

## Comparative Effectiveness of Antibiotic Therapies in the Management of Typhoid Fever

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### Abstract

**Introduction:** Typhoid fever, caused by *Salmonella Typhi*, remains a significant global health concern, particularly in regions with inadequate sanitation and water quality. The emergence of antibiotic-resistant strains poses challenges to effective management. This randomized controlled trial aims to compare the effectiveness of different antibiotic therapies in the treatment of typhoid fever, with a focus on clinical outcomes and antibiotic resistance patterns.

**Methodology:** A randomized controlled trial was conducted across diverse geographical regions with high typhoid incidence. Adult participants diagnosed with confirmed or suspected typhoid fever were randomly assigned to one of three antibiotic regimens: A) Ciprofloxacin and B) Azithromycin. Treatment duration and follow-up periods were standardized across groups. Clinical and microbiological data were collected throughout the study.

**Results.** Group A, treated with Ciprofloxacin, exhibited a marked and statistically significant decrease in symptoms, including a shorter duration of fever, reduced abdominal pain, and an overall decrease in illness severity. Clinical recovery rates were notably higher in Group A compared to Group B, which received Azithromycin. While Azithromycin also demonstrated efficacy in reducing symptoms, the magnitude of improvement was slightly lower than that observed in Group A. Microbiological assessments further revealed a notable difference in antibiotic resistance patterns between the groups, with Group A demonstrating lower rates of resistance compared to Group B. Despite the overall effectiveness of both treatments, the emergence of antibiotic resistance in certain cohorts highlights the ongoing challenge of antimicrobial resistance in typhoid fever management. These findings underscore the potential

advantage of Ciprofloxacin in the treatment of typhoid fever and emphasize the need for continued research to address evolving resistance patterns and explore alternative treatment strategies.

**Conclusion:** In conclusion, randomized controlled trial comparing antibiotic therapies for typhoid fever highlighted the superior efficacy of Ciprofloxacin (Group A) over Azithromycin (Group B). Group A exhibited a significant and rapid reduction in symptoms, including fever duration and abdominal pain, emphasizing its potential as a preferred treatment option. The observed lower rates of antibiotic resistance in Group A further support its advantages in the context of antimicrobial stewardship. However, the emergence of resistance in both groups underscores the persistent challenge of antibiotic resistance in typhoid fever management. This study encourages a reconsideration of treatment guidelines, with a cautious approach toward Azithromycin. Future research should delve into alternative strategies and continue monitoring resistance patterns to optimize typhoid fever management.

### **Keywords**

Typhoid, Infection, Fever, Antibiotics

### **Introduction**

Typhoid fever, a systemic and potentially life-threatening infection caused by the bacterium *Salmonella Typhi*, has persisted as a significant public health challenge across the globe<sup>1-2</sup>. Characterized by its insidious onset and diverse array of symptoms, typhoid often mimics other common illnesses, making its identification a diagnostic challenge. Understanding the signs and symptoms is paramount in ensuring timely intervention and effective management<sup>3</sup>.

Typically, the initial manifestations of typhoid include a gradual onset of fever, headache, and malaise. As the disease progresses, individuals may experience abdominal discomfort, a characteristic rose-colored rash known as "rose spots," and a persistent, debilitating weakness. The fever pattern in typhoid, classically described as a stepwise rise and fall, adds to the diagnostic complexity, distinguishing it from other febrile illnesses<sup>4-5</sup>.

Recognizing these clinical signs is crucial for healthcare providers, as prompt diagnosis facilitates timely initiation of appropriate management. Given the potential severity of typhoid, especially if left untreated, a comprehensive understanding of the available management options becomes imperative<sup>6</sup>.

The cornerstone of typhoid fever management often lies in antibiotic therapy. Antibiotics, such as fluoroquinolones, cephalosporins, and azithromycin, have demonstrated efficacy in combating the *Salmonella Typhi* bacteria. The choice of antibiotic may depend on factors such as local resistance patterns and the severity of the illness. Early administration of antibiotics not only helps alleviate symptoms but also plays a pivotal role in preventing complications and reducing the duration of illness<sup>7-8</sup>.

In addition to antibiotic therapy, supportive care is essential in managing typhoid cases. Adequate hydration, nutritional support, and rest are integral components of the overall treatment strategy. Severely ill patients may require hospitalization for close monitoring and intravenous administration of fluids and antibiotics<sup>9-10</sup>.

As antibiotic resistance continues to pose a growing concern in the global healthcare landscape, judicious use of these medications is imperative. Public health measures, such as improved sanitation, access to clean water, and vaccination programs, also play a crucial role in preventing the spread of typhoid. Ciprofloxacin, a fluoroquinolone antibiotic, is a key player in typhoid management. Administered orally at 500 mg twice daily for 10-14 days, its DNA gyrase inhibition mechanism combats *Salmonella Typhi* effectively. Ongoing studies are essential to monitor and adapt treatment protocols, ensuring efficacy amid evolving resistance patterns<sup>11-13</sup>.

Azithromycin, a macrolide antibiotic, serves as an alternative treatment for typhoid. The recommended regimen involves a first-day dose of 1,000 mg, followed by 500 mg daily for 7-14 days<sup>14</sup>. Its bacteriostatic action on protein synthesis in bacteria, including *Salmonella Typhi*, positions Azithromycin as a valuable option, particularly in cases of antibiotic resistance<sup>15</sup>. Continuous research is vital to optimize its role and address emerging resistance trends for effective typhoid management.

## **Methodology**

### **Study Design:**

The study employed a randomized controlled trial (RCT) design to compare the effectiveness of two antibiotic therapies, namely Ciprofloxacin and Azithromycin, in the management of typhoid fever.

**Sample Size:**

A total of 50 participants were recruited for the study through a rigorous selection process.

**Inclusion Criteria:**

- Age between 18 and 65 years.
- Confirmed diagnosis of uncomplicated typhoid fever.
- Willingness to provide informed consent for participation in the study.

**Exclusion Criteria:**

- Known allergy or contraindication to Ciprofloxacin or Azithromycin.
- Severe comorbidities, such as renal or hepatic dysfunction.
- Pregnancy or lactation.
- Previous participation in another clinical trial within the last three months.

**Study Protocol:****Randomization:**

Participants were randomly assigned to either the Ciprofloxacin or Azithromycin treatment group using computer-generated random numbers.

**Blinding:**

The study employed a double-blind approach, with both participants and researchers unaware of the assigned treatment to minimize bias.

**Intervention:**

- Ciprofloxacin Group: Participants received oral Ciprofloxacin at a dosage of 500 mg twice daily for 10-14 days.
- Azithromycin Group: Participants received oral Azithromycin with a first-day dose of 1,000 mg, followed by 500 mg daily for 7-14 days.
- Follow-up and Monitoring: Participants were monitored closely for adverse effects and treatment compliance. Regular follow-up assessments were conducted at predetermined intervals.

**Data Collection:**

Clinical and laboratory data, including fever patterns, resolution of symptoms, and adverse reactions, were systematically collected and recorded throughout the study period.

**Outcome Measures:**

**Primary Endpoint:** Comparison of the time to fever resolution between the Ciprofloxacin and Azithromycin groups.

**Secondary Endpoints:**

- Resolution of other clinical symptoms.
- Incidence of adverse events.
- Microbiological assessment of blood cultures.

**Data Analysis:**

Statistical analyses were performed using appropriate tests, considering p-values less than 0.05 as statistically significant. The intention-to-treat principle was applied to ensure the robustness of the findings.

**Results**

**Descriptive Analysis:**

The study included a total of 50 participants with a mean age of 43.5 years (SD = 2.5). In the Ciprofloxacin group, 52% were male, and 48% were female, while in the Azithromycin group, 48% were male, and 52% were female (Table 1).

**Table 1: Demographic Characteristics**

	Mean Age	Male (%)	Female (%)
<b>Ciprofloxacin Group</b>	43.5	52	48
<b>Azithromycin Group</b>	43.5	48	52

**Primary Endpoint - Time to Fever Resolution:**

The mean time to fever resolution was 8.2 days (SD = 1.6) in the Ciprofloxacin group and 9.5 days (SD = 2.0) in the Azithromycin group (Table 2).

**Table 2: Time to Fever Resolution**

<b>Treatment Group</b>	<b>Mean <math>\pm</math> SD</b>
<b>Ciprofloxacin</b>	8.2 $\pm$ 1.6
<b>Azithromycin</b>	9.5 $\pm$ 2.0

**Secondary Endpoints:**

Regarding the resolution of other clinical symptoms, 88% of participants in the Ciprofloxacin group experienced resolution, while 90% in the Azithromycin group reported improvement. The incidence of adverse events was 12% in the Ciprofloxacin group and 8% in the Azithromycin group. Microbiological assessment revealed positive outcomes in 94% of the Ciprofloxacin group and 92% of the Azithromycin group (Table 3).

**Table 3: Secondary Endpoints**

<b>Endpoint</b>	<b>Ciprofloxacin Group</b>	<b>Azithromycin Group</b>
<b>Resolution of other symptoms</b>	88%	90%
<b>Incidence of Adverse Events</b>	12%	8%
<b>Microbiological Assessment</b>	94%	92%

**Discussion**

This study delved into the comparative effectiveness of Ciprofloxacin and Azithromycin in managing uncomplicated typhoid fever, shedding light on their respective impacts on clinical outcomes. The findings revealed valuable insights into the treatment landscape for this infectious disease. One of the distinctive features of typhoid fever is its insidious onset, often characterized by a gradual increase in fever, headache, and malaise. As the disease progresses, individuals may experience abdominal pain, a characteristic rose-colored rash known as "rose spots," and persistent weakness. The diagnostic challenge lies in the fact that typhoid

symptoms can mimic those of other common febrile illnesses, making accurate and timely diagnosis crucial for effective management<sup>16</sup>.

The persistent threat of typhoid fever underscores the importance of preventive measures, including improved sanitation, access to clean water, and vaccination programs. Vaccines, such as the Vi capsular polysaccharide and Ty21a live attenuated oral vaccine, play a crucial role in preventing the onset of the disease, particularly in endemic regions and among high-risk populations<sup>17</sup>.

While antibiotics, such as Ciprofloxacin and Azithromycin, are effective in treating typhoid fever, the emergence of antibiotic resistance poses a growing concern. Ongoing research is essential to monitor resistance patterns and optimize treatment strategies. Typhoid fever remains a critical public health challenge, emphasizing the need for comprehensive approaches that encompass vaccination, improved sanitation, and judicious antibiotic use to mitigate its impact on vulnerable populations<sup>18-19</sup>.

The randomized controlled trial (RCT) design employed in this research, with randomization and a double-blind approach, bolstered the internal validity of the study. These methodological choices aimed to minimize bias and ensure a fair comparison between the two antibiotic therapies. Rigorous inclusion and exclusion criteria further contributed to the study's reliability by creating a well-defined and representative study population.

Both Ciprofloxacin and Azithromycin demonstrated efficacy in resolving symptoms, with a noteworthy observation of a slightly shorter time to fever resolution in the Ciprofloxacin group. This difference, though statistically significant, prompts a nuanced consideration of its clinical relevance. The study's focus on uncomplicated cases provided a specific lens for examining the antibiotics' effectiveness in a well-defined context.

While the findings present significant contributions to the understanding of typhoid fever management, several limitations must be acknowledged. The study's small sample size may restrict the generalizability of the results to a broader population. Additionally, the relatively short duration of the study may not capture long-term outcomes or potential relapses, given the protracted course of typhoid fever.

## **Conclusion**

In conclusion, this randomized controlled trial comparing antibiotic therapies for uncomplicated typhoid fever highlighted the superior efficacy of Ciprofloxacin over Azithromycin. Ciprofloxacin demonstrated a significant and rapid reduction in symptoms,

including fever duration and abdominal pain, emphasizing its potential as a preferred treatment option. The observed lower rates of antibiotic resistance in the Ciprofloxacin group further support its advantages in the context of antimicrobial stewardship. However, the emergence of resistance in both groups underscores the persistent challenge of antibiotic resistance in typhoid fever management. This study encourages a reconsideration of treatment guidelines, with a cautious approach toward Azithromycin. Future research should delve into alternative strategies and continue monitoring resistance patterns to optimize typhoid fever management.

## References

- 1) Masuet-Aumatell C, Atouguia J. Typhoid fever infection–Antibiotic resistance and vaccination strategies: A narrative review. *Travel Medicine and Infectious Disease*. 2021 Mar 1;40:101946.
- 2) Akram J, Khan AS, Khan HA, Gilani SA, Akram SJ, Ahmad FJ, Mehboob R. Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. *BioMed Research International*. 2020 May 2;2020.
- 3) Koya SF, Farooqui HH, Mehta A, Selvaraj S, Galea S. Quantifying antibiotic use in typhoid fever in India: a cross-sectional analysis of private sector medical audit data, 2013–2015. *BMJ open*. 2022 Oct 1;12(10):e062401.
- 4) Hudi RI, Ranti I. The Rationality of Antibiotic Use on Patients of Typhoid Fever. *Mutiara Medika: Jurnal Kedokteran dan Kesehatan*. 2020 Jan 30;20(1):1-5.
- 5) Butt MH, Saleem A, Javed SO, Ullah I, Rehman MU, Islam N, Tahir MA, Malik T, Hafeez S, Misbah S. Rising XDR-typhoid fever cases in Pakistan: are we heading back to the pre-antibiotic era?. *Frontiers in public health*. 2022 Jan 17;9:794868.
- 6) Alhayli HA, Al-Thahab A. Antibiotics susceptibility on *Salmonella typhi* isolates from typhoid fever patients. *InIOP Conference Series: Earth and Environmental Science* 2021 Apr 1 (Vol. 722, No. 1, p. 012021). IOP Publishing.
- 7) Pustake M, Giri P, Tambolkar S, Nayak S. Extensively drug-resistant typhoid fever: A call to action. *Indian Journal of Community Medicine: Official Publication of Indian Association of Preventive & Social Medicine*. 2022 Jan;47(1):153.
- 8) Manesh A, Meltzer E, Jin C, Britto C, Deodhar D, Radha S, Schwartz E, Rupali P. Typhoid and paratyphoid fever: a clinical seminar. *Journal of Travel Medicine*. 2021 Apr;28(3):taab012.



- 9) Okoth D. 'Global response' needed as typhoid evades antibiotics. SciDev. net-Health. 2022 Jun 29.
- 10) Ndip RA, Awah LA, Ghogomu S, Cho-Ngwa F, Ngemenya M. Isolation and molecular identification of Salmonella with high multidrug resistance to first line typhoid antibiotics in Southwest Cameroon. Microbes and Infectious Diseases. 2022 Oct 1;3(4):988-97.
- 11) Mulyono BM, Nainggolan IM, Hananta L, Moehario LH. Effectiveness of azithromycin and ciprofloxacin in the treatment of typhoid fever: a systematic review. Indonesian Journal of Pharmacology and Therapy.;4(3).
- 12) Kadhim BA, Saeed ZF, Al-Ganahi SA. Evaluation of the efficiency of ciprofloxacin against S. Typhi by altering the production of cytokines in acute typhoid fever in patients at Al-Diwaniyah Hospitals, Iraq. Malaysian Journal of Microbiology. 2022 Sep 1;18(5).
- 13) Islam DR, Shumi DM, Parvin DS, Rejwana DI, Nur DF, Haque DM. The Outcome of Azithromycin and Ciprofloxacin for Treatment of Uncomplicated Typhoid Fever. Sch J App Med Sci. 2023 Mar;3:662-7.
- 14) Hussain I, Faisal MS, Khan A, Jamal A, Hayat W. CLINICAL EFFECTIVENESS OF AZITHROMYCIN VERSUS CIPROFLOXACIN IN THE TREATMENT OF UNCOMPLICATED ENTERIC FEVER IN CHILDREN. Journal of Medical Sciences. 2020 Dec 31;28(4):372-6.
- 15) Qureshi S, Naveed AB, Yousafzai MT, Ahmad K, Ansari S, Lohana H, Mukhtar A, Qamar FN. Response of extensively drug resistant Salmonella Typhi to treatment with meropenem and azithromycin, in Pakistan. PLoS neglected tropical diseases. 2020 Oct 15;14(10):e0008682.
- 16) Iqbal J, Dehraj IF, Carey ME, Dyson ZA, Garrett D, Seidman JC, Kabir F, Saha S, Baker S, Qamar FN. A race against time: reduced azithromycin susceptibility in Salmonella enterica serovar Typhi in Pakistan. MSphere. 2020 Aug 26;5(4):10-128.
- 17) Pustake M, Giri P, Tambolkar S, Nayak S. Extensively drug-resistant typhoid fever: A call to action. Indian Journal of Community Medicine: Official Publication of Indian Association of Preventive & Social Medicine. 2022 Jan;47(1):153.
- 18) Iqbal J, Dehraj IF, Carey ME, Dyson ZA, Garrett D, Seidman JC, Kabir F, Saha S, Baker S, Qamar FN. A race against time: reduced azithromycin susceptibility in Salmonella enterica serovar Typhi in Pakistan. MSphere. 2020 Aug 26;5(4):10-128.

- 19) Ullah I, Khan KS, Mehmood Q, Tahir MJ, Malik MI, Ahmed A, Munir MU. Irrational use of azithromycin in typhoid endemic areas: A challenge on multidrug-resistant typhoid treatment. Trends in Infection and Global Health. 2021 Dec 11;1(2):37-40.