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Antimicrobial Resistance Pattern and Clinical Spectrum of Blood Culture-Proven Typhoid Fever in Children

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Abstract

Background: Enteric fever remains a major cause of morbidity in children in endemic, resource-limited settings, and emerging antimicrobial resistance (AMR) threatens effective treatment. This study describes the clinical spectrum and AMR pattern of blood culture-proven typhoid fever in children at a tertiary care center. **Materials and Methods:** This retrospective observational study included culture-positive typhoid cases admitted to the pediatrics department of a tertiary care center from January 2023 to 2025. Demographic, clinical, and laboratory data were obtained from hospital records, and case definitions and treatment protocols followed the Indian Academy of Pediatrics protocol. Statistical analysis was performed using the Statistical Package for the Social Sciences version 20. **Results:** Of 64 blood culture-proven cases, 90.6% were due to *Salmonella.* Typhi and 9.4% to *S.* Paratyphi, with equal sex distribution and 40% of cases in children under 5 years. Fever was the most common presentation (95%), followed by vomiting (56%), abdominal pain (46%), diarrhea (19%), cough (17%), convulsions (6.5%), and respiratory distress (3.5%). The Widal test was positive in 35.4% of cases. Complications occurred in 17.1% of children, most commonly hepatitis (6.4%) and shock (4.6%). Resistance was observed too floxacin (25.4%), ampicillin (4.7%), co-trimoxazole (3.17%), ceftriaxone (3.17%), and azithromycin (1.8%); multidrug-resistant strains were seen in 3.1% and extensively drug-resistant strains in 1.56% of cases. **Conclusion:** Typhoid fever continues to cause significant morbidity in children, with high ofloxacin resistance but a notable decline in resistance to first-line drugs, raising the possibility of their future reuse. Continued antimicrobial surveillance is warranted to guide empirical treatment and detect emerging resistant strains.

Keywords: Antimicrobial resistance, Blood culture, Children, Multidrug resistance, *Salmonella* Typhi, Typhoid fever

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Introduction

Enteric fever comprises the clinical spectrum of illness caused by *Salmonella* Typhi and *Salmonella* Paratyphi.[1,2] It remains end emicin areas with low socio economic indices and suboptimal sanitary conditions,[3] with a global annual burden of approximately 12 million cases in 2010.[1,2] The disease preferentially affects children.[4] Case fatality has improved overtime, from 10 to 30% to <1%. In a multi-centered study, the annual incidence of typhoid fever per 100,000 children aged 5–15 years was reported as 180 in North Jakarta, Indonesia; 413 in Karachi, Pakistan; and 494 in Kolkata, India.[5] Changing antibiotic sensitivity and the recent detection and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains pose an increasing challenge for the effective treatment of typhoid fever.[6]

Materials and Methods

This retrospective observational study included culture-positive typhoid cases admitted to the Pediatrics Department of a tertiary care center from January 2023 to 2025, identified using microbiology department software. Data on demographic profile, clinical features, laboratory investigations, and course during hospital stay were obtained from hospital records using each patient's unique identification number. Case definitions and treatment protocols for typhoid were adapted from the Indian Academy of Pediatrics protocol.

Outcomes assessed were complications, time to fever defervescence, need for intensive care, duration of hospital stay, and mortality. Time to fever defervescence was defined as being a febrile for at least 24 h after starting therapeutic doses of culture-sensitive intravenous antibiotics.[7]

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Classification of Typhoid Fever Cases by Drug Resistance Status

MDR typhoid was defined as resistance to the first-line drugs, that is, ampicillin/amoxicillin, chloramphenicol, co-trimoxazole, and nalidixic acid.[8,9]

XDR typhoid was defined as resistance to the classical first-line antibiotics (chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole) as well as to both fluoroquinolones (FQs) and third-generation cephalosporins.[10]

Details of clinical presentation, comorbidities, complications, and culture resistance/sensitivity patterns were extracted and organized using Microsoft Excel. Statistical analysis was performed using the Statistical Package for the Social Sciences statistical software, version 20 (IBM Corporation, Armonk, NY, USA).

Results

There were 64 blood culture-proven typhoid cases; the majority (90.6%) were due to *S*. Typhi and the remaining 9.4% to *S*. Paratyphi, with an equal sex distribution and more cases from semi-urban to urban regions; 40% of cases involved children under 5 years of age.

Fever was the main presenting symptom, observed in 95% of cases. Other presenting features were abdominal pain (46%), vomiting (56%), diarrhea (19%), cough (17%), convulsions (6.5%), and respiratory distress (3.5%). The Widal test was positive in 23 cases (35.40%) [Table 1].

Eleven children (17.10%) developed complications: Hepatitis in 6.4%, shock in 4.6%, anemia in 3.1%, encephalopathy in 1 case (1.5%), and bone marrow suppression in 1 case (1.5%) [Table 2].

The resistance pattern observed in this study was ampicillin (4.7%), cotrimoxazole (3.17%), ofloxacin (25.4%), ceftriaxone (3.17%), and azithromycin (1.8%). MDR was observed in 3.1% and XDR in 1.56% of cases [Table 3].

Discussion

Enteric fever is a community-acquired systemic infection caused by *Salmonella enterica* serovar Typhi and *S*. Paratyphi A, and remains a major health problem in the developing world.[11] Salmonellae are Gram-negative, non-sporulating, flagellate, facultative an aerobic bacilli belonging to the family Enterobacteriaceae, which has more than 2,300 serotypes. Humans are the only reservoir, with the stool of infected persons as the main source, along with contaminated water, food, and possibly flies.[12] Lack of proper sanitation and clean running water is a major concern in resource-poor countries.

Table 1: Baseline characteristics and clinical profile of enteric fever

Parameter	*Cases*	*Percentage*
Median age	6 years (1 month–14 years)	–
Males	32	50
Rural	5	7
Under 5 years	26	40
Fever	60	95
Abdominal pain	30	46
Vomiting	35	56
Diarrhea	12	19
Cough	10	17
Respiratory distress	2	3.5
Hepatosplenomegaly	10	15.4

Table 2: Complications of enteric fever

Symptom	*Cases*	*Percentage*
Liver failure	2	3.1
Shock	3	4.6
Anemia	2	3.1
Pancytopenia	1	1.5
Encephalopathy	1	1.5
Convulsions	4	6.5

Table 3: Antibiotic sensitivity pattern of enteric fever

Antibiotic	*Sensitivity (%)*	*Resistance (%)*
Ampicillin	95.3	4.7
Cotrimoxazole	96.83	3.17
Ofloxacin	74.6	25.4
Ceftriaxone	96.83	3.17
Azithromycin	98.42	1.58
Meropenem	100	0

In this study, fever was the most common presentation, observed in 96% of cases, similar to other studies. Gastrointestinal symptoms observed were abdominal pain (46%), vomiting (56%), and diarrhea (19%), which differed from a study by Kumar *et al*., who reported diarrhea in 74.2% and abdominal pain in 62.9% of children.[13,14] The typical four stages of typhoid observed in adults are rare in children. Thus, enteric fever should be considered in any child presenting with unexplained or prolonged fever and abdominal complaints.

Untreated typhoid fever can sometimes lead to severe complications. In this study, complications observed were hepatitis (6.4%), shock (4.6%), convulsions (6.5%), anemia (3.1%), encephalopathy (1.5%), and bone marrow suppression in 1 case.

The resistance pattern observed in this study was ampicillin (4.7%), cotrimoxazole (3.17%), ofloxacin (25.4%), ceftriaxone (3.17%), and azithromycin (1.8%). Compared with a cumulative study from Kolkata,[13] which showed 100% resistance to ampicillinin 1990 improving to 13% by 2003, cotrimoxazole resistance improving from 100% in 1990 to 15% by 2003, and ofloxacin showing full sensitivity in 1990 but exhibiting 10% resistance by 2003, there have been substantial changes in the resistance pattern of *S*. Typhi over time. In this study, MDR was observed in 3.1% of cases, which was low compared to studies by Parry *et al*. (23%) and Singh *et al*. (63%).[15,16] XDR strains were observed in 1.56% of cases in this study. The decline in resistance to first-line drugs such as ampicillin and cotrimoxazole, from 100% to 3–4%, raises the possibility of their reuse in current treatment practice.

FQ resistance has increased not only in India but worldwide, limiting the scope of their usage. Recent changes in the resistance pattern of ceftriaxone and azithromycin suggest that it is probably only a matter of time before the seorganisms develop wide spread resistance to these drugs as well, as witnessed with first-and second-line drugs, leaving very limited treatment options.

History of Antibiotic Resistance in *Salmonella*

First-line Drugs

Inthemid-1980s, ampicillin, chloramphenicol, and orsulfamethoxazole-trimethoprim were the drugs of choice for enteric fever treatment.[14] Organisms developed resistance to these drugs by acquiring *AMR* genes carried on the IncHI1 group of plasmids. The transferable plasmid carries genes conferring resistance to sulfonamides (sul1, sul2), ampicillin (blaTEM-1), trimethoprim (dfrA7), chloramphenicol (catA), and streptomycin (strAB); a typhoid strain resistant to these three antibiotic classes is termed MDR typhoid.[7]

MDR typhoid has been a major concern in India: A chloramphenicol resistance outbreak was observed in 1972, followed by amoxicillin and co-trimoxazole resistance by the 1990s, associated with a high rate of clinical relapse, complications such as intestinal perforation, and poor treatment response. Similar reports emerged elsewhere, including India,[15] leading FQs to replace these drugs as the treatment of choice.

Second-line Drugs

FQs such as ciprofloxacin and ofloxacin became second-line drugs for treatment duringthe1990s. Overtime, significant resistance to quinolones (nalidixic acid) and intermediate levels of resistance to ofloxacin have been reported.[16]

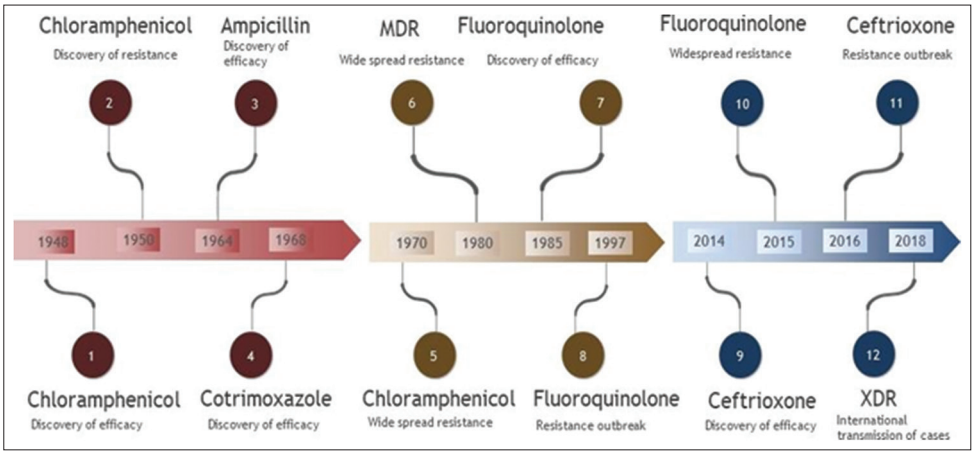

Figure 1: Evolution of drug resistance in enteric fever

These drugs act through DNA gyrase and topoisomerase IV. Non-synonymous single-nucleotide polymorphisms (SNPs) occurring in the genes *gyrA, parC, par E,* and *gyr B* induce conformational changes at the main sites of FQ action, with *gyrA*SNPs correlating strongly with treatment failure.[7]

Third-line Drugs

Following resistance to FQs, third-generation cephalosporins and azithromycin emerged as the treatment of choice. Recently, strains resistant to third-generation cephalosporins have been observed in the Sindh district of Pakistan, warning of a potential future threat. These strains, labeled XDR typhoid, arise from a highly conserved subclade of the H58 haplotype that has chromosomally integrated composite resistance loci and an additional novel IncY plasmid encoding a blaCTX-M-15 extended-spectrum β-lactamase gene and a qnrS FQ resistance gene.

To summarize: (1) Resistance to first-line drugs is mediated by IncHI1 plasmids; (2) resistance to second-line drugs arises from signature mutations in the *gyrA* gene; and (3) resistance to third-generation cephalosporins is mediated by an IncY plasmid [Fig. 1].[10]

The changing resistance pattern of typhoid is a major concern. There cent outbreak of ceftriaxone-resistant typhoid strains in the Sindh province of Pakistan marks the first major outbreak of third-generation cephalosporin-resistant typhoid in the world. Similar patterns of drug-resistant strains have been reported from India, Bangladesh, the Philippines, Iraq, and Guatemala,[7,17,18] providing evidence of the international spread of this strain and highlighting the need for continued study of typhoid sensitivity patterns.

Conclusion

1. Typhoid remains a major cause of morbidity in the urban pediatric age group.
2. Enteric fever should be considered as a differential diagnosis in children with unexplained or prolonged fever.
3. There is a potential threat of wide spread emergence of ceftriaxone-resistant strains in the near future.
4. There is a possibility of reintroducing first-line antibiotics, ampicillin, and co-trimoxazole, which are easily available and affordable, for typhoid treatment.
5. Antibiotic surveillance coupled with molecular analysis of resistance patterns is needed for therapeutic reappraisal and novel drug targeting.

This study was purely observational in nature; a limitation was that only patients with blood culture positivity were included in the analysis, potentially missing culture-negative cases treated for possible enteric fever.

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Not applicable.

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