibility to enteric infection.[14,15] These studies provide indirect evidence that travellers suppressing gastric acidity with regular use of histamine $H_2$ antagonists or proton pump inhibitors would be at increased risk for enteric disease. Although the gastric acid-reducing drugs appear to increase susceptibility of travellers to bacterial diarrhoea, the added risk appears to be less than predicted by volunteer experiments. This is probably explained by the transient rather than sustained change in gastric pH induced by the drugs, and by the recurrent exposure to low or moderate doses of enteropathogens occurring at mealtime during the days at risk for travellers, in contrast to the situation with experimental challenge where a single high-inoculum challenge is administered to volunteers with careful timing of anti-acid pre-treatment.

Epidemiological risk factors for travellers' diarrhoea include young age (both young children and adolescents show high rates of illness), lack of previous travel to high-risk regions in the past 6 months;[2,16] and lack of care in food and beverage selection. In one study, the number of errors in food and beverage selection made by travellers correlated with the rates of illness in the group.[17] Diarrhoea occurrence in a group of travellers is not a result of numerous sporadic events, but appears to be a series of poorly defined illness clusters related to the serv-

ing of meals contaminated with pathogens in hotels, restaurants and homes.[18]

The first evidence that genetics played a role in enteric disease susceptibility was provided by studies showing that persons with blood type O were more susceptible to cholera[19-21] and norovirus (Norwalk) gastroenteritis.[22,23] When it was shown that interleukin (IL)-8 levels were increased in the stool of individuals with travellers' diarrhoea caused by a variety of bacterial enteropathogens,[24] we carried out a study of host IL-8 genetics. In the research, we found that individuals who possessed a single nucleotide polymorphism in the promoter (−251) region of the IL-8 gene were more susceptible to one of the more common forms of travellers' diarrhoea, enteroaggregative *Escherichia coli* (EAEC).[25] Clearly, genetic risk factors help to explain variances in susceptibility among individuals travelling to high-risk areas.

### 3.3 Development of Immunity

It has been observed for more than a century that the high rates of illness seen when persons move from low-risk regions to more high-risk areas become lower with time remaining in the area of high risk.[26,27] In studying US students in Mexico, we found that the rate of illness was reduced by half in those remaining in Mexico for one academic semester or longer, compared with a newly arrived population living in the same dormitories.[28] In the study, newly arrived students from other Latin American regions had low rates of diarrhoea similar to the Mexican students attending classes at the school, suggesting the presence of similar pathogens in their home country and confirming development of immunity in their own locale before travel to Mexico.

## 4. Aetiology

Diarrhoeagenic *E. coli*, particularly enterotoxigenic *E. coli* (ETEC) and EAEC, are the two most important causes of travellers' diarrhoea worldwide, being responsible for approximately 50–60% of cases.[29-32] The second large aetiology group is the invasive bacterial pathogens, *Shigella*, *Salmonella* and *Campylobacter* spp., responsible for about 10–15% of instances in most parts of the developing world, but found more commonly in Asia, where it may explain up to 30% of travellers' diarrhoea.[31,33-35] The other major cause of diarrhoea cases in international travellers to developing regions is a 'no pathogen identified' group, seen in approximately 20%. Antibacterials are effective in shortening the illness compared with placebo,[36-38] suggesting that these cases of illness represent undetected bacterial infection. In support of this notion, when employing the sensitive polymerase chain reaction to the study of these otherwise undefined cases, we found ETEC in a large proportion.[39] While the bacterial enteropathogens show a high degree of similarity throughout the different regions of the developing world, some areas or settings show special associations with pathogens (see table I).

## 5. Clinical Illness

Approximately 80% of travellers with diarrhoea experience watery diarrhoea with abdominal cramps and pain with variable degrees of nausea, vomiting and faecal urgency. This syndrome may include chills and low-grade fever (37.2–37.7°C). All enter-

**Table I.** Geographic considerations of the aetiological agents causing travellers' diarrhoea

| Geographic area | Important aetiological agents |
|---|---|
| All regions of the developing world | Bacterial enteropathogens, of which diarrhoeagenic *Escherichia coli* (ETEC and EAEC) are the most important, found in ~50% of cases, followed by invasive bacterial pathogens (*Shigella*, *Salmonella* and *Campylobacter* spp.) found in 15% of cases |
| Mountainous areas and recreational waters of North America | *Giardia* spp. |
| Southern Asia | Invasive bacterial pathogens (*Shigella*, *Salmonella* and *Campylobacter* spp.) found in up to 30% of cases, of which ciprofloxacin-resistant *Campylobacter* is of special concern |
| Russia (especially St. Petersburg) | *Giardia* and *Cryptosporidium* spp. |
| Nepal, Haiti and Peru | *Cyclospora* spp. |
| Cruise ships | Noroviruses (e.g. Norwalk virus) |

**EAEC** = enteroaggregative *E. coli*; **ETEC** = enterotoxigenic *E. coli*.

ic pathogens causing travellers' diarrhoea cause this form of disease, including the diarrhoeagenic *E. coli*, invasive bacterial pathogens, parasites and viral agents. *Shigella* and *Campylobacter* spp. are the most common causes of dysenteric disease in travellers. Approximately 1–3% of travellers to non-Asian countries will experience febrile dysenteric illness with stools positive for gross blood and mucus.[40-42] In southern Asia, the frequency of dysenteric illness is higher. At least 10% of international visitors will have an illness classified as acute gastroenteritis, where recurrent vomiting is the primary symptom and noroviruses are the most important aetiological agents.[43] Preformed toxins of *Staphylococcus aureus* and *Bacillus cereus* also produce a similar syndrome in international travellers.

The diarrhoeal illness developing in travellers leads to considerable morbidity and results in an average of 24 hours of disability.[44] This length of time can severely disrupt a week-long holiday or business trip since the associated symptoms last considerably longer than the period of disability. Many people avoid travel to high-risk areas because of the threat of illness or because of illness that occurred in previous travels.

Of possibly greater importance than the temporary disability are chronic intestinal complaints seen in a significant subset of travellers. Between 2% and 18% of travellers with diarrhoea continue to have enteric symptoms for several months.[45-47] Between 5% and 10% meet objective criteria for development of post-infectious irritable bowel syndrome (PI-IBS) 6 months after the episode of travellers' diarrhoea.[46,47] Other causes of persistent diarrhoea are parasitic infection,[48] idiopathic Brainerd diarrhoea,[49] unmasked inflammatory bowel disease[50] and celiac sprue.[51]

## 6. Prevention

Disease-preventive strategies, if safe and effective, will have advantages for most travellers over the alternative of empirical self-therapy for this common illness. Prevention strategies include either meticulous care in what is eaten or drunk (see table II) or daily use of a chemoprophylactic agent (see table III) while in an area of risk.

**Table II.** High-risk and low-risk foods and beverages in high-risk regions, tropical and semi-tropical regions

| High-risk foods and beverages | Low-risk foods and beverages |
|---|---|
| Moist foods served at room temperature (e.g. salad) | Any food item or drink (e.g. coffee or tea) served steaming hot (≥59°C) |
| Fruit that cannot be/is not usually peeled (e.g. berries, tomatoes) | Food that is dry (e.g. bread without spreads or butter) |
| Milk from a questionable source | Fruit that can be peeled (e.g. oranges, bananas) |
| Items served in buffet tins without effective heating flame below | Foods with high sugar content (e.g. syrup, jam, honey) |
| Hot sauces on table top | Foods that are self-washed and prepared |
| Tap water or bottled water without a seal | Bottled carbonated drinks |
| Food from a street vendor | Bottled water with seal apparent on twisting top |

### 6.1 Food and Beverage

While it has not been proven that diarrhoeal disease rates can be reduced among travellers by exercising care in food and drink selection during travel, it is logical to assume that illness rates would be modified by exercising established precautions. This is based on the available knowledge of the low- and high-risk food groups,[8,10,58] and the available information indicating that the number of food selection errors made by tourists translates directly into higher rates of diarrhoea.[17] Travellers are not careful about what they eat during travel to high-risk areas,[59] which means either that we have been ineffective in educating them about the risks or that they are more interested in enjoying local foods and drinks than restricting their intake to reduce the risk of illness. Travellers should be informed of the risks, in the hope that they will elect to consume the safer foods and beverages and avoid the high-risk items during travel (table II).

### 6.2 Antibacterial Drugs

Studies in the 1950s and 1960s demonstrated the value of prophylactic antibacterial drugs in reducing the occurrence of travellers' diarrhoea.[3,4,6] In a study carried out in 1957, more than one-third of tourists from the US took preventive antibacterials during their trip to Mexico.[5] When antibacterial resistance to the sulfonamide drugs used early on for prophylaxis became widespread among prevalent bacterial enteropathogens, doxycycline was evaluated as a preventive drug in Peace Corps volunteers

**Table III.** Chemoprophylaxis of travellers' diarrhoea: protection rates and current usefulness of available drugs effective in controlling disease morbidity[52-57]

| Preventive drug | Protection rate (%)[a] | Comment |
|---|---|---|
| Bismuth subsalicylate (two 263mg tablets with meals and at bedtime [8 tablets per day]) | 65 | Large dose required will cause harmless darkening of stools and tongues, and may lead to mild tinnitus |
| Fluoroquinolone (one tablet per day) | 80 | Concern about adverse effects with absorbed drugs; encouragement of resistance among microbes important in systemic infection; and major alterations of colonic flora, causing superinfection |
| Rifaximin (200mg twice a day or 600mg once a day) | 72–77 | Comparatively safe, little concern about resistance; overall best option for chemoprophylaxis |

a Protection rate determined by the following equation: % illness in placebo group minus % illness in drug group divided by % illness in the placebo group multiplied by 100.

living in high-risk regions.[60,61] Doxycycline was effective as a diarrhoea preventive until resistance to that drug was encountered.[62] In more recent years, studies were carried out with either norfloxacin or ciprofloxacin, resulting in protection rates of approximately 80%.[52-55] A Consensus Development Conference held at the National Institutes of Health in the US in 1985 concluded that routine prophylaxis with absorbed drugs should not be encouraged. This conclusion was based on two lines of reasoning: systemic adverse effects of absorbed antibacterial drugs were important; and widespread use of the drugs could hasten development of resistance by endogenous microbes, limiting the future value of the drugs in treating extra-intestinal infections, including pneumonia and urinary tract infection.[63] The Consensus Development Conference did support the use of the drugs for certain high-risk groups. The travel groups for which prophylaxis with one of the absorbed drugs might be employed were further defined in later reviews of the subject.[1,64]

Renewed interest in chemoprophylaxis of travellers' diarrhoea occurred when the nonabsorbed (<0.4%) oral rifamycin, rifaximin, with *in vitro* activity against enteric pathogens, became available.[65] In 2003, a trial was carried out in 210 US students upon arrival in Guadalajara, Mexico. The students received rifaximin 200mg once, twice or three times daily with meals, or a matching placebo for 2 weeks in a randomised, double-blind trial.[56] Diarrhoea was defined as the passage of three or more unformed stools within a 24-hour period plus a symptom or sign of enteric infection (fever, abdominal cramps or pain, excessive intestinal gas-related symptoms, nausea, vomiting, faecal urgency, tenesmus or dysentery). When diarrhoea occurred, the subjects were removed from the study. Equal protection occurred with each of the three doses of rifaximin compared with the placebo group. The resultant protection rate against occurrence of diarrhoea was 72%. The protection rate for treatable diarrhoea, defined as active diarrhoea in subjects coming to the clinic where they were given antimicrobial therapy, was 77%. In those without diarrhoeal disease, rifaximin also reduced the occurrence of mild diarrhoea (one or two unformed stools plus one or more signs or symptoms of enteric infection) and moderate to severe abdominal pain/cramps or excessive intestinal gas-related symptoms. Rifaximin led to minimal alteration of colonic flora and coliform or enterococcal antimicrobial susceptibility patterns.

In considering which groups should be offered rifaximin prophylaxis during travel to high-risk regions, one recent review suggested that the approach be employed for those on tight schedules (e.g. musicians, diplomats and lecturers), those with a history of the illness during travel and those who request chemoprophylaxis.[66] Prophylaxis with rifaximin might also be advised for patients with underlying medical conditions that make them more susceptible to diarrhoea or to complications of illness (e.g. those who are immunocompromised, have chronic gastrointestinal disease or an unstable medical condition, such as type 1 diabetes mellitus or heart failure).

There are two remaining questions regarding rifaximin prophylaxis:

- Will rifaximin prophylaxis prevent illness caused by invasive bacterial pathogens?
- Will rifaximin prophylaxis prevent post-travellers' diarrhoea irritable bowel syndrome?

There are reasons to believe that the answer will be yes to both questions. First, prevention of an invasive bacterial infection by a lumen-active drug should be far easier than treatment of an extensive intra-mucosal inflammatory disease. In support of the notion that the non-absorbed drug would prevent invasive bacterial forms of enteric infection, rifaximin prevented enteric disease in volunteers given a fully virulent *Shigella flexneri* 2a strain, while 40% of placebo-treated subjects developed shigellosis and 10% experienced dysenteric disease.[67] With regard to prevention of PI-IBS, we have seen in our previous studies that symptomatic illness was required for the complication to occur,[47] suggesting that rifaximin-prevented illness should not progress to PI-IBS.

### 6.3 Non-Antibacterial Preparations

Other drugs and products have been employed to prevent travellers' diarrhoea. Bismuth subsalicylate (BSS) was tested because the drug[68] and the intestinal bismuth reaction products[69] had demonstrable antimicrobial properties. When 2oz of BSS were taken four times a day with meals and at bedtime (4.2g of active drug per day) for 3 weeks, a protection rate of 62% was achieved.[70] When the study was repeated with a dosage of two tablets of BSS (263 mg/tablet) four times a day (2.1g of active drug per day) with meals and at bedtime for 3 weeks, a protection rate of 65% resulted (table III).[57] The subjects experienced black tongues and black stools from the harmless bismuth sulfide salt reaction product. A few described nonobjectionable tinnitus while taking the drug.

Commercial *Lactobacillus* preparations have been used. Strains of *L. acidophilus* and *L. bulgaricus* were not found to be effective in prevention of travellers' diarrhoea,[71] while *Lactobacillus* GG was minimally effective, resulting in protection rates of 12% and 45% when used as a prophylactic agent.[72,73] Given that the use of probiotics is an interesting concept and in view of the safety profile, further research with new probiotics is indicated.

Table III lists the currently active drugs shown to be effective in prevention of travellers' diarrhoea, together with the recommended dosage and the value and limitations of each.

## 7. Treatment

When bacterial pathogens were found to predominate as causes of travellers' diarrhoea,[74,75] we employed co-trimoxazole (trimethoprim-sulfamethoxazole) and non-absorbed bicozamycin in successful treatment of the disease.[38,76] Over the past 25 years, a number of drugs have been evaluated in oral therapy of travellers' diarrhoea, including co-trimoxazole, bicozamycin, furazolidone, fluoroquinolones, aztreonam, azithromycin and, most recently, rifaximin.[35-38,76-87] Antibacterial drugs have been shown to shorten the average or median duration of post-initiation of therapy diarrhoea by 20–65 hours compared with placebo. In various clinical trials, the measurement of duration of diarrhoea has been calculated from the time the subjects took the first dose of study medication until they passed their last unformed stool, after which they were declared well.[88] The parameter is referred to as 'time to last unformed stool' or TLUS. With the absorbed drugs, we found that 3 days' treatment was as effective as the US FDA-approved 5 days,[37] and that single-dose treatment was effective in most cases.[77,81,82,85] An unpublished observation we have made is that single-dose therapy with either absorbed fluoroquinolone or azithromycin is effective in most patients but not all and, when symptoms persist, it is necessary for subjects with travellers' diarrhoea to take a second and third dose.

When the nonabsorbed drugs bicozamycin and aztreonam were found to be effective in shortening the duration of travellers' diarrhoea, we felt that use of a nonabsorbed antimicrobial would become the optimal approach to self-treatment because of the safety of such preparations in all population groups and lack of contribution to antibacterial resistance for drugs important in the treatment of systemic infection. Unfortunately, bicozamycin is now marketed exclusively for veterinary use and is no longer available for human use. The manufacturer of oral aztreonam lost interest in the oral use of the drug after a company merger. In 1993, Charles Ericsson and I wrote an editorial describing the ideal antimicrobial agent for travellers' diarrhoea.[1] The drug should be orally administered, be active *in vitro* against prevalent pathogens, and be nonabsorbed so

**Table IV.** Advantages and limitations of currently active drugs useful in the treatment of travellers' diarrhoea

| Antimicrobial | Empirical therapy | Advantages | Limitations |
|---|---|---|---|
| Rifaximin | 200mg three times a day or 400mg twice a day for 3 days | As effective as other treatments, safest preparation | Reduced effectiveness against febrile dysenteric diarrhoea |
| Ciprofloxacin | 500mg twice a day for 1–3 days; 750mg once a day for 1–3 days | Generic drug that should be the least expensive | Resistance rate for *Campylobacter* spp. rising throughout the world, with most strains encountered in southern Asia being resistant |
| Levofloxacin | 500mg once a day for 1–3 days | Effective and single daily dose, convenient administration | *Campylobacter* spp. resistance rates may be similar to ciprofloxacin |
| Azithromycin | 500mg once a day for 1–3 days | Effective against all pathogens including ciprofloxacin-resistant *Campylobacter* spp., good backup medication | Speed of response slower than for other treatments |

that it could be given safely to all individuals without adverse effects or promotion of resistance to organisms important in extra-intestinal disease. A week after writing the article, a call was received from the Italian pharmaceutical company, Alfa Wassermann Ltd, saying that in the review article we had described their drug, rifaximin. We began evaluating this agent and found in a trial in Mexico that rifaximin was as effective as co-trimoxazole at a time when this drug was active *in vitro*. Later, in Mexico and Jamaica, we found that rifaximin was as effective as standard ciprofloxacin treatment in shortening the duration of and curing travellers' diarrhoea.[79,80]

Rifaximin is now licensed in the US for uncomplicated travellers' diarrhoea at a dosage of 200mg three times a day for 3 days. Rifaximin is also effective when given in a dosage of 400mg twice a day for 3 days.[80]

Table IV lists the advantages and limitations of the various antibacterial drugs used in self-treatment of travellers' diarrhoea.

## 8. Bacterial Resistance: Implication for Future Therapy and Chemoprophylaxis

Antimicrobial drugs that have been broadly used to treat a variety of bacterial infections have generally shown value for only a limited period of time because of increasing resistance. Ampicillin and co-trimoxazole, which were once of value in enteric disease therapy, are no longer useful in bacterial diarrhoea, including travellers' diarrhoea. For bacterial enteric infection, the fluoroquinolones have become the most widely used class of drugs for treatment of adults. Currently, ciprofloxacin resistance is occurring among enteric bacterial pathogens, of which the highest rate of resistance is seen with *Campylobacter* spp.[34,35,89,90] Some feel that use of this class of drugs in animal populations is important to the increasing rate of ciprofloxacin resistance in cases of human campylobacteriosis.[91] Fluoroquinolones are used broadly in individuals with a range of infections, including not only bacterial diarrhoea, but lower respiratory tract and urinary tract infections. It is likely that human use of fluoroquinolones is an important factor in stimulation of general resistance patterns among *Campylobacter* strains. We have seen a disturbing number of individuals with travellers' diarrhoea acquired in many regions of the world who did not respond clinically to fluoroquinolone treatment. In areas such as Thailand, where ciprofloxacin-resistant *Campylobacter* spp. are frequently encountered, short-course azithromycin has been employed with success,[35] although azithromycin resistance has occurred among some of the strains identified in US troops in Thailand.[92]

Table V presents the resistance patterns associated with antibacterial drugs used in prevention and treatment of travellers' diarrhoea.

## 9. Conclusion and Future Developments

There is no reason to think that the general environment of the high-risk areas into which tourists and business travellers venture will be hygienically improved in the foreseeable future. Thus, we must provide travellers with the best information on staying well and consider the use of chemoprophylactic drugs to avoid the illness. In the future, prophylactic

**Table V.** Patterns of bacterial resistance to antibacterial drugs used in chemoprophylaxis and therapy of travellers' diarrhoea[34,35,65,80,92,93]

| Antibacterial | Resistance concerns |
|---|---|
| Rifaximin | Resistance development is unusual during rifaximin therapy; most enteric bacteria pathogens other than *Campylobacter* spp. are susceptible *in vitro* to rifaximin |
| Ciprofloxacin and levofloxacin | Ciprofloxacin and levofloxacin resistance to *Campylobacter* spp. has become worldwide, particularly in Spain and Thailand |
| Gatifloxacin and moxifloxacin | The newer fluoroquinolones are active against ciprofloxacin-resistant *Campylobacter* spp. and may have value in travel medicine kits for diarrhoea and lower respiratory tract infections |
| Azithromycin | Azithromycin-resistant strains of *Campylobacter* spp. are not common but have been seen in US troops in Thailand |

rifaximin is likely to be used more extensively in view of its value against diarrhoeagenic *E. coli* and efficacy in preventing most of the illness that would otherwise occur in travellers to high-risk regions. All travellers to high-risk areas should be provided with medication for self-treatment of resultant disease.

Self-treatment will continue to be important among international travellers who develop illness in remote areas away from reliable medical care. Absorbed drugs have an advantage over poorly absorbed drugs because shorter courses of treatment are often effective. However, they may not be the preferred drugs for most travellers because of safety concerns for a range of different groups, including children, pregnant women, and the elderly and infirm. Also, there is an important public health reason to limit the use of fluoroquinolones and azalides to therapy of serious infections, rather than the broad range of less important infections where alternative drugs exist; this helps to decrease selective pressure and the emergence of resistance in pathogens causing life-threatening, extra-intestinal infections. The absorbed drugs also show greater potential for producing adverse effects. One approach is to provide all future travellers with nine 200mg tablets of rifaximin for standard treatment of illness, and to also provide three 500mg tablets of azithromycin for use in the unlikely case that they develop febrile dysentery. The unused azithromycin can be kept for future trips, and rifaximin can be used for the more common nondysenteric illness.

Those working in travel medicine should work to improve the hygiene levels in regions into which travellers enter. The most fundamental way to do this is to work with local governments to educate hotel and restaurant employees on food and personal hygiene principles. The Jamaican government has taken an interest in reducing the occurrence of diarrhoea among their visitors and, through education and implementation of strict public health measures in hotels and restaurants, has been able to reduce the rate of travellers' diarrhoea by >70% over a period of 6 years.[94,95]

Other interventions to reduce the occurrence of travellers' diarrhoea are under development in research centers. ETEC vaccines are being evaluated to prevent ETEC diarrhoea in view of the importance of this organism as a cause of illness. One approach is to incorporate the binding subunit of cholera toxin, which is similar to the corresponding moiety of the heat labile toxin of ETEC strains, in an orally administered vaccine against both ETEC and cholera.[96] A second approach is to use ETEC heat-labile enterotoxin as an adjuvant in transcutaneous delivery of ETEC antigens.[97] A third immunological approach is to use milk immunoglobulin with specific activity against ETEC virulence factors.[98] Each of these approaches are novel and worthy of pursuit. The challenge for immunoprophylaxis is to develop a multivalent vaccine that will prevent an important proportion of disease during high-risk travel time periods.

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