Original Article

Treatment Response and Fever clearance time of Typhoid Patients in a North Indian Tertiary Care Setting

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Abstract

Background: Typhoid fever, caused by Salmonella Typhi and Paratyphi, remains a significant public health issue in India. This study assessed the clinical and microbiological profile of Salmonella bacteremia and examined the association of fever clearance time (FCT) with antibiotic regimens. **Material and Methods:** This prospective study was conducted at Christian Medical College and Hospital, Ludhiana, over one year (November 2016–October 2017). Patients ≥12 years of age with blood culture–proven Salmonella infection were enrolled. Clinical details, prior antibiotic exposure, laboratory results, and FCT were documented. Blood cultures were processed using BD Bactec, and MICs were determined as per CLSI guidelines. Repeat cultures on day 7 assessed microbiological cure. **Results:** Fifty patients were studied; 38 (76%) had S. Typhi and 12 (24%) had S. Paratyphi A. The mean age was 28.4±10.1 years, and 64% were males. Headache (60%) and abdominal pain (46%) were common presentations. Prior antibiotic use was noted in 24%, most frequently cefixime. Among S. Typhi patients, mean FCT was 64.07±13.36 hours with monotherapy and 67.4±19.87 hours with combination therapy (p=0.557). In S. Paratyphi A, mean FCT was 63.64±12.71 hours with single therapy and 84 hours with combination therapy (p=0.156). Hospital stay duration was comparable across both S. Typhi and S. Paratyphi (median 7 days each, p=0.878). **Conclusion:** To conclude, S. Typhi predominated over S. Paratyphi A. Both single and dual therapies were effective, with no significant differences in FCT or hospitalisation, emphasising rational antibiotic use in endemic settings.

Keywords: bacteremia, blood culture, cefixime, Salmonella infections, Salmonella typhi, typhoid fever.

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Introduction

Typhoid fever is a significant infectious disease caused by Salmonella Typhi or Paratyphi, typically transmitted through contaminated food or water. Symptoms appear within 8–14 days, ranging from mild fever to severe complications with abdominal discomfort and systemic involvement. The incubation period can vary from 3 to over 60 days.[1,2] Worldwide, typhoid fever impacts approximately 11 to 21 million individuals annually.[3] A recent study reported a prevalence rate of 3.28% in India.[4]

Each year, an estimated 200 million to 1 billion cases of Salmonella infections occur globally. Based on their pathogenic potential in humans and animals, Salmonella serovars are categorized as either typhoidal or nontyphoidal (NTS).[5] Typhoidal serovars responsible for typhoid and paratyphoid fever in humans include S. Typhi, S. Paratyphi A, B, C, and S. Sendai. These strains exhibit strong host specificity and are transmitted exclusively from infected individuals or carriers via contaminated food or water sources.[6] Typhoidal salmonellosis is marked by relatively lower morbidity but a high risk of mortality.[7] Salmonella Typhi continues to be the leading cause of enteric fever in India. Its primary mode of transmission is vehicle-borne, typically through ingestion of contaminated food or water. Globally, S. Typhi infections account for around 20 million new typhoid cases annually. In India, prevalence rates have been reported at 3.24% and 4.24% across various regional studies.[4,8] The reported prevalence rates of Salmonella Paratyphi serovars across various studies highlight notable regional variability and overall lower occurrence compared to S. Typhi. In the study by Talukder H. et al,[4] S. Paratyphi B was identified in 2.66% of cases, whereas Bhumbla U. et al,[8] reported a prevalence of 2.12% for both S. Paratyphi A and B. These relatively low figures suggest that paratyphoid infections remain less common than typhoid fever in many settings. Supporting this, another Indian study showed a significantly higher prevalence of S. Typhi at 54.4%, compared to 45.6% for S. Paratyphi A.[9]

A major challenge remains the emergence of antibiotic resistance, which makes effective treatment of Salmonella infections difficult. Moreover, this leads to multidrug resistance

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and increased morbidity among patients, with longer fever duration and higher hospital-associated costs.[10] Overall, outcomes vary with increasing severity and microbiological differentiation in Salmonella bacteremia.[11-14]

In this regard, the present study was conducted to assess the clinical and microbiological spectrum in patients with Salmonella bacteremia in our region, with the primary objective of determining the association of fever clearance time and antibiotic use in blood culture–proven Salmonella infections.

Materials and Methods

This prospective study was conducted at Christian Medical College and Hospital, Ludhiana, after obtaining permission from the Institutional Ethical Committee. Patients ≥12 years of age with high-grade fever, including those with blood culture–proven Salmonella infection admitted during the period of one year (1st November 2016 to 31st October 2017), were enrolled after providing informed consent. Patients who were not willing to consent to the study were excluded.

The study by Balasubramanian K. et al.[14] observed that blood culture was done in 80 patients, 6 grew S. Typhi and 28 grew S. Paratyphi. Taking this value as a reference, the minimum required sample size with a 10% margin of error and 5% level of significance was 88 patients. Due to time constraints and non-availability of patients, the finite population correction factor was used. For a finite sample size, taking the population as 60, the total sample size calculated was 36. To reduce the margin of error, the total sample size taken was 50.

Patients were evaluated as per a pre-designed proforma regarding presenting symptoms, physical and laboratory findings. A complete clinical examination was done. The data recorded included prior antibiotic use, dose and duration, and fever clearance time. Repeat blood culture was sent after 7 days of initiation of treatment to assess microbiological cure. Relevant investigations recorded included complete blood profile, serum creatinine, transaminases, blood culture report along with sensitivity, and MIC values.

Microbiological methods

Blood cultures were processed using the BD Bactec system, and all isolates were identified with Beckman Coulter Microscan dried gram-negative MIC/combo and breakpoint combo panels, which use miniaturized broth dilution methods. Antimicrobial agents were diluted in Mueller-Hinton broth, inoculated with standardized bacterial suspensions, and incubated at 35°C for at least 16 hours. Minimum inhibitory concentrations (MICs) for Salmonella were determined as per CLSI 2015 guidelines. Isolates were tested for susceptibility to chloramphenicol (30 µg), nalidixic acid (30 µg), ciprofloxacin (5 µg), and cefotaxime (30 µg). MICs for nalidixic acid, quinolones, and cefotaxime were also assessed using Microscan commercial strips.

Blood Culture technique

Blood culture collection involved strict aseptic precautions using BD Bactec vials that were checked for expiry and contamination. In patients with acute febrile illness, blood was drawn before starting antibiotics. The sample was collected via peripheral venipuncture, away from any existing venous or arterial lines. The venipuncture site was disinfected using 70% alcohol in a 5 cm circular area, scrubbed for 30 seconds, followed by 10% povidone-iodine applied in expanding circles. The iodine was left for 60 seconds to ensure proper antisepsis. BD vial caps were disinfected with alcohol swabs and dried. Blood was drawn using a sterile needle and syringe, inoculated into the BD vials, and gently mixed by inversion to ensure even distribution in the medium.

Definitions

Case: A case of Salmonella infection was defined as one that presented with a febrile illness, whose blood culture yielded S. Typhi or Paratyphi.

Fever clearance time: Fever clearance time was defined as the time from the start of appropriate antibiotic therapy to the first instance when oral temperature fell to 37.5°F (99.5°F) and remained below that level continuously for 48 hours.

Antibiotic therapy: The choice of antibiotic therapy was at the discretion of the treating physician. The decision to prescribe ceftriaxone (adults: 2 g BD; children: 75 mg/kg/day) or a combination regimen of ceftriaxone and azithromycin was made by the treating physician.

Outcome: The final outcome was to correlate fever clearance time with the MIC of cefotaxime and to assess clinical and microbiological outcomes in Salmonella bacteremia.

Clinical failure: Clinical failure of antimicrobial therapy was defined as continuing fever even after five days of continuous treatment with an antimicrobial.

Microbiological cure: Microbiological cure was defined as a negative blood culture taken after 7 days of antimicrobial therapy.

Relapse: Microbiologically confirmed relapse was defined as a blood culture positive for more than 48 hours after the last dose of antimicrobials.

Treatment failure: Patients with treatment failure were defined as those who received an antimicrobial anticipated to be effective for the treatment of typhoid fever and who remained in hospital for ≥7 days without fever clearance.

The final outcome was to correlate fever clearance time with antibiotic use and to assess clinical and microbiological outcomes in Salmonella bacteremia.

Statistical analysis: Categorical variables were expressed as numbers and percentages, while quantitative data with a normal distribution were presented as mean ± standard deviation (SD), and those with a non- normal distribution as median with interquartile range (25th–75th percentile). Normality of data was assessed using the Shapiro–Wilk test, and non-parametric tests were applied for variables not following a normal distribution. For comparisons, the Mann–Whitney test was used for non-normally distributed quantitative variables, and the independent t-test for normally distributed ones. Qualitative variables were compared using Fisher's exact test, as at least one cell had an expected value <5. Data entry was performed in Microsoft Excel, and final analysis was carried out using SPSS software (IBM, Chicago, USA, version 25.0). A p-value <0.05 was considered statistically significant.

RESULTS

The mean±SD age of study patients was 28.4±10.1 years. There were 32 (64.00%) males. The most common presenting complaint was headache in 30 (60.00%) cases, followed by abdominal pain in 23 (46.00%), diarrhoea in 16 (32.00%), cough in 9 (18.00%), and sore throat in 6 (12.00%). The mean±SD days of fever were 5.06±3.35 days, and temperature was 102.11 ± 1.18 °F [Table 1].

Prior antibiotic use was reported in 12 (24.00%) cases. Among those who received antibiotics, the most commonly used antibiotic was cefixime in 5 (41.67%), followed by ofloxacin in 3 (25.00%), ciprofloxacin in 2 (16.67%), augmentin and azithromycin in 1 (8.33%) case each. On examination, hepatomegaly was observed in 10 (20.00%) cases, splenomegaly in 3 (6.00%), and petechiae and pleural effusion in 1 (2.00%) case each. No cases had purpura, ecchymosis, consolidation, perforation or obstruction.

Patients underwent baseline investigations, the mean values of which are shown in Table 2. The mean hemoglobin level was 12.25±1.87 g/dL, TLC was 6186±1838.37 cells/µL, platelet count was 1.85 ± 1.25 lakhs/µL, SGOT was 72.58 ± 103.77 U/L, SGPT was 65.6 ± 45.24 U/L, and serum creatinine level was 0.78 ± 0.21 mg/dL [Table 2].

Culture showed growth of S. Typhi in 38 (76.00%) cases and S. Paratyphi A in 12 (24.00%) cases [Figure 1].

Compared to S. Paratyphi A, S. Typhi had comparable distribution of use of single antibiotic: ceftriaxone only (73.68% in S. Typhi vs. 91.67% in S. Paratyphi A) and combination therapy (26.32% vs. 8.33%) (p=0.257). Distribution of specific antibiotics used was also comparable between S. Typhi vs. S. Paratyphi A: azithromycin (60% vs. 100%), ciprofloxacin (10% vs. 0%), doxycycline (10% vs. 0%), metronidazole (10% vs. 0%) and vancomycin (10% vs. 0%) (p=1) [Table 3].

The mean fever clearance time (FCT) for S. Typhi was 64.07±13.36 hours with single antibiotic therapy and 67.4±19.87 hours with combination therapy (p=0.557). For S. Paratyphi A, FCT was 63.64±12.71 hours with single therapy and 84 hours with combination therapy, showing no significant difference (p=0.156). Overall, combined analysis revealed an FCT of 63.95±13.01 hours for single therapy and 68.91 ± 19.5 hours for combination therapy (p=0.927). The median duration of hospital stay in both S. Typhi and S. Paratyphi A infected patients were 7 days (p = 0.878) [Table 4].

Table 1: Demographic characteristics distribution.

Demographic characteristics	n(%)	Mean ± SD	Median(25th- 75th percentile)	Range
Gender				
Female Male	18 (36.00%) 32 (64.00%)	-	-	-
Abdominal pain	23 (46.00%)	-	-	-
Headache	30 (60.00%)	-	-	-
Diarrhoea	16 (32.00%)	-	-	-
GI bleed	0 (0.00%)	-	-	-
Cough	9 (18.00%)	-	-	-
Sore throat	6 (12.00%)	-	-	-
Age (years)	-	28.4 ± 10.1	26(21-32.75)	12-71
Days of fever	-	5.06 ± 3.35	4(3-6)	2-18
Temperature (ºF)	-	102.11±1.18	102(101.05-103)	99.7-104.2

Table 2: Descriptive statistics of investigations.

Investigations	Mean ± SD	Median(25th-75th percentile)	Range
Hb	12.25 ± 1.87	12.4(11.3-13.3)	7.2-16.3
TLC	6186 ± 1838.37	6150(4800-7350)	3100-10100
Platelet count	1.85 ± 1.25	1.62(1.24-2.21)	0.17-8.99
SGOT	72.58 ± 103.77	50.5(40-66)	24-727
SGPT	65.6 ± 45.24	53(40-82)	24-278
Creatinine	0.78 ± 0.21	0.79(0.6-0.9)	0.4-1.7

Table 3: Association of antibiotics used with S. Typhi and S. Paratyphi A.

Antibiotics given	S. Typhi	S. Paratyphi A	Total	P value
Ceftriaxone only	28 (73.68%)	11 (91.67%)	39 (78%)	0.257*
Combination	10 (26.32%)	1 (8.33%)	11 (22%)	
Combination antibiotic				
Azithromycin	6 (60%)	1 (100%)	7 (63.64%)	
Ciprofloxacin	1 (10%)	0 (0%)	1 (9.09%)	
Doxycyline	1 (10%)	0 (0%)	1 (9.09%)	1*
Metronidazole	1 (10%)	0 (0%)	1 (9.09%)	
Vancomycin	1 (10%)	0 (0%)	1 (9.09%)	
* Fisher's exact test				

Table 4: Comparison of patient in-hospital outcomes.

Organisms	FCT (hours) Single antibiotic	Combination	P value	Duration of hospital stay (days)
S. Typhi	64.07 ± 13.36	67.4 ± 19.87	0.557‡	7(6-7)
S. Paratyphi	63.64 ± 12.71	84 ± 0	0.156‡	7(5.5-8)

A				
Total 63.95 ± 13.01		68.91 ± 19.5	-	7(6-7.75)
P value 0.927‡		0.446‡	-	0.878†

† Mann Whitney test, ‡ Independent t test

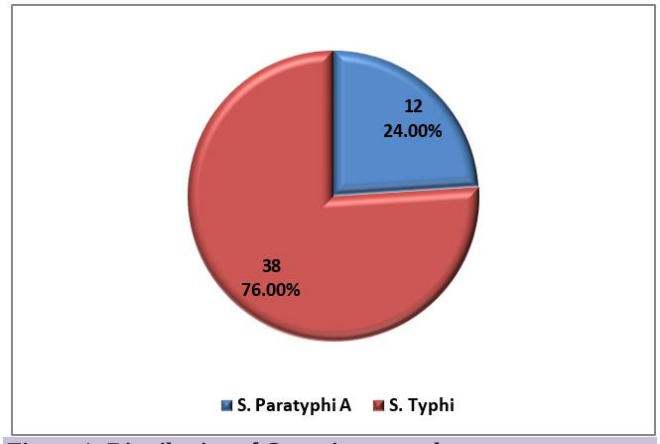

Figure 1: Distribution of Organism growth.

Discussion

Enteric fever should be suspected in individuals presenting with fever persisting beyond three days, with the probability rising as the duration of fever lengthens. Given its gradual progression, patients with severe enteric fever often remain febrile for over a week before seeking medical care or being clinically recognized.[9]

The age distribution of the patients remains wide, encompassing both children and adults. In the present study, the mean age of the typhoid-infected population was 28.4 ± 10.1 years, with a range of 12–71 years. In comparison, the mean age of typhoid cases varied across studies, generally occurring in young adults. Chatterjee et al,[12] reported most infections in 19–30 years (37.72%), while Zmora et al,[13] observed a mean age of 27.9 years (18–81 years). Balasubramanian K. et al,[14] found 56.2% in 13–30 years, 36.4% in 31–50 years, and 7.4% above 50, with a mean of 30.55 years. Kandikuppa et al,[9] reported 44% children and 56% adults (11 months–56 years), most (46.4%) between 16–40 years. Amsalu et al.[15] noted a mean of 34.1 years (8–80 years).

The gender distribution showed male predominance, as 64% of the patients were males, indicating a clear male predominance. Likewise, Chatterjee et al,[12] (61.3% males), Zmora et al,[13] (57% males), Balasubramanian et al,[14] (62.81% males), Lo C.K. et al,[16] (51% males), and Kandikuppa et al,[9] (59.2% males) also reported male predominance in typhoid infection.

Headache was the most common presenting complaint (60% of cases), followed by abdominal pain, diarrhoea, cough, and sore throat. In comparison, Chatterjee et al,[12] reported fever in all cases (100%), with abdominal pain (32.7%), splenomegaly (29.5%), and vomiting (26.7%) as major symptoms. Similarly, Balasubramanian et al,[14] found fever (100%), headache (62%), chills (62%), arthralgia (49%), myalgia (49%), vomiting (48%), and abdominal pain (40%) as common features. Kandikuppa et al,[9] noted fever in all patients, nausea/vomiting (53.6%), abdominal pain (25.6%), headache (23.2%), and cough (24.8%). Lo CK et al,[16 also reported fever (97.8%), abdominal and gastrointestinal complaints (73.5%), headache (35.8%), chills (32.5%), and malaise (24.3%). Variations reflect demographic, geographic, and healthcare-related differences.

The median duration of fever was 4 days, and the median temperature was 102°F, which was shorter compared to Chatterjee et al,[12] (9.53 ± 0.6 days) and Balasubramanian et al,[14] (11.61 ± 7.4 days). Kandikuppa et al,[9] observed fever lasting less than a week in 40.8%, 1–3 weeks in 55.2%, and beyond 3 weeks in 4% of patients. The observed variation may stem from early presentation, prompt antibiotic therapy, or differences in study population, healthcare accessibility, and regional practices.

In our study done on 50 cases, S. Typhi was seen in 76% of cases and S. Paratyphi in 24% of cases, similar to the distribution of typhoid in other regions. This closely aligns with Chatterjee et al,[12] who reported 76.8% S. Typhi and 23.2% S. Paratyphi A among 501 patients. Balasubramanian et al,[14] however, noted only 6 S. Typhi and 28 S. Paratyphi A isolates out of 80 patients, with 44 showing no growth, reflecting lower culture positivity. Lo CK et al,[16] reported 271 cases, with 61% S. Typhi, 36% S. Paratyphi A, and 3% S. Paratyphi B. Similarly, Amsalu et al,[15] found 75% S. Typhi and 25% S. Paratyphi A among 8 patients. Differences are likely due to geographical variations, temporal patterns of infection, laboratory practices, and prior antibiotic use affecting culture yield.

For management, we used either ceftriaxone or its combination with other antibiotics, primarily azithromycin, with others including ciprofloxacin, doxycycline, metronidazole, and vancomycin.

However, whether the antibiotic was used singly or in combination, FCT was statistically non- significant in S. Typhi (p=0.557) and S. Paratyphi (p=0.156), with the mean value of FCT being 63.95 hours with single-use antibiotics and 68.91 hours with combination therapy. Both values were slightly higher with combination therapy, but statistically there was no significant difference. Overall, the median duration of hospital stay was 7 days in either group.

Similarly, Kadhiravan T et al,[17] assessed 51 patients, with treatment regimens including ceftriaxone alone (35 cases), ceftriaxone plus another antibiotic (6), ofloxacin alone (7), and ofloxacin plus combination (3). The average FCT was 5 ± 3.5 days, ranging from 1 to 18.5 days. Fever persisted for ≥7 days in 20% of patients, and FCT showed no correlation with antibiotic sensitivity, MIC values, or treatment regimen. Nalidixic acid–resistant strains showed longer FCT (5.5 ± 3.8 days) compared to susceptible strains (3.7 ± 1.3 days). MDR strains cleared fever in 4.9± 2.7 days, similar to non-MDR strains (5.3 ± 3.9 days). Their findings align more closely with ours, showing no significant benefit of combination therapy over monotherapy.

Our findings contrast with Zmora et al,[13] who studied 105 patients and reported significant FCT reduction with dual therapy

versus monotherapy both in inpatients (ceftriaxone plus azithromycin: 80 hours vs. ceftriaxone alone: 98.25 hours, p=0.014) and outpatients (azithromycin plus cefixime: 86.5 hours vs. azithromycin alone: 96.75 hours, p=0.042). Overall, median FCT was significantly shorter in patients receiving dual therapy compared to monotherapy (88 vs. 95 hours, p=0.004). Their overall results demonstrated a consistent benefit of dual therapy, with FCT shortened by approximately 12 hours. Importantly, no significant difference in FCT was observed between infections caused by S. Typhi and S. Paratyphi (p>0.05). Unlike our results, they found dual therapy superior, possibly due to earlier initiation, patient selection, or differing resistance patterns.

It must be mentioned here that ceftriaxone with azithromycin is commonly given empirically to febrile inpatients when diagnosis is uncertain, as it also covers pneumonia and scrub typhus. In typhoid fever, this combination may be superior to monotherapy, reducing FCT and hastening bacteremia resolution.[9,18]

Limitations of the study: The study has certain limitations. As this is a single-center study, its results cannot be generalized. The study population was restricted to individuals aged 12 years and above, making the findings inapplicable to children. Moreover, prior antibiotic exposure was present in nearly one-fourth of patients, potentially influencing culture yield, sensitivity patterns, and treatment outcomes.

Conclusion

To conclude, this study demonstrated that S. Typhi was the predominant isolate, followed by S. Paratyphi A, with headache and abdominal pain being the most common clinical presentations. Prior antibiotic exposure was noted in a quarter of patients, most frequently with cefixime. Fever clearance time showed no significant difference between single-drug and combination regimens across both Salmonella species, and hospital stay duration remained comparable. These findings indicate that both monotherapy and combination therapy are effective in managing Salmonella bacteremia, with no clear advantage in FCT reduction for dual regimens.

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Conflicts of interest

There are no conflicts of interest.

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