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ANTIMICROBIAL RESISTANCE PATTERN OF ENTERIC FEVER

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ABSTRACT

Introduction: Enteric fever caused by Salmonella Typhi and Paratyphi is a significant public health concern, especially in developing countries. The emergence of antimicrobial resistance complicates its management. Resistance to first-line antibiotics like ampicillin, chloramphenicol, and co-trimoxazole is increasing, leading to the use of third-generation cephalosporins and fluoroquinolones. Yet, there is also a growing resistance to these newer antibiotics. This study assesses antimicrobial resistance in Salmonella Typhi isolates from pediatric patients.

Methodology: In this study, 200 pediatric patients with enteric fever were included. Blood cultures were collected to test Salmonella Typhi isolates for antibiotic susceptibility using the Kirby-Bauer method. The antibiotics tested included first-line drugs, third-generation

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cephalosporins, fluoroquinolones, and aminoglycosides. Resistance patterns were analyzed based on demographic variables like gender, age, and residence.

Results: Among the 200 cases, 63.5% were male and 36.5% female, with a mean age of 7.54 ± 3.12 years. Most cases (51.0%) were in children aged 1-7 years, with 49.0% in the 8-14 years group. Rural areas had a higher prevalence (52.5%) than urban areas (47.5%). Antibiotic resistance was high across various drug classes: Ampicillin (99.0%), ciprofloxacin (97.5%), ceftriaxone (97.0%), ceftazidime (94.5%), chloramphenicol (94.0%), aztreonam (93.5%), moxifloxacin (85.5%), levofloxacin (86.0%). Co-trimoxazole had lower but significant resistance (46.0%).

Conclusion: A study found an alarming increase in drug resistance among Salmonella Typhi, especially to third-generation cephalosporins and fluoroquinolones. This stresses the need for antimicrobial programs, careful antibiotic use, and new treatment approaches for enteric fever.

KEYWORDS: Enteric Fever, Salmonella Typhi, Antimicrobial Resistance, Multidrug Resistance, Pediatric Infections.

INTRODUCTION

Enteric fever, a global community-acquired bacterial infection from Salmonella serotypes, is widespread.[1] Enteric fever poses a significant health threat, especially in developing countries, leading to high rates of illness and death. Untreated, it can advance to severe complications like low blood pressure, mental status changes, liver and brain inflammation, intestinal perforation, and potentially fatal outcomes.[2] In South and Southeast Asia, enteric fever is a major source of community-acquired bloodstream infections. In developed countries like the U.S., it's a notifiable disease and a significant health risk, ranking just below malaria in severity and potential for life-threatening illness among travel-related infections.[3]

Each year, about 21 million people worldwide get an enteric fever, leading to over 150,000 deaths.[4] Pakistan, a developing nation, reports an annual typhoid incidence rate of 493.5 per 100,000 individuals, with Punjab and Sindh being the provinces at highest risk.[2,5] Asia carries 80% of cases and deaths. India sees a wide range of enteric fever cases. Typhoid fever, if untreated, poses high risks, with a 30% fatality rate.[6] Antimicrobial resistance is a major challenge in modern medicine, causing over 35,000 deaths annually in the United States.[7] Management of enteric fever varies globally based on culture and sensitivity results, causing rising MDR and XDR strains in developing countries due to antibiotic misuse.[8]

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Initially, ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole were common treatments, but bacterial resistance has reduced their effectiveness. Multi-drug resistant strains emerged in the 1970s, with broad resistance seen in the 1980s and 1990s.9 The treatment transitioned to quinolones and cephalosporins, initially effective until XDR strains developed resistance to these drugs.[10] The XDR typhoid outbreak started in Hyderabad in 2016, spreading quickly to other cities in Sindh, leading to over 10,000 cases in Pakistan. This highlights the concerning spread of this highly drug-resistant strain.[11-12]

The research assessed Salmonella Typhi sensitivity and resistance. Understanding antimicrobial patterns is key for treatment optimization and health policies. This study evaluates antibiotics' effectiveness, offering insights on current resistance trends. This information aids clinicians in treatment choices and researchers in designing new protocols against antimicrobial resistance in enteric pathogens. Identifying sensitive and resistant antibiotics helps optimize treatment decisions, outcomes, and enteric fever management.

METHODOLOGY

The Pediatric Department at CMH, Muzaffarabad, provided the framework for this cross-sectional observational investigation. The research was carried out over a duration of six months, spanning from June 2024 to December 2024. Employing a non-probability consecutive sampling technique, we incorporated a total of 200 blood cultures that tested positive. The focus of the study was on pediatric patients aged between 1 and 14 years who were admitted to the pediatric department and exhibited blood cultures that were positively identified solely as Salmonella Typhi. To distinguish among various species of Salmonella enterica, an agglutination test was performed at the hospital laboratory. Blood cultures that indicated Salmonella paratyphi and those conducted for alternative conditions were excluded from our analysis. The hospital laboratory successfully cultured Salmonella Typhi utilizing the BACTEC system and assessed antibiotic susceptibility on Muller-Hinton agar through the Kirby-Bauer disc diffusion methodology.

Data were documented in Microsoft Excel and subsequently imported into SPSS Software version 25. Analyses were conducted utilizing this SPSS software. Antibiotic susceptibility and resistance profiles were generated, and frequency analyses were performed for variables such as age, gender, and geographic region. Quantitative variables were evaluated using the mean and standard deviation, while qualitative data were examined through frequencies and

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percentages. Certificate from ethical committee was obtained - Ref No. Ethical committee / DME 754.

RESULTS

Table 1 displays the demographic data of the 200 study patients. Male children dominated at 63.5% (n=127), while females were 36.5% (n=73). The age split was 51.0% (1-7 years, n=102) and 49.0% (8-14 years, n=98), with a mean age of 7.54 ± 3.12 years, evenly distributed. Rural patients constituted 52.5% (n=105), urban 47.5% (n=95), showing enteric fever in both regions, slightly higher in rural areas.

Table 2 shows resistance patterns among Salmonella Typhi isolates where many are resistant to common antibiotics. Ampicillin, Ciprofloxacin, Ceftriaxone, and Ceftazidime had high resistance rates over 94%. Other antibiotics like Chloramphenicol and Aztreonam also showed substantial resistance. Fluoroquinolones like Moxifloxacin and Levofloxacin faced challenges with high resistance rates. Co-amoxiclav had an 83.5% resistance rate, limiting treatment options. Co-trimoxazole had a 46.0% resistance rate. These findings reveal a critical antimicrobial resistance issue in enteric fever requiring cautious antibiotic selection based on susceptibility testing. This high resistance emphasizes the need for effective antibiotic stewardship and alternative treatment strategies.

Table-1: Frequency distribution of different variables (n=200)

Variables		Frequency	Percent
Gender	Male	127	63.5%
	Female	73	36.5%
Age groups	1-7 years	102	51.0%
	8-14 years	98	49.0%
	7.54±3.12 years		
Residence	Rural	105	52.5%
	Urban	95	47.5%

Table-2: Frequency distribution of resistance pattern of different antimicrobials

Antimicrobials		Frequency	Percent
Co-trimoxazole	Resistant	92	46.0%

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	Sensitive	108	54.0%
Chloramphenicol	Resistant	188	94.0%
	Sensitive	12	6.0%
Ceftriaxone	Resistant	194	97.0%
	Sensitive	6	3.0%
Ciprofloxacin	Resistant	195	97.5%
	Sensitive	5	2.5%
Ampicillin	Resistant	198	99.0%
	Sensitive	2	1.0%
Moxifloxacin	Resistant	171	85.5%
	Sensitive	29	14.5%
Aztreonam	Resistant	187	93.5%
	Sensitive	13	6.5%
Cefotaxime	Resistant	185	92.5%
	Sensitive	15	7.5%
Co-amoxiclav	Resistant	167	83.5%
	Sensitive	33	16.5%
Ceftazidime	Resistant	189	94.5%
	Sensitive	11	5.5%
Levofloxacin	Resistant	172	86.0%
	Sensitive	28	14.0%
Cefepime	Resistant	181	90.5%
	Sensitive	19	9.5%
Gentamicin	Resistant	181	90.5%
	Sensitive	19	9.5%

DISCUSSION

The findings of this study highlight a concerning antimicrobial resistance pattern in *Salmonella Typhi* isolates from pediatric patients with enteric fever. The high resistance rates observed in

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this study align with previous research, suggesting a global trend of increasing multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Salmonella Typhi*.[13-14]

In this study, male children (63.5%) were more frequently affected than female children (36.5%). This male predominance has been consistently reported in other studies on enteric fever,[15-16] possibly due to differences in outdoor exposure and hygiene practices. The mean age of 7.54 ± 3.12 years also corresponds with previous findings, where enteric fever is primarily a childhood disease, with peak incidence occurring between 5 to 14 years of age.[17]

Additionally, a higher proportion of cases were from rural areas (52.5%), which could be attributed to poor sanitation, lack of access to clean drinking water, and limited healthcare facilities in rural communities.[18]

The most alarming finding of this study is the high resistance to first-line antibiotics, including ampicillin (99.0%), chloramphenicol (94.0%), and co-trimoxazole (46.0%). These drugs were once the primary treatment for enteric fever but have been largely abandoned due to widespread resistance. The re-emergence of *Salmonella Typhi* strains susceptible to these drugs has been reported in some regions, but their clinical efficacy remains uncertain given the persistence of MDR strains.[19-20]

Resistance to third-generation cephalosporins, particularly ceftriaxone (97.0%), cefotaxime (92.5%), ceftazidime (94.5%), and cefepime (90.5%), is a significant concern. These antibiotics have been the mainstay of treatment for enteric fever in recent years.[21]

The increasing resistance may be attributed to overuse and misuse of cephalosporins in both community and hospital settings. The emergence of cephalosporin-resistant *Salmonella Typhi* has been associated with extended-spectrum β-lactamase (ESBL)-producing strains, which limit treatment options further.[22-23]

The fluoroquinolone resistance rates observed in this study were also remarkably high, with ciprofloxacin (97.5%), moxifloxacin (85.5%), and levofloxacin (86.0%) showing limited efficacy. Similar findings have been reported in South Asia and other endemic regions.[24-25]

The widespread resistance to fluoroquinolones is linked to mutations in the *gyrA* and *parC* genes of *Salmonella Typhi*, leading to reduced drug susceptibility. This has prompted a shift toward alternative treatment strategies, such as azithromycin and carbapenems for severe cases.[26-27]

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The findings of this study emphasize the urgent need for antimicrobial stewardship programs to regulate the use of antibiotics in enteric fever management. With the rising resistance to cephalosporins and fluoroquinolones, treatment options are becoming increasingly limited. Azithromycin remains a viable alternative, as recent studies have reported lower resistance rates compared to cephalosporins and fluoroquinolones. However, monotherapy with azithromycin should be carefully monitored to prevent the emergence of resistance.[28]

Additionally, carbapenems such as meropenem and imipenem may be required for severe XDR cases, but their use should be restricted to hospitalized patients with life-threatening infections to prevent the spread of carbapenem-resistant *Salmonella Typhi* strains.[29]

Public health interventions should focus on preventive strategies, including improved sanitation, access to clean drinking water, and vaccination programs. The Typhoid Conjugate Vaccine (TCV) has shown promising results in reducing the incidence of enteric fever and should be widely implemented in endemic regions.

This study has certain limitations. Firstly, it was conducted in a single-center hospital setting, which may limit the generalizability of findings to broader populations. Secondly, molecular characterization of resistant strains was not performed, which could have provided further insights into the genetic mechanisms underlying resistance. Future studies should incorporate whole-genome sequencing and molecular analysis to better understand the epidemiology of drug-resistant *Salmonella Typhi*.

CONCLUSION

The study shows increasing resistance in Salmonella Typhi to important antibiotics like third-generation cephalosporins and fluoroquinolones. This highlights the crucial need for antimicrobial stewardship programs, careful antibiotic use, and the development of new treatment approaches to effectively combat enteric fever.

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