

## Antimicrobial Sensitivity Trend in Blood Culture Positive Enteric Fever

Rajesh Dhoj Joshi,<sup>1</sup> Sachin khadka,<sup>1</sup> Deepak Man Joshi,<sup>1</sup> Basudha Shrestha,<sup>2</sup> Ganesh Dangal,<sup>3</sup> Kiran Prasad Acharya,<sup>1</sup> Sanjit Shrestha,<sup>2</sup> Yashad Dongol<sup>4</sup>

<sup>1</sup>Department of Medicine, <sup>2</sup>Department of Microbiology, <sup>3</sup>Department of Obstetrics and Gynecology, Kathmandu Model Hospital, Kathmandu, <sup>4</sup>Department of Biochemistry, KIST Medical College, Lalitpur, Nepal.

### ABSTRACT

**Background:** For diagnosis of enteric fever, the culture of the organism from different body fluids is the gold standard. After diagnosis, it is important to treat with the right antibiotic before any complications can occur. The retrospective study is designed to explore the antibiotic sensitivity trend in blood culture positive typhoid fever cases and the extent of drug resistance before treatment is administered.

**Methods:** A retrospective study was carried out for culture isolated enteric fever patients admitted in Kathmandu Model Hospital. The discharged records from January 2012 to December 2016 were analyzed. The patients above 15 years and with culture isolated enteric fever were included in the study.

**Results:** One hundred fifty-nine strains of *Salmonella typhi* and *paratyphi* were isolated from Jan 2012 to Dec 2016 at Kathmandu Model Hospital. Out of 159 isolated, 125 (78.6%) were *Salmonella typhi* and 34 (21.4%) were *paratyphi*. Among them co-trimoxazole, chloramphenicol, ceftriaxone, cefotaxime, cefixime, and ofloxacin demonstrated 100% sensitivity. Similarly, amoxicillin sensitivity was 98.1% (n=156) while ciprofloxacin was sensitive in 6.3% (n=10), intermediately sensitive in 49.1% (n=78) and resistance in 44.7% (n=71). The newer quinolone levofloxacin showed 78.5% (n=11) sensitivity. Azithromycin was sensitive in 99.2% (n=132) of total isolated *Salmonella* species both *typhi* and *paratyphi*.

**Conclusions:** A high degree of sensitivity was noted to chloramphenicol and co-trimoxazole, showing sensitivity has returned to conventional antibiotics. The drug-like ofloxacin is still the best responding drug in our contest whereas ciprofloxacin resistance is still high, but five years patterns show a trend of rollback of sensitivity.

**Keywords:** Cephalosporin; enteric fever; sensitivity.

### INTRODUCTION

Typhoid or enteric fever causes prolonged illness characterized by bacteremia with *Salmonella typhi*. Disease is basically presented as fever with chills and rigor, anorexia, cough, weakness, sore throat, dizziness, muscle pain, abdominal discomfort with either diarrhea or constipation.<sup>1</sup> Over the past decade, antibiotic resistance in *Salmonella enterica* is increasing and changing from one antibiotic to other. Since the introduction of chloramphenicol in 1948, it had been the drug of choice in most parts of the world. However, in the late 1980s, some *Salmonella typhi* strains developed simultaneous plasmid-mediated resistance to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole.<sup>2</sup> The quinolones group of drugs then emerged as the treatment of choice for typhoid fever but resistance

developed eventually which led to a shift in the third-generation cephalosporins.<sup>3</sup> The present retrospective study is designed to explore the antibiotic sensitivity trend in blood culture positive typhoid fever cases and the extent of drug resistance before treatment is administered.

### METHODS

A retrospective study was conducted at Kathmandu Model Hospital. A total of 159 cases of culture-proven *Salmonella typhi* and *paratyphi* were considered for the study. The study period was from January 2012 to December 2016 and data were collected from inpatient culture-positive cases and patients above 15 years of age. Due necessary permission from the concerned department and IRC *phect*-NEPAL were obtained. The

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**Correspondence:** Dr Sachin khadka, Department of Medicine, Kathmandu Model Hospital, Kathmandu, Nepal, Email: sachin\_khadka18@hotmail.com, Phone: +9779840051772.

discharged records of the specified period were analyzed for demographic data and antibiotic susceptibility patterns. Any patient records with incomplete information were excluded from this study. An antibiotic susceptibility pattern was further confirmed from the laboratory records. Data were entered and analyzed using SPSS version 21. Data has been summarized using percentage, graph, bar diagram, and table.

## RESULTS

**Table 1. Age-Specific Group in enteric fever (n=159).**

Age group	Frequency	Percent
>15 - 20	64	40.3
21 - 30	69	43.4
31 - 40	14	8.8
41 -50	8	5.0
<50	4	2.5

Out of 159 isolated cases of *Salmonella enterica*, 125 (78.6%) were *Salmonella typhi* and 34 (21.4%) were *paratyphi*. There were 59.1% (n=94) male and 40.9% (n=65) female patients. The majority of the patients were in the age groups 16-30 years (83.7%) as shown in Table 1. The mean age of the population studied were 24.8 years.

**Table 2. Laboratory and USG findings in enteric fever (n=159).**

Parameters	<i>S. typhi</i>	Bacteria Isolated		Total (%)
		Parameters <i>S. typhi</i>	<i>S. para-typhi</i>	
Leucocytes Count	<4000	15 (9.4%)	1 (.7%)	16 (10.1%)
	4000-11000	105 (65.4%)	31 (19.5%)	135 (84.9%)
	>11000	6 (3.8%)	2 (1.2%)	8 (5%)
USG Finding	Normal	95 (59.7%)	27 (27%)	122 (76.7%)
	Spleno-megaly	30 (18.9%)	7 (4.4%)	37 (23.3%)
Widal Test	<1:320	97 (61%)	32 (20.1%)	129 (81.1%)
	>1:320	28 (17.6%)	2 (1.3%)	30 (18.9%)

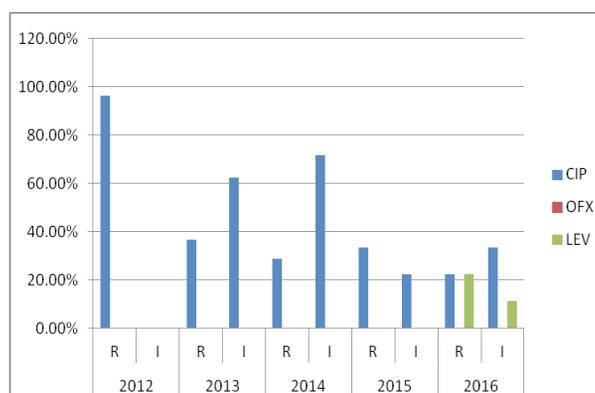
In this study, most of the patients (84.9%, n=135) had leucocytes count between 4000-11000/ccmm. with the mean WBC count of 6322.64/ccmm. Widal test was positive in 18.9 % (n=30) cases. Splenomegaly was seen in only 23.3 % (n=37) cases.

**Table 3. Susceptibility patterns of *Salmonella* species (n=159).**

Antibiotics	Sensitive (%)	Intermediate (%)	Resistant (%)
Amoxicillin	156 (98.1%)	0 (0%)	3 (1.9%)
Co-trimoxazole	159 (100%)	0 (0%)	0 (0%)
Ciprofloxacin	10 (6.3%)	78 (49%)	71 (44.7%)
Chloramphenicol	159 (100%)	0 (0%)	0 (0%)
Ceftriaxone	159 (100%)	0 (0%)	0 (0%)
Cefotaxime	159 (100%)	0 (0%)	0 (0%)
Azithromycin	132 (99.2%)	0 (0%)	1 (0.8%)
Cefixime	159 (100%)	0 (0%)	0 (0%)
Ofloxacin	159 (100%)	0 (0%)	0 (0%)
Levofloxacin	11 (78.5%)	1 (7.1%)	2 (14.3%)

\*Levofloxacin: Started to use from 07 2015; Azithromycin: Started to use from 01 2013

Antibiotic sensitivity to co-trimoxazole, chloramphenicol, ceftriaxone, cefotaxime, cefixime, and ofloxacin were 100%. Similarly, amoxicillin was sensitive in 98.1% (n=156) while ciprofloxacin is sensitive in 6.3 % (n=10), intermediate sensitive in 49 % (n=78) and resistant in 44.7 % (n=71) patients. Sensitivity to levofloxacin was 78.5 % (n=11), azithromycin 99.2% (n=132), as shown in table 3.



**Figure 1. Year wise resistance pattern of *Salmonella* isolates to common quinolones.**

CIP: ciprofloxacin, OFX: ofloxacin and, LEV: levofloxacin

The year wise comparison of commonly used fluoroquinolones resistance patterns of 5 years is shown in Table 4. This comparison demonstrated that ciprofloxacin resistance was 96.1% in 2012 which decreased to 36.6% in 2013 that further decreased to 28.57% in 2014 while it became resistant to 33.3% in 2015. In 2016 ciprofloxacin was resistant in 22.2% of patients only. On the other hand, ofloxacin was completely sensitive during our study period, but levofloxacin, which was started to use from July 2015 was already resistant in 22.2% patients, as shown in figure 1.

## DISCUSSION

Typhoid fever or acute febrile illness caused by *Salmonella typhi* is an important cause of community-acquired septicemia with high morbidity and mortality in Nepal as is seen in many Asian countries. It continues to be a public health problem in Nepal, being compounded by emerging resistance to antibiotics that were effective earlier.<sup>4</sup>

Wide variation in the sensitivity pattern of various strains circulating in different geographic regions of Nepal makes it necessary to assess the sensitivity of typhoid bacilli to antibiotics before instituting therapy.

Out of 159 cases, 94 (59.1%) were males and 65 (40.9%) were females and 83.7% were under 30 years of age with the mean age of 24.8 years which was similar with another study.<sup>5</sup> Total leucocytes count most of the times remained within a normal limit with mean leucocytes count 6322.6/cumm., which was similar finding to with the study done in children by Sudharsan et al<sup>6</sup> that showed WBC count between 5000- 10000/cumm in 70.9% and in adults by Gupta et al<sup>7</sup>, which showed mean WBC 5928/cumm. Similarly, in our study leucocyte counts below 4000 was seen in 16% patients which slightly differs from the other studies done in the past, which showed 11%.<sup>8</sup> In a study conducted by Dhulikhel hospital by Sharma et al<sup>9</sup>, splenomegaly was found in 3% of patients, whereas splenomegaly was present in 21.4% of patients in our study. This difference in sonographic finding could be due to the routine use of sonography in all fever patients in our hospital.

In the present study, among 159 isolated patients, co-trimoxazole, chloramphenicol ceftriaxone, cefotaxime, cefixime, and ofloxacin were 100% sensitive, whereas amoxicillin and azithromycin were sensitive in 98.1% and 99.2% respectively. At the end of 1980s and 1990s salmonella developed resistance to first line antibiotics, namely, amoxicillin, co-trimoxazole and chloramphenicol simultaneously.<sup>2</sup> In our study, co-

trimoxazole and chloramphenicol are 100% sensitive to all salmonella species, which is similar to the study done in 2002.<sup>10</sup> Similarly, in another study done by Khanal et al.,<sup>11</sup> the conventional first line antibiotics, namely, co-trimoxazole and chloramphenicol showed 100% sensitivity to *salmonella* species. The quinolones group of drugs emerged as useful drugs in the 90s for the treatment of multiple drug resistant cases.<sup>12</sup> Resistance to ciprofloxacin is now being reported both from the Indian subcontinent and the West.<sup>6</sup> Our study showed ciprofloxacin was resistant in 44.7% cases and intermediately sensitive in 49.1% patients, but the study done by Dhurba et al<sup>13</sup> in 2012 showed both ofloxacin and ciprofloxacin were resistant in only 1.8% each and intermediately sensitive in 7% and 18.4% of patients respectively. Compared to other quinolones, namely ciprofloxacin and levofloxacin, the ofloxacin showed 100% sensitivity in our study, which is almost similar to the another study with 98.2% sensitivity.<sup>14</sup>

In 2003, the World Health Organization published guidelines that recommended azithromycin, ceftriaxone, or cefixime for quinolone-resistant *Salmonella typhi* and *paratyphi* A infections.<sup>15</sup> Our studies showed ceftriaxone, cefotaxime and cefixime had a sensitivity of 100%, which on the contrary, with the study done at the Dhulikhel hospital by Dhurba et al<sup>13</sup> in 2012, where ceftriaxone was 96.6% and cefotaxime was 87.8% sensitive. Similarly, a study done by Dahiya et al<sup>16</sup> showed third-generation cephalosporins were 100% sensitive to *Salmonella typhi* and *paratyphi* A. In another study conducted by Misra et al,<sup>17</sup> more than 99% of *Salmonella typhi* and 86.3% of *paratyphi* A isolated in their study were susceptible to azithromycin which is similar with this study where 99.2% of patients were susceptible to azithromycin.

Recent reports from India, Far-east, Africa and Pakistan showed that more and more *Salmonella* strains are developing resistance to quinolones especially ciprofloxacin and that the sensitivity pattern of *Salmonella typhi* has been changing, i.e. a decline in the number of MDR isolates was noted which is also reflected by our study with no MDR cases. Concurrently, there has been an increase in the number of isolates sensitive to ofloxacin,<sup>18</sup> which is also proven by another study done by Bajracharya et al<sup>19</sup> which is similar to our study, where ofloxacin is 100% sensitive.

Our study compared the year wise resistance patterns of quinolones (ciprofloxacin, ofloxacin and, levofloxacin). Since levofloxacin was only started to use from July 2015, the number of cases was only 14. This comparison also demonstrates that ciprofloxacin resistance was 96.1% in 2012 which decreased to 36.6% in 2013, which further

decreased to 28.57% in 2014 while it became resistant in 33.3% of patients in 2015. In 2016, ciprofloxacin was resistant in 22.2% of patients only. All this indicates that resistance to ciprofloxacin is decreasing years wise, which is similar to the study done by Patel et al<sup>20</sup> where he studied the resistance patterns from 2011 to 2013 and found 25.5% ciprofloxacin resistance. They also report the declining pattern of multidrug resistance *Salmonella typhi* from 79.6% in 1980-98 study period to 24.6% in their study period of 2011-13. We also observed the reversal of ciprofloxacin resistant in our study from 96.1% in 2012 to 33.3% in 2015, indicating a possible comeback of ciprofloxacin in the near future as a first line drug. On the other hand, ofloxacin was not resistance throughout the study period in this study. However, recently started to use levofloxacin was already resistant in 22.2% patients, which was different from a study done by Chhetri et al<sup>21</sup> which showed levofloxacin was sensitive in 98% patients.

## CONCLUSIONS

A high degree of sensitivity was noted to chloramphenicol and co-trimoxazole, showing sensitivity has returned to conventional antibiotics. The drug-like ofloxacin is still the best responding drug in our context, whereas ciprofloxacin resistance is still high, but five year pattern shows a trend of rollback of sensitivity. Levofloxacin and azithromycin can be used to treat uncomplicated enteric fever as a first line therapy while the cephalosporin group in the treatment of both complicated and uncomplicated enteric fever in our settings.

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