Original Article

Antimicrobial resistance among blood culture isolates of *Salmonella enterica* in New Delhi

Sarika Jain, Tulsi Das Chugh

BLK Superspeciality Hospital, Pusa Road, New Delhi, India

Abstract

Introduction: Enteric fever is a global public health problem, especially in developing countries. Antimicrobial resistance is a major issue enteric fever management. This study examined current pattern of antimicrobial susceptibility among *Salmonella enterica* isolates from enteric fever cases at a tertiary care centre in New Delhi, India.

Methodology: Blood cultures from patients with enteric fever during January 2010- July 2012 were processed using the BACTEC automated system. Antimicrobial susceptibility was tested using Kirby Bauer's disc diffusion method and/or Phoenix 100 automated system.

Results: Of 344 isolates of *Salmonella enterica*, 266 (77.3%) were *S.* Typhi, 77 (22.4%) were *S*. Paratyphi A, and one (0.3%) was *S.* Paratyphi B. Resistance to nalidixic acid (NA^R) (96.7%) was most common, followed by ciprofloxacin (37.9%), and azithromycin (7.3%). Multi-drug resistance was observed only in *S*. Typhi (3.4%). Among NA^R strains, 61.8% were sensitive, 11.1% were moderately sensitive, and 23.9% were resistant to ciprofloxacin (0.8%, 57.4%, and 37.9% respectively according to revised CLSI breakpoint criteria for ciprofloxacin). Resistance to third-generation cephalosporin was found in seven (2%) strains of *S. enterica.*

Conclusion: Increasing rates of nalidixic acid, fluoroquinolone and azithromycin resistance among *S. enterica*, particularly in *S.* Paratyphi A strains, is of concern, as *S.* Paratyphi A infection is becoming increasingly common and is not prevented by current vaccinations. Our results favour use of cefexime or possibly chloramphenicol as first choice for uncomplicated enteric fever. MICs for third-generation cephalosporins and susceptibility pattern must be closely monitored in view of its emerging resistance among *Salmonella enterica*.

Key words: enteric fever; Salmonella enterica; antimicrobial resistance

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Introduction

Enteric fever is a global public health problem with an annual incidence of at least 21.7 million cases reported worldwide, of which 90% occur in Southeast Asia, and resulted in about 216,000 annual deaths [1]. India and Pakistan account for a very high incidence of typhoid fever compared to other Southeast Asian countries such as Vietnam, Indonesia and China [2]. The mortality rate for typhoid fever without appropriate treatment is estimated to be 30%; with specific therapy, the mortality rate is reduced to 0.5% [3].

Salmonella enterica serovar Typhi accounts for a major proportion of enteric fever cases. The incidence and relative contribution of *S.* Paratyphi A, which causes less severe infection than *S.* Typhi, is not properly understood, as most studies from India have focused largely on *S.* Typhi. *S.* Paratyphi A was reported in 3-17% of enteric fever cases in earlier studies [4]. However, a surge in the number of cases due to *S.* Paratyphi A since 1996 in various parts of India has been documented [5].

Antimicrobial resistance is a major issue in the management of enteric fever. Resistance to chloramphenicol emerged in *S.* Typhi strains in the early 1970s and was soon followed by resistance to ampicillin and co-trimoxazole. Several epidemics of typhoid fever due to multi-drug resistant (MDR) *S.* Typhi have occurred worldwide, especially in Southeast Asia, since the 1990s [6]. A single large, high molecular weight, self-transferable plasmid belonging to incompatibility group H I1 is responsible for such en-bloc resistance [3]. This resistance led to frequent worldwide use of fluoroquinolone (FQ) for the treatment of enteric fever. The situation was further complicated by the emergence of quinolone-resistant strains with reduced susceptibility to ciprofloxacin (MIC 0.125-1 μg/mL). Since then, several studies have reported a continuous rise in ciprofloxacin MIC levels associated with treatment failure or prolonged defervescence time with

ciprofloxacin [7]. Beginning in 2004, high-level ciprofloxacin resistance was reported across India [8]. Third-generation cephalosporins and azithromycin are alternative choices for FQ-resistant enteric fever; however, a rise in MICs of these drugs for *Salmonella* has also been observed [9,10]. As drug resistance has been emerging steadily in the species, it is necessary to continuously monitor the local antimicrobial susceptibility patterns of *Salmonella enterica* isolates to update therapeutic guidelines.

This retrospective study aimed to evaluate the trends of antimicrobial resistance among blood culture isolates from enteric fever cases in a tertiary care centre in New Delhi, India.

Methodology

Salmonella enterica isolates were retrieved from blood cultures received in the microbiology laboratory during January 2010-July 2012. This retrospective study was performed in a 700-bed tertiary care hospital in New Delhi. A total of 13,672 blood samples were received for culture during the study period. Data pertaining to age, sex, location of patients, serotype of isolates and their antimicrobial susceptibility profiles was collected. Blood culture was done using BACTEC 9120 vials (Becton, Dickinson and Company, Franklin Lakes, USA) incubated in the instrument for five days. After the blood culture vial signaled positive, isolates were routinely subjected to identification (ID) and antimicrobial susceptibility testing (AST) by direct inoculation of the Phoenix 100 ID and AST panels (Becton, Dickinson and Company, Franklin Lakes, USA). Isolates identified as *Salmonella* were confirmed manually by standard biochemical tests and the slide agglutination test with polyvalent O antiserum and serovar specific antisera (Salmonella agglutinating serum, Remel, Europe, Dartford, UK). Time to positivity (TTP) was measured from the time of blood culture vial inoculation to the time it signaled positive.

As part of the Phoenix AST panel, susceptibility results (MICs) were obtained for ampicillin, chloramphenicol, trimethoprim-sulphamethoxazole (ACCo) and ciprofloxacin. Manual antimicrobial susceptibility testing was also performed simultaneously using the Kirby Bauer's disc diffusion method for antimicrobials not included in the Phoenix panel --nalidixic acid (NA, 30 µg), ceftriaxone (30 µg), azithromycin (15 µg), cefixime (5 µg) (Hi-Media Laboratories, Mumbai, India) -- in addition to the antimicrobials mentioned above. Results were interpreted using Clinical and Laboratory Standards Institute (CLSI, USA) breakpoints [11]. British Society of Antimicrobial Chemotherapy (BSAC) guidelines (sensitive ≥ 19 mm and resistant ≤ 18 mm) were followed for the interpretation of azithromycin results [12]. A standard strain of *E. coli* ATCC 25922 was included as quality control. Isolates resistant to ACCo were defined as multi-drug resistant *S.* Typhi (MDRST).

Results

A total of 344 blood culture positive *Salmonella enterica* isolates were recovered over the span of two years and seven months. Of these, 266 isolates were identified as *Salmonella enterica* serovar Typhi, 77 were *Salmonella enterica* serovar Paratyphi A, and one was *Salmonella enterica* serovar Paratyphi B. The proportions of *S.* Typhi and *S.* Paratyphi A strains isolated were similar each year (Table 1). The median time to positivity of blood culture for *Salmonellae* was 13.5 hours; the turn-around time for culture reports, including antimicrobial sensitivity results, was between 24 and 48 hours. Patients' ages ranged from nine months to 55 years (mean age = 14.2 years); 61.9% of enteric fever cases occurred in males. Pediatric (< 15 years) patients (66.3%) and young adults (20-30 years) (18%) accounted for the majority of enteric fever cases. A comparison of demographic profiles and antimicrobial resistance patterns between *S.* Typhi and *S.* Paratyphi A is shown in Table 2.

Details of antimicrobial susceptibility of *Salmonellae* isolates are shown in Tables 3, 4 and 5. Highest resistance was observed for nalidixic acid (96.7%, 332/344), followed by ciprofloxacin (37.9%, 130/344), and azithromycin (7.3%, 25/344). Multi-drug resistance (MDR, ACCo resistance) was seen in only 2.6% (9/344) of the *Salmonella enterica* isolates, and all these isolates were *S.* Typhi (3.4%). *S.* Paratyphi B was susceptible to all the antimicrobials tested.

Nalidixic acid resistance (NA^R) was observed in 95.8% of *S.* Typhi (255/266) and 100% of *S.* Paratyphi A isolates. To determine the difference in ciprofloxacin susceptibility trends by former [13] and revised CLSI breakpoints [11] (Table 6), both interpretive criteria were applied to all the isolates. Among the NA^R *Salmonella enterica* strains, 62.7% of strains were ciprofloxacin susceptible, 11.1% were intermediate susceptible, and 23.9% were resistant by the former breakpoints versus 0.8%, 57.4%, 37.9%, respectively, by revised breakpoints (Tables 4, 5).

Table 1. Percentage of *Salmonella enterica* isolates from 2010 to 2012

Year	***S*. Typhi**	***S*. Paratyphi A**	***S*. Paratyphi B**	**Total**
2010	108 (79.4%)	28 (20.5%)	0	136
2011	107 (76.4%)	33 (23.5%)	0	140
2012 (Jan-July)	51 (75%)	16 (23.5%)	1 (1.5%)	68
Total	266 (77.3%)	77 (22.4%)	1 (0.3%)	344

Table 2. Comparison of demographic and antimicrobial resistance profile of *S.* Typhi and *S.* Paratyphi A

Characteristics	***S*. Typhi (n=266)**	***S*. Paratyphi A (n=77)**	**Total (n=343)**
Isolation %	77.3	22.4	99.7
Age range (Mean)	9 mo-55 y (14.9)	3y-54 y (22.7)	9 mo-55 y (14.2)
Hospitalized n (%)	114 (43)	17 (22)	131 (38.1)
MDR n (%)	09 (3.4)	Nil	09 (2.6)
NA^R n (%)	255 (95.8)	77 (100)	332 (96.7)
Ciprofloxacin R in MDR isolates n (%)	02 (22.2)	NA	02 (22.2)
Azithromycin R in MDR isolates n (%)	01 (11.1)	NA	01 (11.1)
Ciprofloxacin R* n (%)	92 (34.5)	38 (49.3)	130 (37.9)
Azithromycin R n (%)	17 (6.4)	08 (10.4)	25 (7.3)
NA^R in Azithromycin R isolates n (%)	17 (100)	08 (100)	25 (100)
Ciprofloxacin + Azithromycin R n (%)	15 (5.6)	01 (1.3)	16 (4.7)
Ceftriaxone resistance n (%)	1.0 (0.3)	1.0 (1.2)	02 (0.5)

R= Resistance; NA= not applicable *Revised CLSI ciprofloxacin breakpoints

Table 3. Trends of Antimicrobial resistance pattern among *S.* Typhi and *S.* Paratyphi A isolates (in percentage) from January 2010 - July 2012

Antibiotics	***S*. Typhi (n=266)**				***S*. Paratyphi A (n=77)**				**Total**
	2010	2011	2012	Total	2010	2011	2012	Total	
Ampicillin	4.0 (3.7)	7.0 (6.5)	2.0 (3.9)	13 (4.7)	1.0 (3.5)	1.0 (3.0)	1.0 (6.2)	3.0 (3.8)	16 (4.6)
TMP-SMX	0	4.0 (3.7)	1.0 (2.0)	5.0 (1.8)	0	0	0	0	5.0 (1.4)
Chloramphenicol	3.0 (2.7)	5.0 (4.6)	2.0 (3.9)	10 (3.7)	0	0	0	0	10 (2.9)
Nalidixic acid	101 (93.5)	103 (96.2)	51 (100)	255 (95.8)	28 (100)	33 (100)	16 (100)	77 (100)	332 (96.7)
Azithromycin	3.0 (2.8)	5.0 (4.7)	9.0 (17.6)	17 (6.4)	1.0 (3.6)	3.0 (9.0)	4.0 (25)	8.0 (10.4)	25 (7.3)
Cefexime	1.0 (0.9)	1.0 (0.9)	1.0 (2.0)	3.0 (1.1)	1.0 (3.6)	0	1.0 (6.2)	2.0 (2.5)	5.0 (1.4)
Ceftriaxone	0	0	1.0 (2.0)	1.0 (0.3)	0	0	1.0 (6.2)	1.0 (1.2)	2.0 (0.5)

Table 4. Nalidixic acid and Ciprofloxacin susceptibility profile among *Salmonella enterica* isolates using former CLSI breakpoints

Year	NAS			NARCS*			NARCI			NARCR		
	ST	**SPT**	**Total**	**ST**	**SPT**	**Total**	**ST**	**SPT**	**Total**	**ST**	**SPT**	**Total**
2010	07 (6.5%)	0	**07 (5.1%)**	70 (64.8)	13 (46.4%)	**83 (61%)**	09 (8.3%)	15 (53.6%)	**24 (17.6%)**	22 (20.4%)	0	**22 (16.1%)**
2011	04 (3.7 %)	0	**04 (2.8%)**	64 (59.8%)	19 (57.5%)	**83 (59.2%)**	04 (3.7%)	10 (30.3%)	**14 (10%)**	35 (32.7%)	04 (12.1%)	**39 (27.8%)**
2012	0	0	**0**	33 (64.7%)	13 (81.2%)	**46 (67.6%)**	0	0	**0**	18 (35.3%)	3 (18.7%)	**21 (30.8%)**
Total	11 (4.1%)	0	**11 (3.2%)**	167 (62.7%)	45 (58.4%)	**212 (61.8%)**	13 (4.8%)	25 (32.4%)	**38 (11.1%)**	75 (28.1%)	07 (9.1%)	**82 (23.9%)**

ST- *S.* Typhi; SPT A - *S.* Paratyphi A *MICs among these isolates were found to mostly range from 0.125 to 1.0 µg/ml.

Table 5. Ciprofloxacin susceptibility profile among Nalidixic acid resistant *Salmonella enterica* isolates using revised CLSI breakpoints

Year	**NARCS**			**NARCI**			**NARCR**		
	ST	**SPT**	**Total**	**ST**	**SPT**	**Total**	**ST**	**SPT**	**Total**
2010	02 (1.8)	0	**02 (1.4)**	67 (62)	13 (46.4)	**78 (57.3)**	32 (29.6)	15 (53.6)	**47(34.5)**
2011	01 (0.9)	0	**01 (0.7)**	61 (57)	17 (51.5)	**78 (55.7)**	41 (38.3)	16 (48.4)	**57 (40.7)**
2012	0	0	**0**	32(62.7)	09 (56.2)	**41 (60.2)**	19 (37.2)	07 (43.7)	**26 (38.8)**
Total	03 (1.1)	0	**03 (0.8)**	160 (60.1)	39 (50.6)	**197 (57.4)**	92 (34.5)	38 (49.3)	**130(37.9)**

ST- *S.* Typhi; SPT A - *S.* Paratyphi A

Table 6. CLSI clinical breakpoints for Ciprofloxacin in extra-intestinal *Salmonella* isolates

Ciprofloxacin	**Sensitive**	**Intermediate**	**Resistant**
MIC (µg/ml)			
2012 (New)	≤0.06	0.12-0.5	≥1.0
2011 (Old)	≤1.0	2.0	≥4.0
Zone of inhibition size (mm)			
2012 (New)	≥31	21-30	≤20
2011 (Old)	≥21	16-20	≤15

Ciprofloxacin resistance increased during the study period (between January 2010 and July 2012) from 20.4% to 35.3% in *S.* Typhi, and from nil to 18.4% in *S*. Paratyphi A (Table 4). However, with revised breakpoints, this increasing trend of ciprofloxacin resistance was observed only with *S*. Typhi; interestingly, overall resistance rates were higher with *S*. Paratyphi A (49.3%) compared to *S*. Typhi (35.3%) (Table 5).

Increasing rates of resistance to azithromycin from 2.8% to 17.6% and from 3.6% to 25% were detected in *S.* Typhi and *S.* Paratyphi A isolates respectively during the study period. Resistance to third-generation cephalosporin was noted in seven strains (2%) of *S. enterica*; two isolates, one each of *S.* Typhi and *S.* Paratyphi A, were resistant to ceftriaxone, and five isolates (three *S.* Typhi and two *S.* Paratyphi A) were resistant to cefexime (Table 3).

Discussion

Salmonella Typhi and *S*. Paratyphi A were isolated in the present study in a proportion of about 4:1 with a high percentage isolation of *S.* Paratyphi A cases (23%). Such increasing isolation rates of *Salmonella* Paratyphi A have been reported across India [5,7,14]. This likely reflects a high degree of clinical suspicion for enteric fever, even in milder clinical presentation. The increase may also be attributed to the high and rapid recovery rate of organisms by the BACTEC blood culture system used in the present study, even in the presence of antimicrobials. A high proportion of enteric fever cases in children suggest a greater burden of enteric fever in a younger age group as compared to adults. *S*. Typhi was isolated mostly from children, while *S.* Paratyphi A was isolated mostly from young adults in this study; this finding illustrates the distinct routes of transmission of both diseases. In contrast to *S*. Typhi, which is associated with risk factors within the household i.e. recent typhoid fever in the house and lack of hygienic practices, paratyphoid fevers largely follow an extra-household transmission, mostly by consumption of contaminated food prepared outside home; as children tend to consume street food or eat in restaurants, they are likely to be infected with *S*. Paratyphi A [15]. The percentage of patients hospitalized with enteric fever was two times higher with *S*. Typhi (43%) than with *S*. Paratyphi A (22%), suggesting a milder clinical course of paratyphoid fever.

Restricted use of ACCo has led to a decline in the incidence of MDR *S.* Typhi across India [10,14,16]. A recent multi-centre study from India reported an incidence of MDR in fewer than 5% of *S*. Typhi isolates [9]. Similarly, MDR was observed in only 3.4% of our *Salmonella* Typhi strains. The absence of MDR in *S*. Paratyphi A throughout the study period is consistent with the reports from India and Nepal [7,17], and as 100% of these isolates were susceptible to chloramphenicol and cotrimoxazole, the possibility of their reuse can be considered for management of paratyphoid fever.

With the emergence of MDR in *S*. Typhi, ciprofloxacin became the drug of choice; however, there have been several reports of therapeutic failure with ciprofloxacin in patients with enteric fever. These strains were ciprofloxacin-susceptible by former CLSI breakpoints, but were nalidixic acid resistant (NA^R). These strains were shown to be associated with tenfold higher ciprofloxacin MICs (decreased ciprofloxacin susceptible, ranging from 0.25 to 1.0 μg/mL) [18,19] compared to NA-sensitive isolates. NA^R is therefore an indicator of poor therapeutic response (significantly longer time to defervesce, high treatment failure rates or relapse or complication rates) to FQ therapy [7]. A single mutation in quinolone-resistance–determining region of gyr A gene is sufficient to confer resistance to NA and reduced susceptibility to fluoroquinolones. The continued use of ciprofloxacin against NA^R strains has led to a steady creep in ciprofloxacin MICs [7,16,19] along with further mutations at the same locus, resulting in recent emergence of fully resistant strains [7,8,20-22]. Saha *et al*., in 2006, reported a highly ciprofloxacin-resistant *S*. Typhi strain with the MIC as high as 512 μg/mL from Bangladesh [23]. Similar to several reports across India, the results of present study showed that NA^R *Salmonellae* strains (NA^RST, 95.8% and NA^R *S*. Paratyphi A, 100%) are highly prevalent in our community [7,24,25]. Most (99.2%) of the NA^R strains of *S. enterica* strains susceptible to ciprofloxacin by the former interpretive criteria (MIC $\leq$ 1.0 μg/mL) were recategorised as ciprofloxacin intermediate susceptible (57.4%) and resistant (37.9%) according to revised lowered breakpoints for ciprofloxacin. The high ciprofloxacin resistance rates observed in *S*. Typhi as well as *S*. Paratyphi A, by both former and revised breakpoints, in our study are concerning. Increasing trends of FQ resistance were observed in *S*. Typhi during the study period; however, resistance rates were notably higher in *S*. Paratyphi A (49.3%) than in *S.* Typhi (35.3%) strains by the revised breakpoints. A high level ciprofloxacin resistance (MIC, 8 μg/mL) in *S*. Paratyphi A has been reported from south India in

2006 [8]. In another study, increasing FQ resistance trends were observed in *S*. Typhi and in *S*. Paratyphi A during the six-year study period, both in terms of frequency and MIC levels [26]. Higher MICs of ciprofloxacin (≥ 1 μg/mL) were seen in 56% (14/25) of *S*. Typhi and 80% (20/25) of *S*. Paratyphi A in a study from south India in 2004 [27]. Our findings suggest that FQs should have no role in the empirical treatment of uncomplicated enteric fever. Other authors have also conveyed a similar point of view through their observations [7,22].

In the regions where MDR and NA^R *S. enterica* strains are endemic, azithromycin and third-generation cephalosporins are potential treatment options. By virtue of its high intracellular concentration and long elimination half life of 72 hours, azithromycin achieves rapid defervescence, reduces relapse rates, and eradicates faecal carriage [28]. An overall resistance of 7.3% for azithromycin in *S. enterica* isolates was observed in the present study, and increasing trends of resistance were seen during the study period among both *S*. Typhi and *S*. Paratyphi A isolates (2.8% to 17.6% and 3.6% to 25%, respectively). Furthermore, azithromycin resistance occurred at a slightly higher rate in *S*. Paratyphi A (10.4%, 8/77) than in *S.* Typhi (6.4%, 17/266). Similar to these findings, a higher rate of resistance and higher MICs (MIC90 16 μg/mL) was observed in *S.* Paratyphi A than in *S.* Typhi (MIC90 4.0 μg/mL) in another Indian study; however, all patients with *S.* Paratyphi A infection showed clinical response to azithromycin therapy [28]. The limitation of the present study was that disc diffusion results were not confirmed by MIC testing. Discrepancies between disc zone diameters and MICs have been reported due to the tendency of zones around azithromycin discs to show a trailing of light growth rather than a sharp edge; this causes technical difficulty in obtaining reproducible results by disc diffusion [28]. Nevertheless, this important finding of higher azithromycin resistance rate in *S*. Paratyphi A than *S*. Typhi is consistent with other studies [17,28]. As this was a retrospective study, the therapeutic efficacy of this drug was not determined.

Indian studies have reported higher MIC90 for azithromycin in *S*. Typhi and *S*. Paratyphi A (24 μg/mL) [10,29] compared to Western studies (MIC90 8 μg/mL, MIC range 4-16 μg/mL) [30,31]. In one Indian study, taking a MIC interpretive breakpoint of >16 μg/mL, 36 (33.6%) of *Salmonella* isolates were azithromycin-resistant, while clinical non-response to azithromycin therapy was observed in 19 patients (both azithromycin susceptible and resistant isolates with MIC range 6-64 μg/mL, MIC90 24 μg/mL were included) [10]. Randomized clinical trials (RCT) have shown higher or equivalent clinical cure rates with azithromycin compared to chloramphenicol, fluoroquinolones, and extended-spectrum cephalosporins for therapeutic management of uncomplicated typhoid fever [32,33]. This discordance between *in vitro* susceptibility and *in vivo* effectiveness is probably attributable to hundredfold intracellular concentrations of azithromycin in macrophages compared with serum, as intracellular MICs may not be represented fully by *in vitro* MIC testing methods [29]; additionally, lower MICs are seen with small inocula on *in vitro* testing that may correspond to the low grade bacteremia in typhoid fever [34]. Large-scale RCTs with follow-up and laboratory correlations are needed to evaluate azithromycin usage in the Indian population to address the apparent lack of correlation between *in vivo* and *in vitro* findings and to help formulate treatment policies for typhoid fever.

Cefexime is a favourable empiric choice for outpatient management of enteric fever cases, while ceftriaxone should be reserved for complicated cases. However, there have been sporadic reports of ceftriaxone resistance [9,23]. In the present study, 2% of *S. enterica* strains were observed to be resistant to third-generation cephalosporins (cefexime and ceftriaxone), similar to the proportions reported in a multi-centre Indian study and a report from Pakistan [9,35]. The recent reports of emerging extended spectrum beta lactamase-mediated resistance to ceftriaxone in *S.* Typhi and ACC-1 AmpC beta-lactamase producing *S.* Typhi strain conferring resistance to broad spectrum cephalosporins are alarming [36,37] as their spread among typhoidal salmonellae could seriously limit therapeutic options, and clinicians would likely have to resort to traditional first-line drugs or second line agents such as carbapenems and tigecycline.

In conclusion, the high prevalence of nalidixic acid resistance and emerging FQ resistance is a major problem in Asia; furthermore, azithromycin has an unclear role in enteric fever, particularly with *S.* Paratyphi A, which is being increasingly isolated and is not prevented by current vaccination. First-line agents or third-generation cephalosporin, therefore, are the choices worth considering for empirical management of enteric fever in developing countries. The results of the present study favour the use of

cefexime or chloramphenicol as a choice for uncomplicated enteric fever. However, these drugs require long treatment courses (7-14 days and 14 days, respectively), as short course therapy is frequently associated with relatively high rates of relapses. ACCo use further requires clinical and molecular studies to evaluate their efficacy and to document bacteriological eradication. MICs for third-generation cephalosporins and the susceptibility pattern also need to be closely monitored in view of their emerging resistance among *Salmonella enterica* isolates. Treatment of enteric fever should be guided by *in vitro* antimicrobial susceptibility testing of clinical isolates.

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Corresponding author
Sarika Jain
BLK Superspeciality Hospital
Pusa Road
New Delhi, 110005, India
e mail: drsarika6@gmail.com

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