Original article:

Increase in FluoroQuinolone resistance in *Salmonella enterica* isolated from blood in a tertiary care hospital in Uttarakhand

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Abstract:

Introduction: Enteric fever is a systemic infection caused by the bacteria *Salmonella enterica* serovar Typhi (*S.* Typhi) or *Salmonella enterica* serovar Paratyphi (*S.* Paratyphi). Resistance to chloramphenicol emerged in *S.* Typhi strains in the early 1970s and was soon followed by resistance to ampicillin and co-trimoxazole. The emergence of MDR *Salmonella enterica* isolates led to the use of Fluoroquinolones (ciprofloxacin and Ofloxacin) as the first- line drugs for its treatment. The situation was however complicated by the emergence of quinolone resistant strains. .

Material and methods: A cross-sectional study was carried out in clinically suspected enteric fever patients between Ist May 2015 to 30th April 2016 at Shri Guru Ram Rai Institute of Medical and Health Sciences Dehradun. A total of 4054 blood culture samples were collected and processed. For *Samonella enterica* spp, the antimicrobial agents tested were Ampicillin, Chloramphenicol, Co-trimoxazole, Ciprofloxacin, Levofloxacin ,Ceftriaxone, Cefixime and Nalidixic acid.

Results: Of the 4,054 blood culture samples, a total of 100 strains of *Salmonella enterica* were isolated. Of these, 88 were *Salmonella enterica* serotype Typhi, 12 were *Salmonella enterica* serotype Paratyphi A. 43% isolates of S. typhi were resistant to Ampicillin while *S.* Paratyphi A showed 67% resistance to Ampicillin. 100% sensitivity for chloramphenicol was observed for both, while 97% sensitivity for Salmonella Typhi and 83% sensitivity for Paratyphi A was seen for cotrimoxazole. Increased levels of resistance to Ciprofloxacin was seen in both the *Salmonella enterica spp.* All isolates (100%) were dramatically resistant to nalidixic acid.

Conclusion: Increasing rates of nalidixic acid and fluoroquinolone resistance among *S. enterica*, is of concern. Our results favour use of Cefexime or possibly Chloramphenicol as first choice for uncomplicated enteric fever. Ciprofloxacin can no longer be considered as the drug of choice in treating *Salmonella* infections.

 Key words: Nalidixic Acid, Enteric fever, Blood Culture, MIC

Introduction

Enteric fever (typhoid and paratyphoid fever) is a systemic infection caused by the bacteria *Salmonella enterica* serovar Typhi (*S.* Typhi) or *Salmonella enterica* serovar Paratyphi (*S.* Paratyphi). In humans it is transmitted through the feco-oral route. Enteric fever is a major public health problem in the developing world including Indian subcontinent and there is a need for an efficacious, safe and affordable oral

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treatment[1]. However if not treated appropriately, has a mortality rate of 30%. Appropriate treatment reduces the mortality rate to as low as 0.5% [2] It affects 6 million people worldwide with more than 600,000 deaths a year. Almost 80% of the cases and deaths are in Asia and the rest occur mostly in Africa and Latin America [3]. *Salmonella enerica* 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[4].Chloramphenicol was introduced in 1948 as the Ist effective antibiotic in the treatment of typhoid fever. Even though resistance started to develop within two years of its introduction, it did not emerge as a major problem until 1972[5].Resistance to chloramphenicol was soon followed by resistance to ampicillin and Co-trimoxazole[2]. Several epidemics of typhoid fever due to multi-drug resistant (MDR) *S.* Typhi have occurred worldwide, especially in Southeast Asia, since the 1990s [1]. A single large, high molecular weight, self-transferable plasmid belonging to incompatibility group H I1 is responsible for such en-bloc resistance[2]. The emergence of MDR *Salmonella enterica* isolates led to the use of fluoroquinolones (ciprofloxacin and ofloxacin) as the first-line drugs for its treatment. Fluoroquinolones have good *in vitro* and clinical activity against salmonellae and became the treatment of choice in cases of MDR Salmonellosis[6]

frequently mediated by single-point mutations in the quinolone resistance determining region of the gyr A gene, characteristically occurring at position 83 of the DNA gyrase enzyme (changing serine to phenylalanine) and position 87 (changing aspartate to tyrosine or glycine)[8]. Until recently, quinolone resistance was believed to arise solely from chromosomal mutations in genes encoding target enzymes or due to decreased accumulation of the drug inside the bacteria. In 1998, mobile elements with the potential for horizontal transfer of quinolone resistance genes were described.[9] This plasmid-mediated quinolone resistance was unknown in *Salmonella enterica* until recently. Plasmid-mediated quinolone resistance in *Salmonella* is of great concern, since horizontal transfer of quinolone resistance would facilitate rapid dissemination of the quinolone resistance genes, further compromising the use of these antimicrobial agents [3]. 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 [10].

Given the variation in the susceptibility patterns reported for *Salmonella enterica*, it is important to constantly monitor its susceptibility so as to provide suitable guidelines for treatment. The present study was undertaken to find out the susceptibility pattern of *Salmonella enterica* isolates in a tertiary health care facility in dehradun uttarakhand, India [3].

Materials and Methods

A cross-sectional study was carried out in clinically suspected enteric fever patients between Ist May 2015 to 30th April 2016 at Shri Guru Ram Rai Institute of Medical and Health Sciences Dehradun. The cases defined by physicians as a probable cases of enteric fever with fever (38°C and above) for at least three days and showing clinical signs and symptoms of enteric fever were included in this study. Patients who had already started antibiotic therapy prior to samples being taken were excluded from the study.

A total of 4054 blood culture samples were collected in BacT/ALERT culture bottles and processed in the microbiology division, of central lab SMI hospital dehradun, Shri Guru Ram Rai Institute of Medical and Health Sciences Positive blood cultures (signalled by the BacT/ALERT machine) were processed; subcultured on blood and MacConkey agar (HiMedia Laboratories, Mumbai, India) and incubated at 37°C for 24 hours. Non-lactose-fermenting colonies from MacConkey agar were further processed and identified as *Salmonella enterica* serotype Typhi and Paratyphi A by Vitek 2 automated system (bioMéuriex, France). Salmonellae were confirmed serologically with specific O and H antisera(Denka Seiken co ltd). The antimicrobial agents tested were Ampicillin, Chloramphenicol,), co- trimoxazole ciprofloxacin, levofloxacin ,Ceftriaxone, Cefixime and Nalidixic acid). Minimum inhibitory concentration (MIC) was determined by Vitek-2 automated system, as per the manufacturers' specifications based on CLSI Guidelines 2014.

Results

Of the 4,054 blood culture samples, a total of 100 strains of *Salmonella enterica* were isolated. Of these, 88 were *Salmonella enterica* serotype Typhi, 12 were *Salmonella enterica* serotype Paratyphi A (figure 1).

Of the 100 salmonellae, 61% were isolated from males and 39% from females (male: female ratio 1.7:1) (figure 2). The highest number of isolates (43%) was obtained from patients in 11 to 20 years age group (figure 3). However the least no of isolates were obtained from the age group of 41-50 years. Typhoid fever cases occurred in all months throughout the year, however they peaked during the months of May and June.
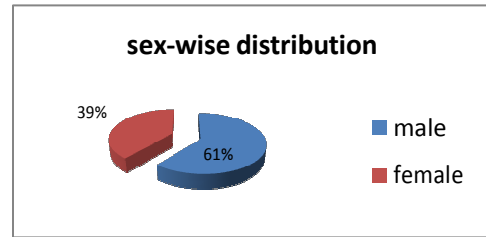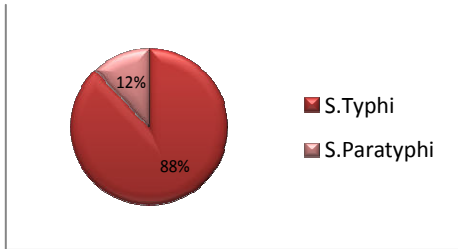

Figure 1. Species distribution of *Salmonella enterica*

Figure 2. Sex-wise Distribution of *Salmonella enterica*

S. Typhi showed 57% sensitivity to ampicillin and 43% isolates were resistant to the same while S. Paratyphi A showed 33% sensitivity and 67% resistance to Ampicillin. 100% sensitivity for chloramphenicol was observed for both, while 97% sensitivity for Salmonella Typhi and 83% sensitivity for Paratyphi A was seen for cotrimoxazole. Ceftriaxone showed 82% sensitivity for Salmonella typhi and 100% sensitivity for Salmonella paratyphi. For cefixime the sensitivity was 88% in *Salmonella Typhi* and 100% for *Salmonella* Paratyphi A. Levofloxacin showed moderate sensitivity (53%) for Salmonella Typhi and 83% for *Salmonella* Paratyphi A. For *Salmonella* Typhi Ciprofloxacin sensitivity was 16%, intermediate sensitivity was 49% and 35% were resistant. We defined decreased susceptibility to ciprofloxacin as a MIC of ≥0.12 μg/ml. For *Salmonella* paratyphi A sensitivity to Ciprofloxacin was 28%, intermediate sensitivity was 41% and 31% were resistant. All isolates (100%) were dramatically resistant to nalidixic acid. CLSI interpretive criteria were used (nalidixic acid resistance is defined as a MIC of ≥32 μg/ml). No MDR *Salmonella enterica spp*. was seen which may be linked to a drastic decrease in the number of chloramphenicol- resistant strains and cotrimoxazole resistant strains. (Table 1)

Antibiotics	S.Ty	S.Ty	S.Paratyp	S.Paratyp
Ampicillin	43	57	67	33
Chlorampheni	0	100	0	100
Cotrimoxazole	3	97	17	83
Nalidixic acid	100	0	100	0
Ciprofloxacin	84	16	72	28
Levofloxacin	47	53	17	83
Ceftriaxone	18	82	0	100
Cefixime	12	88	0	100

Table 1. Antibiotic resistance pattern in S.Typhi and S.Paratyphi A

NARCS		NARCI		NARCR	
S.Typhi	S.Paratyphi A	S.Typhi	S.Paratyphi A	S.Typhi	S.Paratyphi A
16%	28%	49%	41%	35%	31%

Table 2 Nalidixic acid and Ciprofloxacin susceptibility profile among *Salmonella enterica* isolates using revised CLSI breakpoints. NARCS(Nalidixic acid resistant Ciprofloxacin susceptible), NARCI (Nalidixic acid resistant Ciprofloxacin intermediate), NARCR (Nalidixic acid resistant Ciprofloxacin resistant).

16% isolates of *Salmonella* Typhi had minimum inhibitory concentration of nalidixic acid (>16 μg/ml) and that of ciprofloxacin ($\leq$ 0.06 μg/ml) in susceptible range while 28% was for Paratyphi A **(NARCS)** as per the revised guidelines of CLSI.Similarly, 49% of the isolates of *Salmonella* Typhi had minimum inhibitory concentration of nalidixic acid ($\geq$ 16 μg/ml) in resistant range and that of ciprofloxacin (0.12 μg/ml to 0.5 μg/ml) in intermediate susceptible range, while that for *Salmonella* Paratyphi A it was 41% as(**NARCI)**. 35% of the *Salmonella* Typhi isolates had minimum inhibitory concentration of nalidixic acid ($\geq$ 16 μg/ml) and ciprofloxacin ($\geq$ 1 μg/ml) in resistant range while for *Salmonella* Paratyphi A 31% resistance to Nalidixic Acid with Ciprofloxacin resistance was seen **(NARCR)**. (Table 2)

Resistance patterns	S.Typhi (%)	S.Paratyphi A A(%)	Salmonella enterica spp
MDR salmolellae	Nil	Nil	0
Nalidixic acid R	100%	100%	100%
Ampicillin R	43%	67%	55%
Ciprofloxacin resistant	84%	25%	60%
Ceftriaxone R	18%	0%	18%

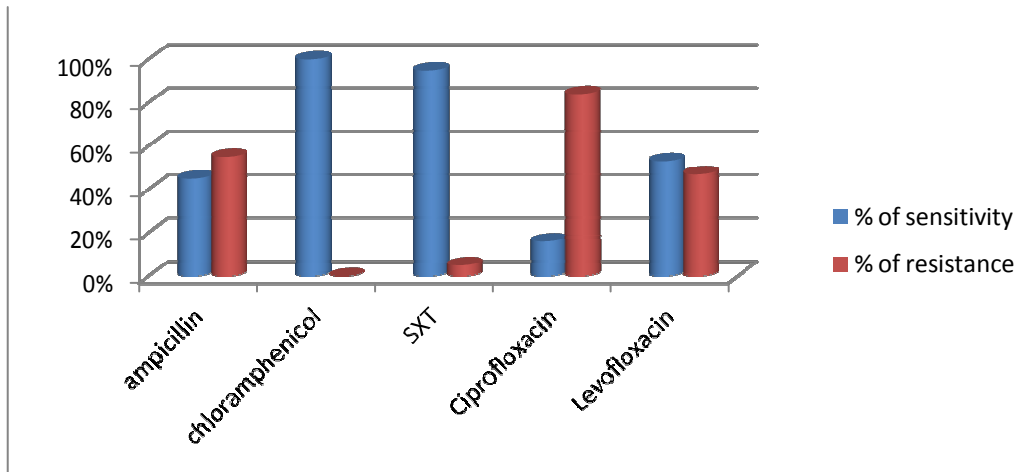Table 3. Resistance patterns seen in *Salmonella enteric spp.*

Figure 3. Comparison between ACCo and Fluoroquinolones resistance pattern.

Discussion:

Enteric fever is a major public health problem in our country. Proper sanitation, public health education and vaccination are long term preventive measures that would improve this situation. The emergence of antibiotic resistant strains of bacteria is closely linked to the irrational usantibiotics in treating human infections, especially ciprofloxacin [11].

In our study 88% isolates were of Salmonella Typhi whereas 12% isolates were of *Salmonella* Paratyphi A showing the preponderance of *Salmonella enterica* serotype Typhi in our region. This is in concurrence with Sidrammapa R etal wherein 86 % of *Salmonella enterica* serotype Typhi were isolated whereas 14% of *Salmonella* Paratyphi A were isolated[12]. 80% of the global burden of *S*.Typhi is mainly seen in the Asian and African countries[4]. It is a serious problem in endemic countries and travelers to these areas. It may be due to a combination of factors including poor sanitation and health care infrastructure[13]. Of the 100 salmonellae, 61% were isolated from males and 39% from females (male: female ratio 1.7:1) and similar findings have been noted in a study by Jain S etal [2] wherein the male female ratio is 1.6: 1 and Mohanty S etal with a male female ratio of 1.7 :1[14]. The highest number of isolates (43%) was obtained from patients in the age group of 11 to 20 years. This can be attributed to the fact that after age 20, the incidence falls, due probably to acquisition of immunity from clinical or subclinical infection [15]. However the least no of isolates were obtained from the age group of 41-50 years. Our findings are similar to those reported in a study by Rudresh S.M etal wherein maximum number of isolates were found in 11-20 yrs age group [7]. Least number of cases in the age group > 40 Years has also been reported by Singhal .L etal [16]. We noted the maximum incidence of typhoid fever in the

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summer months (April–June). Recent studies from India [17]have also noted increased isolation particularly at the end of the summer months. During the dry season, the water level gets progressively lower, becomes more stagnant and potable quality deteriorates as the weather becomes hotter. Under these conditions the likelihood of ingesting Salmonella from contaminated water is high[18].

Our study showed 43% resistance to Ampicillin by *Salmonella* Typhi and 67% resistance by Salmonella paratyphi A i.e 57% sensitivity to Ampicillin shown by Salmonella Typhi and 33% sensitivity by paratyphi A. 100% sensitivity to Chloramphenicol was seen for both typhi and paratyphi A isolates. Cotrimazole also depicted high sensitivity rates for both the types of isolates (97% for S.Typhi and 83% for *S*.Paratyphi A). These first-line drugs ampicillin, chloramphenicol, and cotrimoxazole were used as a standard treatment regimen for enteric fever until the mid-1980s[4]. However, the indiscriminate use of these drugs and

acquisition of plasmid-mediated resistance led to the development of typhoid resistant to ampicillin, chloramphenicol, and cotrimoxazole – multi-drug resistant (MDR) typhoid – in 1989. Due to the emergence of multi-drug resistant *Salmonella*, quinolones such as ofloxacin and ciprofloxacin became the drugs of choice in the treatment of typhoid fever[19].

However, since the early 1990s, several reports of decreased susceptibility to ciprofloxacin or ciprofloxacin resistance leading to treatment failure from Bangladesh, India, Nepal, Pakistan, Thailand, Tajikistan, United States, Vietnam, and other parts of the world have been documented[20]. In recent years, the re-emergence of susceptibility to ampicillin,

chloramphenicol, and trimethoprim has been reported. In this realm where therapeutic options for treating enteric fever have been reduced, the re-emergence of susceptibility to ampicillin, chloramphenicol, and cotrimoxazole needs to be evaluated to determine the therapeutic importance of these drugs[13].Thus, our study revealed a re-emergence of susceptibility to these drugs. In our study, cephalosporins showed an increased sensitivity where Ceftriaxone showed 82% sensitivity for *Salmonella* Typhi and 100% sensitivity for *Salmonella* Paratyphi A. While cefixime showed 88% senstivity in *Salmonella* Typhi and 100% for *Salmonella* Paratyphi A, this in concurrence with Laxmi V etal.[11]. In the recent past, cephalosporins have gained importance for the treatment of enteric infections. Parenterally administered third generation cephalosporins are effective in the treatment of typhoid fever. Ceftriaxone, administered either intravenously or intramuscularly for 10 14 days is equivalent to oral or intravenous chloramphenicol administered for treatment of susceptible *S*.Typhi strains. It is now considered to be the first drug of choice for the treatment of enteric fever unless the in vitro susceptibility tests prove otherwise. First and second generation cephalosporins are ineffective and should not be used to treat typhoid fever. Ceftriaxone and cefixime are both effective in typhoid fever, including nalidixic acid resistant infections[11].

Interestingly, in our study, none of the Salmonella isolates were MDR, even in the era of antibiotic resistance which is in accordance with Chand H.J etal[13]. Furthermore, the higher frequency of nalidixic acid-resistant Salmonella isolates found in our study indicates the possibility of fluoroquinolone resistance occurring currently and in near future as a consequence of the rampant use of fluoroquinolones [21]. This increase in high-level ciprofloxacin resistance probably reflects the overuse or irrational use of ciprofloxacin in the treatment of typhoid as well as in other unrelated infections. Incomplete treatment may be another factor contributing to development of resistance.

In view of the poor response to ciprofloxacin therapy for *S*. Typhi, Clinical and Laboratory Standards Institute (CLSI) published evidence-based revision of the ciprofloxacin MIC. The MIC value was lowered from 1 to 0.06 μg/mL. Decreased ciprofloxacin susceptibility (DCS) is defined as ciprofloxacin MIC of 0.12 – 1 μg/mL [1]. The locus responsible for this plasmid- mediated quinolone resistance, designated qnr A, qnr B and qnr S, has been identified in Enterobacteriaceae species.The qnr A gene confers nalidixic acid (NA) and low-level fluoroquinolone resistance and its presence has been shown to facilitate selection of chromosomal mutations that confer higher levels of resistance[22].

100% isolates of both *S*.Typhi and *S*.Paratyphi A are found to be resistant to nalidixic acid. Among the nalidixic acid resistant strains ciprofloxacin susceptible strains were only 16% in S.Typhi and 28% in S.Paratyphi A (NARCS), while majority of strains i.e 84 % of S.Typhi and 28% S.Paratyphi A (NARCI & NARCR) were in decreased susceptibility range (Table 2). These findings are in concurrence with Jain S. et al from New Delhi. With the emergence of fluoroquinolone resistant strains, their identification was done by determining susceptibility to nalidixic acid. Nalidixic acid resistant Salmonella isolates were found to have almost tenfold higher MIC to ciprofloxacin[23]. It was enthralling to compare the change in resistance pattern of conventional ACCo group of drugs to the flouroquinolones. There was an upward trend in sensitivity to ACCo with Ampicillin showing 45 %, chloramphenicol 100%, and cotrimoxazole 95 % sensitivity in *Salmonella enterica spp*. Contrastingly there was an increase in resistance for flouroquinolones with ciprofloxacin showing 84% resistance and levofloxacin showing 47% resistance in *Salomonella enterica spp*. (Fig 3)This finding has been reported from various parts of the country like Lakshmi V. etal from Hyderabad and Jain S etal from delhi [2,11], however our study is first of its kind reported from Uttarakhand.

Conclusion

Over the last decade there has been the re-emergence of susceptibility to ampicillin, chloramphenicol and co-trimoxazole in *S*. Typhi and a notable decline in MDR strains. The high prevalence of nalidixic acid resistance and emerging Fluoroquinolone resistance is a major problem in Asia. First-line agents or third-generation cephalosporin, therefore, are the choices worth considering for empirical management of enteric fever in developing countries. Results of this study favour use of cefexime or chloramphenicol as a choice for uncomplicated enteric fever. However, these drugs require long treatment courses (7-14

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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. Overall, treatment of enteric fever should be guided by *in vitro* antimicrobial susceptibility testing of clinical isolates.

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