Clinical Spectrum and Drug Sensitivity Pattern in Multi Drug-Resistant Typhoid Fever

Warda Afzal, Ameena Saba, Syed Taqi Hasan Zaidi, Hamid Jamal Siddiqui, Muhammad Tahir

Karachi Institute of Medical Sciences, Karachi/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objectives: To study the clinical presentation, complications and drug sensitivity patterns of multi drugs- resistant enteric fever.

Study Design: Prospective longitudinal study.

Place and duration of study: Combined Military Hospital, Malir Cantt Karachi Pakistan, from Mar to Oct 2019.

Methodology: A hundred cases of multi-drug resistant enteric fever were enrolled. Their demographic data, clinical and laboratory features and drug sensitivity pattern was recorded.

Results: Out of 100 cases, 67 were within 5 to 11 years of age. Twenty-one patients presented with loose motion and splenomegaly each. Seventy cases had a fever of 1 to 2-weeks duration. Complications were seen in 42 cases, out of which hepatitis was most commonly observed (in 27 cases). Ciprofloxacin and Ceftriaxone sensitivity were found to be only 3% and 9%, respectively. Sensitivity to Azithromycin was 95%, while all cases were sensitive to Meropenem and Imipenem.

Conclusion: Very high frequency of extensively drug-resistant typhoid fever was found. Most cases of enteric fever had a fever as the only presenting feature. Typhidot test has very low sensitivity.

Keywords: Clinical presentation, Complications, Drug susceptibility pattern, Multi drugs resistant typhoid fever.

INTRODUCTION

Typhoid fever is a potentially fatal infection caused by Salmonella typhi that produces multi-systemic illness. It is a major public health problem that affects 12-27 million cases annually. Prevalence is more in developing countries. In South Asia, 75000 people die of typhoid fever-related complications each year.[1] In the Indian sub-continent, Pakistan has the highest incidence of enteric fever (451.7/100000 persons/year).[2] Treatment of typhoid fever is a major medical issue because of resistance to most available treatment options.[3] In Pakistan, from 2012-2014, more than half of typhoid fever cases were found multi-drug resistant, meaning resistant to Ampicillin, Chloramphenicol and Trimethoprim-Sulphame-thoxazole.[4] The situation worsened over time, and outbreaks of extensively drug-resistant typhoid fever emerged, which means resistance to quinolones and third-generation Cephalosporins in addition to recommended first-line drugs.[5] Almost universal resistance to quinolones has been observed in recent studies from India.[6,7] In Pakistan (Sindh) Provincial Disease Surveillance and Response Unit (PDSRU) conducted a study from November 2016 to December 2018 in which out of 8188 cases, 5274 cases of typhoid fever turned out to be extensive drug-resistant. At the same time, 69% of these were from Karachi.[8] Consequently, we are left with Azithromycin and Carbapenem, the only treatment options for typhoid fever.[9] Untreated typhoid fever has a mortality of 10%-30%.[10]

Adequate knowledge about drug sensitivity patterns may result in a decrease in morbidity and early initiation of appropriate treatment. This can also avoid the unnecessary use of broadspectrum antibiotics for treating enteric fever, preserving the economy and avoiding adverse effects. Continuous surveillance is necessary to know about changing drug sensitivity patterns. Considering the magnitude of the problem, we conducted a hospital-based study to gather information regarding patterns of presentation and complications of typhoid fever and drug sensitivity patterns based on blood culture reports. Once the current patterns are identified, future protocols for treatment and prevention of enteric fever will be easier to establish. The objectives of the study were to describe the pattern of clinical presentation of cultureproven enteric fever, to assess the frequency of diffe-rent complications of enteric fever in the study population and to describe the sensitivity of Salmonella Typhi to different anti-microbial agents.

METHODOLOGY

It was a prospective longitudinal study conducted at Combined Military Hospital, Malir Cantt Karachi

Correspondence: **Dr Syed Taqi Hasan Zaidi,** Assistance Prof Pediatrics, Combined Military Hospital, Malir, Pakistan.

Pakistan from March 2019 to October 2019. An approval from the Ethical Review Board (Reference Number 1440/2019/Trg/Adm dated 14th Feb 2019) was taken before starting the study.

Inclusion Criteria: Patients of multi-drug resistant enteric fever were included in the study.

Exclusion Criteria: Blood culture-proven cases of enteric fever not fulfilling the criteria of multi-drug resistance were excluded from the study.

In the study duration, only 100 cases of multi drugs resistant enteric fever were reported and were included in the study after taking verbal informed consent from parents. They were enrolled in the Out-patient Department and Child Ward using consecutive convenient sampling. Multi drugs resistance was labelled as simultaneous resistance to Ampicillin, Chloramphenicol and Trimethoprim-Sulphamethoxa-zole in an isolate from blood culture.

In contrast, extensive drug resistance was labelled if isolated Salmonella Typhi was found resistant to third-generation Cephalosporin and Quinolones in addition to first-line drugs.[10] Sample for blood culture and sensitivity was obtained according to standard protocol.

Variables like clinical features of patients, compli-cations of enteric fever (if present), and drug sensitivity patterns were recorded on a predesigned proforma. Statistical Package for Social Sciences (SPSS) version 19.0 was used for the data analysis. Descriptive statis-tics like frequency and percentages of different vari-ables were calculated.

RESULTS

A total of 100 cases of multi drugs resistant typhoid fever were enrolled. Out of these, 68 were males, and 32 were females. Eleven cases were less than five years old. Sixty-seven were 5-11 years old and 22 cases were 10-13 years old. History of loose motion was found in 21 cases, while the rest of the children presented only with a history of pyrexia of unknown origin. Duration of fever was less than one week in 14 cases, 1-2 weeks in 70 cases, while 16 cases presented with more than two weeks of fever (Figure-1). None of the sample cases was previously vaccinated against enteric fever, while 15% of cases received one dose of intramuscular typhoid fever vaccine (Typherix). The spleen was palpable in 21% of cases, out of which 70% (15 cases) had a fever of 1-2 weeks. Leucopenia (according to their age-related reference range) was found in 38% of cases. In 76% of cases, no anti-Salmonella Typhi

antibodies were detected in typhoid testing. About 18% of cases had an IgM type, while 6% had only IgG-type antibodies. The pattern of complications in the Table revealed that hepatitis was the most common typhoid-related complication detected in 27% of cases. Most complications were seen in the second week of illness, while the rest were seen in the third week. About 91% of cases were extensively drug-resistant (XDR) typhoid (Figure-2). Most cases (76%) responded to treatment in 3-7 days, while 23 cases took more than one week to become afebrile. One case showed improvement in less than three days. All of them were receiving Meropenem and Azithromycin. No mortality was seen during the hospital stay and month follow-up in the Outpatient Department.
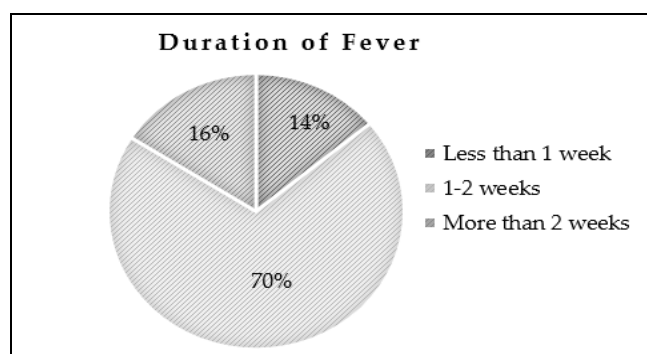

Figure-1: Duration of Fever in Sample Cases (n=100)

Table: Complications of Enteric Fever (n=100)

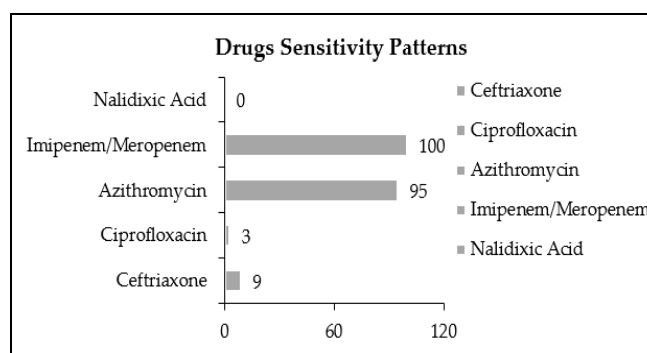| Complications	Percentage
Hepatitis	27%
Arthritis	2%
Local Complications	3%
Encephalopathy	3%
Bone Marrow Suppression	7%
None	58%

Figure-2: Drug Sensitivity Pattern (n=100)

DISCUSSION

Our study results depicted an alarming picture, showing 97% and 91% resistance to Ciprofloxacin and

ceftriaxone, respectively, the two prime antibiotics widely used for the treatment of enteric fever for the past two decades. Significant quinolone resistance was also observed in previous studies,[4,6,7] but the emergence of Ceftriaxone resistance is quite disappointing as its sensitivity was quite high (>99%) in the same city five years back.[4] A possible explanation could be the indiscriminate use of ceftriaxone for minor illnesses by general practitioners and clinicians. On the other hand, azithromycin sensitivity was quite encouraging (95%) though still, its resistance is increasing, which is a devastating situation as we have to resort to Imipenem and Meropenem as the only available options for treatment of enteric fever. This therapy is quite expensive, requiring hospitalisation for intravenous administration and putting a significant economic burden on the patient. Similar situations are also prevailing in India,[6,7,11] while results from Bangladesh and Nepal are quite hopeful, where the prevalence of even multi drugs resistant enteric fever was still found to be low.[12,13]

Another significant finding of our study regarding the clinical presentation of enteric fever was a low prevalence of diarrhoea and splenomegaly as presenting features that are prime clinical features of enteric fever. In 79% of cases, pyrexia of unknown origin was the only presenting feature. Most of our study population was within the age range of 5-10 years. This finding was contradictory to the results of various studies from Bangladesh, where the affected population was less than five years of age.[13,14] The risk of typhoid-related complications in our studies was quite high (42%), again higher than in studies from other south Asian countries.[12,13,14] Chief complications were hepatitis (most common) followed by pancytopenia, encephalopathy, local complications like intestinal haemorrhage and necrosis, and arthritis. These results were comparable to those found in the previous regional study.[15]

Typhidot test was found positive for IgM in only 18% of cases, while it was negative in 76% of cases. This finding was similar to that of another local study conducted in Lahore in 2015, which did not recommend the Typhidot test as a rapid diagnostic tool for enteric fever on account of low sensitivity and specificity.[16]

Since the results of our study showed a very high frequency of extensively drug-resistant enteric fever requiring costly and cumbersome treatment, stress should be laid on prevention at the community level.

Since Salmonella Typhi spreads by ingesting undercooked meat, contaminated food, water and milk,[17,18] health and hygiene promoting strategies like frequent hand washing, proper food cooking, clean and boiled water and vaccination should be encouraged. Furthermore, antibiotic use should be selected, cautious and with appropriate dosage. Indiscriminate prescriptions should be avoided. Awareness-raising programs should be conducted at the community level. Further studies at a broader level are required for future policy making at the national level regarding the diagnosis and management of enteric fever.

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CONCLUSION

A very high frequency of extensively drug- resistance was found. The commonest identified presentation of enteric fever is with pyrexia of unknown origin. Hepatitis was the commonest complication identified in the study population. Typhidot test has very low sensitivity.

Conflict of Interest: None.

Author's Contribution

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

WA: Study design, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

AS: Drafting the manuscript, interpretation of data, approval of the final version to be published.

STHZ: Conception, study design, drafting the manuscript, approval of the final version to be published.

HJS: Data acquisition, interpretation of data, drafting the manuscript, approval of the final version to be published.

MT: Critical review, drafting the manuscript, 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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