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ENTERIC FEVER IN NORTH DELHI: A RETROSPECTIVE ANALYSIS OF BLOOD CULTURE-CONFIRMED SALMONELLA ISOLATES AND THEIR ANTIBIOTIC RESISTANCE TRENDS

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ABSTRACT

Background: Enteric fever, caused by Salmonella enterica serovars Typhi and Paratyphi, remains a major public health concern in India, particularly among children and adolescents. Rising antimicrobial resistance further complicates management. This study aimed to the prevalence, age and gender distribution, seasonal trends, and antimicrobial susceptibility patterns of Salmonella isolates obtained from blood cultures in a tertiary care hospital in North Delhi. **Materials and Methods:** A retrospective cross-sectional study was conducted in the Department of Microbiology, Jaipur Golden Hospital, Rohini, Delhi, from January to December 2024. All blood culture-positive isolates of S. Typhi and S. Paratyphi A and B were included. Blood samples were processed using the automated BacT/Alert® system, and antimicrobial susceptibility testing was performed as per standard protocols. Data were analyzed using Microsoft Excel and SPSS software. **Results:** Out of 144 culture-positive Salmonella isolates, S. Typhi accounted for 104 (72%) and S. Paratyphi for 40 (27.7%) cases. The highest incidence was observed in the 0–10-year age group, followed by 10–18 years, with males (56.9%) being more affected than females (43.1%). A marked seasonal peak was noted during the summer months (March–May). No multidrug-resistant (MDR) or extensively drug-resistant (XDR) strains were identified. Among S. Typhi isolates, resistance was highest to ciprofloxacin (29.8%) and ampicillin (29%), while most remained sensitive to cefixime (100%), chloramphenicol (100%), and cotrimoxazole (100%). S. Paratyphi isolates exhibited resistance to ciprofloxacin (45%) and ceftriaxone (35%), while remaining sensitive to most other agents. **Conclusion:** Enteric fever continues to predominantly affect the pediatric population in North Delhi, with a higher incidence during summer. Despite a favorable susceptibility profile to first-line and third-generation cephalosporins, significant fluoroquinolone resistance persists. Continuous surveillance of antimicrobial patterns, rational antibiotic use, and early introduction of typhoid conjugate vaccines are crucial in controlling enteric fever and preventing the emergence of resistant strains.

INTRODUCTION

Typhoid fever and paratyphoid fever constitute enteric fever, a widespread systemic bacterial infection produced by Salmonella enterica serovars Typhi and Paratyphi. It is a serious public health problem in most low- and middle-income countries in Asia, Africa, and South America, where sanitation is poor, hygiene is lacking, and access to safe drinking water is restricted, leading to high mortality and morbidity. Among more than 2600 closely-related Salmonella enterica serovars, human-restricted Salmonella enterica serovars Typhi and Paratyphi A, B, and C are etiologic agents of enteric fever. Various Salmonella serovars, such as S. Typhi and S. Paratyphi, differ in terms of unique surface antigen combinations, which include the lipopolysaccharide O (somatic) antigen, flagellar H antigen, and virulence-capsule (Vi) antigen. On the basis of host specificity and corresponding disease conditions, Salmonella enterica serovars are generally divided into typhoidal and nontyphoidal Salmonella (NTS). Typhoidal serovars (S. Typhi and S. Paratyphi) are human-restricted pathogens that are responsible for systemic infections like enteric fever, while nontyphoidal serovars(S. Typhimurium and S. Enteritidis) generally have a more extensive host range and are mostly responsible for self-limiting gastrointestinal Salmonellosis.[1]

The magnitude of Salmonella Typhi infection is highly variable throughout Asia, remaining high in South Asian countries, with East Asia still reporting relatively low rates. South Asia had an age-standardized incidence of 379.6 per 100,000 person-years for typhoid fever in 2021. Site-specific estimates reported significantly higher rates in India (412.9) and Pakistan (493.5), with much lower rates being reported by China and Vietnam (<30 per 100,000 person-years). India contributed approximately four-fifths of the regional incidence and mortality. Hospital-based surveillance in India has subsequently documented incidence of 108–970 per 100,000 person-years among adults (≥15 years) and 12–1,622 per 100,000 child-years among children aged six months to 14 years.[2]

Humans are the only reservoir of enteric fever causative organisms, as no animal or environmental sources have yet been found.[3] Transmission occurs through the traditional "4 Fs"—flies, fingers, feces, and fomites. Infection is mostly found among people living in or visiting low- and middle-income countries with ongoing deficiencies in water, sanitation, and hygiene (collectively known as WASH). Improving WASH infrastructure continues to be the mainstay strategy to decrease enteric fever transmission and other fecal–orally transmitted infections.[4]

Enteric fever has a broad clinical picture that can resemble a multitude of febrile diseases. The classic symptoms are ongoing fever, chills, headache, anorexia, and abdominal pain, frequently supported by relative bradycardia, change in bowel habits, hepatosplenomegaly, leukopenia, and thrombocytopenia. Variations in presentation also occur based on age, making diagnosis more challenging. Serious complications include gastrointestinal bleeding, intestinal perforation, bone marrow hypoplasia, encephalopathy, DIC, and shock.[5]

Seasonal trend analysis identified the spring and summer of 2024 as periods with peaks in enteric fever incidence, indicating that environmental factors like poor water quality and inadequate hygiene play a prominent role in transmission. Notwithstanding increasing antimicrobial resistance levels worldwide, the majority of isolates in this analysis were still sensitive to conventional antibiotics—Ampicillin (93%), Cefixime (97.4%), Ceftriaxone (95.4%), Ertapenem (98.6%), Cotrimoxazole (97.5%), Azithromycin (98.8%), and Chloramphenicol (97.8%). Of note was the near-universal resistance to fluoroquinolones (Ciprofloxacin 99.8%), highlighting the need for appropriate antibiotic stewardship and treatment based on susceptibility.[6]

Blood culture is the standard diagnosis for typhoid fever and paratyphoid fever, but sensitivity is highly variable (40–87%), averaging 50%. Detection is greatest in the first week of illness (90%) and decreases progressively with increasing delay in testing or with previous antibiotic use. As the clinical presentation of enteric fever is nonspecific, serological tests like the Widal test (sensitivity 34.1%, specificity 42.8%) and Typhidot M (sensitivity 92.6%, specificity 37.5%) are often used as adjuncts despite their poor reliability.[7]

In a retrospective analysis at Dr. Lal Path Labs from 2021 to 2024, 245,600 positive bacterial cultures were analyzed, and 6,332 (2.6%) Salmonella isolates were found. The majority (99.1%) came from blood, highlighting the systemic nature of the infection. The most common isolate was S. Typhi (90.1%), followed by other Salmonella spp. (4.9%), S. Paratyphi A (3.8%), and S. Paratyphi B (1.1%). The isolates were sometimes obtained from abscess, stool, and urine samples. Cases were predominantly found in males (58.9%) and children aged ≤12 years (49.1%), while multidrug-resistant strains were found solely in children aged under five years.[6]

In uncomplicated cases managed in the outpatient, cefixime is given in two divided doses for 10 days. Hospitalization is required in patients with severe abdominal symptoms, protracted vomiting, or complications such as hepatitis or encephalopathy. In these, intravenous ceftriaxone is given for 14 days or until the patient became afebrile and clinically improved.[8] Treatment with antibiotics is still the mainstay of treatment; however, Salmonella Typhi and S. Paratyphi have become progressively resistant to widely used antimicrobials. The global public health concern is the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, especially in low- and middle-income countries. Multidrug-resistant typhoid (MDR) is S. Typhi isolates resistant to all three traditional first-line drugs—chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole,[9] while XDR is S. typhi strains resistant to chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones, and third-generation cephalosporin.[10] A research study from Hyderabad, Pakistan revealed that among 1452 culture-confirmed typhoid cases, 947 (66%) XDR typhoid cases and 505 (34%) non-XDR typhoid cases were detected. In all, ≥1 complications were noted in 360 (38%) patients with XDR typhoid and 89 (18%) patients with non-XDR typhoid. The most frequently reported complication was ileal perforation, both in patients with XDR typhoid (n=210, 23%) and in patients with non-XDR typhoid (n=71, 14%). Total mortality was reported in 17 (1.8%) patients of XDR S Typhi infection and 3 (0.6%) patients of non-XDR S Typhi infection,[11] Given India's geographical proximity and porous border with Pakistan, there is a substantial risk that the prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) typhoid may rise in the coming years. Continuous surveillance and periodic antimicrobial susceptibility testing of Salmonella species are therefore essential to monitor emerging resistance trends and to guide evidence-based clinical management at regional and national levels.

MATERIALS AND METHODS

We reviewed the hospital laboratory records retrospectively from the Department of Microbiology at Jaipur Golden Hospital, Rohini, Delhi and conducted a retrospective cross-sectional study. From January to December 2024, all patients including children and adults with S. typhi and S. paratyphi A and B strains isolated from the laboratory-based culture of blood samples were included in the study. This included all patients visiting the outpatient as well as the inpatient ones. Laboratory tests along with other required investigations were done on the basis of physician's suspicion of enteric fever. We took around 3 mL of venous blood sample under aseptic condition and inoculated and cultured the sample by an automated BacT/Alert® System (MicroScan by Beckman Coulter)

Statistical Analysis

The collected data from the hospital records were logged into a Microsoft Excel spreadsheet and then interpreted by Statistical Package for the Social Sciences (SPSS) software. The inferred data were tabulated. Figures were made as per the data.

RESULTS

Among the culture-positive results for Salmonella spp. (n=144), Salmonella ser. typhi was detected in 104 cases (72%), while paratyphi A was detected in 40 cases (27.7%). The maximum affected age-group was 0–10 years, followed by 10–18 years, followed by 18-45 years with the least affected age-group being >45 years. The prevalence of infection was higher in males (n = 82, 56.94%) than in female patients (n = 62, 43.05%). From January to December 2024, maximum number of cases were seen during summer season (March–May) and the least during winter season (November–January). Among the tested antimicrobial resistance observed were tabulated. Strains resistant to all three first-line antibiotics are called multidrug resistant (MDR) strains and constituted 0% of total cases, and resistant to both first-line and second-line antibiotics are called extensively drug-resistant (XDR) strains and constituted 0% of total cases.

Table 1: Incidence of Salmonella spp. (n=144) with MDR and XDR percentages

	N	%
S.typhi	104	72%
S.paratyphi	40	27.70%
MDR	0	0
XDR	0	0

Table 2: Antibiotic Resistance trend of Salmonella.typhi

	S.typhi
Ampicillin	29%
Azithromycin	5.77%
Cefixime	0%
Ceftriaxone	9.60%
Chloramphenicol	0%
Ciprofloxacin	29.80%
Levofloxacin	24%
Norfloxacin	29%
Trimethoprim-sulfamethoxazole	0%

Table 3: Antibiotic Resistance trend in Salmonella.paratyphi

	S.paratyphi
Ampicillin	0%
Azithromycin	0%
Cefixime	30%
Ceftriaxone	35%
Chloramphenicol	0%
Ciprofloxacin	45%
Levofloxacin	2.50%
Norfloxacin	0%
Trimethoprim-sulfamethoxazole	0%

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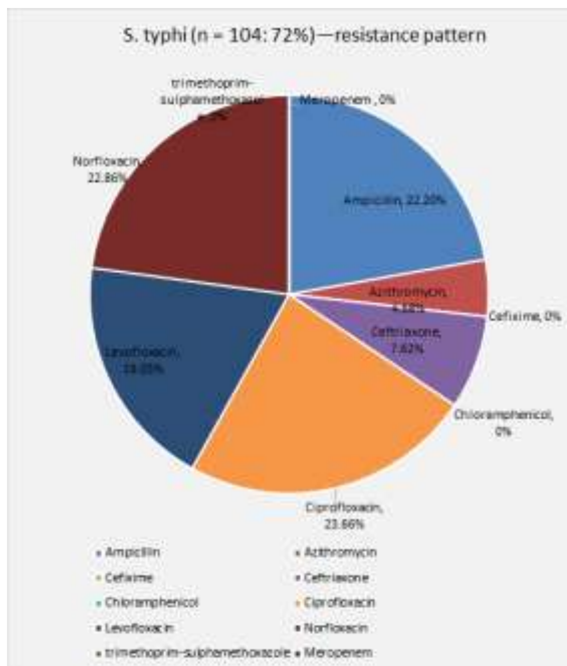

Figure 1: S.typhi (n=104: 72%)-resistance pattern

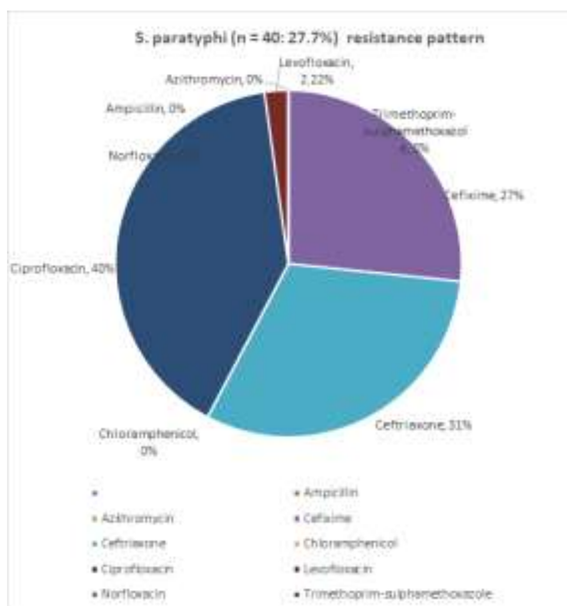

Figure 2: S.paratyphi (n=40: 27.7%) resistance pattern

DISCUSSION

The World Health Organization (WHO) categorizes typhoid fever as a life-threatening systemic disease caused by Salmonella enterica serovar Typhi (S. Typhi), spread mainly by the ingestion of contaminated food and water. Upon ingestion, the organism penetrates the intestinal mucosa, grows, and transmits through the bloodstream, leading to continuing fever, headache, nausea, and loss of appetite. Untreated, it could lead to severe complications or even death. The pathogenicity of the bacterium is controlled by its Type III Secretion System (T3SS), which injects effector proteins into host intestinal epithelial cells and macrophages, altering cytoskeletal structures, facilitating intracellular replication, and assisting the organism in evading immune clearance.[12]

In India, enteric fever has a greater urban prevalence, with rates of incidence up to 1% of the population per year in some endemic areas. Children under the age of 15 years are the most impacted group, presumably because older individuals develop partial immunity by having repeated or subclinical attacks. A large study in an Indian urban slum yielded an incidence of 2 per 1,000 per year in children younger than five years and 5.1 per 1,000 in children younger than ten years. Another study conducted in Northern India reported that the majority of the cases were among the age group 5–12 years, and almost one-fourth (24.8%) of infections were among children below five years.[13] Our study findings were similar to other studies, which showed a higher rate of enteric fever in younger age groups in comparison to adults. An age-related distribution pattern was seen in Salmonella serovars as well, with paratyphoid fever being seen more commonly in adults, while typhoid fever was more common among children.

The classic first-line drugs for the treatment of enteric fever are co-trimoxazole, chloramphenicol, and ampicillin. In the early 1990s, however, the frequency of Salmonella isolates resistant to all three drugs—referred to as multidrug-resistant (MDR) strains—increasingly became the norm, mandating a therapeutic change toward the use of fluoroquinolones (FQs). With time, especially between the years 2001 and 2015, there was a reduction in the prevalence of MDR isolates over time, presumably due to shifting prescribing attitudes and the application of antibiotic stewardship initiatives. Our research also disclosed 0% resistance towards both chloramphenicol and cotrimoxazole reason being reduced usage of these antibiotics. A rising prevalence of fluoroquinolone resistance was noted, which is consistent with their extensive clinical usage. Resistant rates of Salmonella Typhi were 29.8% to ciprofloxacin, 29% to norfloxacin, and 24% to levofloxacin, while S. Paratyphi showed resistant rates of 45%, 0%, and 2.5% to the same antibiotics, respectively. In addition, because of the unfavorable side effect profile of fluoroquinolones and their relative unsuitability in children, their use has fallen out of favor in favor of third-generation cephalosporins, which are now chosen as first-line therapy for enteric fever. Indian reports have confirmed the isolation of Salmonella enterica serovar Typhi with extended-spectrum β-lactamase (ESBL) genes giving resistance to third-generation cephalosporins. In our research, resistance to ceftriaxone was found in 35% of isolates, yet the drug remains commonly used because of its overall high clinical effectiveness, with cure rates being as high as 90%. Azithromycin is a good oral option and is often utilized as a reserve drug for the treatment of enteric fever. In the event that azithromycin resistance is found, carbapenems like meropenem can be used as a treatment option.[14]

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A multicenter surveillance study was carried out in seven Indian cities between the years 2021 to 2024 to determine shifts in antimicrobial susceptibility patterns of Salmonella Typhi and S.Paratyphi. After the outbreak of the COVID-19 pandemic, found that nearly all S. Typhi isolates (99.3%) were non-susceptible to ciprofloxacin, and S. Paratyphi A isolates also possessed comparable resistance patterns with 98.9% of isolates being non-susceptible. In addition to this, only 1.8% (n = 21) of S. Typhi isolates were MDR. 18 S. Typhi isolates from Ahmedabad during Jun 1, 2022-Apr 30, 2023, were resistant to the 3rd generation cephalosporin used (ceftriaxone), as well as ampicillin, sulfamethoxazole + trimethoprim, and ciprofloxacin, but susceptible to azithromycin and chloramphenicol. One S. Paratyphi A isolate from AIIMS Delhi in May 2023 was ciprofloxacin and azithromycin resistant, but susceptible to ampicillin, chloramphenicol, sulfamethoxazole + trimethoprim, and ceftriaxone.[15]

The multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of Salmonella typhi are more common in neighboring nations like Pakistan and Nepal than India, where antimicrobial resistance patterns are still relatively favorable. Muhammad Yousaf et al., during a study in Peshawar, Pakistan, revealed that the traditionally advised first-line antibiotics of amplicillin, chloramphenicol, and co-trimoxazole showed high rates of resistance at 91.5%, 68.1%, and 81.9%, respectively.[16] This was in agreement with the outcome of another study by Aslam et al in Pakista.[17] The XDR Salmonella typhi outbreak reported from Pakistan from 2016 to 2018 was resistant to cephalosporins as well as fluoroquinolones, with susceptibility only to azithromycin and carbapenems.[18] Meropenem has been reported as the most effective antibiotic in this study with only 3% resistance and 97% sensitivity, which aligns with the present study. This finding indicates that the XDR Salmonella typhi strain detected during the 2016–2018 outbreak most likely continues to be the dominant circulating strain in Pakistan.

Blood culture is the gold standard for the diagnosis of enteric fever. Its sensitivity is maximal in the first week of illness and sequentially decreases as the illness evolves. The overall sensitivity is about 50%, but this can be significantly reduced after previous exposure to antibiotics. A number of factors can lead to culture negativity, such as poor culture media, low quantity of blood drawn, the presence of antimicrobial agents, and delay in inoculation of the sample. In order to provide maximum yield, it is crucial that the blood sample should be inoculated into the culture medium immediately upon withdrawal.

Regular performance of blood cultures in cases suspected of enteric fever has numerous benefits. They are 100% specific and yield valuable information regarding antimicrobial susceptibility, which is especially valuable in today's age of increasing multidrug resistance. Other methods of diagnosis like serology are usually unreliable and inconsistent, as shall be explained later. Additionally, blood cultures are economical in the long run, since a positive culture result definitively confirms the diagnosis of enteric fever, enabling doctors to prevent futile investigations for pyrexia of unknown origin (PUO).[19,20]

Widal test as a diagnostic tool has poor sensitivity and specificity. It may be negative in as high as 30% of culture proven typhoid fever. Widal test is not sensitive because it is negative in the initial infection, it may be affected by prior antibiotic treatment and some individuals do not develop immune response to the disease. It must be performed after 5-7 days of fever by tube technique and the titre of 1 in 160 for both H and O antibodies are generally accepted as diagnostic.[21,22,23]

Typhidot test detects IgG and IgM against outer membrane protein of S. typhi. The sensitivity and specificity of this test has been reported to vary from 70-100% and 43-90% respectively. As IgG can persist over a long time it is difficult to distinguish between acute infection and convalescent cases. This test has been improved in modified typhidot M test which detects only IgM antibodies and is more specific.[24,25,26]

The seeming concealment of typhoid disease with the extensive application of potent antibiotics makes a strong impression on the immense danger of rising extensively drug-resistant (S. typhi) strains. This serves to affirm the imperative of increasing the use of typhoid conjugate vaccines (TCVs) as a preventive measure. The greatest incidence of disease was found to occur among children who were between 0 and 10 years of age, emphasizing the need for early immunization. Regular administration of a single dose of TCV at >6 months of age, according to WHO guidelines, would offer prompt and efficient protection, whereas a one-off catch-up campaign in children aged up to 15 years would extend protection to a wider high-risk age group.[27] Also there's a significant need for vaccination against paratyphoid fever because current typhoid vaccines do not provide protection and paratyphoid is a major health concern, especially in Asia.

CONCLUSION

Enteric fever continues to predominantly affect the pediatric population in North Delhi, with a higher incidence during summer. Despite a favorable susceptibility profile to first-line and third-generation cephalosporins, significant fluoroquinolone resistance persists. Continuous surveillance of antimicrobial patterns, rational antibiotic use, and early introduction of typhoid conjugate vaccines are crucial in controlling enteric fever and preventing the emergence of resistant strains.

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