


**Original Article**

# A Retrospective Real-World Evidence Study Evaluating the Clinical Effectiveness and Safety of Cefixime in Managing Typhoid Fever in Indian Population

Dr. Pratyush Kumar<sup>1</sup>, Dr. Amitrajit Pal<sup>\*,2</sup>, Dr. Dattatray Pawar<sup>2</sup>, Dr. Akhilesh Sharma<sup>2</sup>

## Abstract

**Background:** Typhoid fever, caused by *Salmonella enterica* serovar Typhi, remains a significant public health issue in endemic areas like India. Rising multidrug and fluoroquinolone resistance limit treatment options, highlighting the need for effective oral alternatives. Cefixime, a third-generation cephalosporin, is commonly used, but large-scale data on its effectiveness and safety in typhoid treatment are limited.

**Methods:** This multicenter, retrospective, real-world evidence study analyzed anonymized records of 21,515 patients with clinically and/or microbiologically confirmed typhoid fever treated predominantly with cefixime 200 mg. Data were collected at three time points: baseline (start of therapy), intermediate assessment (7 days), and post-treatment follow-up (day 7–14). Clinical and microbiological cure rates, vital signs, laboratory parameters, and adverse events were assessed. Statistical analysis included Chi-square tests and one-way ANOVA with Tukey's post-hoc test.

**Results:** Clinical cure was achieved in 93.5% of patients at EOT and 100% at follow-up ( $p < 0.001$ ). Microbiological cure increased from 90.7% at EOT to 100% at follow-up ( $p < 0.001$ ). Vital signs (pulse, BP, temperature, respiratory rate, SpO<sub>2</sub>) and lab markers (Hb, WBC, CRP, liver enzymes) showed significant improvement across visits ( $p < 0.0001$ ). Adverse events were minimal, occurring in 0.05% of patients at the end of treatment (EOT) and 0.019% during follow-up. The most commonly observed ADRs were mild gastrointestinal disturbances, such as nausea and diarrhea, with no serious or treatment-limiting events reported.

**Conclusion:** Cefixime showed strong effectiveness and safety in a large, diverse patient group, reaffirming its role as a reliable oral treatment for typhoid fever in routine settings.

**Keywords:** Typhoid fever, cefixime, real-world evidence, antimicrobial resistance, microbiological cure

## Introduction

Typhoid fever, a potentially life-threatening systemic infection caused by *Salmonella Typhi*, remains a significant public health concern in many endemic regions. Estimates from 2021 indicate nearly 10 million reported cases globally, with a substantial burden concentrated in high-incidence areas such as India, which has emerged as a major contributor to the global prevalence [1]. Treatment of typhoid fever traditionally involves fluoroquinolones such as ciprofloxacin and ofloxacin, alongside older agents like chloramphenicol,

### Affiliation:

<sup>1</sup>Consulting Physician, Patna Physician and Diabetes Clinic, Ward No. 01, Durga Nagar, Abdullah Chak Gaon, Patna, 800007, Bihar, India.

<sup>2</sup>Medical Affairs Department, Alkem Laboratories Ltd., Alkem House, Senapati Bapat Marg, Lower Parel, Mumbai, 400013, Maharashtra, India

### \*Corresponding author:

Dr. Amitrajit Pal, Medical Affairs Department, Alkem Laboratories Ltd., Alkem House, Senapati Bapat Marg, Lower Parel, Mumbai, 400013, Maharashtra, India.

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amoxicillin, and co-trimoxazole, as recommended by the World Health Organization (WHO). However, the increasing prevalence of multidrug-resistant (MDR) *S. Typhi* strains; resistant to chloramphenicol, ampicillin, and trimethoprim-sulphamethoxazole, has considerably restricted treatment options. Resistance to fluoroquinolones further complicates management, necessitating effective oral alternatives [2].

Third-generation cephalosporins have shown robust antimicrobial activity against *S. Typhi*, offering a promising therapeutic potential [3-5]. Among them, cefixime has gained prominence due to its suitability for oral administration, making it a practical choice for outpatient care [3-5]. Cefixime acts by inhibiting bacterial cell wall synthesis through  $\beta$ -lactam-binding proteins and also triggers bacterial autolysis. Uniquely, it exhibits intracellular activity, penetrating host monocyte-derived THP-1 cells and exerting bactericidal effects at both intra- and extracellular sites. Studies have demonstrated that orally administered cefixime (8 mg/kg) maintains serum concentrations above the MIC for over 12 hours, supporting its sustained action [6]. These pharmacokinetic and pharmacodynamic advantages are supported by real-world clinical outcomes. A study by Chaudhary et al. reported a 92.5% clinical cure rate in patients treated with cefixime, while another study by Mohammad et al. showed a 90% cure rate with minimal relapses and no reported adverse events [3,7]. The Indian Academy of Pediatrics also endorses cefixime as a first-line agent in pediatric typhoid, with doses up to 1,200 mg/day [5].

Despite its widespread clinical use, large-scale real-world evidence evaluating cefixime's clinical and microbiological effectiveness, safety, and tolerability remains scarce, particularly in high-burden, resource-constrained settings. A systematic literature review revealed only a handful of community-based investigations and just seven hospital-based studies conducted over the past decade [8]. In light of the aforementioned literature, this multicenter, retrospective study was designed to address this evidence gap by assessing cefixime's effectiveness and safety in the management of typhoid fever across both inpatient and outpatient populations.

## Methods

### Study design

This was a multicenter, retrospective, and real-world evidence study involving medical records of the patients with typhoid fever managed with cefixime tablets.

### Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and Indian Council of Medical Research (ICMR) principles after receiving ethical approval from the Independent Ethics

Committees (IEC) at each study site. Since the study was a retrospective study, informed consent was not required.

### Population

Adult patients clinically diagnosed with typhoid fever, with laboratory confirmation (e.g., positive blood culture for *Salmonella enterica* subspecies *enterica* serovar Typhi), patients who received cefixime as monotherapy, and had complete medical records documenting the initiation of therapy, an intermediate assessment at 7 days, and a follow-up evaluation between 7 to 14 days post-treatment, were included in this study. Patients with incomplete medical records were excluded from this study.

### Data collection

Data were collected for all patients diagnosed with typhoid fever who presented to the OPD or were admitted to the inpatient department (IPD) and received cefixime therapy at a standard dose of 200 mg twice daily (BD). Study investigators and site personnel identified eligible patients meeting the study selection criteria by reviewing available medical records at each participating site. Patient prescriptions and laboratory investigation reports were screened, and relevant clinical data were extracted and recorded in standardized case record forms (CRFs). Data entry was based solely on the availability of documented information; no additional or retrospective data generation was required. The date on which cefixime therapy was initiated was considered the index date or baseline visit. Data were collected at three time points: the baseline visit (start of cefixime therapy), intermediate assessment, and post-therapy follow-up visit (if available).

Assessment 1 at the beginning of therapy including demographics, infection type, clinical presentation, prior antibiotic use, vitals, lab results, and microbiological data.

Assessment 2 (Intermediate Assessment: Day 7) including treatment duration, symptoms, vitals, clinical outcomes, lab results, microbiological data and adverse events during treatment.

Assessment 3 (if available) during post-therapy follow-up 7-14 days after treatment to capture relapse, clinical outcomes, vitals, lab results, and any secondary infections or adverse events.

As this was a retrospective study based on existing medical records, the post-treatment follow-up period; initially defined as 7-14 days, was extended in some cases depending on the availability and completeness of patient records. Whenever additional follow-up days were available for certain patients, those data were included as appropriate. Given that the mean treatment duration was approximately 15 days, a follow-up window extending up to 30 days from treatment initiation (i.e., about 14 days post-therapy) was considered appropriate

to capture relapse or delayed adverse events. Data entry was done by skilled site investigators using case report forms (CRFs), as each patient was given a unique anonymized ID. Missing or incomplete data submissions were clarified with investigators wherever feasible.

The safety of the study medication was assessed by recording the adverse events (AEs) that occurred during the patient's treatment period. Hematological and biochemical laboratory investigations were carried out at the investigator's discretion during the treatment of the patient. All abnormalities found in the physical examination (including vital signs) and laboratory investigations were treated as AEs. All observed AEs, regardless of the suspected causal relationship to the study drug, were recorded.

### Endpoints

The primary endpoint was to evaluate the clinical and microbiological cure rate in typhoid patients administered with cefixime. The secondary endpoint was to evaluate the adverse effects reported during the treatment period.

### Definitions

**Clinical cure:** The clinical cure will be defined as the completion of the treatment regimen with the resolution of all symptoms and signs of typhoid infection.

**Microbiological Cure:** The microbiological cure will be defined as the absence of the causative pathogen from appropriately obtained specimens at the site of infection.

### Statistical analysis

Statistical analysis results were reported as mean  $\pm$  standard deviation (SD) or standard error (SE) for continuous variables and as frequencies or percentages for categorical variables. A p-value of  $<0.05$  was considered statistically significant. Statistical analyses included Chi-square tests for comparing clinical cure rates (between Assessments 1 and 2) and for trend in microbiological cure rates (across three assessments). One-way ANOVA followed by Tukey's HSD post-hoc test (for  $p < 0.05$ ) was used to compare group means. Safety outcomes (AEs/SAEs) were descriptively summarized due to low event frequency. Analyses were conducted using MS Excel 2019 and SPSS V20.

## Results

A total of 21515 patients were included in this study.

### Demographic characteristics of the patients

The mean age of the patients was 38.2 (14.1). The proportion of female patients 15268 (70.9%) was higher than the male patients 6247 (29.1%). The mean height, weight, and BMI were 158.1 (14.4) cm, 60.5 (14.3) kg, and 24.5 (5.5) kg/m<sup>2</sup>, respectively. This data is summarized in Table 1.

**Table 1:** Demographic characteristics of patients

Parameter	No. of patients (N=21515)
Age (years), mean (SD)	38.2 $\pm$ 14.1
Sex	
Male	6247 (29.1)
Female	15268 (70.9)
Height (cm)	158.1 $\pm$ 14.4
Weight (kg)	60.5 $\pm$ 14.3
BMI (kg/m <sup>2</sup> )	24.5 $\pm$ 5.5
Data given as mean (SD), unless otherwise specified.	

### Symptom profile of the patients

The mean duration of symptoms was 4.2 days. Most patients presented with overlapping symptoms, including pain (99.3%), fever (98.9%), vomiting (97.2%), and cold and cough (97.0%). These findings are summarized in Table 2.

**Table 2:** Symptom profile of the patients

Symptom	No. of patient (N=21515)
Pain	21317 (99.3)
Fever	21283 (98.9)
Vomiting	20921 (97.2)
Cough and Cold	20889 (97.0)

### Vital signs data

A statistically significant and progressive reduction in pulse rate was observed from Assessment 1 to Assessment 3. The mean pulse rate declined from 88.5 (12.3) bpm at baseline to 82.4 (9.8) bpm at Assessment 2,  $p < 0.0001$ , and further to 76.2 (8.5) bpm at Assessment 3 ( $p < 0.0001$ ). Respiratory rate demonstrated a significant downward trend, with a mean of 22.5 (3.2) breaths per minute at baseline, decreasing to 18.6 (2.5) ( $p < 0.0001$ ) and 16.2 (2.0) breaths per minute at subsequent assessments ( $p < 0.0001$ ). Temperature exhibited a consistent decline, with the mean value reducing from 102.1 (1.3) °F at Assessment 1 to 99.1 (0.6) °F at Assessment 2 ( $p < 0.0001$ ), and to 98.4 (0.3) °F at Assessment 3 ( $p < 0.0001$ ). Oxygen saturation (SpO<sub>2</sub>) showed a significant upward shift, increasing from a baseline mean of 93.2% (3.5) to 96.7 (1.6) % at Assessment 2 ( $p < 0.0001$ ), and further to 98.2 (0.9) % at Assessment 3 ( $p < 0.0001$ ). This is shown in Table 3.

### Laboratory parameters

At baseline (Visit 1), patients demonstrated laboratory abnormalities typical of acute typhoid infection, which showed progressive normalization at Visit 2 and Visit 3. WBC counts, initially low at 3,800 (1100.0) cells/ $\mu$ L at Visit 1, rose to 5,200 (900.0) at Visit 2 and further to 6,300 (700.0) cells/ $\mu$ L by Visit 3, reflecting immune recovery. A notable decline

**Table 3:** Vital signs data

Vital Sign	Mean	SD	LS Mean	95% CI	P Value (ANOVA)
Pulse (bpm)					
Assessment 1	88.5	12.3	88.2	87.9 – 88.9	-
Assessment 2	82.4	9.8	82.1	81.6 – 82.7	<0.0001*
Assessment 3	76.2	8.5	76	75.5 – 76.6	<0.0001*
Respiratory Rate (breaths/min)					
Assessment 1	22.5	3.2	22.3	22.1 – 22.6	-
Assessment 2	18.6	2.5	18.4	18.2 – 18.7	<0.0001*
Assessment 3	16.2	2	16.1	15.9 – 16.4	<0.0001*
Temperature (°F)					
Assessment 1	102.1	1.3	102	101.8 – 102.3	-
Assessment 2	99.1	0.6	99	98.9 – 99.2	<0.0001*
Assessment 3	98.4	0.3	98.3	98.2 – 98.5	<0.0001*
SpO <sub>2</sub> (%)					
Assessment 1	93.2	3.5	93	92.7 – 93.4	-
Assessment 2	96.7	1.6	96.6	96.4 – 96.9	<0.0001*
Assessment 3	98.2	0.9	98.1	98.0 – 98.3	<0.0001*

\*- statistically significant as compared to assessment 1 in Tukey HSD Post-hoc Test

in C-reactive protein (CRP) was observed, decreasing from a mean of 72.5 (80.1) mg/L at Visit 1 to 28.2 (25.6) mg/L at Visit 2, and reaching at 6.4 (5.8) mg/L at Visit 3, indicating resolution of systemic inflammation. Liver function markers

including SGPT and SGOT showed a consistent decline: SGPT dropped from 85.6 U/L to 55.4 U/L and then to 36.0 U/L, while SGOT decreased from 78.9 (31.4) U/L to 48.2 (18.5) U/L and then to 30.5 (10.2) U/L. This is shown in Table 4.

### Treatment profile of patients

The mean duration of treatment was 15.2 (5.6) days and the mean hospital stay of 6.2 (2.3) days. The majority of patient (97.6%) were administered with 200 mg of cefixime, followed by 1.8% of patients with 400 mg of cefixime, and 0.6% of 100 mg of cefixime. This is shown in Table 5.

### Effectiveness endpoints

The clinical cure rate was 93.5% at Assessment 2 and 100.0% at Assessment 3 (p < 0.001). Similarly, the microbiological cure rate was 90.7% at Assessment 2 and 100.0% at Assessment 3 (p < 0.001), as shown in Figure 1. Notably, these high cure rates observed by Day 7 were achieved prior to completion of the full prescribed treatment course (mean duration: 15.2 days).

### Safety endpoints

Considering the adverse events, at assessment 2 (intermediate assessment), 11 (0.05%) of patients reported adverse events which further reduced to 4 (0.019%) at assessment 3 (follow-up). The most commonly observed ADRs were mild gastrointestinal disturbances, such as nausea and diarrhea, with no serious or treatment-limiting events reported. This is shown in Figure 1.

**Table 4:** Laboratory parameters

Parameter	Assessment 1 (Start of therapy)	Assessment 2 (EOT)	Assessment 3 (follow-up)	P-value (ANOVA)
WBC (cells/μL)	3,800 (1,100), 2,200–6,000	5,200 (900), 3,800–7,200	6,300 (700), 5,000–7,800	<0.001
CRP (mg/L)	72.5 (80.1), 12–320	28.2 (25.6), 2.5–90.0	6.4 (5.8), 0.5–18.0	<0.001
SGPT (U/L)	85.6 (25.3), 40–170	55.4 (20.1), 30–100	36.0 (12.0), 20–60	<0.001
SGOT (U/L)	78.9 (31.4), 35–160	48.2 (18.5), 22–88	30.5 (10.2), 18–50	<0.001

Mean (SD), min - max, Assessment 2 & 3 were statistically significant as compared to assessment 1 in Tukey HSD Post-hoc Test

**Table 5:** Treatment profile

Dose and strength	N/ mean	Percentage/ SD
Cefixime - 200 mg	20,988	97.6
Cefixime - 400 mg	395	1.8
Cefixime - 100 mg	132	0.6
<b>Duration of treatment, Mean (SD)</b>	<b>15.2</b>	<b>5.6</b>
<b>Duration of hospital stay, Mean (SD)</b>	<b>6.2</b>	<b>2.3</b>

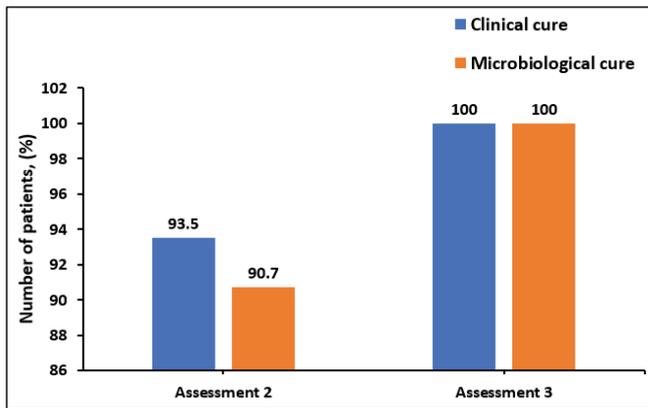


Figure 1: Effectiveness and Safety endpoints

## Discussion

This multicenter, retrospective real-world evidence study represents one of the largest datasets evaluating the clinical and microbiological effectiveness of cefixime in patients with typhoid fever, enrolling over 21,500 individuals from both inpatient and outpatient settings. The study's strength lies in its broad and diverse population base, which enhances the generalizability of the findings across routine clinical practice in India. The longitudinal design with three structured assessment points enabled the comprehensive evaluation of treatment outcomes, including statistically significant improvements in clinical symptoms, vital parameters, and laboratory markers such as hemoglobin, CRP, and liver enzymes. Notably, the clinical cure rate reached 93.5% by the intermediate assessment and 100.0% at follow-up, while the microbiological cure rate improved from 90.7% to 100.0% ( $p < 0.001$ ), supporting the effectiveness of cefixime. The study also demonstrated a favorable safety profile, with adverse events reported in less than 0.05% of cases.

These findings align with earlier evidence from randomized controlled trials that demonstrated cefixime's superiority over other conventional agents such as chloramphenicol. In one such trial involving pediatric patients, cefixime achieved a significantly higher clinical cure rate (90%) compared to chloramphenicol (45%;  $p = 0.0049$ ) [9]. Additional studies conducted in patients with multidrug-resistant *Salmonella Typhi* infections reported 95–96% cure rates with cefixime monotherapy, even in cases presenting with systemic illness [3, 10, 11]. Together with the present data, these findings support the continued relevance of cefixime as an effective oral therapy, particularly in uncomplicated or drug-resistant typhoid fever where parenteral options may be limited. While the growing concern of antimicrobial resistance necessitates vigilant surveillance, this study reaffirms cefixime's role as a safe, accessible, and efficacious treatment option in the contemporary management of typhoid fever. The safety findings from this real-world study are consistent with

previously published evidence on cefixime's tolerability in typhoid fever. Adverse events were infrequent, with only 11 patients (0.05%) reporting events at the intermediate assessment and 4 (0.019%) during follow-up. These low rates align with earlier studies, including pediatric cohorts treated with cefixime monotherapy, where mild gastrointestinal symptoms (e.g., nausea, diarrhea) were observed in fewer than 8% of patients, with no serious or treatment-limiting events reported [10]. A broader safety review involving over 38,000 patients across various indications similarly identified gastrointestinal symptoms as the most common adverse effects, while severe reactions remained rare [12]. Collectively, this evidence supports cefixime as a safe and well-tolerated option for managing typhoid fever.

While the findings are encouraging, several limitations warrant consideration. The retrospective nature of the study introduces potential for missing data, unmeasured confounders, and physician-dependent treatment variability, including the non-standardized duration of cefixime administration. The absence of a comparator arm limits the ability to contextualize these outcomes against other commonly used agents such as azithromycin or fluoroquinolones. A key limitation of this retrospective study is that dosage frequency was not uniformly documented across participating sites; only tablet strength was consistently available. Future prospective studies should ensure that both tablet strength and dosing frequency are systematically recorded to enable more robust evaluation of dose–response relationships and treatment outcomes. To address these gaps, future studies should aim to address these limitations through prospective, randomized controlled designs incorporating standardized treatment protocols and comparator arms. Integration of resistance profiling and cost-effectiveness analysis would further enhance clinical utility. Moreover, expanding follow-up duration and stratifying outcomes by demographic or clinical subgroups may help identify patient populations that derive the greatest benefit from cefixime therapy. Establishing real-world treatment registries could support ongoing surveillance and informed decision-making in the management of typhoid fever.

## Conclusion

This multicenter, retrospective real-world evidence study highlights the effectiveness and safety of cefixime in the treatment of typhoid fever. The study demonstrated high clinical and microbiological cure rates by the intermediate assessment, and complete resolution at follow-up. Patients showed progressive improvement in clinical signs, laboratory parameters, and overall symptom burden, reinforcing the therapeutic value of cefixime. The incidence of adverse events was minimal, further supporting its safety profile. These findings affirm the role of cefixime as a reliable oral monotherapy in routine clinical management of typhoid

fever. Future prospective studies may help to validate these observations and assess its broader impact on healthcare delivery and outcomes.

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