

Antibiotic Self-treatment of Travelers' Diarrhea: Helpful or Harmful?

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Keywords. travelers' diarrhea; ESBL Enterobacteriaceae; post-infectious irritable bowel syndrome; antibiotics.

In recent years, numerous studies have focused on the importance of imported drug-resistant bacteria, especially extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-PE) and carbapenemase-producing Enterobacteriaceae [1]. Although initial reports were related to travelers who sought healthcare in developing countries, it is now clear that healthy returned travelers are at risk for colonization with ESBL-PE and potentially spreading these into the community, especially to those whose underlying health problems put them at risk for severe infection due to antibiotic-resistant organisms. Travel, travelers' diarrhea (TD), and antibiotic use independent of travel have all been shown to be associated with carriage of ESBL-PE; however, previous studies have not looked at these risk factors in concert, particularly the role of antibiotic self-treatment of TD.

In this edition, Kantele and colleagues present the results of an excellent prospective study that provides very compelling

evidence that antimicrobials increase a traveler's risk of colonization by ESBL-PE [2]. In their study of 430 Finnish travelers, 21% became colonized by ESBL-PE. Remarkably, 80% of travelers who self-treated TD with antibiotics in the Indian subcontinent were found to be colonized with ESBL-PE. They found that geographic region, occurrence of TD, and the use of antimicrobials for TD were independent risk factors associated with acquisition of ESBL-PE, and call for caution in the reflexive use of antibiotics for mild or moderate TD. Unsurprisingly and quite reasonably, the authors' primary concern is that colonized travelers might contribute to the spread of resistant intestinal bacteria to the population at large in developed countries.

In reality, however, one can see why a traveler who spends a considerable amount of money on an exotic international trip would want to carry and use an antibiotic for self-treatment for rapid relief of TD. Furthermore, the widespread problem in developing countries of counterfeit drugs, and the use of injections not infrequently administered with unsterile equipment to treat TD, would be a strong impetus for travelers to carry an antibiotic for self-treatment. A survey of healthcare providers in tourist resorts showed that 20%–86% of travelers would have undergone an invasive procedure (infusions, injections, and diagnostic venipuncture) if

they had presented with diarrhea and fever [3]. "So what?" you say. A global World Health Organization survey has shown that 10%–75% of injections administered in developing countries may be given with unsterile equipment [4].

Although it is clear from this study that more judicious use of antibiotic self-treatment of TD is necessary, the question that needs further study is: what criteria should be used to recommend the use of antibiotics? More stringent criteria for self-treatment might include the presence of fever or other constitutional symptoms, or associated gastrointestinal symptoms such as severe abdominal pain, blood in stool, cramping, tenesmus, and vomiting. In a study from the Netherlands, high fever and bloody diarrhea were considered to be serious enough to recommend antibiotic self-treatment [5]. However, most travelers have neither of these symptoms, as enterotoxigenic *Escherichia coli* (ETEC) and enteroadherent *E. coli* are the most frequent causes of TD. What do we recommend to travelers with significant watery diarrhea that interferes with daily activity on short trips? Even though travel medicine experts at home can set criteria for symptoms that are needed before self-treatment should be initiated, from a practical point of view, it will be the individual traveler in the field and not the travel medicine advisor who will decide on what constitutes

Received 18 November 2014; accepted 22 November 2014.

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Clinical Infectious Diseases®

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DOI: 10.1093/cid/ciu961

“severe” enough symptoms to use an antibiotic.

Although the results of this study point out a legitimate concern about spread of antibiotic resistance, an argument may also be made that the consequences to the individual traveler who uses antibiotics may be significant as well. Early self-treatment with a fluoroquinolone or macrolide has been shown to be effective in ameliorating the symptoms of travelers’ diarrhea and reducing the time to last unformed stool to within 24 hours of onset of illness. However, the consequences to the traveler who uses antimicrobial therapy have been largely ignored. Concurrent with self-treatment of TD has been an increasing incidence or recognition of postinfectious sequelae of TD episodes, specifically, a syndrome that is now being called postinfectious irritable bowel syndrome (PI-IBS).

From the perspective of travel medicine, there are several questions that relate to sequencing the gut microbiome, and Kantele et al provide some early answers. How does travel affect the human gastrointestinal microbiome? What is the duration of these changes after travel? How do changes in flora from travel correlate with clinical gastrointestinal illness, both acute and chronic? And what travel-associated and other factors are associated with changes in gastrointestinal flora and the development of PI-IBS?

A change in gut microflora has also been shown to increase the susceptibility of the traveler to certain pathogenic infections. Nelson et al showed that a subset of children with norovirus-associated diarrhea had significantly altered microbiota characterized by a reduction in Bacteroidetes and increase in Proteobacteria [6]. Diversity or absence of certain key species might predict disease severity as well as the risk of long-term sequelae such as

altered gut function and/or impaired mucosal immunity, requiring reconsideration of basic concepts of colonization, infection, and disease.

We are now only beginning to learn the significance of alterations in gut microflora. Whether colonization by resistant bacteria might predispose to an individual’s failure to downregulate intestinal inflammation and lead to the development of a postinfectious inflammatory condition such as PI-IBS is a provocative hypothesis that needs to be tested.

Of note, as there is increasing resistance among enteric bacteria to the fluoroquinolones and with an increase in prevalence of *Campylobacter* as an etiologic agent of TD, focus has turned to the use of macrolides such as azithromycin for self-treatment of TD. In recent animal studies, however, Cho et al have shown that the disruption of the gut microflora by macrolides is significantly greater than that seen with the fluoroquinolones, and this should give pause to the clinician who reflexively recommends the use of antibiotics for self-treatment for mild or moderate cases of TD [7].

So if we are to limit the use of antibiotics to cases of TD that are more severe, what can we offer the traveler? We may need to focus on preventive measures that are non-antimicrobial in nature. Recent work has begun on the evaluation of prebiotics, probiotics, and synbiotics in prevention of TD. It would be interesting to evaluate whether these interventions prevent the colonization by resistant bacteria in travelers as well. Notably, vaccines and hyperimmune bovine colostrum containing antibodies that protect against ETEC are already available in some countries. In the antimicrobial realm, chemoprophylaxis with a nonabsorbable, nonsystemic antibiotic may also be an appropriate

recommendation, although there are no published data on microbiome alterations with luminal antibiotics such as rifaximin.

It is clear that antibiotic self-treatment of TD may contribute to the global spread of ESBL-PE and may be a factor in the etiology of PI-IBS. Are travel medicine advisors and travelers prepared to change their approach to the management of the single most frequent cause of illness during international travel? Stay tuned!

Note

Potential conflict of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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