Correspondence

Evidence of Efficacy Is Not Enough to Develop Recommendations: Antibiotics for Treatment of Traveler's Diarrhea

To the Editor—In a recent article comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen for the treatment of traveler's diarrhea, Tribble et al. [1] conclude that "Single-dose azithromycin is recommended for empirical therapy of traveler's diarrhea acquired in Thailand and is a reasonable first-line option for empirical management in general" (p. 338). We would like to challenge this statement, which is based on a small improvement in the cure rate at 72 h (96% for single-dose azithromycin and 85% for the 3-day azithromycin-based regimen, compared with 71% for the 3-day levofloxacin regimen). We believe that Tribble et al. [1] do not provide sufficient evidence to support their conclusions.

First, the study was conducted among a highly selected population (US military personnel). The disease was more severe (17%–31% of patients had documented fever, and 12%–16% had gross blood in stools) than in studies conducted among the standard traveler population [2]. The enteric pathogens that were recovered and the pattern of microbial resistance were not representative of that found in studies conducted in Thailand and elsewhere in the world [3]. Moreover, the impact of concomitant use of doxycycline in 87% of the patients is unclear. It is obvious that, therefore, their findings cannot be generalized to the entire population of travelers.

Second, they did not include a placebo arm as a control. This is worrying, especially when showing that single-dose azithromycin had greater efficacy than the 3-day azithromycin regimen. Without a placebo group, it is impossible to calculate the number needed to treat, which is essential to evaluate the benefit of the intervention proposed. The basic assumption of the authors is that antibiotic use is appropriate in treating traveler's diarrhea. In fact, a Cochrane review showed that antibiotic use for treatment of traveler's diarrhea has only a very small benefit (reducing the duration of diarrhea by 0.7–1.5 days and the number of loose stools by 1.6 on the first day of treatment, 2.1 on the second day, and 1.4 on the third day) [4]. When extrapolating these findings to the general population of travelers, for every 6 individuals with traveler's diarrhea, 3 will be cured at 72 h if none of them take antibiotics; 4 of them will be cured at 72 h if all of them take antibiotics, at the cost of 1 patient with adverse events.

To develop evidence-based guidelines for the management of traveler's diarrhea, we believe that there is a need to conduct placebo-controlled effectiveness studies involving unbiased populations traveling to different destinations. Even if effectiveness is demonstrated, this is not enough. To develop sound recommendations, there will still be numerous questions that need to be answered, such as: is there any clear benefit to treating traveler's diarrhea at an early stage? Does the small benefit associated with antibiotic treatment of clinical symptoms outweigh the risk of adverse events? Is it worth giving antibiotics to travelers when there is good proof that, in vivo, these drugs select drug-resistant pathogens in the gut flora? Why should traveler's diarrhea be treated with antibiotics, given the demonstration that patients with drug-resistant enteropathogens have clinical outcomes similar to those with fully susceptible enteropathogens? What is the impact of large-scale (irrational) use of antibiotics on the dynamics of bacterial resistance in host countries, given that such countries cannot afford expensive drugs to manage multidrug-resistant pathogens? Lastly, why should travel medicine experts continue to ignore World Health Organization recommendations that restrict antibiotic use to patients with increased risk of complications or with signs of severe disease? Unless these issues are addressed in an unbiased way, we will continue to have recommendations that rely on low-quality evidence and are based on expert opinions or—even worse—on commercial interest.

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