

## Changing spectrum of antibiotic sensitivity in enteric fever

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### Abstract

**Aims and objectives:** The study was designed to analyze clinical profile and Antibiotic sensitivity pattern in case of culture positive typhoid fever and compare response of quinolones in vitro and in vivo.

**Methodology:** Forty eight cases of culture positive enteric fever presented in outpatient and emergency department of Kathmandu Medical College, Sinamangal, and Kathmandu were included in the study. Sensitivity pattern of isolates from blood culture was done by antibiotic disc diffusion method and this was compared with clinical response.

**Results:** Response was based on Fever Clearance Time (FCT) and it was found that mean FCT was 3.58 days with standard deviation of 1.84. Comparison was made separately for FCT $\geq$ 5 days and it was found that vomiting as the symptom and stool occult blood positive as the investigation to predict prolong FCT. Nalidixic acid as compared with other quinolones showed that other quinolones (ciprofloxacin, ofloxacin) are effective even in Nalidixic acid resistant cases when FCT was taken as the criteria of response, and it doesn't include the relapse rate.

**Conclusion:** Enteric fever is one of the leading causes of fever in Nepal. The diagnosis in most of the cases is done empirically by clinical features, but culture and sensitivity of blood or bone marrow is the gold standard way of diagnosis and providing treatment. The antibiotic sensitivity pattern is changing and resistance cases are emerging with indiscriminate use of drugs.

**Key words:** Enteric fever, *Salmonella typhi*, fever clearance time (FCT), antibiotic sensitivity test (AST)

*Salmonella typhi* infects only human and human transmission occurs through consumption of contaminated food and water. Multiple serotypes of *Salmonella* cause the syndrome of enteric fever, of which typhoid fever is the best studied and described.

It is encountered worldwide but is primarily found in those countries of developing world where sanitary conditions are poor. WHO estimates annual global incidence of typhoid fever at 0.3%<sup>1</sup>. 16 million cases occur annually worldwide and 7 million in South East Asia causing 600,000 deaths/ year<sup>2</sup>. Enteric fever is an important cause of illness and death in the overcrowded and unsanitary areas and is the leading cause of morbidity during summer season in Kathmandu<sup>3</sup>. It is one of the major public health issues in Nepal. It is reported from almost every part of Nepal from Mountain to Terai belt<sup>4,5,6,7</sup>.

Improved living conditions and the introduction of Chloramphenicol in 1948 resulted in a drastic reduction of cases and mortality. But in 1989 due to indiscriminate use of drugs and acquisition of plasmid mediated R factor has led to development of typhoid resistant to Amoxycillin, Chloramphenicol, Cotrimoxazole (ACCo) called Multiple Drug Resistant (MDR) typhoid<sup>8,9</sup>. The first major epidemic of MDR typhoid was reported in 1972 in Mexico. So use of Fluoroquinolone (ciprofloxacin initially and later ofloxacin) peaked up due to low cost, advantage

of oral route and twice daily dose and good tolerability<sup>10</sup>.

Though quinolone group of drugs emerged as useful drug for treatment of MDR typhoid, unfortunately ciprofloxacin resistant cases has emerged high<sup>11</sup>. The resistance to quinolone is not plasmid coded but due to altered DNA gyrase subunit. In last few years different studies have shown treatment failure or prolonged fever clearance time with ciprofloxacin, as well as increased Minimum Inhibitory Concentration (MIC) in culture media<sup>12,13,14</sup>. After that Nalidixic acid susceptibility testing was started routinely for all salmonella sensitivity tests. In Nalidixic acid resistant strains MIC to fluoroquinolone was found to increase in vivo along with prolonged fever clearance time<sup>15,16,17,18</sup>. So Nalidixic acid resistance is a marker of increased MIC of fluoroquinolone against salmonella<sup>19,20</sup> and depicts a step in progression towards fluoroquinolone resistance.

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**Material and method**

A prospective cross sectional study was designed to include all febrile cases with culture positive enteric fever in the year 2005 July -2006 July. Hence all patient presenting to outpatient and Emergency department of KMCTH who were suspected to have enteric fever had a blood culture and sensitivity sent at the time of presentation. Those cases with Salmonella species isolated in culture were included and the cases diagnosed as enteric fever on clinical ground or Widal tests were excluded. In the study period of 1 year; 48 cases of culture positive cases and patient >15years of age were taken.

All blood samples were grown in MacConkey’s agar or Blood agar for at least 72 hours and for sensitivity of culture Muller Hinton Agar was used with Kirby Bauer Disc diffusion method. Salmonella organism was confirmed with TSI test, however species identification was not done<sup>21</sup>.

All cases were prescribed fluoroquinolones unless the AST showed other drugs. The Fever Clearance Time (FCT) was noted for Nalidixic Acid Resistant (NAR) and Sensitive (NAS) cases. Patient having FCT more than 5 days and having AST otherwise were changed to different antibiotics if needed. Hospital course, fever clearance time after starting antibiotics and clinical outcome were also studied.

**Results**

Average Age of presentation: 23.5 years. It was found that 83% were in age group 15 – 30 years and 75% were male (Table 1). Fever, headaches were the two most common symptoms followed by GI upsets while on examination splenomegaly and coated tongue were more prevalent. Compared to other studies we found relative bradycardia in only 4% (Table 2). Regarding investigation, we found 82% patient had normal total leucocyte count with 10%leucocytosis and 8% leucopenia. Stool occult blood positive was there in 4 cases (8%).

**Antibiotic sensitivity testing**

Percentage of sensitivity was taken into account of those antibiotics which are included in at least 30 AST. The sensitivity pattern shows high resistance of Salmonella to nalidixic acid unlike good sensitivity to other quinolones in vitro. Surprisingly we had two ceftriaxone resistant cases all of which were ofloxacin sensitive. However there were 100 % (n=36) chloramphenicol sensitive isolates.

Ceftriaxone resistant cases in vitro were sensitive to fluoroquinolones and response to fluoroquinolones was good (Table 3). Sample size regarding NA sensitive and fluoroquinolone sensitive or partially sensitive cases was small, however in NA resistant cases it can be compared (Table 4). Table 5 shows that if vomiting is there as symptom or if Stool occult blood is positive then FCT is prolonged. Patient with more signs/ symptoms were found to have NAR and longer FCT.

**Table 1: Age and Sex distribution**

Age group (years)	Male	Female	Total
15 – 20	16	6	22
21 – 30	14	4	18
31 – 40	4	2	6
41 – 50	2	0	2
<b>Total</b>	36	12	48

**Table 2: Clinical characteristics**

Symptoms	No of patients	Percentage
Fever	48	100
Headache	35	73
Abdominal pain	6	12.5
Diarrhoea	7	14.5
Constipation	2	4
Vomiting	6	12.5
Altered consciousness	1	2
Signs		
Relative bradycardia	2	4
Splenomegaly	16	33
Coated tongue	21	43

**Table 3:** Antibiotic sensitivity pattern

Drugs	Sensitive	Partially Sensitive	Resistant	Total No	Percentage of sensitivity
Nalidixic Acid	9	1	36	46	25
Ciprofloxacin	41	2	1	44	93
Ofloxacin	46	2	0	48	96
Amikacin	34	-	-	34	100
Amoxycillin	39	-	4	43	90
Ceftriaxone	39	2	2	43	90
Cephalexin	24	-	-	24	-
Cephotaxim	16	-	-	16	-
Chloramphenicol	36	-	-	36	100
Cotrimoxazole	24	1	-	25	

**Table 4:** Comparison of Nalidixic acid sensitivity with ciprofloxacin and ofloxacin as shown by fever clearance time (FCT)

Cipro/Ofloxacin	Nalidixic Acid(NA)		
	Sensitive	partially sensitive	Resistant
Sensitive	4 days	4 days	4.13 days
Partially sensitive	-	0	4 .33 days
Resistant	-	0	Other drugs given acc. to AST

**Table5:** Seven NAR cases chosen with FCT $\geq$ 5 days. (Mean FCT: 6.28 days)

Clinical feature	No. in FCT $\geq$ 5 days	Percent prolonged FCT in	Total No of symptoms studied	Percent of symptom present in FCT $\geq$ 5 days
Fever	7	100%	48	14.5%
Headache	5	71%	35	14.2%
Vomiting	4	57%	6	66.6%
Splenomegaly	3	42%	16	18.7%
Stool occult blood positive	3	42%	4	75%

## Discussion

This study was conducted to highlight the incidence and response of Nalidixic acid resistant cases and change in antibiotic sensitivity pattern of salmonella species. Though the sample size was limited and typing was not done, this study indicates some relevant changing pattern in antibiotic response of Salmonella isolates. We have shown significant improvement in the sensitivity of salmonella isolates to chloramphenicol and drugs like amoxicillin, cotrimoxazole as also shown by a bigger study done in India by Mohanty et al and Walia et al<sup>22,23</sup>.

According to Joshi et al identification of Nalidixic acid resistance by the disk diffusion method has sensitivity of 100% and specificity of 87.3% as a tool to screen for isolates having MIC of Ciprofloxacin

0.125gm/ml<sup>13</sup>. Their study showed NAR in 88% of salmonella isolates. Our study has shown 75% NAR salmonella isolates. This corresponds with our study as we found increase FCT in NA resistance cases associated with partial sensitivity (increase MIC) to fluoroquinolone whereas NA sensitive cases were fluoroquinolone sensitive and were clinically characterized by FCT less than 5 days.. There was similar result in the study by Njuda NA et al, where ciprofloxacin sensitivity in vitro was not effective in vivo if the isolate was Nalidixic acid resistant. Many studies have now shown that fluoroquinolone resistant cases are not easily detected by routine disc diffusion method unless Nalidixic acid sensitivity is used.

Interestingly different studies<sup>3,4,20,21</sup> have showed 100% ceftriaxone responsive cases but like other studies done in Kathmandu Medical college<sup>6,21</sup> we found ceftriaxone resistant cases emerging in our community.

However we can agree that enteric fever shows wide variation in presentation and its empirical treatment without antibiotic sensitivity can be hazardous. Since we still have salmonella isolates sensitive to drugs like fluoroquinolone third generation cephalosporin can be avoided and best kept for treatment of serious infections.

### Conclusion

Nalidixic acid resistant isolates of salmonella is quite prevalent in our setting. Since fluoroquinolones are widely used, sensitivity of Nalidixic acid should be routinely asked for and used for deciding treatment with fluoroquinolones as the isolates that are NAR may not show response in vivo with fluoroquinolones even though the strain is sensitive to it in vitro.

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