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**Original Research Article**

# Expert Opinion on the Clinical use of Antibiotics for the Management of Infections and Enteric Fever in Indian Settings

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**Abstract:** ***Objective*:** The present survey-based study aims to gather clinicians' perspectives regarding the antibiotic prescription pattern for the management of infections and enteric fever in Indian settings. ***Methodology*:** The current multiple-response questionnaire-based survey consisted of 17 questions pertaining to clinical observations, clinical experience, and antibiotic prescription practice of specialists involved in the management of infections and enteric fever. ***Result:*** Out of 246 participants, 89% recommended cefixime as the preferred monotherapy drug for enteric fever. The recommended combination therapies for enteric fever were cefixime and ofloxacin, cefixime and azithromycin, and cefpodoxime and ofloxacin, as indicated by 38%, 32%, and 25% of clinicians, respectively. Approximately 61% of the clinicians reported frequently prescribing cefixime for urinary tract infections (UTI). According to 68% of the clinicians, the recommended cefixime dose for treating typhoid fever is 15-20 mg/kg. More than half (55%) of the clinicians recommended amoxicillin/clavulanic acid for the treatment of respiratory infections. Majority (78%) of the clinicians chose cefixime as an effective option for managing recurring infections. A considerable proportion (76%) of clinicians reported no side effects following antibiotic therapy. ***Conclusion*:** The study provides valuable insights into the use of antibiotics in infection and enteric fever in Indian settings. Cefixime therapy is recommended by clinicians in the treatment of enteric fever, UTI, and recurring infections. The preferred treatment option for enteric fever includes a combination of cefixime with either ofloxacin or azithromycin. The recommended cefixime dose for typhoid fever is in the range of 15-20 mg/kg. Respiratory infections are typically treated with amoxicillin/clavulanic acid.

**Keywords:** Antibiotics, Infection, Typhoid, Cefixime, Amoxicillin.



## INTRODUCTION

Typhoid fever poses a significant public health challenge globally, with outbreaks and high disease rates occurring in countries such as India, South Asia, the Middle East, Central Africa, and South America [1]. An estimated 26.9 million cases of typhoid fever occur annually worldwide [2]. In 2019, an updated modeling study estimated that 9.2 million typhoid fever cases and 110,000 deaths occurred globally, with the highest incidence in the WHO South-East Asian (306 cases per 100,000 persons), Eastern Mediterranean (187), and African (111) regions [3]. Typhoid fever is a major contributor to illness and mortality in tropical regions across the world, with the Indian subcontinent being significantly affected. This impact is more pronounced in urban areas of the country [4].

Recurrent urinary tract infections (UTIs), a prevalent form of infection in both in the community and healthcare settings, have significant personal and societal implications. The societal impact encompasses the clinical and economic burden of the illness, while the personal impact includes negative social and psychological effects that can impair the quality of life (QoL). As a modifiable factor, reducing the high prevalence of recurrent UTIs can alleviate both societal and personal burdens [5]. In 2019, it was estimated that there were 404.61 million cases of UTI globally, resulting in 236,790 deaths and 520,200 years of healthy life lost (DALYs) [6].

According to the World Health Organization (WHO), respiratory infections constitute 6% of the global disease burden [7]. In 2019, there were around 17.2 billion cases of upper respiratory infections (URIs) worldwide, accounting for 42.83% of all reported cases in the Global Burden of Disease study [8].

Antibiotics play a crucial role in the management of enteric fever, UTIs and respiratory infections in Indian settings. India is recognized as the world's largest consumer of antibiotics when measured by absolute volume and studies have highlighted significant concerns regarding prescription quality, including the unwarranted use of broad-spectrum antibiotics in the absence of bacterial infection. Such practices have raised substantial public health concerns, especially in the light of India's high rates of antibiotic resistance among bacteria responsible for common infections [9].

The objective of the present survey-based study is to understand the clinicians' perspective regarding the use of antibiotics for the management of infections and enteric fever. Understanding the prescribing practices of antibiotics used in Indian settings may facilitate the development of evidence-based guidelines and recommendations for more effective patient management.

## METHODOLOGY

The cross-sectional, multiple-response questionnaire-based survey conducted between June 2022 and December 2022 among clinicians with expertise in infectious disease management across various regions of India.

### Questionnaire

The questionnaire booklet named TRUST (The expert opinion in using Ritecef in Urinary tract infectionS and enTeric fever) study was sent to the physicians who were interested to participate. The questionnaire consisted of 17 questions pertaining to clinical observations, clinical experience, and prescription practice of antibiotics indicated for infections and enteric fever. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

### Participants

An invitation was sent to leading clinicians with expertise in infectious disease management in the month of March 2022 for participation in this Indian survey. 246 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. Clinicians were instructed to answer the questionnaire on their own, without contacting any of their colleagues. Prior to the study, written informed consent was obtained from each study participant.

### Statistical analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear understanding of their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, pie, and bar charts were created using Microsoft Excel 2013 (version 16.0.13901.20400).

## RESULTS

The present survey involved 246 participants. More than half of the respondents (57%) cited the 20-40 age group as having the highest prevalence of enteric fever. According to 49% of the respondents, the prevalence of multidrug-resistant enteric fever cases noted in routine practice ranges from 6% to 15%. According to 44% of the participants, 10-20 cases of typhoid fever are treated in a month in clinical practice. Majority of the clinicians (61%) cited UTI as the most frequently observed infection in Indian settings. Approximately 42% of the clinicians stated fever as the key symptom reported by patients with UTI. More than half of the clinicians reported that UTI is more prevalent in women and within the age group of 20-40 years. According to 48% of the clinicians, nearly 11-20% of the patients present with UTIs in routine practice.

According to 45%, 28%, and 20% of clinicians, reasons for switching antibiotics during the course of anti-infection therapy include clinical response, culture and sensitivity reports, and unabated fever. Nearly 34% of the clinicians considered the antimicrobial spectrum as the selection criterion when prescribing antibiotics. A significant (89%) proportion of clinicians recommended cefixime as the preferred monotherapy for enteric fever. According to 38%, 32%, and 25% of the clinicians, the preferred combination therapies for enteric fever are cefixime and ofloxacin, cefixime and azithromycin, and cefpodoxime and ofloxacin, respectively (Table 1).

Majority (61%) of the clinicians reported cefixime as the commonly prescribed drug for UTI (Figure 1). According to 68% of the participants, 15-20 mg/kg is the preferred dosage of cefixime for the management of typhoid fever (Table 2). More than half (55%) of the clinicians preferred amoxicillin/clavulanic acid for the management of respiratory infections (Table 3).

**Table 1: Distribution of response to monotherapy and combination therapy drugs preferred for managing enteric fever**

| Monotherapy | Response rate (n = 246) | Combination therapy | Response rate (n = 246) |
|---|---|---|---|
| Cefixime | 218 (88.62%) | Cefixime & ofloxacin | 93 (37.8%) |
| Cefpodoxime | 15 (6.1%) | Cefixime & azithromycin | 78 (31.71%) |
| Ceftriaxone | 12 (4.88%) | Cefpodoxime & ofloxacin | 61 (24.8%) |
| All of the above | 1 (0.41%) | Any other | 13 (5.28%) |
| Any other | 0 (0%) | Not attempted | 1 (0.41%) |

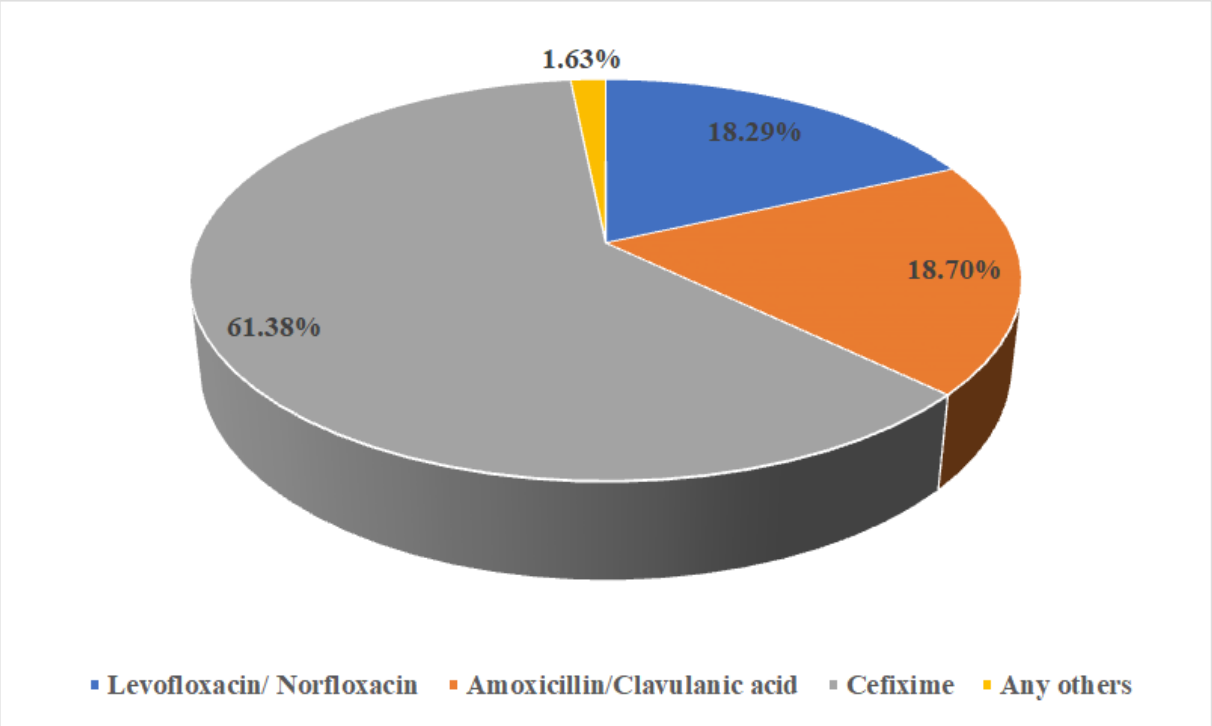


**Figure 1: Distribution of response to commonly prescribed drug in UTI**

**Table 2: Distribution of response on recommended cefixime dose for managing typhoid patients**

| Dosage | Response rate (n = 246) |
|---|---|
| 8-10 mg/kg | 67 (27.24%) |
| 15-20 mg/kg | 165 (67.07%) |
| All of the above | 9 (3.66%) |
| Any other | 2 (0.81%) |
| Not attempted | 3 (1.22%) |

**Table 3: Distribution of response to preferred antibiotic for the management of respiratory infections**

| Antibiotics | Response rate (n = 246) |
|---|---|
| Amoxicillin/clavulanic acid | 133 (54.07%) |
| Azithromycin | 33 (13.41%) |
| Cefpodoxime | 21 (8.54%) |
| Cefuroxime | 6 (2.44%) |
| Cefixime | 50 (20.33%) |
| All of the above | 1 (0.41%) |
| Any other | 0 (0%) |
| Not attempted | 2 (0.81%) |

Majority (78%) of the clinicians reported that cefixime is effective in the treatment of recurrent infections (Figure 2). A significant proportion (76%) of clinicians reported no major side effects following antibiotic treatment (Table 4).

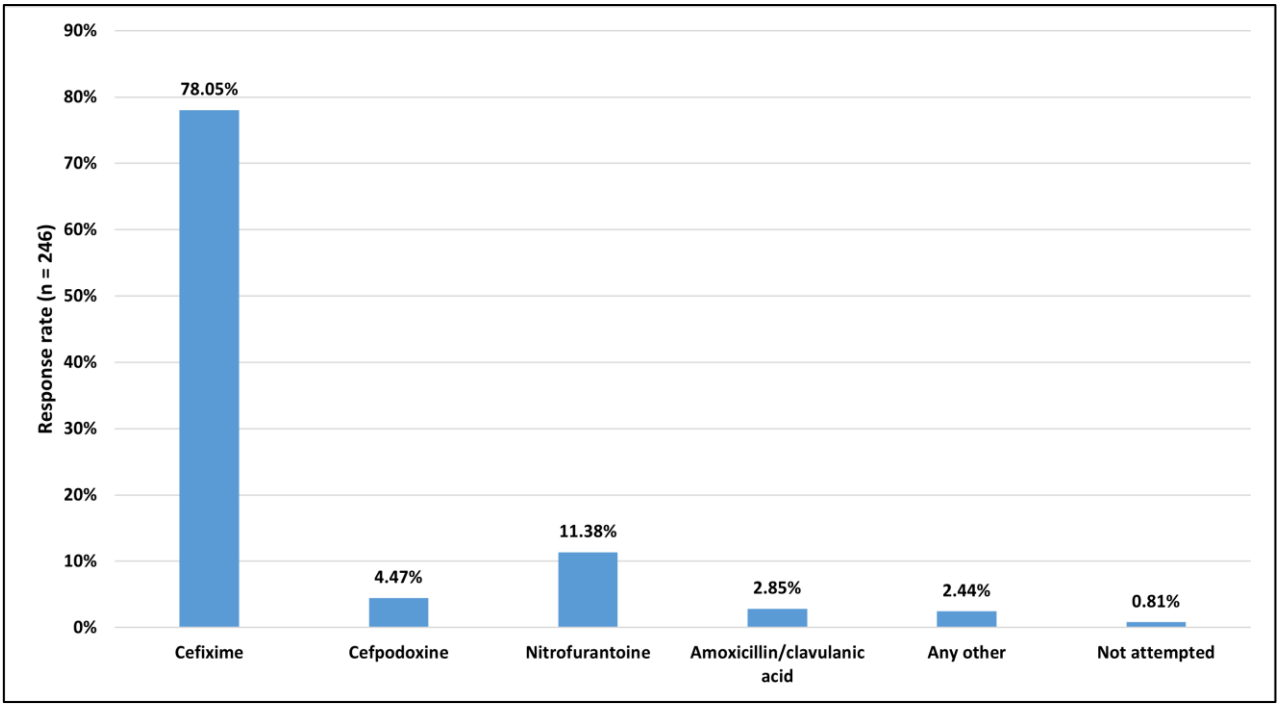


**Figure 2: Distribution of response to effectiveness of the drug indicated for the management of recurrent infections**

**Table 4: Distribution of response on the incidence of side effects post-antibiotic treatment**

| Response | Response rate (n = 246) |
|---|---|
| No | 186 (75.61%) |
| Yes | 59 (23.98%) |
| Not attempted | 1 (0.41%) |

## DISCUSSION

The study emphasizes the substantial preference for antibiotic therapy, especially cefixime, in the treatment of infections and enteric fever. The findings also underscore the effectiveness of combination therapies involving cefixime and ofloxacin, cefixime and azithromycin in enteric fever, as well as amoxicillin/clavulanic acid in the treatment of respiratory infections.

In the present survey, majority of clinicians preferred using cefixime for the treatment of enteric fever, UTI, and recurring infections. Studies conducted by Memon *et al.*, Girgis *et al.*, and Matsumoto *et al.*, have reported that cefixime is a reliable, affordable, efficient, and safe option for treating multidrug-resistant enteric fever [10-12]. A study conducted by Chaudhary *et al.*, involving 112 subjects, assessed the effectiveness and safety of cefixime, administered at a dose of 5 mg/kg or 200 mg twice daily for 7 days, for the treatment of typhoid fever. The study observed clinical cure in 98 (92.5%) of these individuals, and no serious adverse events were reported. These findings indicate that cefixime is a safe and effective option for treating typhoid fever [13]. There is substantial literature evidence to validate the effectiveness and safety of cefixime for treating typhoid fever [14-17]. A review study by Fanos *et al.*, reported that cefixime may be used as monotherapy or switch therapy for pediatric subjects with non-complicated UTI [18]. In another study, around 98% of the patients reported complete recovery from UTI following cefixime treatment [19]. Several other studies have also reported the effectiveness of cefixime for the UTI treatment [20-23].

The present study findings indicate the therapeutic effectiveness of combination therapy involving cefixime and ofloxacin, and cefixime and azithromycin for the management of enteric fever. Tiwaskar *et al.*, reported that in Indian settings, cefixime-ofloxacin is a safe, dependable, and effective therapy choice for clinicians treating uncomplicated typhoid fever [24]. An Indian survey study by Patil *et al.*, which comprised 78 family physicians, reported that the cefixime-ofloxacin 400 mg sustained-release fixed-dose combination is an effective option for treating refractory enteric fever patients, especially when comorbid diseases like diabetes or hypertension increase the pill burden [25]. A comparative study by Chandey *et al.*, reported that both azithromycin monotherapy and the combination of azithromycin and cefixime are equally effective oral therapies for typhoid fever [26].

Most of the clinicians in the current survey recommended amoxicillin/clavulanic acid for the management of respiratory infections. It is effective against respiratory tract and otitis media infections due to its activity against *Streptococcus pneumoniae*, *β*-

*lactamase-producing Hemophilus influenzae*, and *Moraxella catarrhalis* [27]. A randomized controlled trial by Wald *et al*., comprising patients with acute bacterial sinusitis reported that compared to children who received the placebo, those who received the amoxicillin with potassium clavulanate had higher cure rates (50% vs. 14%) and lower rates of treatment failure (14% vs. 68%) [28]. Another clinical trial study by Calver *et al*., reported the effectiveness and safety of amoxicillin/clavulanate in the treatment of lower respiratory tract infections [29]. The present survey has recommended a dosage of 15-20 mg/kg of cefixime for typhoid fever. Previous trials have utilized cefixime at doses ranging from 10 to 20 mg/kg/day for the treatment of typhoid fever [14-17, 30].

A significant proportion of current survey clinicians reported no side effects following antibiotic therapy. Generally, amoxicillin-clavulanate is considered safe and well-tolerated, with the majority of side effects being minor gastrointestinal problems [31]. Chandey *et al*., reported no serious side effects after treatment with the azithromycin+cefixime combination therapy in their study [26]. Similarly, the cefixime-ofloxacin combination is also considered safe, with mild to moderate adverse events [24]. Multiple studies have consistently reported the safety and tolerability of cefixime, with minimal to no severe side effects [10, 12, 14, 16, 17, 19].

The survey findings provide valuable insights into the antibiotic prescribing patterns and preferences of clinicians in Indian healthcare settings. These insights can help develop evidence-based guidelines for better patient management and promote the judicious use of antibiotics, which is crucial in the context of antibiotic resistance. The survey results were obtained through a meticulously crafted and validated questionnaire-based survey, which allowed professionals to provide opinions based on evidence-based practices. However, it is critical to acknowledge some of the study's limitations. Given that individual viewpoints and preferences may have influenced the stated conclusions, the reliance on expert judgments heightens the risk of bias. Therefore, it is essential to interpret the results with these constraints in mind and to contemplate further research to validate and expand upon the findings.

## CONCLUSION

The study offers insightful information on the application of antibiotics in infection and infection-related fever in Indian settings. Most clinicians recommended cefixime therapy to treat enteric fever, UTI, and recurrent infections. Azithromycin and cefixime or cefixime and ofloxacin are additional suggested combination treatments for enteric fever. Cefixime is used at a dosage of 15-20 mg/kg for the treatment of typhoid fever. It was recommended to use amoxicillin/clavulanic acid, to treat respiratory infections. Following the administration of antibiotic medication, no side effects were noticed.

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## DECLARATIONS

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**Conflict of Interest:** None declared.

**Ethical Approval**: This study was approved by the Independent Ethics Committee.

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