Antimicrobial Resistance of *Shigella* Isolates Causing Traveler’s Diarrhea

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*Shigella* isolates were identified as a cause of traveler's diarrhea in 67 (10%) of 675 patients and were tested for resistance to seven antimicrobial agents in a comparative study with those causing nontraveler's diarrhea in Spain. Ampicillin and chloramphenicol resistance was more frequent in *Shigella flexneri* (60 and 46%, respectively) than in *Shigella sonnei* (32 and 18%, respectively) and in travel-related isolates (*P* < 0.05 and 0.04, respectively). Of *S. sonnei* isolates from patients with traveler's diarrhea, 73 and 54% showed tetracycline and trimethoprim-sulfamethoxazole resistance, respectively, compared with only 8% of isolates from patients without a history of travel to developing countries (*P* < 0.0007 and *P* < 0.0002). Low-level resistance to cephalosporins was found, whereas quinolone-resistant strains were not detected among travel-related *Shigella* isolates. Thus, quinolones may be an effective alternative therapy for travel-related shigellosis.

*Shigella* species remain an important cause of gastrointestinal illness manifested by watery diarrhea that may progress to mucoid bloody diarrhea or dysentery (7). The severity of the disease is determined in part by the infecting species; infections due to *Shigella dysenteriae* usually progress to dysentery, which may also occur with infections caused by *Shigella flexneri*, whereas *Shigella boydii* and *Shigella sonnei* generally cause a self-limited, watery diarrhea. *Shigella* species cause gastroenteritis in industrialized as well as in less-developed countries and are also a cause of traveler's diarrhea. It has been shown that the treatment of shigellosis with an appropriate antibiotic to which the *Shigella* species is susceptible can successfully reduce the diarrhea and systemic symptoms as well as induce shedding of the organism in stool (19, 20).

Each year 12 million persons travel from an industrialized country to a developing country in the tropics or subtropics (3). These travelers experience a high rate of diarrhea caused by a wide variety of enteric pathogens acquired by ingestion of contaminated food or water (9). Around 50% of Spanish travelers to developing countries develop diarrhea (8). The purpose of this study was to determine the prevalence of antimicrobial resistance among *Shigella* strains associated with traveler's diarrhea in comparison with the strains isolated from nontravelers from Spain.

A total of 675 patients who attended the outpatient travelers' clinic suffering from traveler's diarrhea after a trip to developing countries were included in this study, in addition to 850 patients without such travel history. Of the patients with traveler's diarrhea, six had previously taken cotrimoxazole and three had taken ampicillin. Traveler's diarrhea was defined, according to the criteria of Merson et al. (13), as the occurrence between 12 h after arrival in and 5 days after departure from the country visited of three or more episodes of watery diarrhea within a 24-h period with or without other symptoms or as the occurrence of unformed stools accompanied by one of the following: abdominal cramps, nausea, vomiting, tenesmus, fever, chills, or prostration. To isolate *Shigella* species, stool samples were inoculated into MacConkey's agar and Salmonella-Shigella agar (Becton Dickinson, Heidelberg, Germany), and the resulting colonies which exhibited characteristics of *Shigella* spp. were identified by conventional biochemical methods. Subsequently the species were identified with specific antisera against *S. flexneri*, *S. sonnei*, and *S. dysenteriae* (Diagnostic Pasteur, Marnes-la-Coquette, France) and *S. boydii* (Difco Laboratories, Detroit, Mich.). Antimicrobial susceptibility tests were performed by an agar diffusion disk method as advocated by the National Committee for Clinical Laboratory Standards (14). Mueller-Hinton agar was obtained from Becton Dickinson, and antimicrobial disks (ampicillin, 10 μg; chloramphenicol, 30 μg; tetracycline, 30 μg; trimethoprim-sulfamethoxazole, 1.25/23.75 μg; norfloxacin, 10 μg; ciprofloxacin, 5 μg; and cephalothin, 30 μg) were obtained from BBL Microbiology Systems, Becton Dickinson, Cockeysville, Md.

*Escherichia coli* ATCC 25992, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control organisms and tested weekly. Each time a new lot of Mueller-Hinton agar was introduced, *Enterococcus faecalis* ATCC 29212 was tested to detect the presence of inhibitors of trimethoprim-sulfamethoxazole.

The MIC of ciprofloxacin (Bayer, Leverkusen, Germany) was determined by using an agar dilution method with an inoculum of 106 CFU per spot and in accordance with the guidelines established by the National Committee for Clinical Laboratory Standards (15). In contrast to other published studies, many of which are selective in terms of traveler types and are restricted to certain geographical areas, this study includes a travelers to a variety of tropical countries and regions. *Shigella* species were isolated as a cause of traveler's diarrhea in 67 patients (10%) (Table 1). *S. flexneri* was isolated more frequently (52%) than *S. sonnei* (33%). A total of 40 isolates (5%) were recovered from 850 nontraveler patients; in this case, *S. sonnei* was found more frequently (65%) than *S. flexneri* (35%). *S. boydii* (6%) and *S. dysenteriae* (9%) were also found as a cause of traveler's diarrhea but were not found in nontravelers in Spain. Isolates were recovered from travelers to all geographical areas; how-

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ever, those from travelers to India (13%) and East Africa (17%) were isolated more prevalently, and three of four strains of S. boydii were from travelers to India. These results are in accordance with those presented by Black (3), who reported that in Latin America, a median of 8% (range, 0 to 30%) of traveler’s diarrhea episodes were caused by Shigella species, whereas in the Asia and Africa, the percentage of episodes with Shigella species ranged from 0 to 13% and from 0 to 15%, respectively. Antibiotic resistance to ampicillin and chloramphenicol was more frequent in S. flexneri (60 and 46%, respectively) than in S. sonnei (32 and 18%, respectively) and in travel-related isolates (P < 0.05 and P < 0.04, respectively) (Table 2). The resistance to ampicillin was similar to that in other reports (for a review see reference 1), although the majority of those publications do not differentiate between species. Trimethoprim-sulfamethoxazole resistance was more frequent in S. sonnei than S. flexneri travel-related isolates (54 and 37%, respectively), but without a significant difference. These results are similar to or higher than the percentages described by Bennish and Salam (1). Ampicillin was the drug of choice for the treatment of shigellosis (11) until ampicillin-resistant Shigella strains became widespread in several geographical areas. The high prevalence of resistance to ampicillin made trimethoprim-sulfamethoxazole the drug of choice. Although trimethoprim has been recommended for the therapy of shigellosis (6, 21), its use should be reconsidered in view of the high frequency of resistance to trimethoprim-sulfamethoxazole in isolates from travelers returning from all regions documented. Of S. sonnei isolates from patients with traveler’s diarrhea, 73 and 54% showed tetracycline and trimethoprim-sulfamethoxazole resistance, respectively, compared with only 8% of isolates from nontravelers (P < 0.007 and P < 0.0002). However, tetracycline alone is no longer useful for the treatment of shigellosis because the majority of Shigella isolates found in diverse geographical locations are now resistant as a result of the intensive use of this antibiotic in developing countries (4). Multiple resistance was observed in 72% of S. sonnei and 63% of S. flexneri isolates from travelers. The most common multiresistance pattern in S. sonnei was resistance to trimethoprim-sulfamethoxazole and tetracycline, whereas for S. flexneri it was resistance to ampicillin, chloramphenicol, and tetracycline. Three of the four isolates of S. boydii presented a pattern of resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, and tetracycline. Although only a small number of S. dysenteriae strains were studied, their resistance to ampicillin (33%), trimethoprim-sulfamethoxazole (50%), tetracycline (83%), chloramphenicol (33%), and cephalexin (17%) is worthy of mention. Resistance to cefalexin was very low in both S. flexneri (2%) and S. sonnei (4%). At least three controlled studies of the use of cefalosporins for the treatment of shigellosis have been conducted (12, 16, 17). The utilization of narrow- and extended-spectrum cephalosporins was found to be ineffective (16, 17), whereas ceftriaxone produced a moderate reduction in the frequency of stools and duration of fever but not in the duration of diarrhea compared with placebo (12). Nevertheless, all Shigella species tested were susceptible either to norfloxacin or to ciprofloxacin. Quinolones accumulate in high concentrations in serum and stool and have been found to be effective in previous studies of patients with shigellosis (2, 5, 10). Quinolones, therefore, may be effective alternative therapy for travel-related shigellosis. Recently, Ries et al. (18) found that the MIC of ciprofloxacin for 13 S. dysenteriae isolates was 0.25 μg/ml, whereas the MIC of this antibiotic for S. flexneri and S. sonnei was <0.06 μg/ml. In our study, the MIC of ciprofloxacin for all the isolates was <0.007 μg/ml, regardless of which species was tested.

Resistant strains emerging anywhere in the world can be of direct importance in public health, as they may be introduced repeatedly by travelers. In general, in this study, the Shigella strains isolated from patients with traveler’s diarrhea exhibited a higher rate of resistance than those in previous studies (1). It has also been shown that S. sonnei from patients with traveler’s diarrhea, the most frequently isolated Shigella species in Spain, is more resistant to chloramphenicol, trimethoprim-sulfamethoxazole, and tetracycline than isolates from nontraveler’s diarrhea. Therefore, future monitoring of antimicrobial resistance in Shigella species both in our country and abroad will be necessary to control the increase in the level of resistance.

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REFERENCES


