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Emergence of nalidixic acid-resistant *Salmonella enterica* serovar Typhi resistant to ciprofloxacin in India

Fluoroquinolones have good *in vitro* and clinical activity against isolates of *Salmonella* spp. and are often the treatment of choice in cases of life-threatening salmonellosis due to multi-drug resistant strains (Miller *et al.*, 1995). The literature includes a few reports of fluoroquinolone-resistant salmonella strains in humans (Chiu *et al.*, 2002; Marimon *et al.*, 2004; Mehta *et al.*, 2001). In recent years, several treatment failures with fluoroquinolones have also been reported, due to decreased susceptibility to ciprofloxacin (Asna *et al.*, 2003; Threlfall & Ward, 2001). Isolates with decreased susceptibility to ciprofloxacin appear susceptible with routine disc diffusion tests (Asna *et al.*, 2003; Le Lostec *et al.*, 1997). Routine application of these tests for each strain is not convenient, and the literature suggests that resistance to nalidixic acid may be an indicator of decreased susceptibility to ciprofloxacin (Asna *et al.*, 2003; Hakanen *et al.*, 1999; Kapil & Das, 2002; Threlfall *et al.*, 2001).

AIDS has become a worldwide epidemic and a multitude of opportunistic infections have been documented in virtually every organ system of patients afflicted with the condition, due to defective cellular and humoral immune responses. The gastrointestinal tract is a major target for pathogens in HIV infection. *Salmonella enterica* serovar Typhi (*S.* Typhi) is endemic in India. Until the mid-1980s, ampicillin, chloramphenicol or co-trimoxazole was the standard treatment for typhoid fever (Asna & Haq, 2000). Since then ciprofloxacin or third generation cephalosporins, namely ceftriaxone, have become the first line of treatment for typhoid fever. Nalidixic acid-resistant *S.* Typhi (NARST) with decreased susceptibility to ciprofloxacin has already been reported from India (Jesudason *et al.*, 1996), Vietnam (Wain *et al.*, 1997), Tajikistan (Murdoch *et al.*, 1998) and the UK (Threlfall *et al.*, 1999, 2001). However, NARST resistant to ciprofloxacin have not been reported until now. We describe the isolation of five clinical strains of *S.* Typhi from HIV-infected patients that were also resistant to ciprofloxacin, another quinolone derivative.

During our search for *Campylobacter* spp. in the stool specimens of 200 HIV-infected patients and 200 HIV-negative control cases with diarrhoea, we inadvertently encountered five *S.* Typhi isolates that were concurrently resistant to nalidixic acid (30 μg) and ciprofloxacin (5 μg) by the conventional Kirby-Bauer disc diffusion method. Among nine isolates from control patients, only two were sensitive to nalidixic acid and seven were resistant. Further, among these seven NARST, four were resistant to ciprofloxacin. A total of 12 NARST isolates were encountered of which 9 were concurrently resistant to ciprofloxacin. This is an indication of the emergence of NARST that are resistant to ciprofloxacin. All the five isolates from HIV patients were also resistant to erythromycin, cephalothin, ceftriaxone, augmentin, gentamicin and

Table 1. Profile of antibiotic resistance of *S.* Typhi in HIV-positive ($n=200$) and -negative ($n=200$) subjects

Antibiotic	Resistant		Sensitive	
	S. Typhi from HIV-positive group ($n=5$)	*S.* Typhi from HIV-negative group ($n=9$)	*S.* Typhi from HIV-positive group ($n=5$)	*S.* Typhi from HIV-negative group ($n=9$)
Ciprofloxacin	5	4	–	5
Erythromycin	5	6	–	3
Cephalothin	5	9	–	–
Nalidixic acid	5	7	–	2
Ceftriaxone	5	6	–	3
Chloramphenicol	3	6	2	3
Cefataxime	–	6	5	3
Augmentin	5	6	–	3
Gentamicin	5	6	–	3
Co-trimoxazole	2	4	3	5
Cefuraxine	3	8	2	1
Doxycycline	5	5	–	4
Amikacin	3	6	2	3

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doxycyclin (Table 1). Chloramphenicol resistance was prominent among six of the isolates from HIV-negative subjects and three from HIV-positive subjects.

Asna *et al.* (2003) reported that decreased susceptibility to ciprofloxacin among strains of *S.* Typhi could not be detected by the disc diffusion method; their isolates were fully susceptible to 5 μg ciprofloxacin (zone of inhibition >21 mm), but were resistant to 30 μg nalidixic acid. Nalidixic acid resistance determined by the disc diffusion method may be an indication of decreased susceptibility to ciprofloxacin. Extensive usage of fluoroquinolone derivatives in HIV patients may predispose to the emergence of NARST resistant to ciprofloxacin. However, the emergence of NARST in HIV-negative individuals with typhoid fever necessitates immediate attention to alternative treatment regimens. We recommend that laboratories should also test all *S.* Typhi strains with a nalidixic acid disc to detect resistant strains as treatment failure might occur in cases of typhoid fever with strains of *S.* Typhi that are resistant to nalidixic acid and may be resistant to ciprofloxacin. Alternative treatment strategies must be adopted to prevent the emergence of NARST resistant to ciprofloxacin.

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Asna, S. M. & Haq, J. A. (2000). Decrease of antibiotic resistance in *Salmonella typhi* isolated from patients attending hospitals of Dhaka City over a 3 year period. *Int J Antimicrob Agents* **16**, 249–251.

Asna, S. M., Haq, J. A. & Rahman, M. (2003). Nalidixic acid-resistant *Salmonella enterica* serovar *typhi* with decreased susceptibility to ciprofloxacin caused treatment failure: a report from Bangladesh. *Jpn J Infect Dis* **56**, 32–33.

Chiu, C. H., Wu, T. L., Su, L. H., Chu, C., Chia, J. H., Kuo, A. J., Chien, M. S. & Lin, T. Y. (2002). The emergence in Taiwan of fluoroquinolone resistance in *Salmonella enterica* serotype *cholerasuis*. *N Eng J Med* **346**, 413–419.

Hakanen, A., Kotilainen, P., Jalava, J., Siitonen, A. & Huovienen, P. (1999). Detection of decreased fluoroquinolone susceptibility in salmonellas and validation of nalidixic acid screening test. *J Clin Microbiol* **37**, 3572–3577.

Jesudason, M. V., Malathy, B. & John, T. J. (1996). Trends of increasing levels of minimum inhibitory concentration (MIC) of ciprofloxacin to *Salmonella typhi*. *Ind J Med Res* **103**, 247–249.

Kapil, A. R. & Das, B. (2002). Nalidixic acid susceptibility test to screen ciprofloxacin resistance in *Salmonella typhi*. *Ind J Med Res* **115**, 49–54.

Le Lostec, Z., Fegueux, S., Jouve, P., Cheron, M., Mornet, P. & Boisivon, A. (1997). Reduced susceptibility to quinolones in *Salmonella typhi* acquired in Europe: a clinical failure of treatment. *Clin Microbiol Infect* **3**, 576–577.

Marimon, J. M., Goariz, M., Zigorraga, C., Cilla, G. & Perez-Trallero, E. (2004). Increasing prevalence of quinolone resistance in human nontyphoid *Salmonella enterica* isolates obtained in Spain from 1981 to 2003. *Antimicrob Agents Chemother* **3**, 576–577.

Mehta, G., Randhawa, V. S. & Mohapatra, N. P. (2001). Intermediate susceptibility to ciprofloxacin in *Salmonella typhi* strains in India. *Eur J Clin Microbiol Infect Dis* **20**, 760–761.

Miller, S. I., Hohmann, E. L. & Pegues, D. A. (1995). Salmonella. In *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 4th edn, pp. 2013–2033. Edited by G. L. Mandell, E. Bennett & R. Dolin. New York: Churchill Livingstone.

Murdoch, D. A., Banatvala, N. A., Bone, A., Shoismatulloev, B. I., Ward, L. R. & Threlfall, E. J. (1998). Epidemic ciprofloxacin-resistant *Salmonella typhi* in Tajikistan. *Lancet* **351**, 339.

Threlfall, E. J. & Ward, L. R. (2001). Decreased susceptibility to ciprofloxacin in *Salmonella enterica* serotype *typhi* in the United Kingdom. *Emerg Infect Dis* **7**, 448–450.

Threlfall, E. J., Ward, L. R., Skinner, J. A., Smith, H. R. & Lacey, S. (1999). Ciprofloxacin-resistant *Salmonella typhi* and treatment failure. *Lancet* **353**, 1590–1591.

Threlfall, E. J., Skinner, J. A. S. & Ward, L. R. (2001). Detection of decreased *in vitro* susceptibility to ciprofloxacin in *Salmonella enterica* serotypes *typhi* and *paratyphi A*. *J Antimicrob Chemother* **48**, 740–741.

Wain, J., Hoa, N. T., Chinh, N. T., Vinn, H., Everett, M. J., Diep, T. S., Day, N. P., Solomon, T., White, N. J. & other authors (1997). Quinolone-resistant *Salmonella typhi* in Vietnam: molecular basis of resistance and clinical response to treatment. *Clin Infect Dis* **25**, 1404–1410.

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