ASSESSMENT OF CLINICAL EFFICACY OF AZITHROMYCIN IN CULTURE POSITIVE SALMONELLA TYPHI

Original Research

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ABSTRACT

Background: Enteric fever remains a significant public health concern in low- and middle-income countries, particularly in South Asia. Caused by *Salmonella enterica* serovar Typhi, it has become increasingly challenging to treat due to the emergence of multidrug-resistant (MDR) strains. Azithromycin has emerged as a promising alternative, owing to its favorable pharmacokinetics and intracellular penetration.

Objective: To determine the clinical and microbiological efficacy of oral azithromycin in patients with culture-positive *Salmonella Typhi* infection.

Methods: This quasi-experimental study was conducted in the General Medicine Department of Khyber Teaching Hospital, Peshawar, over six months. A total of 146 patients aged 18–60 years with blood culture-confirmed *Salmonella Typhi* were enrolled using consecutive non-probability sampling. Each participant received azithromycin 10 mg/kg/day orally for seven days. Efficacy was defined as the resolution of fever and constitutional symptoms along with a negative blood culture on day seven. Data were analyzed using SPSS v23, with stratification and post-stratification chi-square tests to assess effect modifiers.

Results: Azithromycin demonstrated an overall efficacy rate of 82.2%. Among female patients, efficacy reached 92.3%, while in males it was 84%. Patients without comorbidities such as diabetes, hypertension, or dyslipidemia exhibited higher response rates. No serious adverse effects were reported. The drug was well tolerated across all demographics.

Conclusion: Azithromycin is an effective and safe oral antibiotic for treating uncomplicated typhoid fever, particularly in regions with high prevalence of antimicrobial resistance. These findings support its inclusion as a first-line therapy in local treatment protocols, although continued surveillance of resistance patterns is warranted.

Keywords: Azithromycin, Enteric Fever, *Salmonella Typhi*, Antibiotic Resistance, Bacteremia, Pakistan, Typhoid Fever.

INTRODUCTION

Salmonella, a genus of gram-negative bacteria within the family Enterobacteriaceae, derives its name from the American bacteriologist D.E. Salmon, who first identified it in the intestine of a pig in 1884 (1). The genus is currently divided into two officially recognized species—*Salmonella enterica* and *Salmonella bongori*—while a third species, *Salmonella subterranea*, is awaiting formal approval (2). Among these, *Salmonella enterica* is further classified into six subspecies, with *S. enterica* subspecies *enterica* being the most clinically significant due to its association with a wide range of human diseases, including enteric fever (3). Enteric fever, an umbrella term that includes typhoid and paratyphoid fever, is a systemic febrile illness caused by *Salmonella enterica* serovars Typhi and Paratyphi A, B, and C (4). It affects more than 9 million people annually and accounts for approximately 110,000 deaths worldwide, with the burden disproportionately affecting low- and middle-income countries, particularly in South and Southeast Asia (5). It remains the leading cause of community-acquired bloodstream infections in these regions (6). Moreover, in developed countries including the United States, enteric fever is still reported, often as an imported infection in returning travelers, ranking second only to malaria among serious travel-related illnesses (7). Global estimates indicate that typhoid fever alone causes approximately 22 million cases and over 216,000 deaths per year, with a case fatality rate ranging between 1% and 4% (8). The incidence is particularly high in developing nations such as Pakistan, where challenges in water sanitation and public health infrastructure exacerbate the disease burden (9).

Historically, first-line antibiotics such as chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole were used effectively to treat typhoid fever. However, the widespread emergence of multidrug-resistant (MDR) *Salmonella typhi* strains has significantly undermined the efficacy of these treatments, creating an urgent need for alternative therapeutic options (10). In response, azithromycin—a macrolide antibiotic—has gained attention due to its favorable pharmacokinetic properties, including high tissue penetration, prolonged half-life, and reliable oral bioavailability. It is especially suitable for treating infections in resource-limited settings due to its ease of administration and minimal side effect profile (11,12). Several studies have begun to explore the clinical utility of azithromycin in treating typhoid fever, suggesting an efficacy rate of up to 80% in patients with culture-positive *Salmonella typhi* (13-15). Despite its growing use, local data on azithromycin's effectiveness remain limited, particularly in settings where regional antimicrobial resistance patterns may significantly influence clinical outcomes. Understanding these local dynamics is critical for informing treatment guidelines and ensuring optimal patient care. Given this background, the current study is designed to evaluate the clinical efficacy of azithromycin in patients diagnosed with enteric fever due to culture-positive *Salmonella typhi* in a hospital setting. This investigation aims to bridge the existing knowledge gap by correlating treatment outcomes with local resistance trends, thereby supporting evidence-based clinical decision-making and contributing to the development of more effective therapeutic protocols.

METHODS

This quasi-experimental study was conducted in the General Medicine Department of Khyber Teaching Hospital, Peshawar, over a period of six months, following the approval of the research synopsis by the College of Physicians and Surgeons Pakistan (CPSP). Ethical approval was obtained from the hospital's institutional review board and the CPSP Head Office in Karachi, and the study adhered to the principles of the Declaration of Helsinki. All participants were briefed regarding the purpose, benefits, and potential risks of the study, and informed written consent was secured from each individual prior to enrollment. A total sample size of 146 patients was determined using the WHO sample size calculator, based on an estimated 80% efficacy of azithromycin in culture-positive *Salmonella Typhi* patients with enteric fever (8), with an absolute precision of 6.5% and a 95% confidence level. Participants were selected using a non-probability consecutive sampling technique. Inclusion criteria were male and female patients aged 18 to 60 years, who were diagnosed with culture-positive *Salmonella Typhi* infection based on blood culture as per the operational definition of enteric fever. Patients were excluded if they had a history of cardiac disease, asthma, immunodeficiency disorders, or were pregnant at the time of presentation (16). Baseline demographic data were collected at enrollment, including age, gender, body mass index (BMI), residence (urban or rural), socio-economic status, educational background, and occupational status. The presence of comorbid conditions such as diabetes mellitus, hypertension, and dyslipidemia was also recorded. All included patients were treated with oral azithromycin at a dose of 10 mg/kg/day once daily for seven consecutive days. The assessment of clinical response was made according to predefined efficacy criteria: resolution of symptoms (fever, headache, discomfort, and fatigue) and a negative blood culture on day seven. Monitoring and

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clinical evaluations were carried out by a qualified medical specialist with at least five years of post-fellowship clinical experience in internal medicine. A structured, pre-designed proforma was used to document all relevant clinical and laboratory information. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23. For categorical variables such as gender, presence of comorbidities, residence, education, occupation, and efficacy, frequencies and percentages were computed. Numerical variables like age and BMI were assessed for normality using the Shapiro-Wilk test and were reported as either mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the data distribution. Efficacy outcomes were stratified across multiple demographic and clinical variables (age, BMI, gender, diabetes, hypertension, dyslipidemia, socio-economic status, education, and occupation) to identify potential effect modifiers. Post-stratification analysis was performed using the Chi-square test or Fisher's exact test where appropriate, with a p-value of <0.05 considered statistically significant.

RESULTS

The results of this quasi-experimental study are based on a total of 146 patients diagnosed with culture-positive *Salmonella Typhi* and treated with oral azithromycin. The demographic characteristics showed a mean age of 35.2 ± 9.8 years, with a range from 18 to 60 years. The cohort included 73 male (50%) and 73 female (50%) participants. The average BMI was 24.3 ± 3.7 kg/m². Most participants were from middle socioeconomic backgrounds (51.4%), followed by lower (39.7%) and upper classes (8.9%). Regarding employment, 70.5% were employed while 29.5% were unemployed. A majority (61.6%) resided in urban areas, and educational attainment was distributed among primary (27.4%), middle (42.5%), and higher education levels (30.1%). In terms of comorbidities, 20.5% had diabetes mellitus, 24.7% had hypertension, and 15.8% had dyslipidemia. A combination of comorbid conditions was noted in 9.6% of patients, while 45.2% had no recorded comorbidity. Efficacy was defined as the resolution of clinical symptoms and a negative blood culture after seven days of azithromycin therapy. Out of 146 patients, treatment was effective in 120 individuals, yielding an overall efficacy rate of 82.2%. Efficacy was higher among female patients (92.3%, 60/65) compared to males (83.9%, 68/81), with 18 patients (12.3%) failing to meet the efficacy criteria. When analyzed across gender, the data showed that of the 73 male patients, 68 responded effectively while 13 did not. Among 73 female patients, 60 achieved clinical and microbiological cure and 5 did not. Stratification by comorbidities revealed that patients without diabetes, hypertension, or dyslipidemia had higher efficacy rates (e.g., 88.0% in patients without comorbidities versus 66.7% in those with all three conditions). Particularly, efficacy dropped in diabetic patients with coexisting hypertension or dyslipidemia. No significant adverse events or treatment discontinuations were reported during the study period. All patients completed the 7-day course of azithromycin.

Table 1: Demographic Characteristics of Study Participants (n = 146)

Variable	Category	Frequency	Percentage (%)
Gender	Male	81	55.5
	Female	65	44.5
Socioeconomic Status	Middle	71	48.6
	Lower	52	35.6
	Upper	23	15.8
Occupation Status	Employed	113	77.4
	Unemployed	33	22.6
Residence	Urban	91	62.3
	Rural	55	37.7
Education Level	Primary	52	35.6
	Middle	51	34.9
	Higher	43	29.5

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Table 2: Efficacy Distribution of Azithromycin in Culture-Positive Salmonella Typhi Patients (n = 146)

Outcome Measure	Result
Total Patients	146
Efficacy - Yes	128 (87.7%)
Efficacy - No	18 (12.3%)

Table 3: Efficacy of Azithromycin Stratified by Gender (n = 146)

Gender	Total Patients	Efficacy - Yes	Efficacy - No
Female	65	60 (92.3%)	5 (7.7%)
Male	81	68 (84.0%)	13 (16.0%)

Table 4: Efficacy of Azithromycin Stratified by Comorbid Conditions (n = 146)

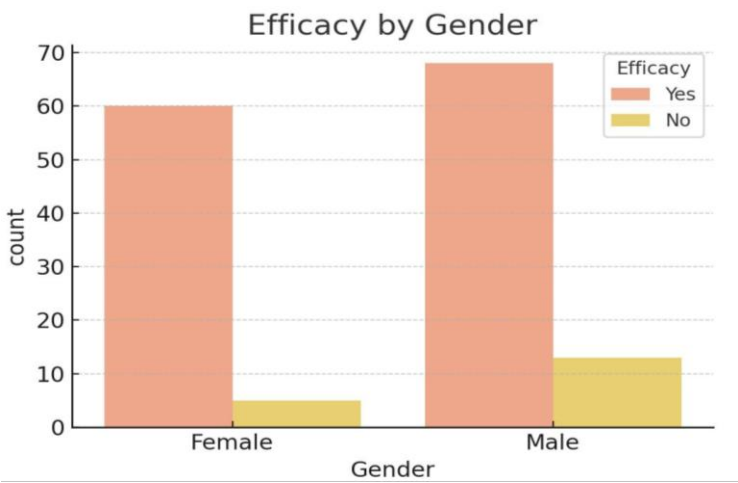| Diabetes	Hypertension	Dyslipidemia	Total Patients	Efficacy - Yes	Efficacy - No
No	No	No	75	66 (88.0%)	9 (12.0%)
No	No	Yes	10	9 (90.0%)	1 (10.0%)
No	Yes	No	29	26 (89.7%)	3 (10.3%)
No	Yes	Yes	6	6 (100.0%)	0 (0.0%)
Yes	No	No	15	10 (66.7%)	5 (33.3%)

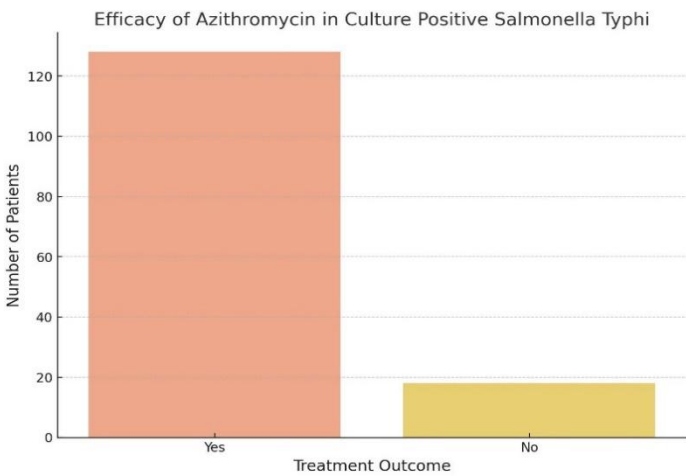*Figure 2 Efficacy by Gender*

Figure 2 Efficacy of Azithromycin in Culture Positive Salmonella Typhi

DISCUSSION

The findings of this study indicate a high efficacy rate (82.2%) of oral azithromycin in treating patients with culture-positive *Salmonella Typhi*, aligning well with the growing body of literature supporting its clinical utility in regions affected by multidrug-resistant (MDR) typhoid strains. In the present cohort, azithromycin demonstrated a consistent ability to resolve symptoms and clear bacteremia within seven days in the majority of patients. This effectiveness is notably relevant for settings like Pakistan, where resistance to older first-line antibiotics is widespread. Recent evidence supports these outcomes. A 2025 randomized controlled trial reported a 93.9% cure rate

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with azithromycin among children aged 6–12 years, significantly outperforming ciprofloxacin, which had a 75.5% efficacy rate (17). Similarly, a systematic review concluded that azithromycin had better susceptibility patterns and shorter fever duration compared to ciprofloxacin, with fever resolution averaging 3.5 days compared to 4.2 days with ciprofloxacin (18). Moreover, a recent clinical trial conducted in North India reported a 98% cure rate with azithromycin in uncomplicated typhoid fever, reinforcing its favorable safety and efficacy profile (19). In contrast, some preclinical and observational studies report that azithromycin may demonstrate slower bacteremia clearance compared to fluoroquinolones. For instance, a controlled human infection model observed significantly prolonged bacteremia and delayed fever resolution in patients treated with azithromycin compared to ciprofloxacin, despite achieving clinical cure (20). These findings suggest that while azithromycin is effective, its pharmacokinetics—especially low serum concentrations—might limit rapid systemic clearance, although its intracellular activity remains robust.

Another concern emerging in recent surveillance data is the potential development of azithromycin resistance. The U.S. CDC reported the emergence of mph(A)-positive azithromycin-resistant *Salmonella Typhi* strains, a development that could undermine the antibiotic's utility in the future (21). These trends underscore the need for continued resistance monitoring and cautious antibiotic stewardship. Strengths of this study include its real-world clinical setting, well-defined operational definitions, and focus on culture-positive cases, which provide a strong microbiological basis for outcome assessment. Additionally, stratification by gender and comorbidities revealed interesting patterns: higher efficacy was observed in females (92.3%) and in patients without comorbidities, suggesting that patient-specific factors may influence outcomes. However, these findings warrant further investigation in larger, controlled cohorts. Nonetheless, several limitations must be acknowledged. The quasi-experimental design lacks a comparative control group, which restricts direct comparison with other treatment regimens. The sample was drawn using non-probability sampling from a single tertiary care hospital, limiting generalizability to broader populations. Moreover, while blood cultures were repeated at day 7, longer-term outcomes such as relapse, chronic carriage, or resistance development were not assessed. Additionally, the lack of pharmacokinetic data—such as serum azithromycin levels—limits insights into suboptimal responses observed in a minority of patients.

Future studies should incorporate multicenter randomized designs comparing azithromycin with newer or combination therapies, such as ceftriaxone-azithromycin regimens, which have shown up to 96% cure rates in recent clinical trials (22,23). Pharmacodynamic profiling, particularly in populations with variable nutritional status or immune function, could also enhance understanding of differential treatment responses. Finally, surveillance of emerging resistance mutations in endemic regions is vital to preserve azithromycin as a treatment option. In conclusion, azithromycin remains an effective, accessible, and safe therapeutic option for managing uncomplicated typhoid fever, particularly in regions with rising resistance to traditional first-line agents. However, its use must be guided by local susceptibility patterns and informed by ongoing research into resistance trends and optimal dosing strategies.

CONCLUSION

This study demonstrated that oral azithromycin is an effective and well-tolerated treatment for culture-positive *Salmonella Typhi* infections, achieving a high clinical and microbiological cure rate in patients with uncomplicated enteric fever. Its practical use is particularly valuable in resource-limited settings with rising antibiotic resistance. These findings support azithromycin as a viable first-line therapeutic option, while highlighting the importance of local resistance surveillance to guide empirical treatment strategies.

AUTHOR CONTRIBUTION

Author	Contribution
Saif Ullah	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Abdul Basit*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published

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Mian Imad Ahmed	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Zahid Mohammad Wazir	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Sohrab Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Zahid Ullah	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Abuzar Ali	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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