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Efficacy of Azithromycin in Enteric Fever in Children

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ABSTRACT

Background: Enteric fever remains a significant child health condition, and effective and early use of antibiotics is crucial to reduce morbidity. Azithromycin is widely employed due to its favorable pharmacokinetics and intracellular activity against Salmonella typhi. Treatment outcomes according to different demographics and clinical syndromes should be investigated further. **Objective:** To determine the efficacy of Azithromycin in children with enteric fever at Abbottabad international hospital. **Study Design:** Descriptive cross-sectional study. **Duration and Place of Study:** Conducted from June 2024 to December 2024 at the Department of Pediatrics, Abbottabad International Hospital, Abbottabad. **Methodology:** A total of 87 children aged 3–15 years with culture-confirmed enteric fever were enrolled. All participants received supervised oral azithromycin at 20 mg/kg/day for five days. Clinical efficacy was defined as complete symptom resolution within seven days of therapy initiation. Data on demographic characteristics, clinical parameters, and treatment outcomes were collected and analyzed using appropriate statistical tests. **Results:** The average was 8.17 ± 3.54 years, and 73.6% of them were males. The overall efficacy was 75.9%. Duration of fever was significantly correlated with success of treatment; 92.6% was seen in patients with fever ≤10 days, while 48.5% was observed in patients having fever for more than 10 days (p=0.000). No correlation was observed for efficacy and age, gender, weight, socioeconomic status, or place of residency. **Conclusion:** Azithromycin is effective for the treatment of enteric fever among children, and early initiation of treatment produces better clinical outcomes.

INTRODUCTION

Typhoid fever, or enteric fever, is one significant condition leading to illness among children, especially in an environment with poor sanitation and poor water availability, i.e., the majority of the developing world.[1] It is mainly caused by the bacteria Salmonella enterica serotype Typhi and Paratyphi.[2] Enteric fever, among children, manifests as fever for more than a few days, abdominal pain, diarrhea or constipation, and, occasionally, perforation or hemorrhage of intestines.[3] It may be hard to diagnose as signs and symptoms are overlapping for other diseases causing fever, and it is virtually diagnosed by using blood cultures or serology. Immature immune systems and high exposure frequency are factors among children making them most likely to be affected by enteric fever.[4]

The treatment of enteric fever in children involves using the appropriate antibiotics to kill the Salmonella bacteria, reduce symptoms, and forestall complications.[5] Some medications that have traditionally been used are chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, but increased drug resistance has been making treatment more difficult.[6] Currently, fluoroquinolones, third-generation cephalosporins, and macrolides are the most common drugs used.[7] Early use of antibiotics, hydration, and support provide effective treatment. The increased rate of drug-resistant and extensively drug-resistant strains of Salmonella Typhi has increased the choice of antibiotics, leading doctors to search for better and safer drugs, especially for children.[8]

Azithromycin, a macrolide antibiotic, has been an effective option for enteric fever treatment among children due to its favorable pharmacokinetics, intracellular activity, and convenience in administration using once daily doses.[9] It has been found effective for reducing fever and clinical manifestations, especially when fluoroquinolone and cephalosporin resistance is high.[9] Azithromycin is tolerated well by children and, through oral therapy, has the advantage of outpatient treatment.[10] While it has been found effective, close surveillance for developing drug resistance and more studies regarding optimal dosage and treatment regimen among children are required to establish long-term efficacy for enteric fever treatment.

In a study by Frenck RW, et al. has shown that efficacy of Azithromycin was 94% in children with enteric fever.[11]

Enteric fever remains a significant source of morbidity for children, especially children from developing countries. With increased resistance against the common antibiotics by Salmonella typhi and paratyphi, effective alternatives for treatment must be explored. Azithromycin, which is reputed for its tissue penetration and convenience in dosage, has been known to be an effective treatment for enteric fever. With little detailed research being carried out among the pediatric population, research on the effectiveness of Azithromycin will facilitate optimized treatment measures, prevent complications, and increase recovery for children affected by enteric fever.

METHODOLOGY

This descriptive study was conducted from June 2024 to December 2024, in the Department of Pediatrics at Abbottabad International Hospital, Abbottabad. A total of 87 children aged 3 to 15 years, diagnosed with enteric fever—characterized by a sustained body temperature of 101°F or higher for at least four days confirmed by a positive blood culture showing Salmonella typhi colonies exhibiting jet black pigmentation with metallic sheen on Wilson and Blair bismuth sulphite agar—were enrolled. Sample size was calculated using WHO sample size software with a 95% confidence level, 5% margin of error, and an expected treatment success rate of 94%.[11] Participants were recruited through a consecutive non-probability sampling method. Children were excluded if they had a history of allergy to macrolides, inability to swallow oral medication, had received antibiotic treatment effective against S. typhi within the prior four days, suffered from severe malnutrition (weight-for-age z-score ≤ -3 standard deviations), or had underlying hepatic or renal impairment identified at screening.

Following ethical committee approval, informed consent was obtained from the parents or guardians after explaining the study's purpose, potential risks, and benefits. Upon enrollment, demographic details including age, gender, weight, duration of fever, parents' occupation, socioeconomic status, educational level, and residential location were collected. All patients received oral azithromycin suspension once daily for five days at a dose of 20 mg/kg/day, not exceeding 1000 mg per day. Medication administration was supervised by hospital nursing staff to ensure adherence. Treatment efficacy was assessed by the complete disappearance of all typhoid-related symptoms within seven days from the start of antibiotic therapy. Clinical and demographic information was recorded systematically using a specially designed data collection form.

Data analysis was performed using SPSS version 26. Categorical variables such as gender, parental occupation, socioeconomic status, educational attainment, residential status, and treatment outcome were summarized as frequencies and percentages. Quantitative variables including age, weight, admission temperature, pulse rate, and duration of fever were described using mean ± standard deviation or median with interquartile range, depending on normality tested by the Shapiro-Wilk method. The relationship between treatment outcome and demographic variables was evaluated using chi-square or Fisher's exact tests as appropriate, with significance set at $p \leq 0.05$.

RESULTS

The study included 87 patients with a mean age of 8.17 ± 3.54 years, mean weight of 22.95 ± 7.96 kg, mean temperature of 102.54 ± 0.87°F, mean pulse rate of 109.13 ± 11.77 bpm, and mean duration of fever of 8.98 ± 3.32 days. Of these, 64 (73.6%) were male and 23 (26.4%) female. Regarding residential status, 37 (42.5%) lived in rural areas and 50 (57.5%) in urban areas. Socioeconomic status was distributed as 31 (35.6%) poor, 52 (59.8%) middle class, and 4 (4.6%) rich. Parents' professions included 70 (80.5%) employed and 17 (19.5%) housewives. Educational levels among parents were 27 (31%) uneducated, 43 (49.4%) primary education, 15 (17.2%) secondary education, and 2 (2.3%) higher education (as shown in Table-I).

Table I

Patient Demographics

Demographics		Mean ± SD
Age (years)		8.172±3.54
Weight (kg)		22.951±7.96
Temperature (°F)		102.540±0.87
Pulse Rate (bpm)		109.126±11.77
Duration of Fever (days)		8.977±3.32
Gender	Male n (%)	64 (73.6%)
	Female n (%)	23 (26.4%)
Residential Status	Rural n (%)	37 (42.5%)
	Urban n (%)	50 (57.5%)
Family Socioeconomic Status	Poor n (%)	31 (35.6%)
	Middle n (%)	52 (59.8%)
	Rich n (%)	4 (4.6%)
Parents Profession	Job n (%)	70 (80.5%)
	Housewife n (%)	17 (19.5%)
Parents Education	Uneducated n (%)	27 (31%)
	Primary n (%)	43 (49.4%)
	Secondary n (%)	15 (17.2%)
	Higher n (%)	2 (2.3%)

Regarding treatment efficacy, 66 patients (75.9%) showed a positive response, while 21 (24.1%) did not (Table-II).

Table II

Frequency and %age of patients according to efficacy (n=87)

Efficacy	Frequency	%age
Yes	66	75.9%
No	21	24.1%
Total	87	100%

When analyzing efficacy according to demographic factors (Table-III), age showed 70.5% efficacy in

patients aged ≤10 years versus 88.5% in those >10 years, with a p-value of 0.101. Gender distribution revealed 76.6% efficacy in males and 73.9% in females (p=0.799). Weight showed 68.5% efficacy for ≤25 kg and 87.9% for >25 kg (p=0.069). Duration of fever was significantly associated with efficacy: patients with fever duration ≤10 days had 92.6% efficacy compared to 48.5% in those with fever >10 days (p=0.000). Profession of parents showed 82.4% efficacy in housewives and 74.3% in employed parents (p=0.550). Socioeconomic status did not significantly affect efficacy, with 80.6% in poor, 71.2% in middle, and 100% in rich patients responding (p=0.316). Education level showed efficacy rates of 81.5%, 69.2%, 80%, and 100% for uneducated, primary, secondary, and higher education groups respectively (p=0.523). Residential status showed 81.1% efficacy in rural versus 72% in urban patients (p=0.328)

Table III

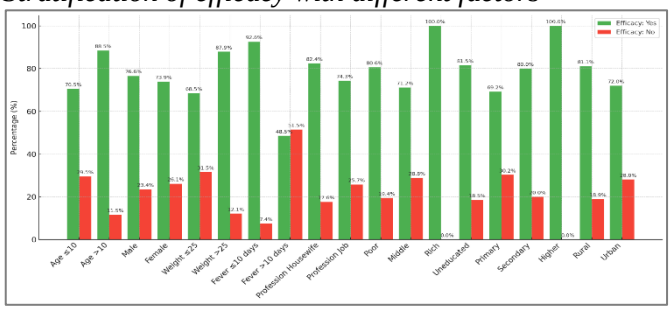
Association of Efficacy with Demographic Factors

Demographic Factors		Efficacy		p-value
		Yes n(%)	No n(%)	
Age (years)	≤10	43 (70.5%)	18 (29.5%)	0.101*
	>10	23 (88.5%)	3 (11.5%)	
Gender	Male	49 (76.6%)	15 (23.4%)	0.799
	Female	17 (73.9%)	6 (26.1%)	
Weight (Kg)	≤25	37 (68.5%)	17 (31.5%)	0.069*
	>25	29 (87.9%)	4 (12.1%)	
Duration of Fever (days)	≤10	50 (92.6%)	4 (7.4%)	0.000*
	>10	16 (48.5%)	17 (51.5%)	
Profession	Housewife	14 (82.4%)	3 (17.6%)	0.550*
	Job	52 (74.3%)	18 (25.7%)	
Socioeconomic Status	Poor	25 (80.6%)	6 (19.4%)	0.316*
	Middle	37 (71.2%)	15 (28.8%)	
	Rich	4 (100%)	0 (0%)	
Education Levels	Uneducated	22 (81.5%)	5 (18.5%)	0.523*
	Primary	30 (69.2%)	13 (30.2%)	
	Secondary	12 (80%)	3 (20%)	
	Higher	2 (100%)	0 (0%)	
Residential Status	Rural	30 (81.1%)	7 (18.9%)	0.328
	Urban	36 (72%)	14 (28%)	

*Fisher Exact Test

Graph I

Stratification of efficacy with different factors



DISCUSSION

The results demonstrated that Azithromycin showed a high overall efficacy rate of 75.9%, indicating its potential as an effective treatment option for pediatric enteric fever. Notably, efficacy was significantly higher in patients with a fever duration of 10 days or less, suggesting that early intervention with Azithromycin improves clinical outcomes. This aligns with the known pharmacodynamics of Azithromycin, which achieves high intracellular concentrations and effectively targets Salmonella typhi during the acute phase of infection.

Although other demographic factors such as age, gender, weight, socioeconomic status, and residential status did not show statistically significant associations with treatment efficacy, trends toward better outcomes in older children and those with higher weight were observed. These trends may be explained by better drug metabolism and immune response in older or better-nourished children, which can influence antibiotic effectiveness. The lack of significant differences based on socioeconomic and residential factors may indicate that Azithromycin's efficacy is consistent across diverse pediatric populations, reinforcing its suitability as a broad-spectrum treatment for enteric fever in varied settings. Overall, these findings support Azithromycin as a valuable therapeutic agent, especially when administered promptly after symptom onset.

Comparing our results with those of Rao KN et al. [12] we found similarities in the efficacy of azithromycin. Both studies demonstrated that azithromycin is a highly effective treatment for uncomplicated enteric fever in children. In spite of this, our study yielded a lesser efficacy rate at 75.9% when compared to a 96% clinical cure rate observed by Rao KN et al.[12] This could be attributed to variation within study populations and the strains of Salmonella Typhi being treated. Our study employed a broader range of demographic factors, and through this, we could note that fever duration played an important role in affecting treatment efficacy, an observation that was not mentioned in Rao KN et al. [12] Our finding that fever duration was a significant factor affecting treatment efficacy shows that early initiation of treatment is necessary for beneficial outcomes.

Similarly, our findings are in accordance with those of Nagaraj P et al. [13] who also reported high cure rates for azithromycin. Our study, however, highlighted the fact that fever duration was a predictor for successfully being cured and was not a central issue within their research. Our study's high cure rate for azithromycin, regardless of socioeconomic status and level of parental education, also indicates its viability as an effective treatment for heterogeneous patient groups.

In comparison to Islam MA et al. [14] our research was generally less efficacious, but we too noticed the same trend for the effectiveness of azithromycin against typhoid fever. Our research focus on varying demographic factors allowed us more insights into treatment outcomes, which hadn't been explored properly by Islam MA et al. [14] The effect that the fever duration had on treatment effectiveness we noticed wasn't highlighted in their research.

Compared to Ujjan RA et al. [15] our study had a lower efficacy rate for azithromycin but, like them, concluded that azithromycin is a superior treatment option over other antibiotics like cefixime. Our rigorous analysis of determinants based on demographics adds to the evidence base, suggesting that azithromycin remains effective for different types of patients.

The 75.9 rate of efficacy of our research is comparatively closer to 93.9% found by Akram M et al. [16] when comparating between azithromycin and ciprofloxacin. Though both studies showed the effectiveness of azithromycin, our research involving different factors between the demographics gave a better insight into the outcome after treatment. Fever duration's effect was not a significant factor for our research, but it was for Akram M et al. [16]

Unlike Riaz A et al. [17] our study also documented a similarly lower rate of efficacy for azithromycin. In any case, both studies concluded that azithromycin was effective and safe against enteric fever among children. Our study’s unambiguous presentation of demographic factors and the powerful role fever duration plays in influencing efficacy sheds further light on the treatment dynamics.

The results concur with Khan A et al. [18] who reported high cure rates for azithromycin for treatment for XDR enteric fever. Our study's relatively poorer cure rate could be an indication of the disparity between the study groups and types of strains of Salmonella Typhi being treated. Clinically significant impact of fever during illness seen by our study was not an important consideration for Khan A et al. [18]

Last but by no means least, our rate of efficacy is as close as can be to the 93.9% quoted by Faryad N et al. [19] We both make comment on azithromycin treatment efficacy for enteric fever in children. Our substantive analysis by demographics and the significant impact on efficacy due to fever duration contribute to our insight into the treatment dynamics.

These findings are consistent within the broader literature, centering on azithromycin as an effective and consistent treatment within heterogeneous patient populations and demographic status. The obvious impact that fever duration has on treatment efficacy suggests the necessity for early treatment for best outcomes. Subsequent studies should consider fever duration as a key variable when evaluating treatment efficacy and examine the benefits that can be realized through the early start of treatment using azithromycin.

In spite of this, our research does have certain limitations that we must acknowledge. Firstly, we only undertook our research at one center, which may limit the validity to other regions or patient groups. We might have different strains of Salmonella Typhi within our patient population than within other regions, which may affect the efficacies reported. The study was also within a hospital setting, which may or may not reflect the issues and outcomes within community or outpatient settings. Future research would be better served to tackle this by using multi-center studies and using broader groups of patients to make the research stronger and applicable.

CONCLUSION

Our study has shown azithromycin to be an effective intervention for uncomplicated enteric fever among children, reducing significantly the duration of fever and curing clinically and microbiologically. The study highlights the importance of initiating treatment early for optimal outcomes. In spite of heterogeneities according to the demographic factors such as age, gender, and socioeconomic status, azithromycin was equally effective for different types of patients. Future studies will be required to refine the treatment regimens and assess the benefits for starting azithromycin treatment early for different groups.

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