Diarrhea at the Summit

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Infectious diarrhea has been with human-kind since the beginning of recorded history. The organisms that cause infection are passed in the stool, and, subsequently, are ingested by a new host. During the past 120 years, industrialized countries have found ways to isolate human feces from the environment through the proper management of sewage and by regulating the public sale of food and meals at restaurants. Through these measures, infectious diarrhea has diminished as a major concern in developed countries, although the risk has not been eliminated entirely.

After World War II, leisure travel to developing countries became more popular, and air travel made it possible for more people to take shorter trips to exotic locales. Approximately 33% of travelers would develop acute diarrhea during the first 1–2 weeks of travel to these destinations [1]. Mexico was the first destination to be formally examined, and our early awareness of traveler’s diarrhea comes mainly from the observations of Dr. Benjamin Kean [1].

The etiology of traveler’s diarrhea at that time was mysterious. The only bacterial pathogens that had been isolated from the stool, besides Vibrio cholerae, were Salmonella and Shigella species, and those pathogens proved to be present only rarely in persons who acquired traveler’s diarrhea in Mexico [1]. A thorough search for protozoal pathogens confirmed that these organisms were not the main cause of traveler’s diarrhea [1]. At the same time, the use of poorly absorbed antibiotics as prophylaxis decreased the rate of infection with traveler’s diarrhea, which suggested that the unknown organisms were likely to be bacteria [2, 3].

A breakthrough came in the 1970s. A previously innocuous-looking Escherichia coli was proved, through insightful and tedious experiments involving loops of rabbit ileum, to produce a cholera-like toxin [4–6]. This organism, subsequently referred to as enterotoxigenic E. coli, was soon found to be one of the most frequent causes of traveler’s diarrhea worldwide [7]. Several years later, the discovery of the role of Campylobacter species filled in a significant blank area of the traveler’s diarrhea map [8, 9]. The demonstration that rotavirus is a significant cause of childhood gastroenteritis rounded out the decade’s contributions, although viruses cause only a small proportion of cases of traveler’s diarrhea [10].

In spite of this progress, uncertainty about the etiology and seriousness of traveler’s diarrhea lingered. The illness was often described using nicknames (e.g., “turst” and “Delhi belly”), which tended to trivialize the problem. Because the disease was known to be self-limited, for the most part, specific treatment was discouraged. Theories about the illness being due to “a change in normal flora,” jet lag, or a change in cuisine further undermined efforts to prevent and treat traveler’s diarrhea [1].

With the confirmation that the main pathogens causing traveler’s diarrhea were bacterial, however, antibacterial treatment now had a basis. Tradition held that, because traveler’s diarrhea was self-limited, treatment was not necessary and might even be harmful by prolonging the excretion of certain organisms after clinical cure had been achieved. Nonetheless, even before the efficacy of antibacterial treatment had been firmly established, there was interest in determining whether prophylactic antibiotics could reduce the risk of traveler’s diarrhea. Studies in the 1970s showed that prophylactic antibiotics indeed reduced the risk of traveler’s diarrhea [11]. How and whether these drugs should be recommended to travelers was debated at a diarrhea consensus panel held in 1985 [12]. With the threat that millions of tourists might start taking full-strength antimicrobial courses for weeks at a time, experts were concerned about adverse effects and increasing antimicrobial resistance. These experts did not end up agreeing with each other fully, but they managed to produce a consensus statement that discouraged the use of prophylactic antibiotics to prevent traveler’s diarrhea. Given that antibiotics had been found to be effective for the treatment of traveler’s diarrhea, experts began to steer travelers away from the use of prophylaxis and toward the use of empirical standby therapy for traveler’s diarrhea once it developed [13, 14].

Gradually, experience and controlled
trials showed that a very short course of antibiotics was enough to treat almost all cases of traveler’s diarrhea. By the beginning of the 1980s, the earliest employed antibiotics, ampicillin and the tetracyclines, had already become less useful because of the development of resistance. Co-trimoxazole filled the gap for several years, until resistance began to limit its utility as well. Nalidixic acid and, subsequently, the newer fluoroquinolones began to be used and are still in use in most of the world. However, quinolone-resistant Campylobacter species have now been documented in Thailand and Nepal, necessitating the use of azithromycin for empirical treatment in those countries [15] (P. Pandey, unpublished communication, May 2004).

The use of antibacterials to treat traveler’s diarrhea has brought a measure of control to travelers, who may be able to avoid spending days in bed, canceling travel or meetings, or having to trust their fate to the uncertainty of local medical care. The inevitable problem of antibiotic resistance has led some investigators to postulate that a nonabsorbed antibacterial might prove to be useful in the treatment or prevention of traveler’s diarrhea. Such a drug would have little use beyond the treatment of intestinal infections, and, thus, resistance would form only slowly. The first studies were done with bicoazamycin, which proved to be promising, but the drug was not pursued by the manufacturer. Recently, rifaximin, a virtually nonabsorbed antimicrobial that had been licensed in Europe for 15 years, was brought to the US market by Salix Pharmaceuticals.

With the advent of rifaximin, the question was raised as to whether nonabsorbed antimicrobial treatment is equivalent to treatment with an absorbed antimicrobial and whether the drug was safe enough to use as prophylaxis in millions of travelers. New interest in prophylaxis of traveler’s diarrhea has been generated by the observation that a small but significant percentage of travelers who experience a severe bout of gastroenteritis can eventually develop long-term symptoms, which are now being investigated under the provisional name of “postinfectious irritable bowel syndrome.” Could the prevention or minimization of a bout of traveler’s diarrhea help prevent this unwelcome outcome?

With the 50-year history of studies of traveler’s diarrhea in mind, and with the fact that this history began with studies using poorly absorbed antibiotics to prevent traveler’s diarrhea, we decided to hold a summit meeting on traveler’s diarrhea to address the half century of history and to see where we can and should go from here. The International Society of Travel Medicine sought and received an unrestricted educational grant from Salix Pharmaceuticals to sponsor the meeting, which was subsequently hosted by me in Jackson Hole, Wyoming. In response to concerns about drug company–sponsored meetings, I would like to say that I had complete freedom to invite whomever I chose and that I designed the program with complete freedom.

The event itself was special—in a hotel overlooking the Grand Teton, we assembled, in a wood-paneled room in comfortable chairs, a handpicked group of diarrhea experts. Many lifetimes of experience and, indeed, much of the modern history of traveler’s diarrhea research had been played out in the fieldwork and laboratories of the persons in attendance. This supplement to Clinical Infectious Diseases has been put together to memorialize the meeting and to share some of the excitement of stopping to take a look at what we have learned about traveler’s diarrhea and where our knowledge might lead us.

It is easy to lose perspective while focusing on traveler’s diarrhea, a disease that is characterized mainly by inconvenience and generally mild morbidity. As fascinating as the topic of diarrhea in travelers can be, it pales in significance when compared with the impact of the same organisms on the world’s children. Although the death of a tourist due to traveler’s diarrhea is almost unheard of, up to 10,000 children die of diarrhea every day. Thus, simply trying to arm tourists against the risk of diarrhea is ignoring the basis of the entire problem—the sanitation problems in developing countries. We need to continue to help rid developing countries of diarrhea, not just arm tourists against the risk.

It is also important to link the study of traveler’s diarrhea with infectious diarrhea in children for another reason. Traveler’s diarrhea has often been thought of as a syndrome—defined as short-lived, watery diarrhea or as occasional dysentery. However, this artificial distinction of traveler’s diarrhea as something that only occurs in travelers is misleading and is not scientifically correct. We need to realize that, as Dr. Mary Wilson points out in her article in this supplement [16], “traveler’s diarrhea is defined by the circumstances of acquisition,” not the particular symptoms or etiology. What we are really dealing with is infectious diarrhea in a susceptible host in a circumstance where the risk of exposure is increased.

Knowing what we do about the etiology of traveler’s diarrhea and the established fecal-oral route of transmission, it should be theoretically possible to teach travelers how to avoid eating contaminated food and thus avoid diarrhea. The fact that identifying and avoiding contaminated food must be possible is so widely believed that it comes as a surprise to discover that there is virtually no support in the literature for the effectiveness of this intervention. Restaurant hygiene practices probably play a much more significant role in the transmission of traveler’s diarrhea than do individual food choices. Thus, the risk of traveler’s diarrhea may diminish only when the preparation and handling of food achieves levels that we associate with industrialized nations.

The subject of antibiotic resistance was discussed at the meeting, although a comprehensive review was not undertaken. Some themes emerged, however, that are worthy of being pursued further. There was a general consensus that the use of...
an antibiotic to treat traveler’s diarrhea will not induce resistance of that organism in the country being visited. Only when that antibiotic is in general use in that country will antibiotic resistance occur. It is currently unclear what role the routine use of antibiotics in animals may be playing in developing countries in relation to the subsequent creation of resistant pathogens. There are several studies in developed countries linking the emergence of quinolone-resistant Campylobacter species with the increasing use of quinolones in animal feed [17].

In the end, the articles in this supplement help to reinforce a key notion in traveler’s diarrhea: traveler’s diarrhea is not a disease of travelers, it is a disease of the developing world (and, to a lesser degree, the industrialized world) for which travelers are an incidental host. The nature of the transmission of the disease has to do with the handling and preparation of food, and travelers remain most subject to traveler’s diarrhea in countries with the poorest traditions of sanitation and restaurant hygiene. The seriousness of the disease depends possibly on host factors and access to definitive treatment. Antibacterials clearly shorten the length and severity of illness due to organisms that have a known treatment. In poorly understood ways, the intestine can be altered by a bout of severe gastroenteritis, leading to months or years of gastrointestinal symptoms. The recognition of the possibility of long-term sequelae resulting from an acute episode of gastroenteritis has led to renewed interest in preventing or minimizing the severity of traveler’s diarrhea.

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References