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Profile of Enteric Fever in Children Admitted to a Tertiary Care Center in North India

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Abstract

Background Enteric fever is a community-acquired systemic infection which is more common in resource-limited overcrowded communities with poor access to sanitation and its management is compounded by the increasing antimicrobial resistance to the first-line antibiotics used.

Materials and Methods This descriptive study reports the clinical profile of children with enteric fever managed at the departments of pediatrics and microbiology of a tertiary care hospital from February 2020 to August 2021. All inpatients who were confirmed (blood culture positive) or probable cases (clinical and serological evidence by Widal test) of enteric fever were included. Profile of all cases and antibiotic sensitivity pattern in culture positive cases were studied.

Results Of the 70 cases enrolled, 40% were females and 60% males, and majority (52.9%) was in the age group of >5 years. At admission, fever was the most common presentation along with abdominal symptoms. Widal test was positive in 84.6% cases and was found to be 80% sensitive when compared to the gold-standard blood culture. Both *Salmonella* Typhi (74.3%) and *S*. Paratyphi (12.9%) isolates were 100% sensitive to azithromycin, cotrimoxazole, and ceftriaxone. Quinolones and second-generation cephalosporin cefuroxime showed high resistance in comparison. None of the isolates was multidrug resistant. All cases were discharged after successful treatment.

Conclusion The burden of disease and antibiotic susceptibility of enteric fever needs to be monitored to guide clinicians in selection of antibiotics.

Keywords
- enteric fever
- children
- *Salmonella*
- blood culture

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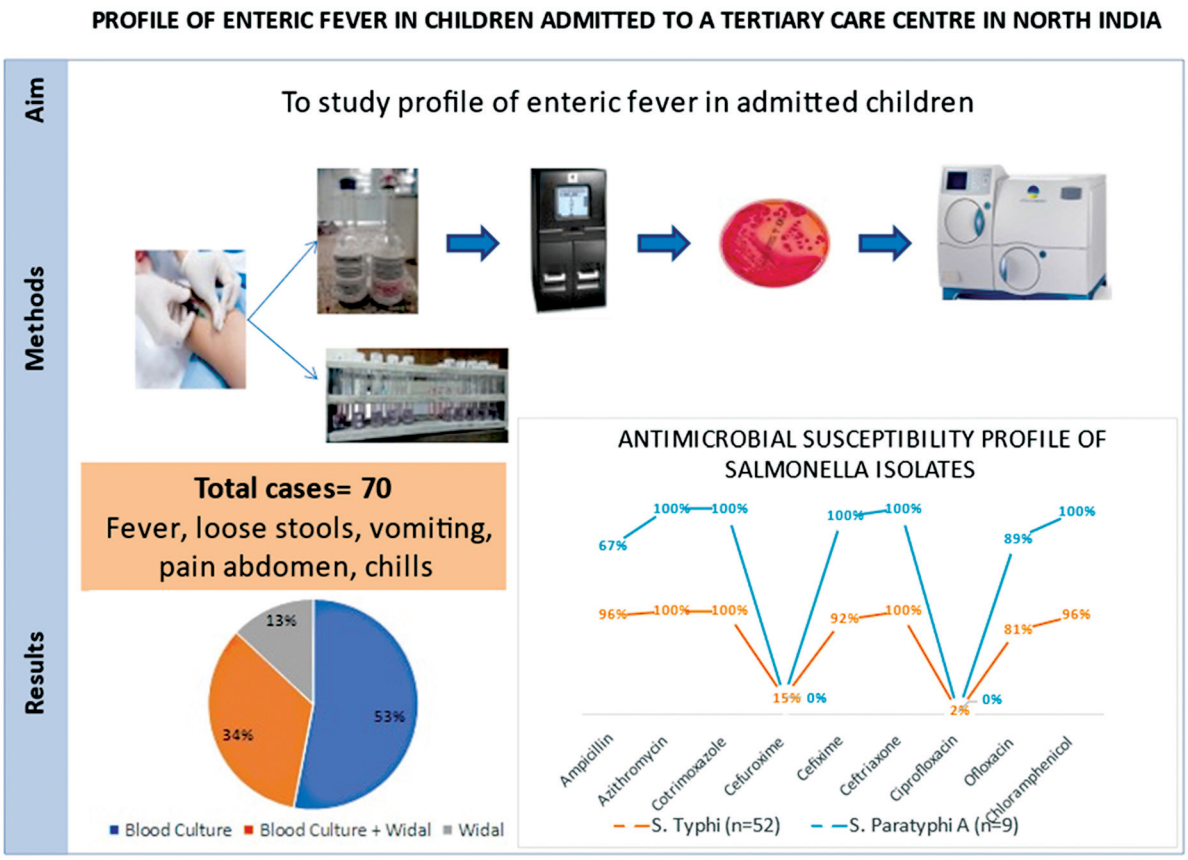

Introduction

Enteric fever is a community-acquired systemic infection which continues to be a public health problem in developing countries and resource-limited communities with poor access to sanitation.[1]

Salmonella Typhi is the leading cause of enteric fever, responsible for 12 to 21 million cases and over 140,000 deaths each year globally.[2,3] The clinical features of enteric fever in children are nonspecific and overlap with a variety of infections in endemic areas.[4] Among blood culture-confirmed cases in children, as low as 4% cases are clinically suspected with enteric fever at initial presentation. A recent systematic review of enteric fever cases showed that the risk of mortality due to enteric fever is four times higher in children < 5 years compared to those > 5 years of age.[5]

The widespread and poorly regulated use of antibiotics and antipyretics in low-to-middle-income countries not only confounds the clinical picture but also leads to the origin and propagation of multidrug resistant (MDR) strains of *Salmonella*. If untreated, the febrile response reaches its peak in the second week of illness in a characteristic "stepladder" pattern. Chills and rigors are less common in children than adults while relative bradycardia, a classical finding in enteric fever, is identifiable in 11 to 30% of children.[5] Diarrhea and febrile seizures are reported more commonly in infants than in older children and adults. A lesser proportion of children may have constipation, which has been associated with disease relapse in children infected with MDR strains. Clinically tender hepatosplenomegaly is seen in 85 to 90% of pediatric cases. Hepatic and splenic abscesses with subsequent splenic abscess rupture are more commonly encountered in younger children, immunosuppressed, and those with hemoglobinopathies. The transient pancytopenia seen in acute illness may be partly because of seeding of *Salmonella* to the bone marrow.[6] While it is challenging to breakdown the complex dynamics between antimicrobial use, antimicrobial susceptibility, and disease burden, estimating the incidence of enteric fever in children will provide a better understanding of current disease burden and its transmission dynamics.[7]

Aim and Objective

To study the profile of children with enteric fever admitted in a tertiary care center in North India.

Material and Methods

This prospective study was conducted between February 2020 and August 2021 after clearance from the institutional ethical committee. All admitted pediatric patients, who were either confirmed or probable cases of enteric fever, were included with informed consent of guardians. Case definitions were adapted from the World health Organization and Indian Academy of Pediatrics (IAP) guidelines. Confirmed case: A patient with fever (38°C and above) for

at least 3 days, with a laboratory-confirmed positive culture of *Salmonella* Typhi or *S.* Paratyphi A. Probable case: A clinically consistent case with positive serodiagnosis but without *Salmonella* isolation. The patients who did not meet case definition of enteric fever and those who did not give consent were excluded.

Samples received in microbiology lab were processed as per standard protocols.[8] Widal tube agglutination test was employed for serodiagnosis in the second week of illness. As per the prevalent local titers, "O" antigen titers of more than 80 and "H" antigen titers of more than 160 were considered significant. Blood cultures were sent at the time of admission, before starting antibiotics and processed in the Bactec or BacT/Alert automated culture systems for a maximum period of 7 days. Bacterial identification and susceptibility testing from positive culture bottles were done using the Vitek2 system. Serological testing was done by slide agglutination using antisera from Central Research Institute, Kasauli. Susceptibility was tested against azithromycin, ceftriaxone, cefixime, cefuroxime, ampicillin, chloramphenicol, cotrimoxazole, ciprofloxacin, and ofloxacin and results were interpreted on the basis of minimum inhibitory concentration breakpoints as per the Clinical and Laboratory Standards Institute guidelines. The isolates showing resistance to ampicillin, cotrimoxazole, and chloramphenicol were labeled as MDR.

Data was described in terms of range, mean ± standard deviation, frequencies (number of cases), and relative frequencies (percentages) as appropriate. Statistical analysis was done using SPSS (Statistical Package for the Social Science) version 21 software.

Results

A total of 70 patients were enrolled of which 61 were confirmed cases based on blood culture and 9 cases were probable cases with clinical features and positive Widal test. Sixty percent of these patients were male and 40% were female, with a male-to-female ratio of 1.5:1. All the children presented with fever, 54 (77.1%) had fever of > 5 days duration, while 16 (22.9%) had fever for < 5 days. The other presenting symptoms were loose stools and vomiting in 35 (50%), pain abdomen in 22 (31.4%), chills and rigor in 11 (15.7%), and abnormal body movements in 5 cases (7.1%). Notably, 25.7% (18/70) children had received oral antibiotics prior to hospitalization (cefixime 14, azithromycin 3, and ofloxacin 1). Apart from this, one patient had received intravenous vancomycin + ceftriaxone, and another intravenous amikacin + oral azithromycin before admission. Only one child had history of typhoid vaccination.

On examination, pallor was observed in 68 children (97.1%), hepatomegaly in 33 (47.1%), hepatosplenomegaly in 18 (25.7%), and edema in 1 patient (1.4%). Laboratory Investigations revealed anemia (hemoglobin < 11 g/dL) in 44 (62.9%), leukopenia (total leukocyte count [TLC] < 4000/µL) in 31 (44.3%), leukocytosis (TLC > 11000/µL) in 10 (14.3%), raised C-reactive protein in 64 of 66 (97%)—mean value 71.3, raised serum glutamic-oxaloacetic transaminase in 49 out of 52 (94.2%)–mean value 109.7, and raised serum glutamate pyruvate transaminase in 40 of 53 (75.5%)—mean value 89.7.

Widal test was reported positive in 33 out of 39 cases (84.6%). Among these, TO + TH was positive in 28 cases and TO + AH in 5 cases.

Blood culture was positive in 61 of the 70 cases (87.1%), 52 of which yielded growth of *Salmonella* Typhi and 9 showed growth of *S.* Paratyphi A. It was observed that azithromycin, cotrimoxazole, cefixime, and ceftriaxone were 100% effective for both *S.* Typhi and *S.* Paratyphi A. Most isolates were resistant to cefuroxime and ciprofloxacin, but 81 to 89% susceptibility to ofloxacin was observed (►**Fig. 1**). None of the isolates were MDR.

Out of 70 cases, 24 were positive by both culture and serology, while 37 were diagnosed by culture alone and 9 by

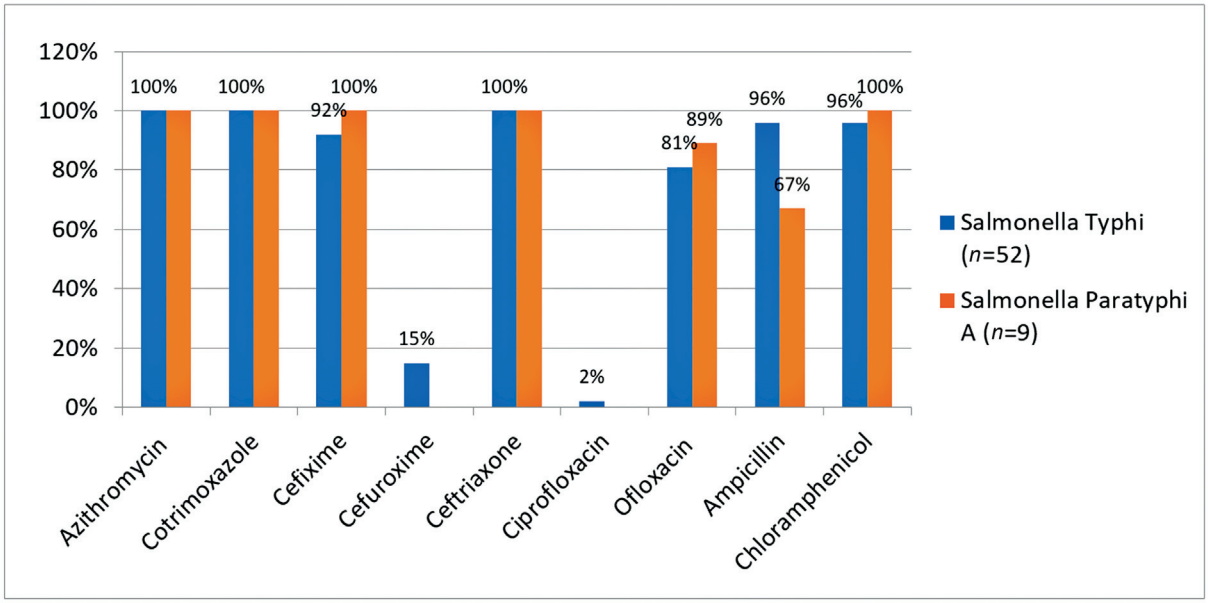

Fig. 1 Antimicrobial susceptibility profile of *Salmonella* isolates.

Table 1 Positivity of blood culture and Widal test

	Blood culture		Total
Widal	**Positive**	**Negative**	
Positive	24	9	33
Negative	6	0	6
Total	30	9	39
Sensitivity: 80%, CI 61.43–92.29% Positive predictive value: 73%, CI 69.04–76.13%			

Abbreviation: CI, confidence interval.

serological test alone. Blood culture is considered as the gold-standard test for enteric fever diagnosis and comparison of the two showed sensitivity of Widal test to be 80%with a positive predictive value of 73% (►**Table 1**).

Antibiotic treatment (intravenous/oral) was given for 14 days as per standard protocol.

Most of the children were given intravenous antibiotics—ceftriaxone (62) and cefepime + tazobactam (4) along with antipyretics and fluids. On the basis of prolonged defervescence and previous antibiotic history, patients were started on cefepime + tazobactam.

After improved oral intake, oral cefixime was started in three cases and azithromycin in one along with intravenous ceftriaxone. The mean duration of defervescence of fever was 10.5 ± 2.86 days. All children recovered and one was given discharge on request of guardians.

Discussion

The present study describes the clinical and microbiological profile of enteric fever in hospitalized children. Majority of the children were aged > 5 years, with typhoid more common than paratyphoid fever. This high incidence in school-going children is in line with the trends reported by Sinha et al in their pediatric cohort study from North India.[9] However, Saigal et al reported maximum cases in the 1- to 5-year-old group. The difference may be because of inclusion of only admitted children in our study.[10]

Fever was the most common presenting complaint in all cases, similar to observations of other authors.[11,12] Anemia was observed in nearly 63% children, and reflects the general anemia rate in Punjab (57.3%), attributed to the iron-deficient diet, childhood illnesses, and parasitic infections.[13] Edema noted in one patient was due to underlying hypoalbuminemia and failure to thrive, and may not be due to enteric fever itself.

In developing countries, Widal test has been used for diagnosis of enteric fever but is reported to have low sensitivity and specificity. In the present study, it was found to have 80% sensitivity when compared to blood culture, since the test was performed in the second week of fever. Similar results were reported by Maheshwari et al.[14] In most cases, fourfold rise or fall of titer in paired sera tested 7 to 10 days apart can provide a more reliable diagnosis.[8]

It was observed that despite prior antibiotic usage, blood culture had a high yield of 87.1%, which may be due to timely presentation, adequate sample collection, and good culture techniques. On the contrary, a low culture positivity of 43.5 and 20.2% was reported by various authors.[12,15]

In our study, *S*. Typhi (74.3%) was predominant while *S*. Paratyphi was predominant in the study by Malini et al. *S*. Typhi in our study showed 100% sensitivity to azithromycin, cotrimoxazole, and ceftriaxone, 96% to ampicillin and chloramphenicol, and 2% to ciprofloxacin. Malini et al reported 100% sensitivity to azithromycin, ampicillin, and ceftriaxone, 89% to cotrimoxazole, and 0% to ciprofloxacin. *S*. Paratyphi isolates in our study showed 67% susceptibility to ampicillin while high susceptibility (91%) was observed by Malini et al.[15]

High susceptibility to first-line antibiotics like amoxycillin, chloramphenicol, and cotrimoxazole supports their use and the principle of antibiotic cycling in the treatment regimens. High levels of quinolone resistance were seen, and is concordant with the resistance patterns reported by several studies from India.[16,17]

The absence of any MDR strains in our study is contrary to the findings of McAteer et al (22% MDR *Salmonella*) and Siddiqui et al (14% MDR *S*. Typhi and 57% MDR *S*. Paratyphi).[18,19]

The IAP standard treatment guidelines for enteric fever recommend use of parenteral ceftriaxone or oral cefixime for 14 days as first-line therapy.[20] Following the guidelines and susceptibility pattern of *Salmonella* isolates, intravenous ceftriaxone was the most commonly used antibiotic in our study, as all cases were hospitalized.

The study describes the profile and local sensitivity pattern in enteric fever and will help guide proper antibiotic use. As majority of the cases get treated on outpatient basis or with over-the-counter antibiotics, this hospital-based study may not reflect the situation of enteric fever in the community. Another limitation of the study is that genomic sequencing of the isolates was not done, which could have provided more information on the emerging strains and antimicrobial resistance. A larger sample size and comparison of yearly trends would provide more useful data.

Conclusion

Enteric fever is a community-acquired systemic infection, common in developing countries with rising antimicrobial resistance. Though blood culture remains the gold standard, Widal test can be used as an inexpensive and reliable test for diagnosis, especially when drawing adequate sample for

blood culture is difficult in smaller children. Though no MDR *Salmonella* were reported from children in our study, there is a need to monitor the burden of disease and antimicrobial resistance to guide treatment choices. The high morbidity, especially among children, underscores the need for improved water and sanitation practices as well as increasing vaccination coverage to control the disease.

Ethical Clearance
This article has been approved by institutional ethical committee(IEC).

Author's Contribution
All authors contributed equally to the article.

Data Availability Statement
There is no data associated with this work.

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Conflict of Interest
None declared.

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