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Nalidixic Acid-Resistant *Salmonella enterica* Serovar Typhi with Decreased Susceptibility to Ciprofloxacin Caused Treatment Failure: A Report from Bangladesh

S. M. Zahurul Haque Asna, J. Ashraful Haq[1]* and Md. Mushfequr Rahman[2]

Department of Microbiology, Chittagong Medical College, Chittagong,
[1]Department of Microbiology, Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine & Metabolic Disorders, Dhaka 1000 and
[2]Department of Immunology, National Healthcare Network, Dhaka 1205, Bangladesh

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Typhoid fever is endemic in Bangladesh (1). Until the mid-1980s, ampicillin, chloramphenicol, or co-trimoxazole was the standard treatment for typhoid fever. Since then, ciprofloxacin or third generation cephalosporins (namely, ceftriaxone) have become the first line of treatment for typhoid fever (2). In 1999, ceftriaxone-resistant *Salmonella typhi* was detected in Bangladesh (3). Here we describe two cases of typhoid fever, that were unresponsive to treatment with ciprofloxacin.

A 25-year-old man was admitted to Chittagong Medical College Hospital (a teaching hospital in the southern part of Bangladesh) with a high fever. Blood culture yielded growth of *Salmonella enterica* serovar Typhi. Antibiotic susceptibility testing was performed by Kirby-Bauer disk diffusion technique (4) with disks from Oxoid, Ltd., Hampshire, UK. The strain was found to be susceptible to ciprofloxacin (5 μg disk) and ceftriaxone (30 μg disk), but resistant to nalidixic acid (30 μg), ampicillin (10 μg), chloramphenicol (30 μg), and co-trimoxazole (25 μg). The patient was treated with ciprofloxacin (1 g daily) for 14 days without improvement. The patient was then given intravenous ceftriaxone (2 g daily), and remission of fever occurred on the third day. Subsequent to this case, another patient with typhoid fever (a 20-year-old male), who was admitted to the same hospital, likewise did not respond to treatment with ciprofloxacin. *S. enterica* serovar Typhi was isolated from his blood. The isolate was found by the disk diffusion test to be susceptible to ciprofloxacin (5 μg) and ceftriaxone (30 μg), but resistant to nalidixic acid (30 μg). Moreover, the isolate was also resistant to ampicillin, chloramphenicol, and co-trimoxazole. The patient responded to treatment with intravenous ceftriaxone.

The antibiotic therapy for typhoid fever in Bangladesh is based on the antibiogram of the isolated organism. The first line of antibiotics for the treatment of typhoid fever in adults is 3 tablets of co-trimoxazole (each contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole) every 12 h, or ampicillin 2-4 g/day orally in four divided doses, for 2 weeks. Chloramphenicol, at a dose of 500 mg orally every 6 h for 2 weeks, is also used as a first-line drug. The second and third regimes include ciprofloxacin (500 mg orally every 12 h for 2 weeks) and ceftriaxone (2 g intravenously once a day for 5 days), respectively. In both cases above, the isolated organisms were resistant to first-line antibiotics.

Later, the minimum inhibitory concentrations (MIC) of ciprofloxacin and of nalidixic acid of the isolates of *S. enterica* serovar Typhi from the two patients mentioned above were determined by agar dilution method (5). The MICs of ciprofloxacin were between 0.4-0.8 mg/L. No plasmid was found in either strain. The *gyrA* mutations mediating fluoroquinolone resistance were not analyzed. Although the MIC range of both strains was below the breakpoint for ciprofloxacin recommended by the National Committee for Clinical Laboratory Standards (4 mg/L), the treatment with ciprofloxacin failed because these patients were infected with strains of *S. entrica* serovar Typhi that had decreased susceptibility to ciprofloxacin (MIC: ≥0.25 mg/L). This decreased susceptibility could not be detected by the disk diffusion method; both strains were found to be fully susceptible to the 5 μg ciprofloxacin (zone of inhibition: >21 mm) disk. However, both strains were found resistant to the 30 μg nalidixic acid disk. Therefore, nalidixic acid resistance determined by the disk diffusion method could be an indication of decreased susceptibility to ciprofloxacin.

Since 1997, infection with nalidixic acid-resistant *S. typhi* (*S. enterica* serovar Typhi) with decreased susceptibility to ciprofloxacin has been reported from Vietnam, Tajikistan, the UK, and India (6-9). In the UK, the percentage of *S. enterica* serovar Typhi strains showing decreased susceptibility to ciprofloxacin increased from 2.7% in 1995 to 21% in 1998. Treatment failure with ciprofloxacin occurred in such cases. The majority of these strains were imported from India and Pakistan. Our two cases have demonstrated that strains of *S. eneterica* serovar Typhi with decreased susceptibility to ciprofloxacin are present in Bangladesh. The routine disk diffusion test with ciprofloxacin disk alone is unable to detect such cases. It is recommended that laboratories should also test all *S. enterica* serovar Typhi strains with a nalidixic acid disk to detect resistant strains as treatment failure might occur in cases of typhoid fever infection with strains of *S. enterica* serovar Typhi that are apparently ciprofloxacin-susceptible but nalidixic acid-resistant.

*Corresponding author: Mailing address: Department of Microbiology, Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM), 122, Kazi Nazrul Islam Avenue, Dhaka 1000, Bangladesh. Tel: +880-2-9661551~5 ext. 2248/2271, Fax: +880-2-8613004, E-mail: jah@bdonline.com

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