Travelers' Diarrhea: The Other Side of the Coin

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According to the United Nations World Tourism Organization, an annual increase of 4% in international travel for several years resulted in 1323 million international travel worldwide in 2017, including visits to low-income countries in Asia and Africa [1]. Global tourism presents enormous social and economic benefits, especially to low-income countries. International travel has been estimated to account for 10% of the world's gross domestic product, 7% of global trade and 10% of employment [1].

International travel also presents negative impacts. One of the most important is health-related conditions, especially among immune-compromised populations [1,2]. Acute diarrhea is the most common medical condition reported among travelers, both adults and children [3-5]. It presents in 10–69% of travelers, depending on the destination and travel characteristics, and is associated with considerable inconvenience, expenses, morbidity, and hospitalizations. Acute diarrhea sometimes progresses to chronic diarrhea and irritable bowel syndrome. These conditions develop in 3–17% of those affected [3,4,6]. Travelers' diarrhea is essentially an infectious disease, caused by bacterial, viral, or protozoal pathogens [4,7]. Positive microbial detection has recently increased from only 50% [4] to 98%, with the use of a highly-sensitive multiplex polymerase chain reaction FilmArray [8].

Travelers' diarrhea is usually defined as passage of three or more unformed stools each day, usually with at least one additional enteric symptom, such as vomiting, abdominal pain, or cramps, occurring within the first 2 weeks of travel [7]. Inherent to the definition is travel from a high-income to a low-income resource-limited destination [7], as the acquisition of the diarrhea reflects the increased likelihood of fecal-oral transmission of gastrointestinal pathogens due to poor food and water hygiene in the travel destination [3,4]. Indeed, travelers' diarrhea in Israel is contacted, discussed, and reported among Israeli adults and children who travel from Israel to low-income countries [9,10].

THE OTHER SIDE OF THE COIN

In their interesting report in the current issue of the *Israel Medical Association Journal* (*IMAJ*), Meltzer and colleagues [11] highlight another aspect of a very special form of travelers' diarrhea. Using a retrospective electronic-based anonymous survey, they examined the rate of acute diarrhea among 97 medical students from the United States and Canada who relocated to central Israel for 4 years of study at Sackler School of Medicine – New York State/American Program of Tel Aviv University. The students were relatively young, with a mean age of 24.2 years. Most of them reported being healthy prior to relocation, although 13.4% had previous chronic gastrointestinal conditions, including irritable bowel syndrome, inflammatory bowel disease, and lactose intolerance. The results of the study were rather impressive. The prevalence of acute diarrhea during the study period among the relocated medical students was 69.1% [11].

The epidemiological and clinical features of the acute diarrheal syndrome among the students who relocated to Israel were similar to those reported in studies of classic travelers' diarrhea, namely:

- The definition of the episode was similar: three or more loose/watery stools per day with or without additional symptoms such as fever, vomiting, or abdominal pain [7,11]
- The overall prevalence was well within the range described for travelers' diarrhea [4,11]
- The incidence of diarrhea was highest in the first month after relocation, 34.8 per 100 student-months, and then declined sharply to 3–6/100 during the rest of the first year, and to 1.3 per 100 student-months during years 2–4; again, similar to travelers' diarrhea
- A higher incidence of acute diarrhea was noted in the younger students, similar to the findings in travelers' diarrhea [4,11,12]
- Street food consumption by the students was very common (> 92%), similar to habits of long-term travelers who often do not stay in hotels
- Regarding the clinical course of diarrhea, most students in the present study recovered within one week, often with self-medication; and nearly 5% had prolonged diarrhea of more than 3 months; again, similar to the course reported in travelers' diarrhea [3,4,11]

This editorial therefore suggests that the study by Meltzer et al. [11] actually represents the other side of the coin of travelers' diarrhea in Israel.

How can the results of the study be explained? Israel is a high-income country with relatively low rates of food- and water-borne enteric infections. It is not perceived

by the U.S. Centers for Disease Control and Prevention [13] or according to the registry of the GeoSentinel Global Network [14] as a usual source of travelers' diarrhea. Travel between two high-income countries should not theoretically be associated with travelers' diarrhea.

However, although data are limited, evidence suggests that travel between two high-income locations can be associated with the acquisition of acute diarrhea. Diarrhea was reported among European travelers to North America and southern Europe [15]. Findings similar to those in the present study were observed in foreign students who relocated to United States [16]. An interview of 215 foreign students matriculating at the University of California, Los Angeles, USA, showed that the attack rate of acute diarrhea during the first month after arrival was 14%. In a comparative group of 238 U.S. students, the attack rate of diarrhea in one month was only 8.4%. Interestingly, in the group of U.S. students, an increased incidence of diarrhea was noted among those who arrived from outside California to Los Angeles [16].

The findings of increased incidence of acute diarrhea after travel to high-income locations may relate to the behavior of the travelers, for example frequent street food consumption and less than usual adherence to personal hygiene, and also to potential differences of enteric pathogens in the new locations as compared to the original ones. These results support the idea that acquiring travelers' diarrhea is not limited to travel to developing countries.

The study by Meltzer and colleagues [11] has significant limitations and thus was appropriately designated as a pilot. No microbiology data are provided. It is therefore unclear if enteric pathogens that are more common in Israel caused the high rates of acute diarrhea and it is therefore unclear which preventive measures – vaccines or antimicrobial agents – might be effective.

The low rate of responders (97/252) could cause a selection bias, with a higher response among students with diarrhea and therefore overestimation of its rate. Moreover, the relatively small sample limits the power of the study and precludes the identification of risk factors for diarrhea. The relatively long lag period from the students' relocation to their respond to the survey – the median time was 3 years, with a range of 0.7 to 6.9 years – raises the possibility of recall bias and reduces the validity of the results. Following this important pilot study [11], well-designed prospective studies, also in other high-income countries, are recommended to overcome these limitations.

TRAVEL MEDICINE AS A MOVING TARGET

The study by Meltzer et al. [11] in the current issue of *IMAJ* actually accentuates the continuous changes occurring in the field of travel medicine, as is evident in most medical specialties.

Measles is probably one of the best examples to highlight this concept of change. According to the World Health Organisation (WHO) European Region, 82,596 measles cases were diagnosed in Europe in 2018, a few decades record high, with 72 deaths [17]. Israelis traveling to Europe were therefore instructed to verify complete vaccination against measles and to take precautions while traveling in Europe, especially for infants who are too young to be vaccinated against measles and for immune-compromised individuals.

Before 2015, Zika virus was not discussed in travel clinics, either in pre-travel consultation or in the post-travel evaluation of medical complaints. Zika virus has since emerged as a major travel-related issue, especially in men and women of reproductive age travelling to South America [18]. A comprehensive nationwide prospective study of 1188 Israeli travelers documented that 30 had Zika virus infection, and that since 2017, a geographic shift was noted, with 60% of the cases occurring after travel to Southeast Asia [18]. Likewise, with the increased worldwide use of the Rota virus vaccine, noroviruses have emerged as a frequent cause of travelers' diarrhea [19]. Regarding the increasing bacterial resistance to antimicrobial agents, travelers' diarrhea can be caused by multiply-resistant *Escherichia coli*, which has become an alarming problem [20]. The human intestinal microbiome, whose role in health and illness has become increasingly recognized, is also considered to contribute to the risk of acquiring travelers' diarrhea, especially after visiting tropical regions.

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Capsule

Gab3 adaptor prevents NK cell dysfunction

Natural killer (NK) cells are innate effector cells that help defend mammals from viral infections and cancer while acting locally in the uterus to support successful pregnancy outcomes. **Sliz** et al. performed a chemical mutagenesis screen in mice and identified Gab3 as a scaffolding protein required for NK cell priming and peripheral expansion in response to cytokines. Gab3 mutant mice exhibited defects in their ability to control tumors and successfully complete pregnancies because of impaired NK cell function. Thus, an adaptor protein is required to achieve full NK cell function, and subtle uterine NK cell perturbations can contribute to pregnancy failure.

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Eitan Israeli

Capsule

Ceramides in focus

Excess calorie intake can ultimately lead to a metabolic syndrome that interferes with fat or lipid metabolism. There are many different types of lipids, and it has been widely debated which are the true culprits underlying metabolic disorders. **Chaurasia** and co-authors reported that ceramides are the major contributor to insulin resistance and fatty liver disease. This appears to be caused by the enzyme dihydroceramide desaturase 1 (DES1) is normally involved in ceramide production by inserting a double bond into the backbone of the molecule. In mice fed a high-fat diet, deletion of DES1 improved glucose and lipid metabolism.

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Eitan Israeli

Capsule

Effects of an FcγRIIA polymorphism on leukocyte gene expression and cytokine responses to anti-CD3 and anti-CD28 antibodies

The low affinity Fcγ receptor, FcγRIIA, harbors a common missense mutation, rs1801274 (G›A, Arg131His) that modifies binding affinity to human IgG2 and mouse IgG1 antibodies and is associated with increased risk of autoimmune disease. Despite the important role of the Arg131His variant, little is understood about heterozygous genotype effects on global gene expression and cytokine production during an FcγR-dependent response. To address this gap in knowledge, **Stein** et al. treated human whole-blood samples from 130 individuals with mouse IgG1 anti-CD3 and anti-CD28 antibodies and characterized the genome-wide gene expression profiles and cytokine production among individuals stratified by rs1801274 genotype. The analysis revealed that the levels of four cytokines (IFN-γ, IL-12, IL-2, TNF-α) and global gene expression patterns differed between all three genotype classes. Surprisingly, the heterozygotes showed suboptimal T cell activation compared to cells from individuals homozygous for the higher-affinity FcγRIIA allele (GG; Arg/Arg). The results of this study demonstrate that IgG response varies among all rs1801274 genotype classes and results in profound differences in both cytokine responses and gene expression patterns in blood leukocytes. Because even heterozygotes showed dampened global responses, these data may provide insight into the heterogeneity of outcomes in cytokine release assays and immunotherapy efficacy.

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