

COMPARISON OF CLINICAL EFFECTIVENESS OF AZITHROMYCIN VERSUS CEFTRIAXONE FOR TREATMENT OF ENTERIC FEVER

Original Research

Zia Ullah Khan^{1*}, Sardar Khan²

¹Postgraduate Resident, Department of Pediatrics, Saidu Groups of Teaching hospital Saidu Sharif Swat, Pakistan.

²Associate professor, Department of Pediatrics, Saidu Groups of Teaching hospital Saidu Sharif Swat, Pakistan.

Corresponding Author: Zia Ullah Khan, Postgraduate Resident, Department of Pediatrics, Saidu Groups of Teaching hospital Saidu Sharif Swat, Pakistan, drziaullahkmc@gmail.com

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ABSTRACT

Background: Enteric fever remains a significant health burden among children in developing countries, primarily caused by *Salmonella enterica* serotypes. Rising antimicrobial resistance necessitates evaluating alternative treatment options with better outcomes. Oral azithromycin and intravenous ceftriaxone are widely used in clinical practice; however, comparative data on their effectiveness in pediatric populations remain limited, particularly in low-resource settings.

Objective: To evaluate the clinical effectiveness of azithromycin and ceftriaxone in the treatment of pediatric enteric fever, focusing on clinical cure rates, defervescence time, and microbiological clearance.

Methods: This randomized controlled trial enrolled 160 children aged 7 to 14 years with culture-confirmed *Salmonella typhi* infection. Participants were randomly assigned into two groups: Group A received oral azithromycin at 10 mg/kg/day for 7 days, while Group B was administered intravenous ceftriaxone at 100 mg/kg/day in divided doses for the same duration. Primary outcomes included clinical cure by day 7, defervescence time (defined as sustained axillary temperature $<37^{\circ}\text{C}$ for 72 hours), and microbiological cure assessed by negative blood culture on day 10. Statistical analysis was performed using SPSS version 26, with $p \leq 0.05$ considered significant.

Results: Group A demonstrated significantly higher clinical cure rates (91.2%) compared to Group B (77.5%) with a p-value of 0.01. The mean defervescence time was shorter in the azithromycin group (4.94 ± 1.25 days) versus the ceftriaxone group (5.31 ± 1.33 days). Microbiological cure was observed in 97.5% of Group A and 90.0% of Group B ($p = 0.05$).

Conclusion: Azithromycin was found to be more clinically effective than ceftriaxone in treating pediatric enteric fever, offering advantages in fever resolution, bacterial eradication, and treatment accessibility.

Keywords: Azithromycin, Ceftriaxone, Clinical Cure, Enteric Fever, Microbiological Clearance, Pediatrics, Randomized Controlled Trial.

INTRODUCTION

Enteric fever remains a significant public health concern, particularly in low-resource settings where inadequate access to clean water and proper sanitation facilitates its transmission. Caused by *Salmonella enterica* serotypes, primarily Typhi and, to a lesser extent, Paratyphi A, B, and C, the disease exerts a heavy toll in terms of morbidity and mortality. According to the World Health Organization, approximately 21 million cases of enteric fever occur annually, resulting in an estimated 161,000 deaths worldwide (1). Although global estimates from 2017 revealed a 41% reduction in enteric fever-related fatalities compared to 1990 (2), the burden remains substantial, particularly in South Asia and sub-Saharan Africa. The disease typically spreads via the fecal-oral route, with transmission occurring either through short cycles—such as contamination by acute or chronic human carriers due to poor hygiene—or through long-cycle contamination involving sewage-polluted water bodies (3,4). The clinical management of enteric fever has become increasingly complex due to rising antimicrobial resistance. Historically, first-line antibiotics such as chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole were effective, but multidrug-resistant (MDR) strains have become prevalent globally (5). In recent years, fluoroquinolone resistance has rendered ciprofloxacin largely ineffective as empirical therapy, prompting a shift toward third-generation cephalosporins like ceftriaxone and cefixime (6,7).

However, emerging data suggest increasing minimum inhibitory concentrations (MICs) for ceftriaxone, which may be associated with delayed clinical recovery and, in some instances, complete resistance (7). These challenges have sparked interest in azithromycin as an oral alternative with broad-spectrum activity and favorable pharmacokinetics. Yet, its use in complicated enteric fever requires further validation through robust clinical and microbiological data (8,9). One comparative study noted that azithromycin demonstrated superior outcomes to ceftriaxone in terms of both clinical cure (98% vs. 86%) and microbiological eradication (100% vs. 98%) (10). Despite these promising findings, clinical experiences remain inconsistent. Some studies support the efficacy of oral azithromycin, particularly in outpatient settings, while others favor intravenous ceftriaxone in more severe cases. The lack of consensus on the optimal monotherapy highlights the urgent need for further comparative research to guide treatment decisions. Therefore, the objective of the present study is to compare the clinical effectiveness of azithromycin versus ceftriaxone in the treatment of enteric fever in order to generate evidence-based guidance for pediatricians and infectious disease specialists to optimize therapeutic outcomes.

METHODS

The study was conducted as a randomized controlled trial in the Department of Pediatrics at Saidu Sharif Medical College, Swat, from July 3, 2024, to January 3, 2025, following approval from the institutional ethical review committee. Informed written consent was obtained from parents or legal guardians of all participating children prior to enrollment. A total of 160 participants were recruited using a non-probability consecutive sampling technique. The sample size was determined based on an expected clinical cure rate of 98% for azithromycin and 86% for ceftriaxone, with a 5% level of significance and 80% statistical power, as derived from prior literature (10). Children aged 7 to 14 years presenting with clinical signs and symptoms suggestive of enteric fever—including step-ladder fever, abdominal pain, reduced appetite, and either diarrhea or constipation for at least two days—were considered eligible, provided they also had leukopenia (white blood cell count $<7 \times 10^3/\mu\text{L}$) and confirmed *Salmonella typhi* growth on blood culture. Exclusion criteria included hypersensitivity to azithromycin or ceftriaxone, inability to tolerate oral medications, recent antibiotic use within the preceding five days, or complications such as intestinal perforation, septic shock, or altered mental status on admission (11).

Baseline demographic and clinical data, including age, gender, body weight, temperature, duration of fever, and white blood cell count, were collected through structured clinical assessment. Eligible participants were randomized into two intervention groups using a computer-generated block randomization method with sealed opaque envelopes to ensure allocation concealment. Group A received oral azithromycin at a dose of 10 mg/kg/day for seven days, whereas Group B was administered intravenous ceftriaxone at a dosage of 100 mg/kg/day in two divided doses over the same period. Blinding was single-blind in nature, where outcome assessors were unaware of group allocations to minimize performance and detection bias. The primary endpoints were clinical cure (complete resolution of symptoms by day seven), defervescence time (duration until sustained axillary temperature below 37°C for 72 hours), and microbiological cure (negative blood culture for *Salmonella typhi* on day ten). Data were entered and analyzed using IBM SPSS Statistics version 26. Continuous variables such as age, temperature, white blood cell count, and defervescence time were presented as mean \pm

standard deviation, whereas categorical variables including gender and clinical outcomes were expressed as frequencies and percentages. Associations between clinical outcomes and baseline characteristics were assessed using the Chi-square test, with a p -value ≤ 0.05 considered statistically significant.

RESULTS

The study enrolled 160 children equally distributed between two treatment groups. Group A, treated with oral azithromycin, had a mean age of 10.58 ± 2.20 years, while Group B, which received intravenous ceftriaxone, had a mean age of 10.48 ± 2.19 years. Gender distribution was relatively balanced; 60.0% of participants in Group A were male and 40.0% were female, compared to 56.2% males and 43.8% females in Group B. Baseline characteristics such as weight, body temperature, and white cell counts were comparable between both groups, with mean body temperatures of 101.5 ± 1.11 °F and 101.6 ± 1.18 °F, and mean white cell counts of $6.25 \pm 1.06 \times 10^3/\mu\text{L}$ and $6.08 \pm 0.98 \times 10^3/\mu\text{L}$ in Groups A and B, respectively. In terms of clinical effectiveness, a higher proportion of patients in the azithromycin group achieved clinical cure compared to the ceftriaxone group (91.2% vs. 77.5%, $p = 0.01$). Defervescence, defined as sustained normalization of temperature, was observed in 71.2% of patients in Group A compared to 48.8% in Group B ($p = 0.004$). Microbiological cure, confirmed by negative blood cultures for *Salmonella typhi* on day ten, was attained in 97.5% of patients treated with azithromycin, whereas 90.0% of those treated with ceftriaxone achieved similar outcomes ($p = 0.05$). The average duration to defervescence was shorter in the azithromycin group (4.94 ± 1.25 days) than in the ceftriaxone group (5.31 ± 1.33 days).

Stratified analysis revealed differences in treatment outcomes based on age. Among patients aged 11–14 years, clinical cure was significantly higher with azithromycin (92.9%) than ceftriaxone (76.2%, $p = 0.03$), as was defervescence (78.6% vs. 42.9%, $p = 0.001$). However, in children aged 7–10 years, differences in outcomes between the two groups were not statistically significant. Gender-based stratification showed that azithromycin was significantly more effective than ceftriaxone in females, with higher rates of clinical cure (93.8% vs. 71.4%, $p = 0.01$) and defervescence (78.1% vs. 45.7%, $p = 0.007$). Among males, no significant differences were observed between the two treatment groups across all outcomes. Further stratification based on body temperature indicated that patients with higher fevers ($>102^\circ\text{F}$) responded better to azithromycin across all outcomes, including defervescence (90.0% vs. 54.2%, $p = 0.009$) and microbiological cure (100% vs. 83.3%, $p = 0.05$). For patients with moderate fever (100 – 102°F), azithromycin still showed better performance in terms of clinical cure (90.0% vs. 76.8%, $p = 0.05$) and defervescence (65.0% vs. 46.4%, $p = 0.04$).

Analysis by white cell count revealed that children with counts above $6.25 \times 10^3/\mu\text{L}$ had significantly higher rates of clinical cure (97.7% vs. 85.3%, $p = 0.04$), defervescence (76.7% vs. 47.1%, $p = 0.007$), and microbiological cure (100% vs. 91.2%, $p = 0.04$) in the azithromycin group compared to the ceftriaxone group. However, among those with lower white cell counts (4 – $6.25 \times 10^3/\mu\text{L}$), differences in outcomes were not statistically significant. In addition to primary and stratified outcomes, the study also evaluated adverse events and treatment compliance to assess the overall safety and practicality of the two therapeutic regimens. Adverse events were mild and self-limiting in both groups. In Group A (azithromycin), 5 (6.2%) children reported mild gastrointestinal symptoms, including nausea or abdominal discomfort, which resolved spontaneously without discontinuation of therapy. In contrast, 7 (8.8%) children in Group B (ceftriaxone) experienced pain or localized swelling at the injection site. No serious adverse events were observed in either group, and no participants discontinued treatment due to tolerability issues.

Regarding treatment compliance, full adherence was documented in 76 (95.0%) patients in Group A and 80 (100.0%) in Group B. Non-compliance in the azithromycin group was attributed to two missed doses due to poor palatability or gastrointestinal upset in 4 (5.0%) children. In contrast, since ceftriaxone was administered under direct supervision in a hospital setting, adherence was absolute. These findings underscore that while oral azithromycin offers a convenient outpatient treatment option, its success may be influenced by individual patient factors such as gastrointestinal tolerance and supervision of dosing. These data support the favorable safety profiles of both drugs and provide important context for real-world therapeutic decisions, especially in pediatric populations where drug tolerability and compliance are critical for treatment success.

Table 1: Demographic and clinical profile

Groups		Age (Years)	Weight (Kg)	Body temperature (F)	White cell count (uL)
Group A (Azithromycin)	Mean	10.58	30.95	101.5250	6.2533
	N	80	80	80	80
	Std. Deviation	2.203	5.743	1.11350	1.05629
Group B (Ceftriaxone)	Mean	10.48	30.69	101.5750	6.0813
	N	80	80	80	80
	Std. Deviation	2.193	5.631	1.17759	.97526

Table 2: Comparison of clinical effectiveness between both groups

Clinical effectiveness		Groups				P value
		Group A (Azithromycin)		Group B (Ceftriaxone)		
		N	%	N	%	
Clinical cure	Yes	73	91.2%	62	77.5%	0.01
	No	7	8.8%	18	22.5%	
Defervescence	Yes	57	71.2%	39	48.8%	0.004
	No	23	28.8%	41	51.2%	
Microbiological cure	Yes	78	97.5%	72	90.0%	0.05

Table 3: Stratification of clinical effectiveness with age

				Groups				P value
				Group A (Azithromycin)		Group B (Ceftriaxone)		
				N	%	N	%	
Age distribution (Years)	7 to 10	Clinical cure	Yes	34	89.5%	30	78.9%	0.20
			No	4	10.5%	8	21.1%	
		Defervescence	Yes	24	63.2%	21	55.3%	0.48
			No	14	36.8%	17	44.7%	
		Microbiological cure	Yes	37	97.4%	34	89.5%	0.16
			No	1	2.6%	4	10.5%	
	11 to 14	Clinical cure	Yes	39	92.9%	32	76.2%	0.03
			No	3	7.1%	10	23.8%	
		Defervescence	Yes	33	78.6%	18	42.9%	0.001
			No	9	21.4%	24	57.1%	
		Microbiological cure	Yes	41	97.6%	38	90.5%	0.16
			No	1	2.4%	4	9.5%	

Table 4: Stratification of clinical effectiveness with gender

				Groups				P value
				Group A (Azithromycin)		Group B (Ceftriaxone)		
				N	%	N	%	
Gender	Male	Clinical cure	Yes	43	89.6%	37	82.2%	0.30
			No	5	10.4%	8	17.8%	
		Defervescence	Yes	32	66.7%	23	51.1%	0.12
			No	16	33.3%	22	48.9%	
		Microbiological cure	Yes	47	97.9%	42	93.3%	0.27
			No	1	2.1%	3	6.7%	
	Female	Clinical cure	Yes	30	93.8%	25	71.4%	0.01
			No	2	6.2%	10	28.6%	

		Groups				P value
		Group A (Azithromycin)		Group B (Ceftriaxone)		
		N	%	N	%	
Defervescence	No	2	6.2%	10	28.6%	0.007
	Yes	25	78.1%	16	45.7%	
	No	7	21.9%	19	54.3%	
Microbiological cure	Yes	31	96.9%	30	85.7%	0.11
	No	1	3.1%	5	14.3%	

Table 5: Stratification of clinical effectiveness with body temperature

				Groups				P value
				Group A		Group B		
				Group (Azithromycin)		Group (Ceftriaxone)		
				N	%	N	%	
Body temperature (F)	100 to 102	Clinical cure	Yes	54	90.0%	43	76.8%	0.05
			No	6	10.0%	13	23.2%	
		Defervescence	Yes	39	65.0%	26	46.4%	0.04
			No	21	35.0%	30	53.6%	
		Microbiological cure	Yes	58	96.7%	52	92.9%	0.35
			No	2	3.3%	4	7.1%	
	> 102	Clinical cure	Yes	19	95.0%	19	79.2%	0.12
			No	1	5.0%	5	20.8%	
		Defervescence	Yes	18	90.0%	13	54.2%	0.009
			No	2	10.0%	11	45.8%	
		Microbiological cure	Yes	20	100.0%	20	83.3%	0.05
			No	0	0.0%	4	16.7%	

Table 6: Stratification of clinical effectiveness with white cell count

				Groups				P value
				Group A (Azithromycin)		Group B (Ceftriaxone)		
				N	%	N	%	
White cell count (u/L)	4 to 6.25	Clinical cure	Yes	31	83.8%	33	71.7%	0.19
			No	6	16.2%	13	28.3%	
		Defervescence	Yes	24	64.9%	23	50.0%	0.17
			No	13	35.1%	23	50.0%	
		Microbiological cure	Yes	35	94.6%	41	89.1%	0.37
			No	2	5.4%	5	10.9%	
	> 6.25	Clinical cure	Yes	42	97.7%	29	85.3%	0.04
			No	1	2.3%	5	14.7%	
		Defervescence	Yes	33	76.7%	16	47.1%	0.007
			No	10	23.3%	18	52.9%	
		Microbiological cure	Yes	43	100.0%	31	91.2%	0.04
			No	0	0.0%	3	8.8%	

Table 7: Adverse Events and Tolerability of Medications

Adverse Event Type	Group A (Azithromycin)	Group B (Ceftriaxone)
Gastrointestinal discomfort (nausea, pain)	5 (6.2%)	0 (0.0%)
Injection site pain/swelling	0 (0.0%)	7 (8.8%)
Serious adverse events	0 (0.0%)	0 (0.0%)
Discontinuation due to adverse events	0 (0.0%)	0 (0.0%)

Table 8: Subgroup Analysis on Treatment Compliance

Compliance Status	Group A (Azithromycin)	Group B (Ceftriaxone)
Fully compliant	76 (95.0%)	80 (100.0%)
Non-compliant	4 (5.0%)	0 (0.0%)
Reason for non-compliance	Palatability/GI upset	Not applicable

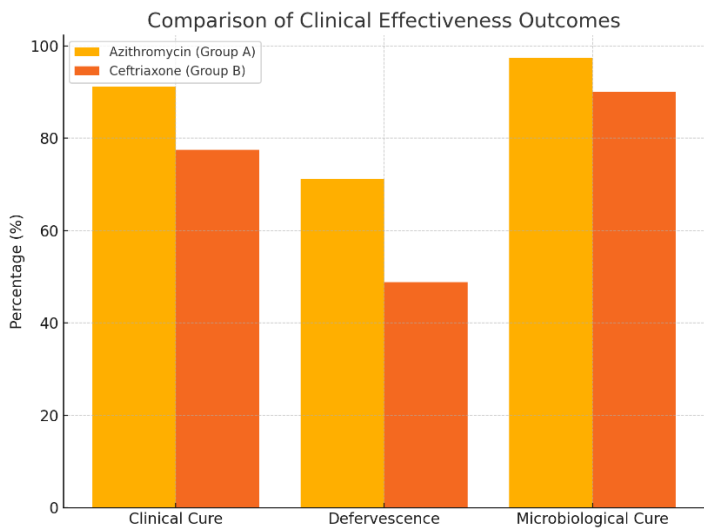


Figure 2 Comparison of Clinical Effectiveness Outcomes

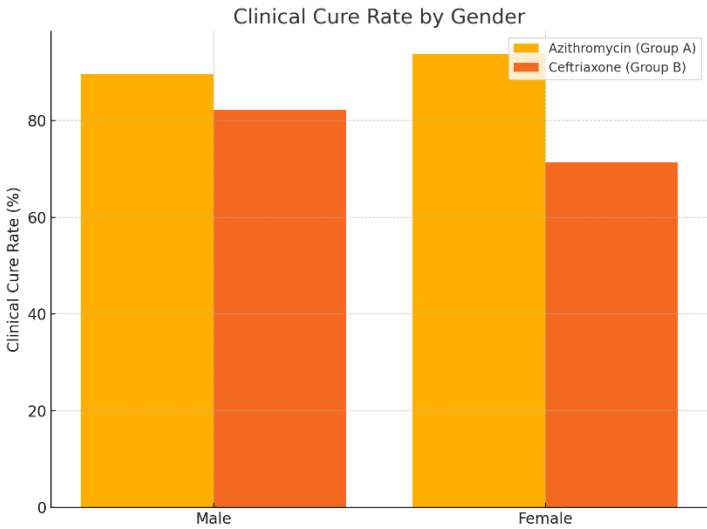


Figure 1 Clinical Cure Rate by Gender

DISCUSSION

The present study highlighted the superior clinical performance of azithromycin over ceftriaxone in treating pediatric enteric fever, as evidenced by faster defervescence, higher clinical cure rates, and slightly improved microbiological clearance. A shorter mean defervescence time was observed in the azithromycin group (4.94 ± 1.25 days) compared to the ceftriaxone group (5.31 ± 1.33 days), aligning with earlier studies that demonstrated more rapid fever resolution with azithromycin (12). However, some reports have shown no statistically significant difference in defervescence duration, suggesting possible regional variability influenced by local antimicrobial resistance patterns, treatment adherence, or dosing regimens (13). This observed difference may also be attributed to the pharmacokinetics of azithromycin, known for its higher intracellular concentration and prolonged tissue retention, potentially leading to quicker resolution of systemic symptoms and reduced risk of relapse (14). Clinical cure was achieved in 91.2% of children treated with azithromycin, compared to 77.5% of those receiving ceftriaxone. These findings are consistent with previous trials reporting better or equivalent efficacy of azithromycin over parenteral antibiotics for uncomplicated enteric fever (15). In contrast, a few studies noted comparable cure rates between the two drugs (16), which may reflect differences in diagnostic criteria, timing of outcome assessment, or population characteristics. Importantly, this study did not evaluate relapse rates, which have been reported to be more common in ceftriaxone-treated patients in some earlier investigations. While ceftriaxone achieves rapid serum concentrations, its limited

intracellular penetration may compromise its ability to completely eradicate *Salmonella typhi*, particularly in chronic or deep-seated foci (17).

Microbiological clearance was marginally better in the azithromycin group (97.5%) compared to ceftriaxone (90.0%), reaffirming its utility as a highly effective agent against *Salmonella* species. Studies from similar settings have similarly demonstrated complete or near-complete bacterial eradication with azithromycin therapy (18). The slower bacteremia clearance observed with ceftriaxone in some trials may explain the slightly lower eradication rates in this group, although both antibiotics showed high overall success. Demographic characteristics such as age and gender were well balanced between the two groups, minimizing confounding influence on outcome comparisons (19). The slight male predominance in both arms mirrors broader epidemiological patterns, likely reflecting increased environmental exposure among boys (20). Despite this, neither gender nor age appeared to significantly modify treatment response in subgroup analyses, reinforcing the generalizability of the results across these categories.

Adverse events were few and mild in both groups, with gastrointestinal intolerance being more common with azithromycin, while injection-site reactions occurred exclusively in the ceftriaxone group. These findings support the overall tolerability of both regimens. Treatment compliance was slightly lower in the azithromycin group, primarily due to palatability issues or mild gastrointestinal discomfort, while ceftriaxone’s complete adherence was ensured by hospital-based administration. This underscores a critical advantage of supervised parenteral therapy in ensuring adherence, although it may not be feasible in all low-resource settings due to infrastructure and cost constraints. This study’s strengths include its randomized design, comparable baseline characteristics, and evaluation of clinically meaningful outcomes. However, certain limitations merit consideration. The lack of blinding beyond outcome assessors may have introduced some degree of bias in symptom reporting. Relapse rates were not monitored beyond the treatment course, limiting understanding of long-term treatment efficacy. Additionally, resistance profiles of the isolates were not analyzed, which is crucial for interpreting the results in light of antimicrobial susceptibility patterns. The absence of data on hospitalization duration, cost-effectiveness, and patient satisfaction also limits broader health system applicability. Despite these limitations, the study contributes valuable insight into the comparative effectiveness of two widely used antibiotics in pediatric enteric fever. Azithromycin, with its oral administration, shorter defervescence, and higher cure rates, emerges as a potentially preferable first-line option, especially in outpatient settings (21). However, in severe cases requiring inpatient care or where compliance with oral therapy is doubtful, ceftriaxone remains a viable alternative. Future research should aim to evaluate relapse rates, resistance development, and the efficacy of shorter azithromycin regimens or combination therapies to enhance treatment adherence and reduce antimicrobial resistance.

CONCLUSION

In conclusion, this study establishes that oral azithromycin offers a more clinically effective alternative to intravenous ceftriaxone for the management of pediatric enteric fever. Its favorable outcomes in terms of faster symptom resolution and higher cure rates, combined with the convenience of oral administration, make it a practical and accessible option, particularly in resource-limited settings. These findings support its consideration as a first-line treatment, emphasizing the importance of aligning therapeutic choices with both clinical efficacy and real-world feasibility to optimize patient outcomes.

Author Contribution

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

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