ORIGINAL ARTICLE

Clinical Profile and Prescription Patterns in Culture-proven Enteric Fever in Children

Divya Priyadharshini[1], Mobill Clinton[2], Nandini Sethuraman[3], Mathrubootham Sridhar[4], Vidya Krishna[5]

Received on: 11 November 2023; *Accepted on:* 19 December 2023; *Published on:* 16 March 2024

Abstract

Aim: We aimed to study the clinical profile of enteric fever in children at an urban tertiary care children's hospital in South India.

Materials and methods: We carried out a retrospective study of culture-proven enteric fever in children aged 0–18 years between January 2018 and March 2023. We included 128 children in total; 109 inpatients (85.2%) and 19 outpatients (14.8%).

Results: Enteric fever accounted for 4.9% of nonrespiratory febrile admissions (n = 2,204). A total of 98 (76.5%) had *Salmonella typhi (S. typhi)*, while 30 (23.5%) had *Salmonella paratyphi (S. paratyphi) A* in their blood. Leukopenia occurred in 28 (21.8%) patients. The average inpatient fever defervescence time was 4.62 days (range: 1–28 days). A total of 26 children (20.3%) experienced fever defervescence after 5 days. The mean C-reactive protein (CRP) was 58.2 mg/dL in the group with fever defervescence in <5 days and 63.3 mg/dL for >5 days (p = 0.540). Single antibiotic was used in only 25 children (19.5%). Mean fever defervescence time was 4.8 days in the single antibiotic group and 4.5 days in the combination group (p = 0.47), and in typhoid vs paratyphoid, it was 4.8 vs 3.3 days (p = 0.04).

Conclusion: *Salmonella paratyphi (S. paratyphi)* caused 23.5% of culture-proven enteric fever cases. Most cases had normal leukocyte counts, eosinopenia, and elevated CRP. CRP does not predict fever defervescence. Fever typically resolved in 4–5 days, with paratyphoid fever resolving earlier. Combination therapy was used in over two-thirds of cases.

Clinical significance: *Salmonella paratyphi (S. paratyphi)* is a significant cause of enteric fever in children. There seems to be no clear benefit for combination therapy from our small retrospective data, but study limitations preclude drawing accurate conclusions. Future areas of research interest will include an effective vaccine for paratyphoid fever and a randomized clinical trial on single vs combination therapy in enteric fever.

Keywords: Culture-proven enteric fever, Drug susceptibility in enteric fever, Enteric fever in children, Prescription patterns in enteric fever, *Salmonella typhi* and *paratyphi* in Indian children.

Pediatric Infectious Disease (2024): 10.5005/jp-journals-10081-1408

Background

According to the multicenter SEFI study, the overall incidence of typhoid in our country is 360 cases per 100,000 person-years, resulting in an estimated 4.5 million cases and 8,930 deaths, with an assumed case fatality rate of 0.2%.[1] Enteric fever is more common in urban than rural areas in India, and Tamil Nadu bears a significant burden of this disease.[1,2] Children remain vulnerable to enteric fever in India, as the typhoid conjugate vaccine is not yet universally administered. While antimicrobial resistance in enteric fever has been widely reported in Pakistan, it has not yet become a widespread problem in India.[3] The role of combination therapy in treating enteric fever remains unclear, although it is often employed due to concerns about delayed defervescence.[4] In light of these factors, our study aims to investigate the clinical profile and prescription patterns in culture-proven enteric fever among children.

Materials and Methods

We conducted a retrospective analysis of hospital records, focusing on children aged 0–18 years with culture-proven enteric fever who received treatment either as outpatients or inpatients at Apollo Children's Hospital, Chennai, Tamil Nadu, between January 2018 and March 2023. We gathered demographic and clinical information, including age, sex, residence, the day of fever when the blood culture was taken, antibiotics administered before the culture, the day of fever defervescence after initiating treatment, associated complications, and the duration of hospital stay. We also examined laboratory parameters, including total white blood cell (WBC) counts with a differential count, C-reactive protein (CRP) levels, and antimicrobial susceptibility patterns. Additionally, we compared these parameters between culture-proven *Salmonella typhi (S. typhi)* and *Salmonella paratyphi (S. paratyphi)*. We also studied antibiotic prescription patterns in enteric fever.

[1,2,4]Department of Pediatrics, Apollo Children's Hospital, Chennai, Tamil Nadu, India

[3]Department of Microbiology, Apollo Hospitals, Chennai, Tamil Nadu, India

[5]Department of Infectious Diseases, Apollo Hospitals, Chennai, Tamil Nadu, India

Corresponding Author: Vidya Krishna, Department of Pediatric Infectious Diseases, Apollo Children's Hospital, Chennai, Tamil Nadu, India, Phone: +91 7845803309, e-mail: drvidya_krishna@apollohospitals.com

How to cite this article: Priyadharshini D, Clinton M, Sethuraman N, *et al*. Clinical Profile and Prescription Patterns in Culture-proven Enteric Fever in Children. Pediatr Inf Dis 2024;6(1):6–9.

Source of support: Nil

Conflict of interest: Dr Vidya Krishna is associated as the Assistant Editor of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of this editorial board member and her research group.

© The Author(s). 2024 Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Statistical Analysis

We presented descriptive statistics with mean ± standard deviation for continuous factors and frequency (percentage) for categorical factors. The normality of the data was determined by the Shapiro–Wilk test. We used the student's *t*-test/Mann–Whitney *U* test to recognize significant differences in the time to fever defervescence between these independent groups. Chi-square/Fisher's exact test was used to assess associations between two independent categorical factors. A *p*-value of <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences statistical software (IBM, version 28.0).

Results

Among the 128 children with culture-proven enteric fever in our study, 109 (85.2%) were admitted as inpatients and 19 children, 14.8%, were treated as outpatients. These 109 children accounted for 4.9% of total admissions (*n* = 2,204) for nonrespiratory origin of febrile illnesses in the period. Table 1 below represents the characteristics of the study group.

Most cases occurred in children above the age of 5 years (54.6%), with boys slightly outnumbering girls (55.4 vs 44.5%). Infants made up only 7.8% of the total study population. The majority of patients (91.4%) came from urban backgrounds. Although it is standard practice in our hospital to obtain blood cultures for all undifferentiated fevers before starting antibiotics, 25 (19.5%) children in the study group had already received antibiotics in the community prior to undergoing blood cultures at our hospital.

Of the patients, 98 (76.5%) had *S. typhi*, while 30 (23.5%) had *S. paratyphi A* in their blood cultures. All isolates were sensitive to amoxicillin, chloramphenicol, ampicillin, ceftriaxone, azithromycin, and cotrimoxazole, with the only noted resistance being to ciprofloxacin. Total WBC count was within the normal range in 87 (67.9%) children, while 28 (21.8%) had leukopenia and 13 (10.1%) had leukocytosis. Eosinopenia was observed in 86 (67.1%) cases. The mean CRP was 58 mg/dL, ranging between 7.4 and 200 mg/dL. The mean CRP in children with fever defervescence in <5 days was 58.2 mg/dL, compared to 63.3 mg/dL in those with fever defervescence after 5 days (*p*-value of 0.540).

Single antibiotics were prescribed in only 25 (19.5%) children. Among inpatients, ceftriaxone was the most commonly used antibiotic (*n* = 109, 100%). Azithromycin served as a second drug in 88 patients (80.7%), while cotrimoxazole was used in four patients (3.7%). Seven (6.4%) inpatients received triple therapy comprising ceftriaxone, azithromycin, and cotrimoxazole. One patient initially received meropenem followed by piperacillin-tazobactam but was later switched to ceftriaxone. Among outpatients, cefixime was the predominant single antibiotic (*n* = 13, 68.4%), while four (21%) received azithromycin alone, two (10.5%) got a combination of cefixime and azithromycin, and one child received a combination of cotrimoxazole and cefixime.

The average time to fever defervescence among inpatients was 4.62 days (range: 1–28 days). A total of 26 children (20.3%) experienced fever defervescence after 5 days. The mean time to fever defervescence was 4.8 days in the single antibiotic group and 4.5 days in the combination therapy group (*p*-value of 0.47). In terms of typhoid vs paratyphoid fever, the mean time to fever defervescence was 4.78 and 3.34 days, respectively (*p*-value of 0.04). Complications were observed in five inpatients (4.6%) with typhoid fever, including transaminitis (1), relapse (1), meningitis (1), cerebellitis (1), and psoas abscess (1). There were no fatalities in the study group.

Discussion

In our retrospective study, we observed that enteric fever predominantly affected males and children above 5 years of age, which is consistent with findings from a study by Walia et al.[5] Infants comprised a smaller proportion of cases, accounting for only 7.8% of all cases. Additionally, a higher percentage of patients in our study hailed from an urban background, potentially due to differences in healthcare-seeking behavior. Urban populations may be more susceptible due to dietary and sanitation practices.[2]

Notably, 19.5% of the children in our study had already received antibiotics in the community before undergoing blood cultures at our hospital. This highlights the issue of underdiagnosis or overtreatment of enteric fever in the community, as prior antibiotic use can affect blood culture results.

Regarding laboratory parameters, we found that 67.9% of children had normal total leukocyte counts (TLC), with leukopenia observed in 21.8% of cases, similar to findings by Behera et al.[6] Eosinopenia was noted in 67.1% of cases. CRP levels were elevated in most children, but we found no significant difference in CRP levels between those with fever defervescence in <5 days and those with fever defervescence after 5 days, underscoring the limited utility of CRP as a predictor for fever defervescence. In a study by Kheng et al., they reported that children culture-positive for *S. typhi* had a mean CRP level of 43 mg/dL, compared to a CRP level of 21 mg/dL in children with nontyphoidal illnesses.[7]

Most patients (76.5%) in our study were culture-positive for *S. typhi*, consistent with a similar study by Walia et al., where 80.6% were culture-positive for *S. typhi* and 19.4% for *S. paratyphi*.[5]

Our study revealed that 85.1% of patients were hospitalized, while 14.8% were treated as outpatients. However, this distribution may be influenced by referral bias since our study was conducted at a tertiary care hospital. In a surveillance study in Dhaka among children, the hospitalization rate for culture-positive enteric fever was 30%, with the highest rate observed among children aged 2–5 years.[8]

Combination therapy was commonly used in our patient population, with single antibiotics prescribed for only 19.5% of children. Among inpatients, ceftriaxone was the most frequently employed antibiotic, often combined with azithromycin. In contrast, outpatients more commonly received cefixime as a single antibiotic. A cross-sectional study by Koya et al. conducted between 2013 and 2015 found that at least ten different antibiotics were prescribed in 72.4% of patients. Cephalosporins were frequently used in children and young adults, except in the southern part of India, where different antibiotics were preferred.[9]

The average duration of fever defervescence in our study was 4.6 days, with a range of 2–16 days. This aligns with the findings of Walia et al., where the duration of hospital stay ranged from 2 to 35 days among 30 inpatients, with an average stay of 10 days.[5] Fever defervescence was notably longer in the typhoid group compared to the paratyphoid group, consistent with paratyphoid fever being generally milder.[7,10]

Interestingly, we observed no significant difference in fever defervescence between single antibiotic therapy and combination therapy (4.8 vs 4.5 days). In a small randomized control trial involving 105 adults with enteric fever in Nepal, where they used

Table 1: Characteristics of the study group

Group	*Characteristics*	*N (%) (n = 128, unless specified otherwise)*	*p-value*
Demography			
Sex	Male	71 (55.5%)	–
	Female	57 (44.5%)	
Age	<1 year	10 (7.8%)	–
	1–5 years	48 (37.5%)	
	>5 years	70 (54.7%)	
Residence	Urban	117 (91.4%)	–
	Rural	11 (8.6%)	
History			
Day of illness when blood cultures were drawn	<5 days	65 (50.8%)	–
	>5 days	63 (49.2%)	
Antibiotic receipt before blood cultures	Yes	25 (19.5%)	–
	No	103 (80.5%)	
Investigations			
TLC	Low Normal	28 (21.9%) 87 (68%)	–
	High	13 (10.1%)	
Eosinopenia	Yes	86 (67.1%)	–
	No	42 (32.8%)	
Platelet count ($\times 10^9$/L)	>150	107 (83.6%)	–
	<150	21 (16.4%)	
Mean CRP (mg/dL)	<5 days	58.2	*p*-value of 0.540
	>5 days	63.3	
Blood cultures	*S. typhi*	98 (76.6%)	–
	S. paratyphi	30 (23.4%)	
Treatment			
Admission	Yes	109 (85.2%)	–
	No	19 (14.8%)	
Antibiotics	Single	25 (19.5%)	–
	>1	103 (80.5%)	
Antibiotic class (inpatients) *n* = 109	Ceftriaxone	109 (100%)	–
	Ceftriaxone + azithromycin	88 (80.7%)	
	Ceftriaxone + cotrimoxazole	4 (3.7%)	
	Ceftriaxone + azithromycin + cotrimoxazole	7 (6.4%)	
	Meropenem	1 (0.9%)	
	Piperacillin- tazobactam	1 (0.9%)	
Antibiotic class (outpatients) *n* = 19	Cefixime	12 (63.1%)	–
	Azithromycin	4 (21.1%)	
	Cefixime + azithromycin	2 (10.5%)	
	Cotrimoxazole + azithromycin	1 (5.2%)	
Outcomes in hospitalized patients			
Fever defervescence in the study group, mean 4.62 days (range: 2–16 days)			
Fever defervescence (days)	Single antibiotic group	4.8	*p*-value of 0.47
	>1 antibiotic	4.5	
Fever defervescence (days)	*S. typhi*	4.8	*p*-value of **0.04**
	S. paratyphi	3.3	
Length of hospital stay	<3 days	36 (33%)	–
	>3 days	73 (67%)	
Complications	Yes	5 (4.6%)	–
	No	104 (95.4%)	

a combination of azithromycin with cefixime for those treated as outpatients and azithromycin with ceftriaxone for admitted patients, the combination therapy arm demonstrated superiority over azithromycin alone, resulting in a lesser duration of fever defervescence.[11] The rationale behind expecting better efficacy from combination therapy is that azithromycin is thought to act intracellularly, while ceftriaxone or cefixime works extracellularly. Additionally, combination therapy may help prevent the emergence of resistance.[4] However, further research, such as the results of the ACT-SA trial, is needed to better understand this aspect.[12]

The average duration of hospital stay in our study was 6 days, similar to a study by Ganesh et al., which reported an average length of stay of 6.5 days.[13] Hospitalization for >3 days was required for 67% of our study population.

Complications were relatively infrequent in our inpatient population, with only 4.6% experiencing complications associated with typhoid fever. No deaths occurred in the study group. Literature suggests that severe complications like ileal perforation, severe gastrointestinal bleeding, and encephalopathy occur in 10–15% of hospitalized patients, usually at around two to three weeks of illness.[10] The case fatality rate is usually <1%.[10] In our study, early diagnosis and treatment may have contributed to the lower rate of complications.

Limitations of our study include its hospital-based nature without a comparator group and its retrospective design.

Conclusion

Salmonella paratyphi (S. paratyphi) accounted for nearly a quarter of culture-proven enteric fever cases in our study. Most cases exhibited normal leukocyte counts, eosinopenia, and elevated CRP levels. CRP was not a reliable predictor of fever defervescence, which typically occurred within 4–5 days of treatment initiation. Paratyphoid fever resolved significantly earlier than typhoid fever. While combination therapy was frequently used in more than two-thirds of cases, its impact on fever resolution remains unclear.

Clinical Significance

Salmonella paratyphi is a significant cause of enteric fever in children. Though combination therapy is often used in clinical practice, there seems to be no clear benefit for combination therapy from our small retrospective data, but study limitations preclude drawing accurate conclusions. Future areas of research interest will include an effective vaccine for paratyphoid fever and a randomized clinical trial on single vs combination therapy in enteric fever.

References

1. Cao Y, Karthikeyan AS, Ramanujam K, et al. Geographic pattern of typhoid fever in India: a model-based estimate of cohort and surveillance data. J Infect Dis 2021;224(224 Suppl 5):S475–S483. DOI: 10.1093/infdis/jiab187
2. John J, Bavdekar A, Rongsen-Chandola T, et al. Burden of typhoid and paratyphoid fever in India. N Engl J Med 2023;388(16):1491–1500. DOI: 10.1056/NEJMoa2209449
3. Qamar FN, Yousafzai MT, Dehraj IF, et al. Antimicrobial resistance in typhoidal Salmonella: surveillance for enteric fever in Asia project, 2016-2019. Clin Infect Dis 2020;71(Suppl 3): S276–S284. DOI: 10.1093/cid/ciaa1323
4. Parry CM, Qamar FN, Rijal S, et al. What should we be recommending for the treatment of enteric fever? Open Forum Infect Dis 2023;10(Suppl 1):S26–S31. DOI: 10.1093/ofid/ofad179
5. Walia M, Gaind R, Mehta R, et al. Current perspectives of enteric fever: a hospital-based study from India. Ann Trop Paediatr 2005;25(3): 161–174. DOI: 10.1179/146532805X58085
6. Behera JR, Rup AR, Dash AK, et al. Clinical and laboratory profile of enteric fever in children from a tertiary care centre in Odisha, Eastern India. Cureus 2021;13(1):e12826. DOI: 10.7759/cureus.12826
7. Kheng C, Meas V, Pen S, et al. Salmonella typhi and paratyphi A infections in Cambodian children, 2012-2016. Int J Infect Dis 2020;97:334–336. DOI: 10.1016/j.ijid.2020.06.054
8. Saha S, Sayeed KMI, Saha S, et al. Hospitalization of pediatric enteric fever cases, Dhaka, Bangladesh, 2017-2019: incidence and risk factors. Clin Infect Dis 2020;71(Suppl 3):S196–S204. DOI: 10.1093/cid/ciaa1356
9. Fazaludeen Koya S, Hasan Farooqui H, Mehta A, et al. Quantifying antibiotic use in typhoid fever in India: a cross-sectional analysis of private sector medical audit data, 2013-2015. BMJ Open 2022;12(10):e062401. DOI: 10.1136/bmjopen-2022-062401
10. Hughes M, Appiah G, Watkins LF. Typhoid and paratyphoid fever. (CDC), Centers for Disease Control and Prevention, Jeffrey B Nemhauser (eds), CDC Yellow Book 2024.
11. Zmora N, Shrestha S, Neuberger A, et al. Open label comparative trial of mono versus dual antibiotic therapy for typhoid fever in adults. PLoS Negl Trop Dis 2018;12(4): e0006380. DOI: 10.1371/journal.pntd.0006380
12. Giri A, Karkey A, Dongol S, et al. Azithromycin and cefixime combination versus azithromycin alone for the outpatient treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia: a randomized controlled trial protocol. Wellcome Open Res 2021;6:207. DOI: 10.12688/wellcomeopenres.16801.2
13. Ganesh R, Janakiraman L, Vasanthi T, et al. Profile of typhoid fever in children from a tertiary care hospital in Chennai-South India. Indian J Pediatr 2010;77(10):1089–1092. DOI: 10.1007/s12098-010-0196-9