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Antibiotic Resistance Pattern in Culture Positive Cases of Enteric Fever at Combined Military Hospital Gujranwala

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ABSTRACT

Objective: To determine the antibiotic resistance in Blood culture positive cases of enteric fever.
Study Design: Cross sectional study
Place and Duration of the Study: Combined Military Hospital Gujranwala, Pakistan from Apr 2023 to Mar 2024.
Methodology: The study enrolled 290 consecutive patients who were clinically suspected of enteric fever as per inclusion criteria. Blood cultures collected before administration of antibiotics. After identification of salmonella colonies, sensitivity tests for seven antimicrobial agents applied including Ampicillin, Azithromycin, Ceftriaxone, Ciprofloxacin, Cotrimoxazole, Chloramphenicol and Meropenem. Data gathered and analysed for specific resistance along with Multi Drug Resistance (MDR), extended drug resistance (XDR) cases.
Results: The study revealed 134(46%) patients as culture positive enteric fever with mean age 25.00 (IQR:13.00) years and 101(75.4%) males, 33(24.6%) females. Resistance pattern identified as Ampicillin in 115(85.8%) cases, Azithromycin in 53(39.6%), Ceftriaxone in 42(31.3%) cases, Ciprofloxacin in 64(47.8%) cases, Chloramphenicol in 61(45.5%), Cotrimoxazole in 61(45.5%) cases. Meropenem showed 100 percent sensitivity and no resistance. the data proved 16.4 % cases as MDR typhoid and 31.34% as XDR cases.
Conclusion: Rising incidence of MDR and XDR enteric fever are a major concern. Resistance to Azithromycin and Ceftriaxone is emerging significantly, meropenem should be used cautiously to avoid resistance against it.

Keywords: Antibiotic resistance, Enteric fever, Salmonella, Multi Drug Resistance, Extended drug resistance.

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INTRODUCTION

Enteric fever also known as typhoid fever is bacterial infection caused by salmonella typhi and Para typhi. It affects approximately 9.3 million people worldwide each year, resulting around 110000 deaths.[1,2] This is transmitted through orofecal rout and more prevalent in countries with poor sanitation and inadequate clean drinking water.[3] Typhoid fever is common in South Asia, Southeast Asia, Africa, and the Western Pacific regions. Children are at the highest risk of contracting typhoid fever.[4] If left untreated or improperly treated, enteric fever can lead to serious complications. Early Complications (within 1-2 weeks) include Intestinal perforation with peritonitis, Gastrointestinal bleeding which can be life-threatening and Toxic encephalopathy leading to confusion, seizures, and coma. Late complications (after 2-4 weeks) include Osteomyelitis, Meningitis, Endocarditis and hepatosplenomegaly.[5,6]

Literature search revealed Irrational empirical antibiotic therapy as the main cause of antibiotic resistance which requires more complicated and expensive treatment options. It is due to poor hygiene, misuse of antibiotics and cultural barriers for vaccination there is emergence of MDR and XDR enteric fever in developing countries.[7] Pakistan is experiencing a significant challenge with a rise in MDR and XDR typhoid fever cases. Previously, Ampicillin, Trimethoprim-Sulfamethoxazole, and chloramphenicol were first line agents to treat enteric fever. Resistance to these first-line antibiotics (MDR) was seen in early 1980s. Multidrug resistance (MDR) enteric fever is prevalent in most of South Asia, with figures reaching 13% in India and 21 % in Pakistan.[8] Then Fluoroquinolones adopted to treat enteric fever, however, resistance to Fluoroquinolones also emerged, and as per SEAP (surveillance of enteric fever in Asia Project), the resistance of Salmonella Typhi to fluoroquinolones in Pakistan reported as 90%. Then third-generation Cephalosporins (Ceftriaxone and Cefixime) came into practice,However, in 2016, during the outbreak of enteric fever in Karachi and Interior Sindh in Pakistan, strains resistant to third-generation Cephalosporins

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emerged.[9] Currently, carbapenems (Meropenem, Imipenem) and Azithromycin remain the most widely used oral agent to treat the XDR enteric fever. So far resistance to these two agents is rare. Govt of Pakistan published health advisory to give Meropenem and Azithromycin to only culture proven XDR cases to avoid emergence of resistance.[10]

while working in combined military hospital Gujranwala, medical team noticed unusual cases of complicated enteric fever with many unresponsive to first- and second-line drugs. Unfortunately, no study at local level was available for the antibiotic resistance pattern, mandating the need for comprehensive study. This study would be helpful in providing insight to the resistance pattern of salmonella typhi and paratyphoid in the region. It would guide clinicians in selection of antibiotics for enteric fever, significance of fair practice, and importance of blood culture/sensitivity in diagnostics.

METHODOLOGY

This Cross sectional study study was conducted by Multidisciplinary team at Combined Military Hospital Gujranwala, Pakistan from April 2023 to March 2024 after IRB Approval from Hospital ethical committee (Reference number: ERB 27/2023 dated 20 march 2023). The target population was all patients coming to the Hospital for evaluation of Fever both male and female more than 12 years of age. The Sample size was calculated as 290 by keeping confidence interval (CI) of 95%, 5%, margin of error and percentage of MDR is 21%.[7] The consultant physicians enrolled 290 cases of enteric fever suspects, based on inclusion criteria, after informed written consent.

Inclusion Criteria: Patients of either gender with age above 12 years, presenting in outpatient department or emergency reception with clinical enteric fever were included in the study. Clinical Enteric fever was defined as a fever of 38 degree centigrade or above for 3 or more days associated with GIT symptoms like nausea, vomiting, diarrhea, constipation or prostration.[11]

Exclusion Criteria: Patients who were found positive for malarial parasite or dengue NS 1 Ag were excluded from study, similarly patients who took antibiotics within 7 days of presentation were also excluded from the study.

The Demographic and socioeconomic data were collected on a preformed questionnaire. All clinically suspected cases were evaluated with blood culture, Dengue NS1 antigen, Malarial Parasite (MP), Complete Blood Picture (CBC) and Liver Function Tests (LFT).

The Blood cultures collected on the spot before antibiotic initiation and sent to the department of pathology. Blood was inoculated into 40-45ml brain-heart infusion broth using BACT/ALERT VIRTUO automated blood culture machine [bioMérieux, Inc]. Incubation was done at 37 degrees. Salmonella isolates were tested for antimicrobial susceptibility by the Kirby-Bauer disk diffusion method on Mueller-Hinton agar with standard antimicrobial disks.

Antimicrobial susceptibility against seven antimicrobial agents-ampicillin, Azithromycin, co trimoxazole, ciprofloxacin, chloramphenicol, Ceftriaxone, and Meropenem was performed. The diameter of the zone of inhibition caused by each antimicrobial disc on the Salmonella isolates was measured in mm and compared with the standard chart recommended by The European Committee on Antimicrobial Susceptibility Testing to classify the organism as either sensitive, resistant, or having intermediate sensitivity pattern to the antibiotic. Culture-positive cases and sensitivity patterns were recorded as per the operational definition. MDR enteric fever was defined as the one caused by S. typhi or Para-Typhi A, B, and found resistant to 3 or more first-line drugs including quinolones. First-line drugs are chloramphenicol, ampicillin, and trimethoprim/sulfamethoxazole [TMP/SMX].[11] XDR enteric fever was the one caused by S. typhi or Para Typhi A, B, or C strains which are resistant to all antibiotics recommended for treatment including Cephalosporins and Quinolones.[11] Culture-positive patients were those having S. Typhi or Para-Typhi growth (1 or more colonies), obtained from blood culture after a maximum of 7 days of incubation.

Data analyzed using Statistic package for Social Sciences Version 23. The Number of Culture positive cases was identified first then analyzed for numerical and categorical variables. Numerical variables such as (age and number of culture-positive patients) presented as mean ± standard deviation (SD), and categorical variables (gender, type of isolate, antimicrobial sensitivity pattern) analyzed as frequency and percentage. For categorical variables, the chi-square test applied. The p-value of ≤0.05 considered statistically significant.

RESULTS

Out of 290 patients with clinically suspected enteric fever, 134(46.2%) patients were isolated as culture positive enteric fever. The patients had a mean age of 25.00 (IQR:13.00) years.101(75.4%) patients were males and 33(24.6%) were females. Salmonella typhi was present in 118 (88%) cases while salmonella Para-Typhi in 16(12%) cases (Figure-1).The antibiotic resistance pattern revealed Ampicillin resistance in 115(85.8%) cases, sensitivity in 9(6.7%) cases, intermediate results in 10(7.5%) cases. Azithromycin resistant in 53(39.6%) cases, sensitive in 60(44.8%) cases and intermediate results in 21(15.7%) cases. Ceftriaxone resistant in 42(31.3%) cases, sensitive in 92(68.7%) cases. Ciprofloxacin resistant in 64(47.8%) cases and sensitive in 70(52.2%) cases. Chloramphenicol resistant in 61(45.5%) cases, sensitive in 73(54.5%) cases. Cotrimoxazole resistant in 61(45.5%) cases and sensitive in 73 (54.5%) cases. Meropenem sensitive in 134 (100%) cases and showed no resistance (Figure-2). Sensitivity of antibiotics also checked against type of pathogen. The ampicillin, Azithromycin, and Ceftriaxone had no significant difference in sensitivity against both type of pathogens. While Ciprofloxacin, Chloramphenicol, Cotrimoxazole showed significantly better sensitivity to Para-typhi than typhi. Meropenem was also equally sensitive to both pathogens (Table).

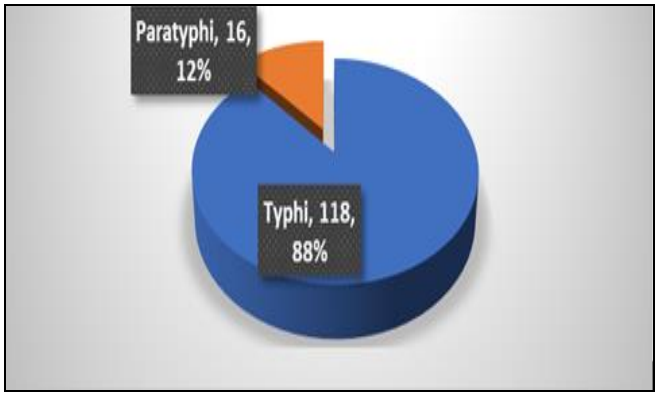

Figure-1: Type of Salmonella detected on Blood Test (total culture positive: 134)

DISCUSSION

The study revealed valuable information about the enteric fever in the locality. It includes the blood culture sensitivity in diagnosing enteric fever, age/gender distribution of cases, strain distribution among all cases, antibiotic resistance patterns, variation with type of strains and prevalence of MDR and XDR cases.

134(44.2%) cases found culture positive enteric fever out of 290 enteric fever suspects. 118(88 %) Salmonella typhi and 16(12%) salmonella Para-typhi. The sensitivity of blood culture in confirming the enteric fever remained 46 percent which is high as compared to tertiary care centers in Lahore and Karachi (25.2%).[9] Careful selection of cases, bedside inoculation of samples and exclusion of cases who had already taken antibiotics are reasons for achieving high levels.

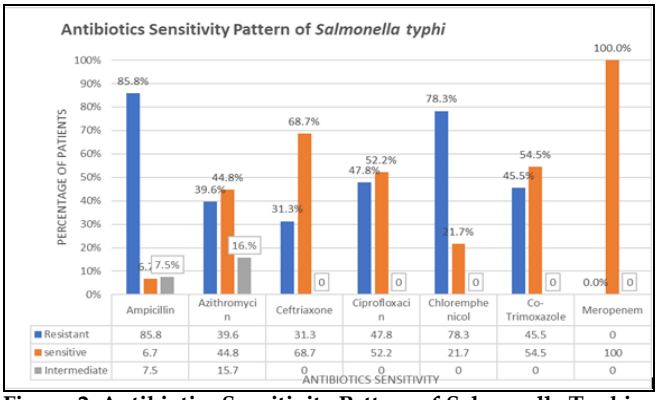

Figure-2: Antibiotics Sensitivity Pattern of Salmonella Typhi

Table: Association of Antibiotics Sensitivity against Type of Pathogen (n=134)

Antibiotic	Sensitivity Level	Type of Pathogen		p-value
		Typhi n=118	Para-Typhi n=16	
Ampicillin	Sensitive	6 (5.1%)	3 (18.8%)	0.070
	Resistant	102 (86.4%)	13 (81.3%)	
	Intermediate	10 (8.5%)	0 (0%)	
Azithromycin	Sensitive	49 (41.5%)	11 (68.8%)	0.109
	Resistant	50 (42.4%)	3 (18.8%)	
	Intermediate	19 (16.1%)	2 (12.5%)	
Ceftriaxone	Sensitive	78 (66.1%)	14 (87.5%)	0.083
	Resistant	40 (33.9%)	2 (12.5%)	
Ciprofloxacin	Sensitive	57 (48.3%)	13 (81.3%)	0.013
	Resistant	61 (51.7%)	3 (18.8%)	
Chloramphenicol	Sensitive	60 (50.8%)	13 (81.3%)	0.022
	Resistant	58 (49.2%)	3 (18.8%)	
Cotrimoxazole	Sensitive	58 (49.2%)	13 (81.3%)	0.016
	Resistant	60 (50.8%)	3 (18.8%)	
Meropenem	Sensitive	118 (100.0%)	16 (100.0%)	NA
	Resistant	0 (0%)	0 (0%)	

In our study MDR salmonella detected in 16.4 percent and XDR salmonella in 31.34 percent. The drug-resistant enteric fever is common in South-East Asia including Pakistan, Nepal, Bangladesh, and India.[12] The resistance to first-line antibiotics like ampicillin, chloramphenicol, and TMP/SMX is universal all over Pakistan and Asian countries. The injudicious use of antibiotics and over prescription of medication by non-qualified medical practitioners are

the reasons for emergence of resistant strains of Typhoid.[13,14] The prevalence of MDR in Asian countries is 23% 12 compared to 16.4% detected at our set. The XDR enteric fever prevalence is 43.4 14 compared to 31.34 % in our set up. XDR cases are also rising in Sindh province of Pakistan. National Institute of Health (NIH) Islamabad reported that a total of 14,360 XDR enteric fever detected in Karachi from January 2017 to June 2021. Whereas in the rest of Sindh, a total of 5741 cases of XDR enteric detected in the same period, with district Hyderabad 69.5% of cases.6 Resistance Pattern for individual drugs revealed ampicillin resistance in 85.8% cases and considered ineffective for treatment of enteric fever. Chloramphenicol resistance in 46.3 % cases. This is less as compared to found in Karachi as 59%.[15] We found 31,3% resistance, whereas this is negligible in central Asia.16 Emergence of resistance to Ceftriaxone can lead to increase in complications and mortality. This restricts the treatment options for enteric fever to more expensive Meropenem leading to economic burden in resource limited countries like Pakistan. A study was conducted at Hyderabad during epidemic in 2016, where significant Ceftriaxone resistance detected and mass level typhoid conjugate vaccine program in Hyderabad city was recommended.[10] Azithromycin is one of the most effective oral medicines for uncomplicated enteric fever. isolates in this study showed resistance in 39.6 % cases while intermediate sensitivity in 15.7% cases. Azithromycin resistance is rapidly increasing in Pakistan. Literature shows Azithromycin resistance for salmonella typhi increased from 10.3% to 24.1% between 2017 and 2020 in Pakistan.6 More over multidrug-resistant salmonella typhi strains showed higher resistance to Azithromycin (34.6%) compared to non-MDR strains (14.1%)[16]. Our study also shows higher resistance to Azithromycin compared to previous studies. This is alarming. This has serious implications. Meropenem found sensitive in all the cases and remains the only antibiotic with no resistance seen so far mimicking inferences from other studies conducted in Pakistan.

Marchello *et al*. conducted systematic review on antimicrobial resistance among salmonella typhi worldwide in 2020 and claimed that Understanding patterns and trends of antimicrobial resistance (AMR) in Salmonella Typhi could guide empiric treatment recommendations and contribute to country decisions about typhoid conjugate vaccine (TCV) introduction. They recommended vaccination to be incorporated along with other preventive measures like good hygiene, safe drinking water and recommended robust stewardship and surveillance program for empirical treatment of enteric fever.[17] Stewardship programs assist in preventing resistance by ensuring antibiotics are used correctly and not excessively or inappropriately. In the end, following proper stewardship practices helps maintain the effectiveness of current antibiotics, lowers healthcare expenses related to resistant infections, and shields future generations from the impacts of widespread antimicrobial resistance. Similarly, data was analyzed from 1990 to 2018 by Annie J brown et al. and concluded that drug resistant enteric fever is widespread in low- and middle-income countries and the situation is worsening. It is essential that public health and clinical measures, which include improvements in water quality and sanitation, the deployment of S. Typhi vaccination, and an informed choice of treatment are implemented.[18]

Limitations of this study include a small sample size. This is tip of the iceberg, and more extensive multicentric studies, as well as population-based studies are required. Only then we can conduct meta-analysis and produce our population-based guidelines.

CONCLUSION

Resistance to Ceftriaxone, Azithromycin, MDR and XDR enteric fever is increasing at alarming speed. It is essential to practice antibiotic stewardship to address the increasing concern of antibiotic resistance. Restricting injudicious carbapenem use to minimum essential. There is need to establish Culture sensitivity guided rationale practice in treatment of enteric fever and more studies to develop antibiogram for each region of Pakistan for empiric treatment recommendations.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MT & AM: Data acquisition, data analysis, critical review, approval of the final version to be published.

NA & IA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

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