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The Outcome of Azithromycin and Ciprofloxacin for Treatment of Uncomplicated Typhoid Fever

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Abstract **Original Research Article**

***Background*:** Enteric fever affects more than 11 million children and adults globally each year. Typhoid fever is treated with antibiotics. Ideally, treatment should be safe and available for adults and children in shortened courses of 5 days, cause defervescence within 1 week, render blood and stool cultures sterile, and prevent relapse. ***Objective*:** To compare the outcome of azithromycin and ciprofloxacin for treatment of uncomplicated typhoid fever. ***Method*:** This comparative intervention was done at tertiary hospital where one hundred patients ranging in age from 5 to 25 years were enrolled in the study and randomly assigned to one of the two treatment groups. Group A constituted of 50 patients receiving azithromycin and group B constituted of the other 50 patients receiving ciprofloxacin. All patients underwent blood cultures or stool cultures from which S. typhi or S. paratyphi was isolated, and these subjects comprised the basis for analysis. ***Results*:** During the study, majority of the patients belonged to 5-15 years age group. 50% cases lived in semi pucca buildings followed by 70% drank supply water without boiling and 80% cases were accustomed to homemade food and outside food. Moreover, significance association was noticed in food habit and water source of the patients. In group A, 50 cases showed positivity in salmonella typhi and their mean duration of hospital stay was 10 days. Similarly, in group B, 50 cases showed positivity in salmonella typhi and mean duration of hospital stay was 9.0 days. In group A, 90% were cured by day 7 plus no relapse cases were found. In group B, 80% were cured by day 7. Mild-to- moderate adverse events, all of which were short-term and self-limited were reported equally in both treatment groups. ***Conclusion*:** Our results indicated that azithromycin and ciprofloxacin were similarly effective, both clinically and bacteriologically, against typhoid fever caused by both sensitive organisms and MDR S. typhi.

Keywords: Azithromycin, ciprofloxacin, uncomplicated typhoid fever.

INTRODUCTION

Typhoid fever, an often-deadly illness of adults and children that causes bacteremia and inflammatory destruction of the bowel and other organs, is widespread in most nations, particularly in Asia and Africa [1]. Due to the increasing development of multidrug-resistant (MDR) Salmonella typhi (resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole), alternative therapeutic alternatives are being sought for the treatment of typhoid fever [2, 3]. Fluoroquinolones have proven effective, but to date they are restricted from use in children, and quinolone-resistant strains of S. typhi have been reported [4]. There is also some hope for the treatment of typhoid fever using antibiotics belonging to the azalide class. The first medicine in this family, azithromycin, is a derivative of the basic macrolide nucleus and is more effective against gram-negative bacteria than erythromycin. Azithromycin's minimal inhibitory concentration (MIC) range against Salmonella typhi in vitro is 4–16 g/ml, indicating its limited value in the treatment of typhoid fever [5]. Azithromycin's extraordinary feature of intracellular concentration in macrophages (>100 times the concentrations in serum) allowed it to be very efficient in eradicating the infection in a mouse typhoid model when administered

once daily [6]. Ciprofloxaciin proved highly effective against salmonella infections in mice, suggesting that it might also be of value in humans [7]. In light of this, researchers decided to compare the efficacy of ciprofloxacin and azithromycin in treating people with uncomplicated typhoid fever.

OBJECTIVE

To compare the outcome of azithromycin and ciprofloxacin for treatment of uncomplicated typhoid fever.

METHOD

This comparative intervention was done at tertiary hospital where one hundred patients, both males and females age ranging from 5 to 25 years were enrolled in the study. Study duration was 10 months from October 2021 to July 2022. To be eligible for study entry, subjects were required to have a documented fever (temperature, ≥38.5°C) for at least 4 days in addition to two or more of the following: abdominal tenderness, hepatomegaly (>2 cm below the right costal margin), splenomegaly (>2 cm below the left costal margin), and rose spots. Exclusion criteria included pregnancy or lactation, allergy to ciprofloxacin or erythromycin (or other macrolides), complication of typhoid fever (pneumonia, intestinal hemorrhage or perforation, shock, or coma), inability to swallow oral medication, significant underlying illness, and treatment within the past 4 days with an antibiotic potentially effective against S. typhi. Only patients with blood and/or stool cultures positive for S. typhi or S. paratyphi were evaluable. All the patients were randomly assigned to one of the two treatment groups. A total of 50 patients received azithromycin and were encountered as group A. The other 50 patients received ciprofloxacin and were categorized as group B. All the cases had blood cultures or stool cultures from which S. typhi or S. paratyphi was isolated, and these subjects comprised the basis for analysis. Informed consent was obtained before each subject was randomly assigned to a treatment group. Group A was given 1 g of Azithromycin orally on the 1st day, followed by 500mg orally once daily for the next 6 days. Group B was treated with 500mg of ciprofloxacin twice daily for 7 days.

Responses of patients to treatment were classified by the following definitions. Clinical cure was resolution of symptoms by the end of 7 days of therapy. Microbiological cure was sterile blood cultures at days 4 and 10. Clinical failure was lack of resolution of symptoms by day 7 or development of a major complication of typhoid fever (such as intestinal hemorrhage or perforation or seizures) after 5 days of therapy. Microbiological failure was a blood culture positive for S. typhi or S. paratyphi on day 4 or 10. Relapse was recurrence of fever with signs and symptoms of typhoid fever within 4 weeks of therapy completion along with isolation of the organism in culture. Defervescence was defined as the first day on which the maximum temperature was ≤38.0°C with maintenance of the temperature at this level for at least 48 h.

RESULTS

Table-1 shows age distribution of the patients. Majority of the cases belonged to 5-15 years age group. Thirty percent of the cases belonged to 16-25 years age group.

Table 1: Age distribution of the patients

Age distribution of the patients	Percentage (%)
5-15 years	70%
16-25 years	30%

Figure-1 shows gender status of the patients where 55% were male and 45% were female.

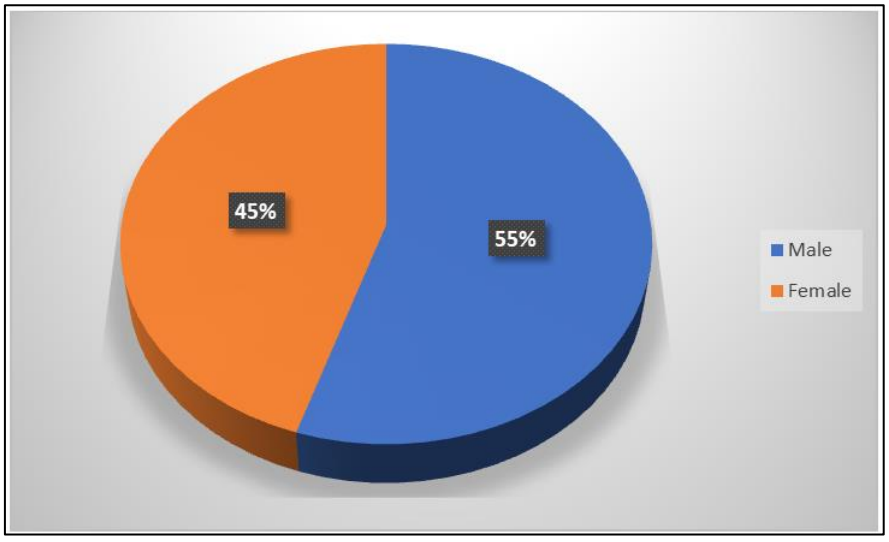

Figure 1: Gender distribution

Table-2 shows demographic status of the patients. Fifty percent patients live in semipucca buildings, 70% drink supply water without boiling and 80% cases were accustomed to both homemade food and outside food. Significant associations were noticed in food habit and water source of the patients.

Table 2: Demographic status of the patients

Demographic status	Percentage (%)	P value
Housing status:		
• Kacca	20%	
• Semi pucca	50%	0.213
• Pucca	30%	
Drinking water source:		
• Tube well	10%	
• Supply water without boiling	70%	0.0001
• Supply water with boiling	20%	
Food habit:		
• Accustomed to solely homemade food	20%	0.002
• Accustomed to homemade food & outside food	80%	

Figure-2 shows Distribution of patients by liver status where 75% had palpable liver status.

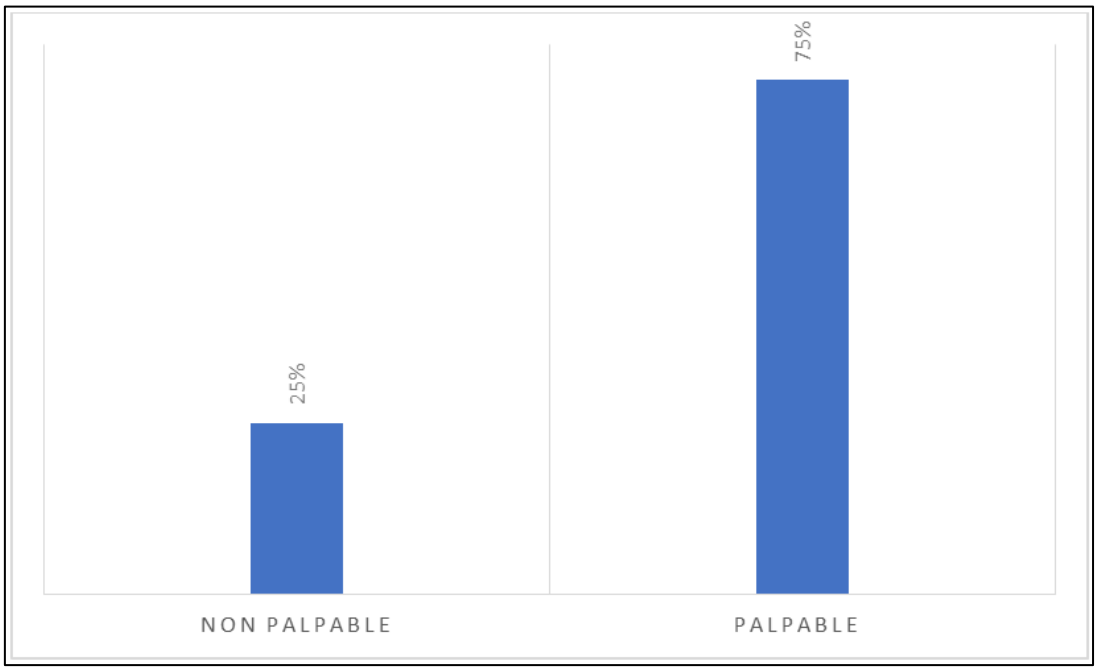

Figure-2: Distribution of patients by liver status

x2= 5.486; df=1; P = 0.014

Table-3 shows clinical characteristics of azithromycin and Ciprofloxacin recipients who had typhoid fever and positive blood cultures. In group A, mean duration of hospital stay were 10 days and 50 cases showed positivity for salmonella typhi. In Ciprofloxacin group mean duration of hospital stay were 9.0 days and 50 cases showed positivity for salmonella typhi.

Table 3: Clinical characteristics of Group A and B recipients who had typhoid fever and positive blood cultures

Clinical characteristics (During admission)	Group A, n=50	Group B, n=50	P value
Mean Duration of fever in days	10	9.0	0.234
Blood culture result			
• Salmonella typhi	50		0.121
• Salmonella paratyphi		50	
Blood culture that yielded MDRS. Typhi	6	7	0.112

Table-4 shows laboratory status of the patients during admission. In Group A, mean hemoglobin level was 10.6±1.4 g/dl followed by mean WBC count was 6.0±2.3 cells/mm3, Total bilirubin level 0.3±0.1 mg/dL. Whereas in group B, mean hemoglobin level was 10.9±1.4 g/dl followed by mean WBC count was 6.5±2.3 cells/mm3, Total bilirubin level 0.4±0.1 mg/dL.

Table 4: Laboratory status of the patients during admission

Laboratory characteristics (During admission)	Group A, n=50	Group B, n=50	P value
Hemoglobin level, g/dL (11–18)	10.6±1.4	10.9±1.2	0.111
WBC count, cells/mm3(4.5–10.53103)	6.0±2.3	6.5±1.6	0.121
Platelet count, cells/mm3(150,000–350,000)	213,000±75,000	215,000±96,000	0.100
Total bilirubin level, mg/dL (0.2–1.0)	0.3±0.1	0.4±0.1	0.321
AST level, U/L (0–33)	89±48	84±70	0.201
Serum creatinine level, mg/dL (0.7–1.5)	0.8±0.1	0.7±0.2	0.506

Table-5 shows mean Laboratory test result on day 10. After 10 days, in group A, mean hemoglobin level was 9.8±1.4g/dl followed by mean WBC count was 6.2±1.6 cells/mm3 and total platelet count 433,000±122,000 cells/mm3. Whereas in group B, mean hemoglobin level was 10.5±1.0 g/dl followed by mean WBC count was 7.4±2.2cells/mm3 and total platelet count 431,000±164,000cells/mm3.

Table 5: Laboratory test result on day 10

Laboratory characteristics, day 10	Azithromycin group, n=50	Ciprofloxacin group, n=50	P value
Hemoglobin level, g/dL (11–18)	9.8±1.4	10.5±1.0	0.111
WBC count, cells/mm3(4.5–10.53103)	6.2±1.6	7.4±2.2	0.120
Platelet count, cells/mm3(150,000–350,000)	433,000±122,000	431,000±164,000	0.101
Total bilirubin level, mg/dL (0.2–1.0)	0.3±0.1	0.4±0.2	0.321
AST level, U/L (0–33)	52±29	60±35	0.0.23
Serum creatinine level, mg/dL (0.7–1.5)	0.6±0.1	0.7±0.2	0.506

Table-6 shows responses to treatment in group A and group B patients. 90% patients of group A were cured by day 7 plus no relapse cases were found. In contrary, 80% patients of group B were cured by day 7 and similarly no relapse cases were found.

Table 6: Responses to treatment in group A and group B patients

Response to treatment	Group A, n=50	Group B, n=50	P value
• Clinical cure by day 7	45 (90%)	40(80%)	0.001
• Duration of fever after starting therapy, mean d±SD	4.0±1.1	3.7±1.1	0.212
• No. of days to defervescence (temp, ≤38°) after start of treatment	3.8 ± 1.1	3.3 ± 1.1	0.021
• Blood culture positive for Salmonella **Day 4** **Day 10**	 1 0	 0 0	0.121
• Stool culture that yielded Salmonella on day 10	0	0	0.0001
• Relapse	0	0	

Table-7 shows adverse effects reported by patients. The adverse effects included nausea, vomiting, lightheadedness, dry mouth, loose stools and constipation. Effects were reported to be mild to moderate, all of which were short-termed and self-limited equally in both treatment groups.

Table 7: Adverse events reported by patients

Adverse effects	Group A, n=50	Group B, n=50
Nausea or vomiting		
Mild	4%	3%
Moderate	1%	-
Lightheadedness		
Mild	2%	2%
Moderate	-	-
Dry throat or mouth		
Mild	2%	4%

Moderate	1%	
Loose stools		
Mild	-	3%
Moderate	3%	-
Constipation		
Mild	2%	1%
Moderate	-	1%

DISCUSSION

In this comparative study, we compared the effectiveness of azithromycin and ciprofloxacin in treating typhoid fever and found that both antibiotics were equally successful, curing all patients clinically within 10 days and eliminating Salmonella from their blood cultures bacteriologically. Due to the similarity in outcomes between the two treatment groups and the lack of problems in either group, there were few differences seen. There was no statistically significant difference between the two groups when it came to the mean time to defervescence (3.3 days for patients treated with ciprofloxacin and 3.9 days for individuals treated with azithromycin; $P > 0.05$). All patients had negative stool cultures during and after treatment, and there were no signs of recurrence. Nausea, vomiting, dizziness, dry mouth, and diarrhea were noted infrequently across both study groups. These adverse effects were either mild or moderate in severity, but they did not warrant a pause in treatment. Some patients' AST levels increased following medication, with a greater increase in the ciprofloxacin group compared to the azithromycin group; however, the difference between the mean values was not statistically significant ($P > 0.05$), and the findings may have been attributable to typhoid fever. These results confirm the earlier finding that azithromycin is effective against infections caused by S. typhi and S. paratyphi A, and they show that it performs well in comparison to other antimicrobial agents recently tested for typhoid fever, such as ceftriaxone, cefixime, and fluoroquinolones [8, 9].

Our data demonstrate that azithromycin is effective in vitro against MDR and ampicillin/chloramphenicol/sulfamethoxazole-susceptible S. typhi strains. Antimicrobial-resistant infections were found in 6 of our azithromycin-treated individuals. Two Egyptian patients' strains of S. typhi and seven Indian patients' strains of S. typhi were found to be multidrug-resistant (MDR) but also sensitive to azithromycin and the patients were healed after receiving azithromycin [10, 11].

Administration, pharmacokinetics, and therapeutic principles of the two medicines were considerably different. Both ciprofloxacin and azithromycin were administered once daily for 7 days, with ciprofloxacin given twice daily at 1,000 mg/day and azithromycin at 500 mg/day. Both medications have substantial therapeutic effectiveness against S. typhi, a primarily intracellular pathogen, and their efficacy may be attributed to their ability to enter and travel throughout the host cell. Although the minimum inhibitory concentration (MIC) for S. typhi is 0.1 mg/liter, the serum concentrations recorded during therapy range from 0.04 to 0.4 mg/liter [12]. Therapeutic effectiveness against typhoid fever seems to depend on azithromycin's capacity to reach intracellular concentrations in monocytes and polymorphonuclear leukocytes 231 and 83 times larger than the quantities in serum [13, 14].

Further clinical research with adults and children are needed to clarify the role of azithromycin in the treatment of typhoid fever. The 7-day course of once-daily oral therapy is practical and should improve adherence among outpatients. Typhoid patients who were unable to participate in the trial due to vomiting or difficulty swallowing oral preparations were excluded. Although azithromycin in parenteral form is now accessible, it has not been utilized to treat typhoid. While this study's sample size indicated no significant difference in clinical reactions between the two groups, more patients would be needed to rule out the potential of a nuanced variation in responses to therapy. Ciprofloxacin and ofloxacin, two fluoroquinolones, have shown promise in adult clinical trials in MDR settings [8, 9]. However, due to the propensity for these medications to harm cartilage in developing bones in animals, their use in children is normally not allowed. Typhoid affects children at a higher rate than it does adults [15]. Ceftriaxone, cefixime, aztreonam, and furazolidone have all been used effectively to treat MDR typhoid fever in both children and adults [16–20]. Azithromycin's availability as a pediatric suspension allows researchers to evaluate the drug's effectiveness and safety in treating multidrug-resistant typhoid in infants and toddlers.

CONCLUSION

Our results indicated that azithromycin and ciprofloxacin were similarly effective, both clinically and bacteriologically, against typhoid fever caused by both sensitive organisms and MDR S. typhi.

REFERENCES

1. Azad, A. K., Islam, R., Salam, M. A., Alam, A. N., Islam, M., & Butler, T. (1997). Comparison of clinical features and pathologic findings in fatal cases of typhoid fever during the initial and later

stages of the disease. *The American journal of tropical medicine and hygiene*, *56*(5), 490-493.
2. Mirza, S. H., Beechmg, N. J., & Hart, C. A. (1996). Multi-drug resistant typhoid: a global problem. *Journal of medical microbiology*, *44*(5), 317-319.
3. Rowe, B., Ward, L. R., & Threlfall, E. J. (1997). Multidrug-resistant Salmonella typhi: a worldwide epidemic. *Clinical infectious diseases*, *24*(Supplement_1), S106-S109.
4. Girgis, N. I., Butler, T., Frenck, R. W., Sultan, Y., Brown, F. M., Tribble, D., & Khakhria, R. (1999). Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrobial agents and chemotherapy*, *43*(6), 1441-1444. doi:10.1128/AAC.43.6.1441
5. Metchock, B. (1990). In vitro activity of azithromycin compared with other macrolides and oral antibiotics against Salmonella typhi. *J Antimicrob Chemother*, 24(Suppl. A), 29–31.
6. Butler, T., & Girard, A. E. (1993). Comparative efficacies of azithromycin and ciprofloxacin against experimental Salmonella typhimurium infection in mice. *J Antimicrob Chemother*, 31, 313–319.
7. Easmon, C. S. (1987). Protective effects of ciprotloxacin in a murine model of salmonella infection. *Am. J. Med.*, 82, 71.
8. Smith, M. D., Duong, N. M., Hoa, N. T., Wain, J., Ha, H. D., Diep, T. S., ... & White, N. J. (1994). Comparison of ofloxacin and ceftriaxone for short-course treatment of enteric fever. *Antimicrobial agents and chemotherapy*, *38*(8), 1716-1720.
9. Wallace, M. R., Yousif, A. A., Mahroos, G. A., Mapes, T., Threlfall, E. J., Rowe, B., & Hyams, K. C. (1993). Ciprofloxacin versus ceftriaxone in the treatment of multiresistant typhoid fever. *European Journal of Clinical Microbiology and Infectious Diseases*, *12*, 907-910.
10. Butler, T., Sridhar, C., Daga, M., Jani, K., Pandit, R., Khakhria, R., Potkar, C., & Johnson, R. (1997). Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C: American Society for Microbiology; 1997. Azithromycin vs. chloramphenicol in the treatment of typhoid fever in India, abstr. LM-18; p. 367.
11. Tribble, D., Girgis, N., Habib, N., & Butler, T. (1995). Efficacy of azithromycin for typhoid fever. *Clin Infect Dis.*, 21, 1045–1046. [Google Scholar]
12. Retsema, J., Girard, A., Schelky, W., Manousos, M., Anderson, M., & Bright, G. (1987). Spectrum and mode of action of azithromycin (CP-62, 993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. *Antimicrob Agents Chemother*, 31, 1939–1947.
13. Pascual, A., Conejo, M. C., Garcia, I., & Perea, E. J. (1995). Factors affecting the intracellular accumulation and activity of azithromycin. *J Antimicrob Chemother*, 1 35, 85–93.
14. Wildfeuer, A., Laufen, H., & Zimmerman, T. (1996). Uptake of azithromycin by various cells and its intracellular activity under in vivo conditions. Antimicrob Agents *Chemother*, 40, 75–79.
15. Butler, T., Islam, A., Kabir, I., & Jones, P. K. (1991). Patterns of morbidity and mortality in typhoid fever dependent on age and gender: review of 552 hopitalized patients with diarrhea. *Reviews of infectious diseases*, *13*(1), 85-90.
16. Acharya, G., Butler, T., Ho, M., Sharma, P. R., Tiwari, M., Adhikari, R. K., ... & Pathak, U. N. (1995). Treatment of typhoid fever: randomized trial of a three-day course of ceftriaxone versus a fourteen-day course of chloramphenicol. *The American journal of tropical medicine and hygiene*, *52*(2), 162-165.
17. Bhutta, Z. A., Khan, I. A., & Molla, A. M. (1994). Therapy of multidrug-resistant typhoid fever with oral cefixime vs. intravenous ceftriaxone. *The Pediatric infectious disease journal*, *13*(11), 990-993.
18. Dutta, P., Rasaily, R., Saha, M. R., Mitra, U., Manna, B., Chakraborty, S., & Mukherjee, A. (1993). Randomized clinical trial of furazolidone for typhoid fever in children. *Scandinavian journal of gastroenterology*, *28*(2), 168-172.
19. Girgis, N. I., Kilpatrick, M. E., Farid, Z., Sultan, Y., & Podgore, J. K. (1993). Cefixime in the treatment of enteric fever in children. *Drugs Exp Clin Res.*, 19, 47–49.
20. Girgis, N. I., Sultan, Y., Hammad, O., & Farid, Z. (1995). Comparison of the efficacy, safety and cost of cefixime, ceftriaxone and aztreonam in the treatment of multidrug-resistant Salmonella typhi septicemia in children. *The Pediatric infectious disease journal*, *14*(7), 603-605.