

Clinical and microbiological investigations of typhoid fever in an infectious disease hospital in Kuwait

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A retrospective analysis of 135 typhoid cases was conducted to review the clinical, epidemiological and microbiological characteristics of enteric fever cases diagnosed and treated at the Infectious Diseases Hospital, Kuwait, from 2002 to 2005. Diagnosis of patients was based on clinical features, serology and blood culture. The susceptibility testing of the isolates to ampicillin, chloramphenicol, trimethoprim–sulfamethoxazole, ceftriaxone, ciprofloxacin and nalidixic acid was performed by the disc diffusion method, and MICs of ceftriaxone and ciprofloxacin were determined by Etest. Of 135 typhoid fever patients, 108 (88 %) were treated with ceftriaxone and 27 (20 %) were treated with ciprofloxacin. The mean time for fever defervescence with ciprofloxacin therapy was 8 days and 6.3 days for those treated with ceftriaxone. Of the 135 *Salmonella enterica* serotypes Typhi and Paratyphi A isolated from patients, 50 (37 %) were multidrug resistant (MDR) and 94 (69.6 %) isolates of both serotypes were nalidixic acid resistant (NAR). Between 90 and 100 % of MDR and NAR strains had decreased susceptibility to ciprofloxacin ($0.125\text{--}1\ \mu\text{g ml}^{-1}$). Low-level resistance to ciprofloxacin ($\text{MIC } 0.125\text{--}1\ \mu\text{g ml}^{-1}$) was also detected in 13.8 and 33.3 % of nalidixic acid-susceptible isolates of *S. Typhi* and *S. Paratyphi A*, respectively. All isolates were susceptible to ceftriaxone. Two relapses occurred in the ciprofloxacin-treated group. MDR strains and strains resistant to ciprofloxacin and ceftriaxone are a major threat in the developing world. A situation is fast approaching where the emergence of highly resistant *Salmonella* isolates is quite likely. Proper steps must be taken to avoid a pandemic spread of MDR *S. Typhi* strains.

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INTRODUCTION

The last two decades have witnessed the emergence and spread of multidrug resistance against conventional antityphoid drugs (ampicillin, chloramphenicol and trimethoprim–sulfamethoxazole) among typhoid salmonellae, especially in South and South-east Asia (Chandel *et al.*, 2000; Rowe *et al.*, 1997). Typhoid fever caused by such multidrug-resistant (MDR) strains of *Salmonella enterica* serotype Typhi presents a serious problem in many developing countries (Ivanoff & Levine, 1997; Rowe *et al.*, 1997). It has left fluoroquinolones as the antimicrobial agents of choice for the treatment of typhoid fever (Parry *et al.*,

2002). Fluoroquinolones, especially ciprofloxacin, have been in use for more than 18 years and have remained an important weapon against typhoid infections. In spite of this, in recent years, several reports have appeared worldwide concerning reduced activity of ciprofloxacin against typhoid salmonellae (Wain *et al.*, 1997; Chandel *et al.*, 2000; Threlfall & Ward, 2001; Hakanen *et al.*, 2001). Nalidixic acid-resistant (NAR) *S. Typhi* and *S. enterica* serotype Paratyphi A with decreased susceptibility to ciprofloxacin is now endemic in India and neighbouring countries, constituting a threat to global health (Chandel *et al.*, 2000; Threlfall & Ward, 2001; Rodrigues *et al.*, 1999; Pountanen & Low, 2003; Hakanen *et al.*, 1999). Since 1994, an increasing number of strains of *S. Typhi* from patients in the UK have exhibited reduced susceptibility to ciprofloxacin, in addition to resistance to chloramphenicol,

Abbreviations: MDR, multidrug resistant; NAR, nalidixic acid resistant; NAS, nalidixic acid susceptible.

ampicillin and trimethoprim–sulfamethoxazole. In 1999, 23 % of 179 strains exhibited low-level resistance to ciprofloxacin, of which 59 % were also MDR (Threlfall & Ward, 2001). The majority of these cases were patients who had recently returned from the Indian subcontinent, particularly Pakistan and India (Threlfall & Ward, 2001). Similarly, Hakanen *et al.* (1999) reported that 90.22 % of *S. Typhi* strains isolated in Calicut, Pakistan, between 1999 and 2003 were resistant to nalidixic acid and expressing low-level resistance to ciprofloxacin, which resulted in treatment failure. The emergence of MDR *S. Typhi* and *S. Paratyphi A*, and concerns about delayed response to quinolones therapy have resulted in anxiety among treating physicians. We report the clinical and microbiological observations on cases of typhoid fever caused by quinolone-resistant *S. enterica* serotypes Typhi and Paratyphi A.

METHODS

Setting. The study was carried out at the Infectious Diseases Hospital (IDH), Kuwait, over a period of 4 years (2002–2005). The IDH is a 151 bed specialized institution serving the entire population of Kuwait.

Study design. A retrospective analysis of 135 patients suffering from typhoid fever was performed. All patients with positive blood cultures for *S. Typhi* and *S. Paratyphi A* from January 2002 to December 2005 were included in the study. Diagnosis of typhoid fever was based on clinical features, Widal test and blood culture. Patients' medical records were reviewed for demographic, clinical and laboratory features. Time to fever defervescence was defined as the interval from initiation of appropriate antibiotic therapy until return to normal body temperature for more than 24 h. Outcomes were divided into cure and relapse. An infection was considered cured, if clinical signs and symptoms resolved, and blood and stool culture became negative. A patient was considered to have relapsed if after an appropriate clinical and bacteriological response, fever or other clinical signs of infection recurred in association with a positive blood culture within 2 months of completion of treatment

Bacterial cultures. Blood cultures were carried out using a Bactec 9120 (Becton Dickinson), a continuous-monitoring blood culture system (Weinstein, 1996), and details have been published in our previous study (Dimitrov *et al.*, 2005).

Stool specimens were plated directly onto MacConkey and SS agar, and inoculated into Selenite F broth for enrichment. Identities of isolates were confirmed to be *S. enterica* serotypes Typhi or Paratyphi A by their API 20E profiles (bioMérieux) and slide agglutination with specific antisera (Denka Seiken).

Antimicrobial susceptibility testing. Susceptibility to antimicrobial agents was performed using the disc diffusion method as described by the Clinical and Laboratory Standards Institute (2005). Antimicrobial agents (discs) tested and reported were obtained from their respective manufacturers and included: ampicillin (10 µg), trimethoprim–sulfamethoxazole (25/23.75 µg), chloramphenicol (30 µg), ceftriaxone (30 µg), ciprofloxacin (5 µg) and nalidixic acid (30 µg). MICs for ciprofloxacin and ceftriaxone were determined by Etest strips (AB Biodisk). *Escherichia coli* strain ATCC25922 was used for quality control. MDR isolates of *S. Typhi* and *S. Paratyphi A* were those resistant to all three first line antityphoid drugs (ampicillin, chloramphenicol and trimethoprim–sulfamethoxazole). Low-level resistance to ciprofloxacin (Cip_L) was defined as an MIC of 0.125–1 µg ml⁻¹

Table 1. Yearly distribution of enteric fever cases

Year	Total no. of isolates	<i>S. enterica</i> serotype	
		Typhi [no. (%)]	Paratyphi A [no. (%)]
2002	29	23 (79.3)	6 (20.7)
2003	34	22 (64.7)	12 (35.3)
2004	41	30 (73.2)	11 (26.8)
2005	31	26 (83.9)	5 (16.1)
Total	135	101 (74.8)	34 (25.2)

Widal test. The Widal tube agglutination test was performed according to the manufacturer's instruction, using plasmatic reagents (Plasmatec Laboratory Products), containing O and H antigens of *S. Typhi* and *S. Paratyphi A*. Positive and negative serum controls were included, a titre of $\geq 1/160$ to either antigen in a single serum specimen (in addition to the seroconversion) was taken to be indicative of typhoid fever. The results were correlated with blood culture results and interpreted in conjunction with the patient's history and recent clinical presentation on admission.

RESULTS AND DISCUSSION

A total of 135 cases of typhoid fever were recorded between 2002 and 2005. The yearly totals ranged from 29 (lowest) in 2002 to 41 (highest) in 2004 (Table 1). The patients' demographic characteristics and clinical features are summarized in Tables 2 and 3. They consisted of 105 (77.8 %) males and 30 (22.2 %) females, with the majority of them being nationals of India (39.3 %), Pakistan (23.7 %) and Bangladesh (25.2 %).

A review of treatment charts revealed that 108 (80.0 %) patients were treated with ceftriaxone (1 g intravenously every 12 h – adult dose, 50–70 mg kg⁻¹ daily intravenously/intramuscularly divided into treatments every 12 h – paediatric dose) and 27 (20.0 %) of them were treated with ciprofloxacin (500 mg orally twice a day – adult, 20–30 mg kg⁻¹ twice a day – paediatric dose). The mean duration of treatment for both groups was 14 days (range).

Table 2. Typhoid patient characteristics

Characteristic	No. (%) of patients (135)
Age in years (mean \pm SD)	26.3 (2–74)
Sex (male : female)	3.5 : 1 (105 : 30)
Nationality	
Indian	53 (39.3)
Pakistani	32 (23.7)
Bangladeshi	34 (25.2)
Sri Lankan	1 (0.7)
Egyptian	4 (2.9)
Nepalese	1 (0.7)
Jordanian	1 (0.7)
Others	9 (6.7)

Table 3. Clinical and laboratory findings at presentation

Characteristic	No. (%) of patients (135)
Clinical symptoms	
Fever	135 (100)
Diarrhoea	71 (52.6)
Chills	34 (25.2)
Vomiting	65 (48)
Abdominal pain	39 (28.9)
Cough	25 (18.5)
Anorexia	24 (17.8)
Constipation	5 (3.7)
Headache	40 (29.6)
Sore throat	16 (12)
Clinical signs	
Hepatomegaly	13 (9.6)
Splenomegaly	28 (20.7)
Rose spots	3 (2.2)
Laboratory findings	
Leucopenia (<4000 white blood cells mm ⁻³)	34 (25.2)
Anaemia (haemoglobin <12 g dl ⁻¹)	74 (54.8)
Thrombocytopenia (<100 000 platelets mm ⁻³)	13 (9.6)
ESR	44 (32.6)
Mean duration of symptoms	6.6 days
History of recent travel	119 (88)

Blood and stool samples were obtained in all cases at admission. The causative micro-organisms were isolated from the blood of all 135 (100 %) patients but in only 21 (15.5 %) of stool samples (Table 4). The distribution of *S. enterica* serotypes is presented in Table 1. *S. enterica* serotype Typhi was isolated from 101 (74.8 %) patients and *S. enterica* serovar Paratyphi A was isolated from 34 (25.2 %) patients. A total of 50 (37 %) of the 135 typhoid cases were caused by MDR isolates of both serotypes, comprising 43 (42.6 %) *S. Typhi* and 7 (20.6 %) *S. Paratyphi A* isolates (Table 5). Ninety-four (69.6 %) of them were resistant to nalidixic acid and ninety-two (97.8 %) expressed increased ciprofloxacin MICs (Table 6). The percentage of MDR *S. Typhi* isolates with decreased susceptibility to ciprofloxacin (MIC 0.125–1 µg ml⁻¹) increased from 90 % in 2002 to 100 % in 2005 (Table 7).

Table 4. Laboratory methods of diagnosis of typhoid fever

Method of diagnosis	No. (%) of patients
Blood culture	135 (100 %)
Stool culture	21 (15.5 %)
Serological test (Widal test)	
Number of cases with only O antibodies at cut-off titre ≥ 1/160	
<i>S. Typhi</i>	6 (5.9 %)
<i>S. Paratyphi A</i>	0 (–)
Number of cases with both O and H antibodies at cut-off titre of ≥ 1/160	
<i>S. Typhi</i>	39 (38.6 %)
<i>S. Paratyphi A</i>	4 (11.8 %)
Number of cases with O antibodies at cut-off titre of ≥ 1/160	
<i>S. Typhi</i>	45 (44.6 %)
<i>S. Paratyphi A</i>	4 (11.8 %)
Number of cases with H antibodies at cut-off titre of ≥ 1/160	
<i>S. Typhi</i>	63 (62.4 %)
<i>S. Paratyphi A</i>	16 (47.1 %)
Number of cases with O antibodies titre of <1/160 and H antibodies at cut-off titre of >1/160	
<i>S. Typhi</i>	24 (23.8 %)
<i>S. Paratyphi A</i>	12 (34.3 %)
Number of cases with only O antibody titre of <1/160	
<i>S. Typhi</i>	56 (55.44 %)
<i>S. Paratyphi A</i>	30 (88.2 %)
Number of cases with only H antibody titre of <1/160	
<i>S. Typhi</i>	38 (37.6 %)
<i>S. Paratyphi A</i>	18 (52.9 %)
Widal test negative:	
<i>S. Typhi</i>	10 (9.9 %)
<i>S. Paratyphi A</i>	10 (29.4 %)

Increased ciprofloxacin MIC was also detected in 54, 47, 92 and 56.3 % of the sensitive (non-MDR) strains of the same serotype isolated in 2002, 2003, 2004 and 2005, respectively (Table 7). The majority (79.4 %) of serotype Paratyphi A isolates were susceptible to the first line antityphoid drugs (ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole). Among them, 22 (81.5 %) had ciprofloxacin MICs of 0.125–1 µg ml⁻¹ (Table 7). There were only two MDR *S. Paratyphi A* strains among the nalidixic

Table 5. Yearly distribution of typhoid cases caused by MDR and sensitive isolates of *S. enterica* serotypes Typhi and Paratyphi A

Year	<i>S. Typhi</i>			<i>S. Paratyphi A</i>			Total <i>S. Typhi</i> and <i>S. Paratyphi A</i>		
	Total no. (MDR + SENS)	MDR [no. (%)]	SENS [no. (%)]	Total no. (MDR + SENS)	MDR [no. (%)]	SENS [no. (%)]	Total no. (MDR + SENS)	MDR [no. (%)]	SENS [no. (%)]
2002	23	10 (43.5)	13 (56.5)	6	2 (33.3)	4 (66.7)	29	12 (41.4)	17 (58.6)
2003	22	7 (31.8)	15 (68.2)	12	2 (16.7)	10 (83.3)	34	9 (26.5)	25 (73.5)
2004	30	16 (53.3)	14 (46.7)	12	2 (16.7)	10 (83.3)	42	18 (42.8)	24 (57.1)
2005	26	10 (38.5)	16 (61.5)	4	1 (25)	3 (75)	30	11 (36.7)	19 (63.3)
Total	101	43 (42.6)	58 (57.4)	34	7 (20.6)	27 (79.4)	135	50 (37)	85 (63)

SENS, Sensitive.

Table 6. Incidence of decreased susceptibility to ciprofloxacin in NAR and NAS strains of *S. Typhi* and *S. Paratyphi A*

Year	<i>S. Typhi</i>					<i>S. Paratyphi A</i>				
	Total no. of isolates	NAR		NAS		Total no. of isolates	NAR		NAS	
		No. (%)	Cip _L [no. (%)]	No. (%)	Cip _L [no. (%)]		No. (%)	Cip _L [no. (%)]	No. (%)	Cip _L [no. (%)]
2002	23	16 (70)	16 (100)	7 (30)	0 (0)	6	3 (50)	1 (33)	3 (50)	3 (100)
2003	22	13 (59)	13 (100)	9 (41)	1 (11)	12	10 (83)	10 (100)	2 (16.6)	1 (50)
2004	30	26 (87)	26 (100)	4 (13)	1 (25)	11	6 (55)	6 (100)	5 (45)	0 (0)
2005	26	17 (65.4)	17 (100)	9 (34.6)	2 (22.2)	5	3 (60)	3 (100)	2 (40)	0 (0)
Total	101	72 (71.3)	72 (100)	29 (28.7)	4 (13.8)	34	22 (64.7)	20 (90.9)	12 (35.3)	4 (33.3)

Cip_L, Low-level resistance to ciprofloxacin (MIC 0.125–1 µg ml⁻¹).

Table 7. Incidence of decreased susceptibility to ciprofloxacin in MDR and sensitive strains of *S. enterica* serotypes *Typhi* and *Paratyphi A*

Year	<i>S. Typhi</i>					<i>S. Paratyphi A</i>				
	Total no. of isolates	MDR		Sensitive		Total no. of isolates	MDR		Sensitive	
		No. (%)	Cip _L [no. (%)]	No. (%)	Cip _L [no. (%)]		No. (%)	Cip _L [no. (%)]	No. (%)	Cip _L [no. (%)]
2002	23	10 (44)	9 (90)	13 (56)	7 (54)	6	2 (33)	0 (0)	4 (67)	3 (75)
2003	22	7 (32)	7 (100)	15 (68)	7 (47)	12	2 (16.7)	1 (50)	10 (83)	10 (100)
2004	30	17 (57)	16 (94)	13 (43)	12 (92)	11	1 (9.0)	0 (0)	10 (91)	6 (60)
2005	26	10 (38.5)	10 (100)	16 (61.5)	9 (56.3)	5	2 (40)	0 (0)	3 (60)	3 (100)
Total	101	44 (43.6)	42 (95.5)	57 (56.4)	35 (61.4)	34	7 (20.6)	1 (14.3)	27 (79.4)	22 (81.5)

Cip_L, low-level ciprofloxacin resistance (MIC 0.125–1 µg ml⁻¹).

acid-susceptible (NAS) strains; one of them showed low-level resistance to ciprofloxacin. Among 41 NAS strains of both serotypes, 8 (19.5 %) of them expressed increased ciprofloxacin MICs (0.125–1 µg ml⁻¹).

The resistance patterns of *S. Typhi* and *S. Paratyphi A* strains were compared with the nationality of the patients in order to establish a relationship. The results showed that most of the MDR strains were from patients from Bangladesh and Pakistan. Of the 43 MDR *S. Typhi* strains (Table 5), 35 (81.4 %) were from nationals of India (9,

20.9 %), Bangladesh (13, 30.2 %) and Pakistan (13, 30.2 %) (Table 8). The distribution of the MDR *S. Typhi* and *S. Paratyphi A* among the strains from India, Bangladesh and Pakistan is presented in Table 8. Of the 34 *S. Paratyphi A* blood isolates, 7 (20.6 %) were MDR and were obtained only from Pakistani patients.

Widal test

A Widal test was performed on serum samples from all 135 patients. The results are presented in Table 4. A total of 56

Table 8. Distribution of MDR *S. enterica* serotypes *Typhi* and *Paratyphi A* isolated from patients of different nationalities

Year	<i>S. Typhi</i>						<i>S. Paratyphi A</i>					
	Indian		Pakistani		Bangladeshi		Indian		Pakistani		Bangladeshi	
	Total no. of isolates	MDR [no. (%)]	Total no. of isolates	MDR [no. (%)]	Total no. of isolates	MDR [no. (%)]	Total no. of isolates	MDR [no. (%)]	Total no. of isolates	MDR [no. (%)]	Total no. of isolates	MDR [no. (%)]
2002	10	1 (10)	3	2 (66.7)	7	5 (71.4)	1	–	4	2 (50)	1	–
2003	18	2 (11.1)	8	4 (50)	2	1 (50)	7	–	2	2 (100)	3	–
2004	15	5 (33)	4	3 (75)	9	7 (77.8)	1	–	4	2 (50)	7	–
2005	6	1 (16.7)	6	4 (66.7)	8	5 (62.5)	1	–	2	1 (50)	1	–
Total	49	9 (18.4)	21	13 (61.9)	26	18 (69)	10	–	12	7 (58.3)	12	–

(55.4 %) of the patients with positive blood culture for typhoid fever (*S. Typhi*) and 30 (88.2 %) of those positive for *S. Paratyphi A* had O antibodies that were lower than the cut-off titre of 1/160. Similarly, 38 (37.6 %) and 18 (52.9 %) that yielded *S. Typhi* and *S. Paratyphi A*, respectively, had H antibodies below the cut-off titre of 1/160. O agglutinins at a cut-off titre of $\geq 1/160$ were detected in 45 (44.6 %) of enteric fever cases caused by *S. Typhi* and in only 4 (11.8 %) of cases caused by *S. Paratyphi A*. An elevated titre of H antibodies ($\geq 1/160$) was detected in 63 (62.4 %) and 16 (47 %) of the patients infected by *S. Typhi* and *S. Paratyphi A*, respectively. Thirty-nine (38.6 %) and only four (11.8 %) of the patients infected with *S. Typhi* and *S. Paratyphi A*, respectively, had both (O and H) agglutinins at a cut-off titre of $\geq 1/160$.

In another 24 (23.8 %) and 12 (34.3 %) of bacteriologically proven cases of enteric fever caused by serotype *Typhi* and serovar *Paratyphi A*, respectively, the anti-O antigen immune response was $< 1/160$, whereas anti-H antigen agglutinin titre showed at least a fourfold rise ($\geq 1/640$). Conversely, a rise in somatic antibody titre alone was observed in only 3.5 % of typhoid cases.

The relative importance of somatic and flagellar agglutinin titres for diagnosis of typhoid fever has been questioned (Senewiratne & Senewiratne, 1977; Saha *et al.*, 1996). The data from our study suggest that O and H antibody titres may have a different diagnostic value in serological diagnosis of enteric fever cases caused by *S. Typhi* and *S. Paratyphi A*. This may be due to bacterial factors such as lower immunogenicity of lipopolysaccharide of *S. Paratyphi A* leading to a weak or negative anti-O antigen immune response. At the same time, not only were H antibody titres elevated against flagellar antigens of both serovars, but also seroconversion could be observed. Therefore, a single Widal test may not be reliable for the diagnosis of typhoid fever because false-positive and false-negative results are common. The incidence of false-negative tests among bacteriologically proven cases in this study was 9.9 and 29.4 % for *S. Typhi* and *S. Paratyphi A*, respectively. These findings are of significance to clinicians, who must often rely solely upon the results of the Widal test in making a diagnosis of typhoid fever. The results of Widal tests should be interpreted in concert with a patient's clinical presentation in making a diagnosis of typhoid fever. Both the agglutinins, somatic and flagellar, are equally important for this purpose.

Drug resistance in typhoid salmonellae is considered as one of the important factors in the morbidity and mortality of the disease. Infections by *S. Typhi*, a potentially lethal organism, were successfully managed for many years with chloramphenicol (Chowta & Chowta, 2005). However, chloramphenicol resistance was reported (Anderson & Smith, 1972; Agarwal *et al.*, 1981), and in the late 1980s and early 1990s, MDR *S. Typhi* appeared and has become a real challenge especially in the developing countries (Khosla *et al.*, 1998; Rowe *et al.*, 1997). The quinolones

emerged as useful drugs for the treatment of multiple-drug resistant cases of typhoid (Parry *et al.*, 2002). As a consequence of extensive use of fluoroquinolone, resistance is being reported with increasing frequency all over the world (Wain *et al.*, 1997; Chandel *et al.*, 2000; Threlfall & Ward, 2001; Hakanen *et al.*, 2001) and a correlation between resistance to nalidixic acid and reduced susceptibility to ciprofloxacin and other fluoroquinolones has been reported (Hakanen *et al.*, 1999). The data from this study also highlight an increasing incidence of enteric fever caused by NAR strains of both serotypes with decreased susceptibility to ciprofloxacin. Increasing MIC for ciprofloxacin and treatment failure in spite of *in vitro* sensitivity have been reported (Rodrigues *et al.*, 1998a, b; Jesudason *et al.*, 1996; Prabha Adhikari & Baliga, 2002). An epidemic of ciprofloxacin-resistant typhoid has also been reported (Murdoch *et al.*, 1998).

MDR *S. Typhi* is endemic in Pakistan, India and Bangladesh (Nadeem *et al.*, 2002; Munir *et al.*, 2001) but has also been reported from other parts of the world (Wain *et al.*, 1997; Chandel *et al.*, 2000; Hakanen *et al.*, 2001; Threlfall & Ward, 2001; Ackers *et al.*, 2000). The incidence of MDR increased in the UK from 21 % in 1991 to 36 % in 1994, declined to 13 % in 1997 and then increased to 26 % in 1999. More than 90 % of patients infected with MDR strains had recently returned from the Indian subcontinent, particularly Pakistan and India (Threlfall & Ward, 2001). In this study, 50 (37 %) of the 135 typhoid cases were caused by MDR *S. Typhi*. (42.6 %) and *S. Paratyphi A* (20.6 %) (Table 5). In contrast, none of 106 strains of *S. Paratyphi A* reported previously in our hospital was MDR (Panigrahi *et al.*, 2003). The major sources for these MDR isolates were nationals of Pakistan and Bangladesh similar to the situation in the UK that was reported by Threlfall & Ward (2001). The emergence of MDR *S. Typhi* and *S. Paratyphi A* infections in the Infectious Diseases Hospital is a consequence of the migration of people from endemic MDR typhoid fever areas.

The defervescence period for ciprofloxacin is about 3–5 days (Mandal, 2001) and for cephalosporins is about 3 days. But in the present study, we observed that the defervescence time was comparatively longer, with a mean of 8 days for ciprofloxacin and 6 days for ceftriaxone. The patients with MDR typhoid fever had a longer duration of fever defervescence (8 ± 5 days) compared to those with drug-susceptible typhoid fever (5.7 ± 4 days). In 10 (37 %) enteric fever cases, caused by *S. Typhi* and *S. Paratyphi A* sensitive to ciprofloxacin (MIC $< 0.125 \mu\text{g ml}^{-1}$), the defervescence period was shorter, 6 days, compared to those (17, 63 %), infected with strains with reduced susceptibility to ciprofloxacin (MIC ≥ 0.125 – $0.38 \mu\text{g ml}^{-1}$), for which the defervescence time was ≥ 12 days. Among them, two relapse cases with *S. Paratyphi A* (ciprofloxacin MIC = $0.75 \mu\text{g ml}^{-1}$) and six failures with *S. Typhi* (ciprofloxacin MIC = $0.38 \mu\text{g ml}^{-1}$) were observed. These findings suggest that the sensitivity of *S. Typhi* and *S. Paratyphi A* to ciprofloxacin is gradually decreasing. Indiscriminate

use of drugs is one of the important factors leading to drug resistance, and in the case of ciprofloxacin, moderate cost, the advantage of an oral route, tolerability and a convenient dosage schedule have contributed towards this. In our study, sensitivity to ceftriaxone was 100 % and there were no cases of treatment or relapses with ceftriaxone. In addition to ciprofloxacin resistance in typhoid *Salmonella*, treatment failures in ciprofloxacin-treated cases of typhoid fever could also be caused by reduced bioavailability of the drug *in vivo* following administration. Recently, Arya & Agarwal (2006) suggested that poor bioavailability of ciprofloxacin would lead to treatment failures and resistance, especially in sick patients, and recommended monitoring the bioavailability of antimicrobials given to patients. Poor bioavailability of ciprofloxacin can be caused by its chelation by divalent and trivalent cations, such as antacids, iron compounds or dairy products, which prevents its absorption (Borcherding *et al.*, 1996). The bioavailability of ciprofloxacin in these patients was not measured. However, the role of poor drug availability in treatment failure should be extensively studied.

The majority of typhoid cases in this study were caused by NAR strains with reduced susceptibility to ciprofloxacin introduced by patients from South-East Asia where these strains are endemic. We are fast heading towards a situation where emergence of highly resistant *Salmonella* isolates is quite likely. We require good choices, proper dosage and proper duration of therapy, and rational prescribing of antibiotics. Possible use of costly drugs like meropenem and imipenem for MDR *Salmonella* is going to impose a huge burden on individuals as well as the community. Hence there is a need for the continued surveillance of resistant strains and proper selection and use of antibiotics.

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