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Original Research Article

A Multicenter, Retrospective, Real-World Evidence Study to Assess the Effectiveness and Safety of Cefotaxime in Patients with Respiratory Tract Infection and Urinary Tract Infection

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Abstract

Objective: The primary objective of the study was to evaluate the clinical effectiveness and safety profile of cefotaxime in the treatment of respiratory tract infections (RTIs) and urinary tract infections (UTIs).

Methods: The study was a single-arm, multicentre retrospective study that analysed the data of 5264 patients. The study included all patients diagnosed with RTIs and UTIs, who have been treated with cefotaxime therapy. Existing medical records were used to collect data on efficacy endpoints (clinical cure rate, duration of treatment and hospitalisation, isolation of bacterial isolates) and safety endpoints (adverse events reported). Descriptive statistics were used for continuous and categorical variables.

Results: A total of 5,264 patients were included for analysis. Out of which 1580 patients were of UTI and 3684 patients were of RTI. Majority of the patients of RTI and UTI had received 1000 mg twice daily (78.26% and 66.30%, respectively). The mean duration of cefotaxime prescription was 5.43 ± 1.72 days. E. coli was the most prevalent pathogen among the 464 samples assessed, initially detected in 170 (36.64%). Its prevalence significantly declined to 68 during treatment and further to 3 (5.17%) in the post-therapy follow-up. Symptoms were cured for 84% and 97% of the population at the end of therapy and post-therapy follow up respectively. The mean duration of hospital stay was 6.02 days. Adverse effects were reported in 107 patients at the end of therapy and in 88 patients at follow up visit.

Conclusion: Cefotaxime demonstrated clinical effectiveness, with the majority of the patients achieving symptom resolution and reduction in microbial infection following treatment. Cefotaxime was well-tolerated, with a low incidence of adverse events reported, ranging from mild to moderate. This indicates that cefotaxime demonstrated a safe and effective drug profile in Indian patients with RTI and UTI.

Keywords: Retrospective Study, Treatment Outcome, Bacterial Infections, Drug Therapy, Adverse Effects.

Introduction

Respiratory tract infection (RTI) constitutes a major health concern as it increases the rate of mortality and morbidity among the general population [1]. According to reports in 2016, acute respiratory infections (ARIs) contributed to 2.38 million global fatalities [2]. Among the Indian population, approximately 41 million cases of RTIs were recorded in 2019 with 3,740 deaths in 2018 [3]. The clinical manifestation of RTIs includes asymptomatic cases, mild infectious cases presenting with cough and fever, and fatal infections with the risk of death. The severity of RTI is determined by the interplay of the causative pathogen, environment, and the susceptibility of the

host [1]. These respiratory tract infections/RTI typically present with acute symptoms such as shortness of breath, irritated throat, cough, coryza, respiratory difficulties, wheezing, and fever, often developing within hours or days of contracting the infectious pathogen [1]. The epidemiological patterns of RTIs are constantly shifting due to changes in the sociodemographic and climatic conditions [4,5]. While RTIs are a significant cause of fatalities among the geriatric and pediatric populations, they are also the leading cause of consultations and admissions in healthcare settings. It contributes significantly to the rising demand for medical evaluations, antimicrobial prescriptions, and hospitalizations [6]. Urinary tract infections (UTIs) also pose a significant public health challenge, adding to the burden of infectious disease. Clinically, UTIs are classified as complicated UTIs and uncomplicated UTIs. Uncomplicated UTIs are frequently observed in patients who are healthy overall without structural or neurological abnormalities within the urinary tract [7,8]. Conversely, complicated UTIs include infection due to a compromised urinary tract or defence mechanism of the host [9].

In women over 65 years of age, the prevalence of UTIs is approximately 20% globally. Furthermore, 50-60% of females are likely to contract UTIs at least once during their life 10. In the United States, UTIs rank as the seventh most common cause of emergency departmental visits, accounting for over 1 million visits per annum. Among these cases, approximately 22% (220,000) are classified as complicated UTIs, with around 100,000 patients requiring hospitalization each year [11,12]. The prevalence of UTI among Indian population ranges between 21.8% and 31.3% [13]. The increased rate of recurrence and the escalating antibiotic resistance observed in the uropathogens raise concerns regarding the global healthcare burden associated with managing these infections [14]. Furthermore, antibiotic resistance has been observed in both RTIs and UTIs which accounts for the majority of the reasons for treatment failure and relapse rate.

Cefotaxime, a third-generation cephalosporin, was initially approved for use on March 11, 1981, by the US FDA and is recommended in the dosage strength of 1-2 g IM or IV every 12 hours. Cefotaxime has shown favorable efficacy and safety profiles in managing various infections caused by both gram-positive and gram-negative bacteria [15]. Given the broad-spectrum antibacterial activity of cefotaxime, it is effective in treating various bacterial infections responsible for causing RTIs, UTIs, neurological infection, intra-abdominal infections (IAI), as well as bone, joint, skin, and genital tract infections [16].

The primary advantage of cefotaxime over other cephalosporins is its low risk of developing coagulopathies and the absence of pseudo cholelithiasis as a drug-related adverse event as compared to ceftriaxone [17]. Previous studies have reported symptom resolution rates between 75% and 100% in patients admitted to the hospital for moderate and severe infections [17,18]. Therefore, according to the existing studies, cefotaxime is an effective and well-tolerated drug.

Despite the well-documented efficacy of cefotaxime for treating RTIs and UTIs in controlled clinical trials, there is a wide gap in real-world evidence. The lack of evidence is particularly higher in India with diverse patient demographics and variable disease profiles. Most of the studies evaluating the use of cefotaxime have been conducted under controlled conditions, which has limited the applicability of the findings to broader patient populations. Furthermore, the increasing instances of antibiotic resistance in both RTIs and UTIs necessitate the assessment of the real-world performance of the alternative antibiotic, cefotaxime, ensuring the applicability of the drug in Indian patients. The current retrospective study aims to evaluate the clinical effectiveness and safety profile of cefotaxime in the management of RTIs and UTIs. By extracting data from the medical records of patients diagnosed with RTIs and UTIs and treated with cefotaxime in diverse clinical and patient profiles, this study offers valuable insights into the performance of the drug in India.

Methods

Study design and population: A single-arm, retrospective, multicentre, medical record-based study was conducted. The study retrospectively analysed the data of 5264 patients treated with cefotaxime therapy from the period of January 2023 to April 2024. Patients with a confirmed clinical diagnosis of RTIs and UTIs receiving cefotaxime were enrolled in the analysis. Those patient with incomplete records were omitted from the analysis. Data was collected from 457 centres across all the different regions of India to ensure comprehensive information.

The inclusion criteria are 1) Patients of any age group, 2) Patients diagnosed with RTIs such as pneumonia and bronchitis or UTIs such as cystitis and pyelonephritis, 3) Patients who received treatment with cefotaxime, and 4) Patients with documented clinical diagnosis, duration of therapy & hospitalization, and treatment outcomes following cefotaxime therapy. Patients for whom clinical diagnosis and medical records were not available were excluded.

Study endpoints: Efficacy endpoints were the clinical outcomes used as a measure of therapeutic efficacy.

These included: 1) Clinical Cure: the completion of the treatment regimen with the resolution of the primary infection and characterized by the cessation of all symptoms and signs of infection following cefotaxime therapy in patients with RTIs and UTIs. 2) Duration of therapy with cefotaxime therapy in RTIs and UTIs patients, 3) Duration of hospitalization, and (4) Isolation of bacterial species: the absence of the causative pathogen from appropriately obtained specimens at the site of infection among patients treated with cefotaxime for RTIs and UTIs, (if available).

The safety endpoint of the study included adverse events reported during the treatment period. Any abnormal findings in laboratory results or physical examination were reported as adverse events, regardless of the causal relationship between the event and the drug.

Data collection: The study investigator and site personnel identified patients fulfilling the study inclusion criteria from the available patient medical records at the study site. Prescriptions and laboratory investigations of the individual patients were screened and data from the medical records was meticulously documented using standard reporting systems.

Patient records at each site were given a unique ID number. The index date on which treatment with cefotaxime was initiated was considered for baseline data. The data was collected at the start of treatment, at the end of therapy, and post-treatment follow-up.

The assessment at the initiation of cefotaxime included patient demographics (age, gender, and medical history), diagnosis, clinical symptoms, cefotaxime dosage, duration of treatment, duration of hospitalisation, and microbiological data (presence of bacteria, identification of the bacteria) wherever it was available.

The assessment conducted at the end of therapy included duration of treatment, clinical outcome (cure/improvement/worsening/mortality), microbiological data (wherever available), and reported adverse events. Another assessment was conducted at post-treatment follow-up included clinical symptoms, vitals, clinical outcome (cure/improvement/worsening/mortality), microbiological data (wherever available), and reported adverse events.

Statistical Analysis: The statistical analysis was done using SPSS (Version 25) software. Descriptive statistics were employed to summarize the cohort's demographic characteristics (age, weight & height), signs & symptoms, and treatment details at the start of therapy, end of therapy, and post-treatment follow-up. Continuous variables were represented using means and standard deviations, while categorical variables were summarized using frequencies and percentages. All statistical analyses were performed with a 95% confidence interval, and p-values less than 0.05 were considered statistically significant.

Ethical considerations: The study followed the directives of good clinical practice (GCP) and ethical guidelines issued by the Indian Council of Medical Research (ICMR). Ethics committee approval was taken before the commencement of the study. Due to the retrospective nature of the study, anonymized data from existing medical records were used waiving informed consent of the patients. Stringent measures were taken to maintain data confidentiality.

Results

Patient demographics and baseline characteristics: A total of 5,264 clinically confirmed cases of UTIs and RTIs were analysed. The final analysis included all 5,264 cases, consisting of 1,674 females (31.80%) and 3,590 males (68.20%) as shown in figure 1.

The patients had a mean age of 38.93 ± 15.82 years, reflecting a wide age range. Additionally, the average height and weight were 154.31 ± 22.29 cm and 61.54 ± 16.12 kg, respectively.

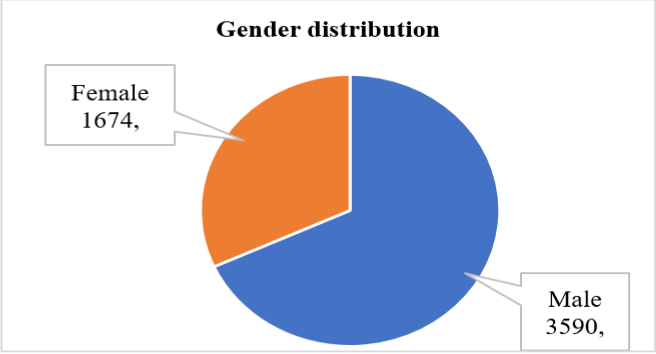

Figure 1: Gender Distribution

Among the total patient population, clinical diagnosis confirmed 3,652 cases (69.4%) of RTI and 1,612 cases (30.6%) of UTI, as illustrated in Figure 2. Fever with cold/cough/pain was the most common signs and symptoms of RTI and UTI with 1373 (26.1%) patients complaining of the same. Other most common symptoms included cold & cough, urine problems, and diarrhea. Sinusitis and GI disturbance were found to be the least common symptoms of RTI and UTI.

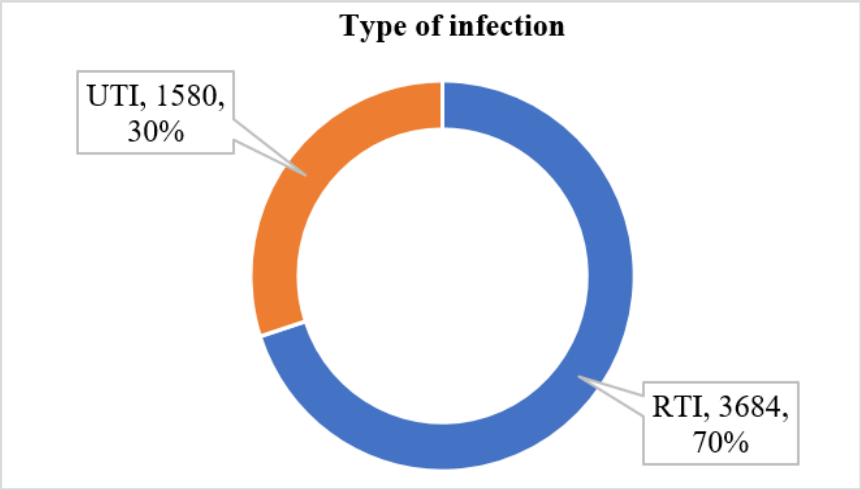

Figure 2: Type of Infection

Clinical outcomes: Majority of the patients 4393 (83.45%) were prescribed cefotaxime 1gm injection. The most common dosing frequency observed was twice daily followed by thrice daily. An average duration of prescription was 5.43 ± 1.72 days. The average duration of therapy received was 5.33 ± 2.00 days. Vitals and microbiological data captured at different time points prior to therapy, at the end of therapy, and during the follow-up period are displayed in table 1. No significant changes in the vitals were observed during the study.

Table 1: Details of prescription

Parameter	**Mean**	**SD**
Dose (mg) per day	1119.5	470.44
Duration (Days)	5.41	1.72
Frequency	**n**	**Percent (%)**
▪ Once a Day	135	2.6
▪ Twice a Day	4327	82.2
▪ Thrice a Day	786	14.9
▪ Four Times a day	16	0.3
	Mean	**SD**
Total Duration of Therapy (Days)	5.33	2.00
Duration of Hospital Stay (Days)	6.02	2.81

Bacterial species were isolated for 464 (8.81%) patients at the start of therapy, 161 (3.05%) patients at the end of therapy, and 58 (1.1%) patients at post-treatment follow-up.

Escherichia Coli was identified as the most prevalent pathogen, detected in 170 (36.64%) cases at the start of therapy, 68 (42.24%) cases at the end of therapy, and 3 (5.17%) cases at the follow-up. Streptococcus pneumoniae was the second most prevalent pathogen at the start and end of therapy, with presence in 62 (13.36%) cases at the start of therapy and 29 (18.01%) cases at the end of therapy.

Other less prevalent pathogens detected were S. pyogenes, H. influenzae, Salmonella, K. pneumoniae, etc. as shown in table 2.

Table 2: Details of bacterial species isolated.

	At baseline	% At the baseline	At the end of treatment	% At the end of therapy	At the follow up visit	% At the follow up visit
Bacterial species	**464**	**%**	**161**	**%**	**58**	**%**
E. Coli	170	36.64	68	42.24	3	5.17
S. pneumoniae	62	13.36	29	18.01	0	0.00
S. pyogenes	51	10.99	0	0.00	0	0.00
H. influenzae	47	10.13	0	0.00	2	3.45
E. faecalis	17	3.66	0	0.00	0	0.00
Staphylococcus Aureus	12	2.59	0	0.00	6	10.34
K. pneumoniae	11	2.37	6	3.73	0	0.00
Salmonella	0	0.00	2	1.24	0	0.00

Treatment outcomes and adverse events reported: The changes in symptoms and occurrence of drug-related adverse events at the end of therapy and the follow-up period are outlined in figure 3 and figure 4. At the end of therapy, symptoms were cured for 4559 (84.0%) patients, improved for 844 (15.5%) patients, worsened for 21 (0.3%), and 4 (0.1%) experienced mortality.

Moreover, symptoms were cured for 5276 (97.20%) patients, improved for 144 (2.65%) patients, and worsened for 6 (0.11%) patients at the post-treatment follow-up with 2 (0.04%) cases of mortality.

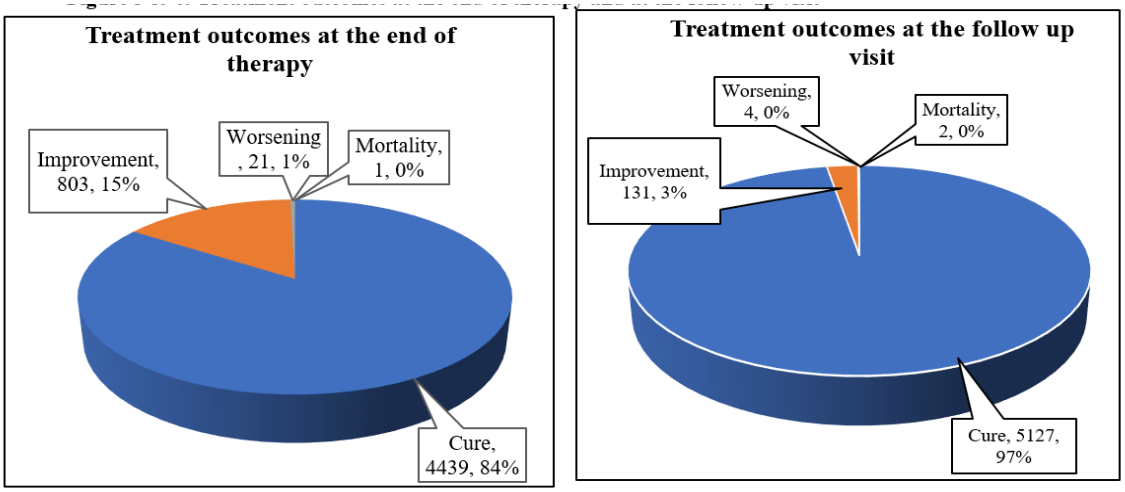

Figure 3 & 4: Treatment outcomes at the end of therapy and at the follow-up visit

As given in table 3, 110 (2.0%) patients experienced adverse events due to medication at the end of therapy while 88 (1.6%) patients experienced the same at the time of follow-up.

Table 3: Adverse event reported at the end of therapy and at the follow up visit

		At the end of therapy	At the follow up
Adverse event Reported	Yes	107	88
	No	5157	5179

Discussion

The present observational study assessed the efficacy and safety of the third-generation cephalosporin, and cefotaxime in UTI and RTI patients. These patients commonly presented with acute symptoms of fever, cold, cough, and pain. Cefotaxime was administered parentally with a quick symptom resolution time. Escherichia coli and Streptococcus pneumoniae were the most prevalent bacterial pathogens.

A significant majority of the patient's experienced cures post-treatment and during the follow-up period. Mortality was significantly less. The incidence of adverse events reported was approximately 2%, demonstrating the overall safety of the drug. The improvements in symptoms were observed after the cefotaxime administration. Thus, cefotaxime reported high therapeutic efficacy in reducing symptoms and curing infections, with a low risk of adverse events. A significant proportion of the current study population reported RTIs as the primary diagnosis. Cefotaxime administered

parentally was effective in infection eradication with over 90% clinical cure. Similar findings were observed in a study by R L Perkins, which shows overall rates of bacteriologic and clinical cure, analysed by pathogen, for the cefotaxime treated patients were 89.9% and 93.9%, respectively [19], However in another study by Naber et al, it was reported that, there were lower rates of bacteriological cure in complicated or hospital-acquired UTIs, with a cure rate of 35% at 4-week follow-up post-cefotaxime parental administration [20]. Well in another study by Simmons et al, 70% clinical sure was observed in serious UTI patients, with infection caused by Escherichia coli [2]. Another study on 100 pediatric patients with pyelonephritis 10 days post-therapy showed a clinical cure and eradication of the causative agent in 82% of the patients [22]. A study in Africa on 50 females having chorioamnionitis and undergoing C-section demonstrated a clinical resolution in 96% of cases after a 10-day treatment course with 2g of cefotaxime twice daily, administered first intravenously and later intramuscularly [23].

The outcome of cefotaxime therapy varies depending on the severity of the infection. Studies Graninger et al. and, Ludwig and Knebel on uncomplicated urinary tract infections have shown bacteriological response rates between 87% and 100% following treatment with cefotaxime 2 g/day [24,25]. In patients with complicated urinary tract infections, bacteriological outcomes varied based on the timing of assessments. After treatment, 93% to 100% of patients had negative urine cultures, although this figure dropped to approximately 60% to 70% one week later, with re-isolation of the original organism occurring in 14% to 29% of cases [26].

Further evidence from Europe and Latin America underscores cefotaxime's efficacy across a variety of RTIs. A study by Young et al. (1980) reported clinical cure in 81% of 410 patients, with a 5% relapse rate and 14% treatment failure [27]. Multicentre studies in the United Kingdom reported cure rates of 82% and 90% in 103 patients with LRTIs, treated either with cefotaxime monotherapy or combined with other antibiotics [28,29]. A brief report by Newsom et al. (1981) highlighted the successful treatment of four patients with ampicillin-resistant Haemophilus influenzae-related pneumonia using cefotaxime at 1g three times daily over a period of 1 week [30]. These studies in addition to the findings of our study, which demonstrated a high rate of clinical cure in the majority of patients treated, it is evident that cefotaxime remains highly effective in managing a range of respiratory infections.

In our findings it was observed that, in patients undergoing microbiological assessment, among the list of isolated bacteria Escherichia coli was the most predominant pathogen, followed by Streptococcus pneumoniae, Streptococcus pyogenes, and Haemophilus influenzae. These organisms were susceptible to cefotaxime with significantly reduced detection of microbes at the end of therapy and during the follow-up period. The similar findings were observed in another study conducted in Southeast Ethiopia by Getenet et at, where they observed E. coli, Klebsiella pneumoniae and S. saprophyticus as most commonly isolated pathogens [31]. Another large cohort study enrolling 421 patients with pneumonia caused by 142 different pathogenic species reported bacteriological cure in 92.7% of the pathogens including Escherichia coli, Staphylococcus aureus, Klebsiella species, and Streptococcus pneumoniae [32]. Some patients reported the presence of Escherichia coli even after completing the course of cefotaxime. This is in alignment with other studies reporting cefotaxime-resistance in certain strains of Escherichia coli. A national surveillance study in the United States identified cephalosporin-resistant strains in 3% of the 94 early-onset Escherichia coli infections [33]. Similar findings were reported in Germany, where 4% of 158 Escherichia coli strains showed resistance to cefotaxime [34]. In England and Wales, a five-year surveillance study revealed that approximately 3% of neonatal bloodstream infections caused by Escherichia coli could not be managed with cefotaxime [35]. Therefore, the presence of Escherichia coli strains which are cephalosporin-resistant necessitates cautious monitoring of drug failure in such patients.

The majority of the patients in the present study over 96% did not experience any adverse events. Bivariate analysis reported that there is no significant association between the occurrence of adverse events and the administration of 1gm cefotaxime injection. However, previous studies have reported higher incidences of drug-related adverse events. Cefotaxime administered parentally is generally well-tolerated with an incidence rate of adverse events ranging between 5 and 8%, out of which 1-2% discontinued the drug [16,18]. The most common side effects associated with cefotaxime therapy include diarrhea, nausea, vomiting, skin reactions like rash and pruritus, and local sensitivity at the injected region, including pain and inflammation [16,18]. Compared to other cephalosporin injections, cefotaxime has a favorable safety profile. Unlike some of these agents, such as cefamandole and cefoperazone, cefotaxime is not associated with a significant risk of developing coagulopathies. Furthermore, unlike ceftriaxone, cefotaxime does not pose a risk of biliary tract sludge formation [17]. Another important advantage of cefotaxime is its lack of nephrotoxicity. Therefore, the present result is consistent with previous literature suggesting the

high safety of cefotaxime with a lower incidence rate and only mild-moderate adverse reactions.

The present study provides recent data using a large sample population on the clinical efficacy and safety of cefotaxime in real-world clinical settings in India. The majority of the studies of this particular drug were performed 2 decades earlier, with the lack of recent evidence and use in the current scenario. However, the study demonstrates high therapeutic efficacy with a good safety profile of the drug even today, with the increasing antibiotic-resistant strains. Therefore, the study is important in highlighting the role of cefotaxime in managing UTI and RTI effectively, recommending further adoption of the drug by physicians in their practice.

Certain limitations of the study must be addressed. First, the retrospective nature of the study potentially introduces confounding biases that could be missed during assessment. Second, the lack of a comparator arm of other cephalosporin or standard practice drugs limits the comparability to other better-performing drugs in the market, if any. Third, the microbiological data for all patients was not available due to the observational design, potentially leading to unidentified cefotaxime-resistant strains in patients with treatment failure.

Conclusion

Cefotaxime was well-tolerated and provided significant clinical and microbiological cures in the majority of the patients. The reported adverse events ranged from mild to moderate, indicating a safe and effective drug profile in Indian patients. The primary reason for treatment failure is hypothesized as the presence of cefotaxime-resistant pathogens, or cephalosporin hypersensitivity of the patients. Therefore, administering cefotaxime is advised in UTIs and RTIs, but cautious monitoring of adverse events is required.

Given that the recent evidence of cefotaxime, particularly in India is scarce, the present study is critical to address the rising antibiotic-resistant bacterial strains and its translation in the clinical efficacy of the drug. Further clinical trials are required to understand the underlying pathogens and patterns of antibiotic susceptibility for informed decision-making by physicians.

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