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ORIGINAL ARTICLE

Efficacy of Azithromycin and Meropenem in Pediatric XDR Salmonella Typhi: A Retrospective Study from Abbottabad, Pakistan

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ABSTRACT

Objective: To evaluate the efficacy of azithromycin as a first-line therapy and the combination of meropenem and azithromycin as the second-line therapy in treating pediatric patients with extensively drug-resistant (XDR) Salmonella Typhi in Abbottabad, Pakistan.

Methods: This retrospective cross-sectional study was conducted at Department of Pediatrics, Abbottabad International Medical Complex, Pakistan from May 2022 to January 2024. Children aged 1-15 years clinically diagnosed with typhoid fever were enrolled if subsequent blood cultures confirmed XDR Salmonella Typhi infection. Initial treatment comprised azithromycin. If there was no response to azithromycin, patients received a combination therapy of meropenem alongside continued azithromycin. Primary outcomes were clinical recovery, recurrence within 30 days post-treatment, and treatment-related adverse effects.

Results: Of total 67 pediatric patients, the mean age of the patients was 10.02 ±2.76 years. The overall mean duration of defervescence was 6.01 ±2.98 days. Initially, all patients were treated with azithromycin alone. Most patients recovered clinically 57 (85.1%). For the 10 (14.9%) who did not respond, meropenem was added to azithromycin, resulting in recovery for all. The mean duration of defervescence found significantly low in patients who received azithromycin monotherapy as compared to patients who received combination therapy i.e., 4.80 ±0.58 days vs. 12.90 ±1.10 days (p-value <0.001). Mild nausea was the only adverse event observed in 29 patients (43.3%) during treatment.

Conclusion: Azithromycin monotherapy demonstrated a high clinical recovery rate, with a significant reduction in fever duration compared to combination therapy with meropenem. Mild nausea was the only treatment-related adverse effect observed.

Keywords: Antibiotic Resistance, Azithromycin, Meropenem, Salmonella Typhi, Typhoid Fever.

INTRODUCTION

Extensively drug-resistant (XDR) Salmonella Typhi has emerged as a significant public health threat, particularly in regions with inadequate healthcare infrastructure and poor sanitation.[1] Typhoid fever, caused by Salmonella enterica serovar Typhi, remains a prevalent infectious disease in many developing countries, with an estimated 9 million cases and 110,000 deaths annually worldwide.[1] Misuse and overuse of antibiotics have contributed to the development of multidrug-resistant (MDR) and XDR strains of Salmonella Typhi, complicating treatment protocols.[2]

The traditional first-line antibiotics for typhoid fever, such as chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, have been rendered ineffective against MDR and XDR strains, necessitating the use of third-generation cephalosporins and fluoroquinolones. However, resistance to these antibiotics has also been reported, further limiting treatment options.[3] In this context, carbapenems such as meropenem and macrolides such as azithromycin have shown promise as effective alternatives for treating XDR Salmonella Typhi infections.[3,4]

Meropenem, a broad-spectrum carbapenem, demonstrates high efficacy against a variety of gram-negative and gram-positive bacteria, including XDR Salmonella Typhi. It is often used in severe cases and in hospitalized patients due to its intravenous administration route. Azithromycin, an oral macrolide, is favored for its

convenient administration and good penetration into tissues, making it a suitable option for outpatient therapy.[5] Combining these two antibiotics may offer synergistic effects, potentially improving treatment outcomes in severe infections.

In Pakistan, typhoid fever remains endemic, with numerous outbreaks reported over the past decade.[6-9] The emergence of XDR Salmonella Typhi has exacerbated the public health challenge.[3,6-9] An outbreak in Hyderabad, Pakistan highlighted the rapid spread of XDR strains, resistant to five or more classes of antibiotics, including third-generation cephalosporins and fluoroquinolones, which were previously the mainstay of treatment.[9] The high burden of typhoid fever in Pakistan is attributed to poor sanitation, contaminated water supply, and overcrowded living conditions, which facilitate the transmission of the pathogen.[9,10]

The rationale of this study is to evaluate the clinical and microbiological efficacy of azithromycin as a first-line therapy and the combination of meropenem and azithromycin as the second-line therapy in treating pediatric patients with XDR Salmonella Typhi. Despite previous research, the evolving nature of antibiotic resistance necessitates ongoing studies to validate and update treatment protocols. Understanding the efficacy of these regimens is crucial for developing effective management strategies for XDR typhoid fever, particularly in endemic regions where the disease burden is high, and treatment options are limited. By comparing the outcomes of these different approaches, this study aims to provide evidence-based recommendations to optimize treatment protocols and improve patient outcomes.

METHODS

This retrospective cross-sectional study was conducted at Department of Pediatrics, Abbottabad International Medical Complex, Pakistan from May 2022 to January 2024. Ethical approval was obtained from the Institutional Review Board of Abbotabad International Medical Institute prior to conducting of the study. Require-ment of the consent form was waived as all data were retrieved from the medical records.

By using OpenEpi sample size calculator taking prevelance of treatment failure rate 4.5%,[8] level of confidence 95%, and 5% margin of error. The estimated sample size was 67. The inclusion criteria for this study were patients aged 1-15 years who were clinically diagnosed with typhoid fever and started on azithromycin based on clinical suspicion before blood culture results were available. Only patients with subsequently confirmed XDR Salmonella Typhi infection via blood culture were included. Patients with known allergies to meropenem or azithromycin, pregnant or breastfeeding women, and those with severe comorbidities or immunocompromised status were excluded. Patients with incomplete medical records, particularly those lacking details on antimicrobial therapy, treatment duration, treatment failure, and time to defervescence, were excluded from the study. Additionally, patients who left against medical advice (LAMA) within 48 hours of admission, those with a positive blood culture who did not receive treatment at either hospital, and those who failed to return for follow-up visits after blood culture confirmation were also excluded.

XDR Salmonella Typhi was defined as a strain of Salmonella enterica serovar Typhi that was confirmed through blood culture to be resistant to at least five of the first-line and second-line antibiotics commonly used to treat typhoid fever. These antibiotics include chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones (such as ciprofloxacin), and third-generation cephalosporins (such as ceftriaxone). The diagnosis is made based on the isolation of Salmonella Typhi from the patient's blood sample, followed by antimicrobial susceptibility testing to identify resistance to the specified antibiotics.

The treatment plan for XDR Salmonella Typhi in this study involved the use of azithromycin as the first-line therapy. Patients received azithromycin at a dosage of 20mg per kg per day intravenously for 7-10 days, depending on clinical response and severity of infection. For patients who failed to respond to azithromycin monotherapy, defined by persistent or worsening symptoms and/or positive blood cultures after 4-5 days of treatment, a combination therapy was initiated. This combination therapy included meropenem at a dosage of 40 mg per kg per dose administered intravenously every 8 hours, along with azithromycin continued at 20 mg per kg intravenously once daily. The combination therapy continued for 10-14 days, with adjustments based on the patient's clinical condition and response to treatment. Data collection included demographic information, clinical presentation, treatment regimens, and outcomes such as defervescence (fever clearance), clinical recovery, treatment failure, recurrence rates, and any adverse effects observed.

The primary outcomes of this study focused on clinical recovery or treatment failure. Clinical recovery was operationally defined as the complete resolution of all

symptoms associated with XDR Salmonella Typhi infection, including fever, headache, abdominal pain, diarrhea, constipation, and vomiting. Patients were considered to have achieved clinical recovery if they were documented as symptom-free for at least 48 hours without requiring further medical intervention for the infection after the completion of the treatment course. This assessment was based on the review of symptom logs and follow-up records documented in the patients' medical records. Treatment failure was defined as the persistence or recurrence of infection-related symptoms and/or positive blood cultures for Salmonella Typhi after completing the prescribed antibiotic treatment course. This included the lack of fever clearance within the expected time frame (typically within 7 days of starting treatment), persistence of other clinical symptoms, a positive blood culture for Salmonella Typhi at the end of the treatment period, or the need to change antibiotic therapy due to lack of response to the initial treatment. Treatment failure was determined by reviewing the patients' clinical course documented in medical records, symptom persistence noted in follow-up visits, and/or blood culture results, indicating no improvement or worsening during or after the treatment period. Patients were classified based on these mutually exclusive outcomes to ensure clear and distinct categorization of treatment responses.

Data entry and statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) version 24. Mean and standard deviation were calculated for all the quantitative variables like age, duration of symtopms, and duration of defervescence. While percentages and frequencies were calculated for gender and symptoms of XDR Salmonella Typhi infection. The mean difference of quantitative variables between groups were explored using the independent t-test. The p-value ≤0.05 was taken as significant.

RESULTS

Of total 67 pediatric patients, the mean age of the patients was 10.02 ±2.76 years. There were 35 (52.2%) males and 32 (47.8%) females. The mean duration of symptoms was 8.09 ±0.81 days. The overall mean duration of defervescence was 6.01 ±2.98 days. Initially, all patients received azithromycin monotherapy. Of these, 57 (85.1%) achieved clinical recovery. For the remaining 10 (14.9%) patients who experienced treatment failure, meropenem was added to their treatment alongside azithromycin, resulting in successful clinical recovery for all 10 patients (Figure 1).

In azithromycin monotherapy group majority of the patients were presented with symptoms such as fever 47 (82.5%), headache 48 (84.2%), abdominal pain 36 (63.2%), diarrhea 38 (66.7%), constipation 4 (7.0%), and vomiting 26 (45.6%) (Figure 2).

The mean duration of defervescence found significantly low in patients who received azithromycin monotherapy as compared to patients who received combination therapy i.e., 4.80 ±0.58 days vs. 12.90 ±1.10 days (p-value <0.001) (Table 1). Gender wise comparison also showed that in males and females defervescence found significantly low in patients who received azithromycin monotherapy as compared to patients who received combination therapy i.e., 4.87 ±0.61 days vs. 12.75 ±1.50 days (p-value <0.001) and 4.73 ±0.53 days vs. 13.00 ±0.89 days (p-value <0.001) (Table 2). Mild nausea was the only adverse event which was observed in 29 (43.3%) patients during treatment.

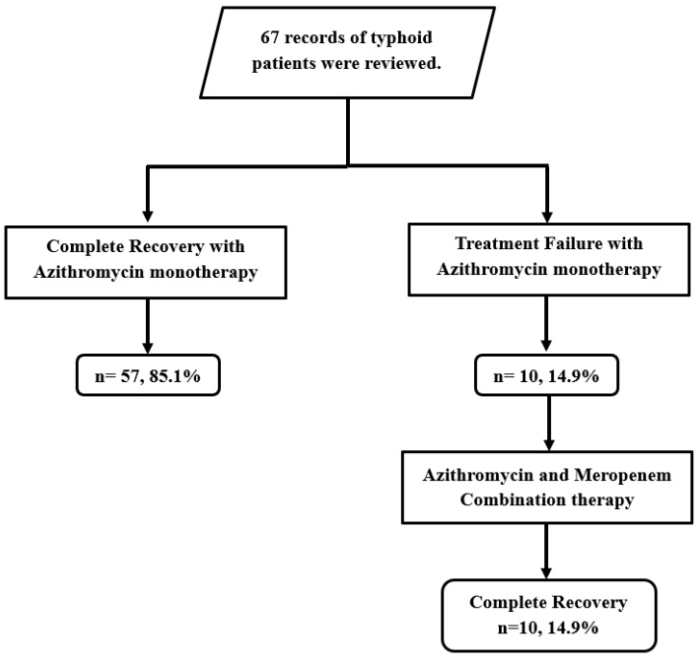

Figure 1: Flowchart showing treatment response to azithromycin monotherapy and combination therapy.

DISCUSSION

This retrospective cohort study aimed to evaluate the efficacy of azithromycin as a first-line therapy and the combination of azithromycin and meropenem as a second-line therapy in treating pediatric patients with XDR Salmonella Typhi. The study findings indicate that azithromycin monotherapy was effective in achieving clinical recovery in the majority of the patients. However, few patients exhibited treatment failure with azithromycin alone, necessitating the addition of meropenem. This combination therapy proved to be

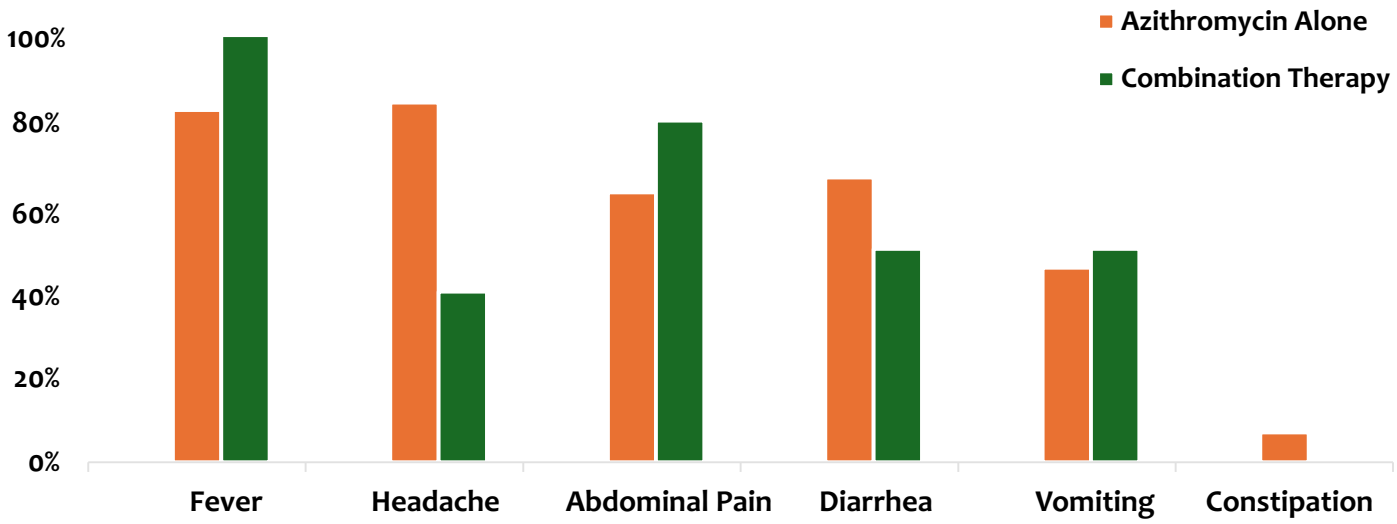

Figure 2: Symptoms present in patients admitted with XDR Salmonella Typhi (n=67)

Table 1: Mean comparison of quantitative variables with treatment groups (n= 67)

	Total	Azithromycin Monotherapy (n= 57)	Combination Therapy (n=10)	p-value
	Mean ±SD	Mean ±SD	Mean ±SD	
Age, years	10.02 ± 2.76	9.65 ±2.75	12.20 ±1.69	0.006*
Duration of symptoms at the time of initiation of therapy, days	8.08 ± 0.81	8.09 ±0.81	8.10 ±0.87	0.965
Duration of defervescence, days	6.01 ± 2.98	4.81 ±0.58	12.90 ±1.10	<0.001*

*p-value ≤ 0.05 (~Independent t-test)

Table 2: Gender wise mean comparison of quantitative variables with treatment groups (n= 67)

	Azithromycin Monotherapy (n= 57)	Combination Therapy (n=10)	p-value
	Mean ±SD	Mean ±SD	
Males (n= 35)			
Age, years	9.45 ±2.71	11.75 ±2.36	0.116
Duration of symptoms at the time of initiation of therapy, days	8.19 ±0.79	8.25 ±0.50	0.891
Duration of defervescence , days	4.87 ±0.61	12.75 ±1.50	<0.001*
Females (n= 32)			
Age, years	9.88 ±2.84	12.50 ±1.22	0.037*
Duration of symptoms at the time of initiation of therapy, days	7.96 ±0.82	8.00 ±1.09	0.923
Duration of defervescence , days	4.73 ±0.53	13.00 ±0.89	<0.001*

*p-value ≤ 0.05 (~Independent t-test)

highly effective, as all patients who received it achieved clinical recovery. These findings are consistent with previous studies that have demonstrated the efficacy of azithromycin alone or in combination with meropenem in treating typhoid fever, particularly in regions with high antibiotic resistance.[8,11-13]

A recent meta-analysis reported that XDR typhoid has become dominant in Pakistan. Moreover, Azithromycin resistance mutations were detected at low prevalence in South Asia.[14] A study reported almost resistance with meropenem alone in almost half of the cases.[15]

The overall duration of defervescence in this study was six days, which aligns with the expected range for effective antibiotic therapy in typhoid fever. Notably, the duration of defervescence was significantly shorter in patients who responded to azithromycin monotherapy compared to those who required combination therapy. This prolonged defervescence in the combination therapy group underscores the severity of infection in patients with initial treatment failure and the effectiveness of adding meropenem to the regimen.[16] Somewhat similar defervescence period for azithromycin alone was reported in previous studies as well.[8,17]

The absence of symptom recurrence within 30 days post-treatment in our cohort is encouraging and suggests that the treatment regimens used were successful in eradicating the infection. This finding is particularly important given the high rate of relapse and complications associated with XDR Salmonella Typhi in other studies.[8,11]

Adverse events were minimal in this study, with mild nausea being the only reported side effect in forty three percent of the patients. This was effectively managed and resolved without impacting the overall treatment outcomes. Previous studies have reported similar safety profiles for azithromycin and meropenem, further supporting their use in pediatric populations.[18-20]

As with any retrospective study, this research has several limitations that must be acknowledged. Firstly, the reliance on medical records may introduce biases due to incomplete or inaccurate data entries, which can affect the reliability of the findings. Secondly, the study's observational nature precludes the ability to establish causal relationships definitively. Thirdly, the sample size, while adequate, may not be large enough to detect all potential differences between treatment regimens, especially for less common outcomes or adverse effects. Additionally, the study is conducted within a specific geographical region, which may limit the generalizability of the results to other settings with different healthcare infrastructures and resistance patterns. Lastly, the potential for selection bias exists, as patients who received meropenem, azithromycin, or combination therapy might differ systematically in ways not fully accounted for in the analysis.

Future research should address the limitations of this study and build on its findings. Prospective, randomized controlled trials are recommended to confirm the efficacy and safety of meropenem and azithromycin, both as monotherapy and in combination, for treating XDR Salmonella Typhi. These studies should aim for larger, more diverse patient populations to enhance generalizability and should include detailed subgroup analyses to identify which patients benefit most from each treatment regimen. Additionally, research should explore the molecular mechanisms underlying antibiotic resistance in Salmonella Typhi to develop more targeted therapeutic strategies. Longitudinal studies examining the long-term outcomes of patients treated with these antibiotics are also warranted to understand the impact of treatment on recurrence rates and resistance development. Finally, public health research should focus on implementing and evaluating interventions aimed at reducing the spread of XDR Salmonella Typhi, including vaccination programs, improved sanitation, and antibiotic stewardship initiatives.

The study's strengths significantly enhance its relevance. Notably, it addresses a critical public health issue in an endemic region, offering valuable and actionable insights for healthcare providers in Pakistan. The study leverages real-world data from medical records, offering insights into the effectiveness of treatment regimens in routine clinical practice. By comparing monotherapy with combination therapy, the study provides a comprehensive analysis of different treatment strategies, which can inform clinical decision-making. The inclusion of a detailed monitoring plan for clinical recovery, treatment failure, and adverse effects ensures a thorough evaluation of patient outcomes. Additionally, the study's findings are timely and critical for guiding the management of XDR Salmonella Typhi, a rapidly evolving threat that necessitates continuous research and updated clinical guidelines.

CONCLUSION

In conclusion, azithromycin monotherapy demonstrated a high clinical recovery rate, with a significant reduction in fever duration compared to combination therapy with meropenem. Both boys and girls did better with azithromycin alone. Nausea was the main

side effect noted. These findings show azithromycin is effective and safe for treating these infections in children. More research can help make treatments better and faster for these challenging cases.

ETHICAL APPROVAL: This study was approved by the Institutional Review Board of Abbottaboad International Medical Institute (Ref. No: Chairman Research Cell-AIMI/IREB, dated: 4th April, 2024).

AUTHORS' CONTRIBUTIONS: KM & K: Conception and study design. K, AK & AR: Data acquisition, analysis and interpretation. K & KB: Drafting of manuscript. All authors critically reviewed and gave final approval of the manuscript.

CONFLICT OF INTEREST: The author declared no conflict of interest.

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