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**Original Research Article**

# A study on the clinical spectrum, prescription pattern and diagnosis of enteric fever in a tertiary care hospital of North India

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## ABSTRACT

**Background:** Enteric fever is a major public health concern in developing countries. Lack of good diagnostic tests and antimicrobial resistance are challenges in treatment of enteric fever. Timely diagnosis and proper management of fever are essential to reduce the complications and emergence antibiotic resistance.
**Methods:** A prospective observational study was conducted on 71 subjects between February 2018 and December 2019. Spectrum of the disease, antimicrobial resistance and prescription pattern were observed and performances of various diagnostic methods (like culture, serology and loop mediated isothermal amplification) were determined.
**Results:** The most commonly observed clinical features included gastrointestinal complaints, anaemia, leukopenia, splenomegaly and hepatitis. Blood culture was positive for 49.3% (35/71) of the cases using conventional culture method. All samples positive by LAMP were also culture positive. Among the culture positive samples 80% (28/35) were *S. typhi* and 20% (7/35) were *S. paratyphi A*. Antimicrobial susceptibility to ciprofloxacin was 39.3% and 28.6% and ampicillin susceptibility was 32.1 and 28.6% in *S. typhi* and *S. paratyphi A* respectively. Only one multidrug resistant isolate was noted, while none was resistant to ceftriaxone or azithromycin. Cefixime and azithromycin combination therapy led to the earliest defervescence of fever.
**Conclusions:** Oral combination therapy may be a good option to treat enteric fever and oral combination therapy may be a good option to treat enteric fever and performance of LAMP seem to be as good as culture with a shorter turnaround time. LAMP can be used to obviate the need of culture in resource limited settings.

**Keywords:** Enteric fever, Typhoid, Salmonella, Loop mediated isothermal amplification, Multi-drug resistance

## INTRODUCTION

Typhoid and paratyphoid fevers, collectively referred to as enteric fever, are caused by *Salmonella enterica* serovars Typhi and Paratyphi A, B, and C.[1] Global burden of disease study (GBD) estimated 14·3 million incident cases and 135.9 thousand deaths due to enteric fever around the world in 2017. An annual incidence of 493.5 typhoid cases per 100,000 persons was reported from India.[2] Typhoid, a multi-system disease leading to complications and mortality, may present with features of involvement of various organs.[3] Blood culture is the gold standard for the diagnosis of enteric fever. The positivity of the blood culture is 90 % in 1st week and the sensitivity range of blood culture remains between 40% and 80%.[4] Polymerase chain reaction (PCR) is a promising molecular diagnostic method that is more than 90% sensitive but is infrastructure and cost intensive. Among serological tests, Widal has a sensitivity of 47 to 77% and a specificity of 50-92%.[4] Immunoassay methods like

Typhidot® and IDL Tubex® are rapid-dot enzyme immunoassays (EIA) that detect antibodies to a specific antigen of *Salmonella typhi*. Loop-mediated isothermal amplification (LAMP) has been applied to diagnosis by targeting STY2879 gene of *S.* Typhi. It is an attractive option for a rapid diagnosis eliminating the need for multiple thermal cycles of PCR.[5] LAMP is a highly sensitive diagnostic tool at low copy numbers of genetic material.[6] Typhoidal salmonella resistant to the drugs chloramphenicol, co-trimoxazole and ampicillin together are called multidrug resistant (MDR) strain. The Indian Network for Surveillance of antimicrobial resistance had reported lower than 5% of MDR *S. typhi* across the country from 2008 to 2010.[7] In India, resistance to fluoroquinolones among enteric fever isolates was reported to be 8.25% in a study that used a collection of strains from two decades [8]. Thereafter, extensive use of ceftriaxone and cefixime led to reports of increasing MIC and defervescence time for these antibiotics.[9] An Indian study showed that 12% *S. typhi* isolates were resistant to ceftriaxone.[10] Another study carried out in India reported cefotaxime-mediated extended-spectrum β-lactamases (ESBL) production among isolated *S. typhi*.[11] H58 clade that is resistant to fluoroquinolones and first line agents such as 3rd generation cephalosporins are an emerging menace.[12] Another study from India reported 6.8% azithromycin resistance among *S. typhi*.[13] Reports of azithromycin clinical failures and *in-vitro* resistance in the different parts of the world exists. The $MIC_{90}$ values for azithromycin against Salmonella isolates from India do not match with the strains isolated from the Western countries.[14] Recently, extensively drug resistant (XDR) *S. typhi* strain has been identified in Pakistan which is resistant to first generation antibiotics, fluoroquinolones as well as third-generation cephalosporins and similar genomic profiles have been reported from India.[12,15,16]

## METHODS

This study was conducted in the Department of Medicine at our institute between February 2018 and December 2019 and was a prospective observational study. Any adult subject in the age group of 18 to 75 years and who had fever for more than 3 days and was clinically suspected to be a case of enteric fever were included in the study. Patients in whom any other cause of fever was proved were excluded from the study. The study was carried out in the samples collected from 71 number of volunteering and consenting patients in the age group of 18-75 years of age. Patients who visited the Department of Medicine at the Institute who fulfilled the inclusion criteria and who agreed to participate in the study were included. A detailed history was taken and clinical examination was carried out. The data were collected using a pre-designed and pre-tested schedule. About 10 ml of blood was collected from the subjects aseptically. Blood culture, IgM antibody test, Widal test and loop mediated isothermal amplification assay were performed from the sample collected at the point of the first contact. LAMP assays were carried out directly from blood sample as well as after four hours of incubation of the blood samples in blood culture bottles.[5,6] An increase in the amplified products confirms the viability of the detected pathogen. Other necessary tests to rule out other common causes of fever and routine investigations (as ordered by the treating physician) were also noted.

### *Case definition*

Confirmed case*:* persistent fever (38°C or more) lasting three or more days, with laboratory-confirmed *S. typhi* organisms (blood, bone marrow, bowel fluid). This is a clinically compatible case that is confirmed in laboratory. Probable case: persistent fever (38°C or more) lasting three or more days, with a positive serodiagnosis but no *S. typhi* isolation. This is a clinical compatible case that is epidemiologically linked to a confirmed case in an outbreak.

### *Blood culture*

Five ml of blood sample was collected from the patient and mixed with 45 mL of brain heart infusion (BHI) media (BD Difco, USA). These blood culture bottles were incubated at 37°C for 24 to 48 hours. These blood culture bottles were further subcultured on MacConkey agar (HiMedia) plates at 37°C for 24 hours. Pale colonies on MacConkey agar were subjected to MALDI-TOF which identified the organisms up to *Salmonella enterica* species level. The identified organism was inoculated in TSI agar for serotyping as per Kauffman White scheme.[17] Antibiotic sensitivity was performed by disc diffusion method (Hi Media Laboratories Ltd, India) as per clinical laboratory standards institute (CLSI) 2017 guidelines.[18]

### *Serology*

Widal test: antigen was prepared as per standard protocol for tube agglutination test. Serum samples were mixed with antigen in serial dilution and incubated as per laboratory protocol. After incubation, the sedimented button of every tube was dislodged very gently and observed for agglutination macroscopically. Titres of 1:80 and above were taken as positive as per laboratory protocol.

*IgM typhi point*

Serum was used for detection of specific IgG and IgM antibodies against extracted *Salmonella* antigens. The test was carried out using commercially available EIA test kit (typhi point, AB diagnopath manufacturing Pvt. Ltd., New Delhi) as per the manufacturer's guidelines.

### *Loop mediated isothermal amplification (LAMP)*

LAMP assays were carried out to detect the presence of S. Typhi and *S. paratyphi A* in blood culture samples of patients suspected of enteric fever. The genomic DNA was isolated of 4 hours sample at pre incubation and post

incubation of four hours from the blood culture bottles using Qiagen DNA isolation kit as per manufacturer's instructions (QIA amp DNA minikit; Qiagen, Germany). LAMP assay was performed as reported previously.[5,6] The commercial LAMP master mix containing geobacillus species DNA polymerase (Optigene, UK), deoxynucleotide triphosphates, ds-DNA binding dye and reaction buffer containing $Mg_2Cl_2$ (Optigene, UK) was used. LAMP reaction was carried out at 65°C for 20 minutes. The final results were detected via a photo sensitive isothermal amplification detection device designed and published elsewhere.[5,6]

***Patient follow up studies***

Out patients were followed up on alternate day courses of antibiotic were completed. We contacted (over phone) those patients who did not turn up for follow up. *In-patients* were followed up daily till discharge/death or till the oral antibiotics were completed (for those in whom there was oral switch before discharge). The patients were enquired about the day of fever defervescence and were observed for any complication of disease or medicines. The data of subjects were collected using a pre-designed and pre-tested schedule.

***Statistical analysis***

The data collected was analysed using statistical *t* test and *z* test.

## RESULTS

Seventy-one patients were included in the study of which thirty-five (49.3%) were treated as in-patients while the rest were managed on out-patient basis. Patients, hemodynamically unstable, who were unable to take orally or who did not respond to oral antibiotics were admitted. Thirty-nine out of our seventy-one patients (54.93%) were females. The age of most of subjects ranged between 21 to 30 years (42.25%) while 23.94% of the subjects were between 18 to 20 years of age. All the patients were febrile and the duration of fever in the study subjects ranged from one to thirty days with an average of ten days. 19.72% of the patients had more two than weeks of fever. The presenting complaints are shown in Table 1.

**Table 1: Presenting complaint of our patients (n=71).**

| Complaint | N (%) |
|---|---|
| **Pain abdomen** | 26 (36.62) |
| **Headache** | 21(29.58) |
| **Only fever** | 21 (29.58) |
| **Cough** | 12 (16.9) |
| **Diarrhoea** | 11 (15.49) |
| **Myalgia** | 2 (2.82) |
| **Haematochezia** | 1 (1.41) |
| **Vomiting** | 12 (16.9) |

Blood culture was carried out in for all the 71 cases and was reported to be positive for *Salmonella spp.* in 35 (49.3%) of the patients (henceforth referred as culture positive). Of the thirty-six-blood culture negative patients (henceforth termed as culture negative), 12 were managed indoor while 24 were treated on outdoor basis. Of the 35 culture positive patients, 23 were admitted (65.71 %). The comparison of clinical and laboratory features of the culture positive and culture negative patients is shown in Table 2.

**Table 2: Table depicts the clinical and laboratory features of culture negative and culture positive patients and results of Chi-square test applied to compare each parameter between the two groups.**

| Characteristics | | Culture negative patients (n=36) Frequency (%) | Culture positive patients (n=35) Frequency (%) | Chi-square test |
|---|---|---|---|---|
| **Transaminitis** | AST >80 U/l | 8 (22.22) | 11 (31.43) | 0.7674 p=0 .381009 |
| | ALT >90 U/l | 9 (25) | 10 (28.57) | 0.1155 p=0 .733975 |
| **Leukopenia** | Leukopenia | 12 (33.33) | 11 (31.43) | 0.0294 p=0.86386. |
| | ANC <1500 $mm^3$ | 5/12 (41.67) | 6/11 (54.55) | |
| | lymphopenia <1000 $mm^3$ | 2/12 (16.67) | 4/11 (36.36) | |
| **Anaemia** | Males | 8/11 (72.73) had Hb <13.5, of these 8.6 (75) also had leucopenia | 15/21 (71.473) had Hb <13.5 of these 15.9 (60) also had leucopenia | 0.1131 p=0.736644 |
| | Females | 18/25 (72) had Hb <12.2/18 (11.11) also had leucopenia | 7/14 (50) had Hb <12. Among these 7.1 (14.29) had leucopenia | 1.8876, p=0.169473 |
| **Splenomegaly** | | 11 (30.56) | 10 (28.57) | 0.0335. p=0.854686. |

**Table 3: Comparison of various diagnostic test according to days of fever.**

| Days of fever | Blood culture (%) | Widal test (%) | IgM typhi point (%) |
|---|---|---|---|
| **1 to 5** | 8/15 (53.33) | 4/10 (40) | 7/12 (71.43) |
| **6 to 10** | 22/38 (57.89) | 28/34 (82.35) | 17/24 (65) |
| **11 to 15** | 5/11 (45.45) | 5/10 (50) | 7/9 (45.45) |
| **>15** | 0/7 (0) | 4/7 (57.14) | 2/7 (28.57) |

The average duration of hospitalization of thirty-five patients who received inpatient treatment was 8.5 days. The average duration was 8.6 days among culture positive patients and 8.3 days among culture negative patients. Among the thirty-five patients who were found culture positive, Salmonella Typhi growth was observed in the culture of 28 (80%) of the subjects and seven (20%) patients had their blood cultures positive for *S. Paratyphi A*. Antibiotic sensitivity pattern of our isolates is shown in Figure 1. Maximum blood culture positivity (57.89%) was found when blood was collected between six to ten days of fever. Maximum Widal positivity was also noted (82.35%) between six and ten days of illness while maximum IgM typhi point positivity (71.43%) was seen within first five days of illness (Table 3).

Out of the thirty-six culture negative patients twenty-three were Widal positive. Out of the seven *S. paratyphi A* culture positive patients five had Widal test done of which two were Widal positive. Among the 28 culture positive S. *typhi* 16 had Widal positive. Sensitivity, specificity, positive and negative predictive values for Widal were found to be 69.23%, 34.29%, 43.9 and 60% respectively with respect to culture. Sensitivity, specificity, positive and negative predictive values for IgM typhi point were calculated to be 90.91%, 56.67%, 60.61% and 89.47% respectively with respect to culture.

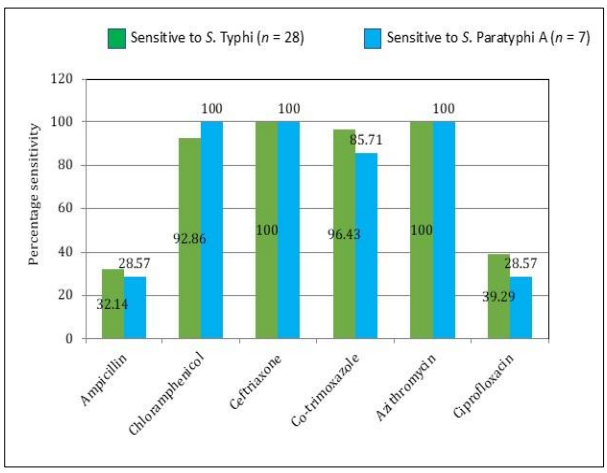


**Figure 1: Antimicrobial susceptibility of the blood culture *Salmonella* isolates against anti-typhoidal drugs.**

The results for twenty-one samples were evaluated with LAMP assay and nine of the samples yielded positive results. All these nine patients were culture positive. Average duration of IPD (In patient department) antibiotics was 7.3 days. Eight patients had IV to oral switch at discharge. Three were discharged on azithromycin 1 gm/ day and five were discharged on cefixime 400 mg twice a day. A flowchart depicting the antibiotic usage in in-patients and out-patients is shown in (Figure 2).

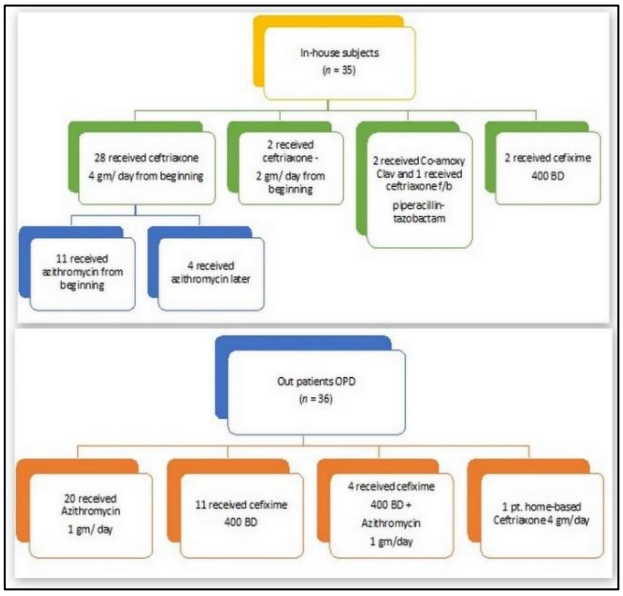


**Figure 2: Antibiotic usage in 35 inpatient cases and in 36 OPD patients included in the study.**

Use of combination of cefixime 400 mg twice a day along with azithromycin 1 gm/day led to earliest defervescence of fever on an average of 2.5 days, followed by cefixime 400 mg twice a day (average 3.5 days) and azithromycin 1gm once a day (average 3.75 days) given alone. Average time to defervescence of fever when Ceftriaxone 4gms per day was found to be 4.45 days, while it was longest (4.78 days on an average) when ceftriaxone 4gms per day was combined with azithromycin 1gm per day. Cefixime was given for an average of 7.4 days while ceftriaxone was given for an average of 6.1 days. Azithromycin was given for an average of 7.3 days. None of the patients were found to have significant drug related adverse event necessitating stopping of antibiotics.

## DISCUSSION

Non-specific cough was presenting complaint in 16.9% of our patients while, a study from Ethiopia had found that 44.4% of patients had a cough at presentation.[19] Splenomegaly was found to be common in the studies and was present in 29.81% of our patients.[20,21] Typhoid

hepatitis was seen in a substantial number of patients as in other studies.[22] Literature pertaining to depth of neutropenia and typhoid as a cause of febrile neutropenia is sparse. We found 16.67% of patients with leukopenia had absolute neutrophil count less than 1000/cumm.

Blood culture positivity of our study corroborates with study of Crump et al (40% to 87%) and various other published data.[23] As observed in various other studies we noted declining sensitivity of blood culture after first week of fever.[23] The observation of high sensitivity and high negative predictive value and early positivity of IgM typhi corroborates with other studies.[24,25] Recently Kaur et al reported 100% sensitivity and specificity (with respect to culture) of LAMP in diagnosing typhoid, which was also seen in the present study. As the sensitivity and specificity was as good as culture, it has the scope of being used in resource limited settings where culture facilities are not available. But further studies are needed to draw a conclusion. Our observations of this study reiterate the data of recent literatures that claim declining resistance to first line agents and high prevalence of quinolone resistance among currently circulating strains.[9,16,26] This has been explained by the decreased use of ampicillin, chloramphenicol and co-trimoxazole and increased use of quinolones. In contrary to various reports, all of our 35 *Salmonella spp.* isolates were sensitive to ceftriaxone. All our isolates were sensitive to azithromycin and there was no apparent azithromycin treatment failure in contrary to some reports of azithromycin resistance and treatment failure.[21] In the current study, ceftriaxone was the most common antibiotic prescribed to the admitted patients out of which 31.43% had received combination of ceftriaxone and azithromycin from the beginning. In total, 45.71% of the in-patients received a combination of two antibiotics at some point. This data of ceftriaxone usage and combination drug usage corroborate with the study of Rathod et al.[27]

In this work, azithromycin was the most commonly prescribed drug in OPD followed by cefixime. Nearly 11% of the patients had received a combination of azithromycin 1gm /day and cefixime 400 mg twice a day. The usage of azithromycin was high as was also seen in an another study, but the use of combination therapy was lower in the present study.[22] In our study, the use of combination of cefixime 400 mg twice a day along with azithromycin 1gm/day led to the earliest defervescence of fever on an average of 2.5 days. This ushers the scope of rational use of combination therapy for faster cure of enteric fever in the near future, but larger well-designed studies are needed to look into this.

## CONCLUSION

Transaminitis, anemia and leucopenia were common among our patients. IgM performed best in the first five days of illness while Widal and blood culture performed better between 6$^{th}$ and 10$^{th}$ day of fever. All LAMP positive samples were also culture positive. Blood culture was positive in 49.3% patients. About 80% of our isolates were *S. typhi* while 20% were positive for *S. paratyphi A.* None of our isolates were ceftriaxone or azithromycin resistant. Use of combination of two or more than two drugs was low in our study (45.71% among in-patients and 11.11% in out-patients). Defervescence was fastest with combination of cefixime and azithromycin. Time to defervescence was shorter with the use of cefixime than with use of azithromycin. Thus, use of combination of azithromycin and cefixime for treatment out-patients is an attractive treatment option, but further studies are needed.

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