# CEFTRIAXONE AS AN EMPIRIC ANTIBIOTIC: PRESCRIBING PRACTICES, RESISTANCE DYNAMICS, AND STEWARDSHIP STRATEGIES

**Qahil IBRAIMI[1], Merita DAUTI[2], Erëza DURMISHI[3], Drita YZAIRI[1], Gjylaj ALIJA[1], Driton SELMANI[1]**

[1]*Faculty of Medical Sciences, Department of Pharmacology - University of Tetovo*
[2]*Clinical Hospital – Tetovo, Department of Internal disease*
[3] *Clinical Hospital – Tetovo, Department of Pediatric*
*Contact: qail.ibraimi@unite.edu.mk*

**Abstract**

Ceftriaxone, a broad-spectrum third-generation cephalosporin, is widely used as empiric antibiotic therapy for severe infections, including pneumonia, sepsis, and complicated urinary tract infections [1,2]. Its clinical relevance is supported by favorable pharmacokinetics, broad antimicrobial activity, and convenient once-daily dosing. However, increasing global use has been accompanied by a significant rise in antimicrobial resistance, particularly mediated by extended-spectrum β-lactamases (ESBL), AmpC β-lactamases in Gram-negative bacteria, and penA mutations in Neisseria gonorrhoeae [3,4]. These developments raise concerns regarding the continued effectiveness of ceftriaxone in empiric treatment.

This study aimed to evaluate the rational use of ceftriaxone in empiric therapy and its relationship with resistance development. The importance of this paper lies in addressing the growing gap between widespread ceftriaxone use and evidence-based prescribing, which directly contributes to antimicrobial resistance, increased healthcare burden, and compromised patient outcomes. Ceftriaxone was selected as the model antibiotic due to its global prevalence, well-characterized pharmacological profile, and central role in clinical guidelines for empiric therapy. The rationale was supported by evidence of substantial inappropriate use [5-7]. Common empiric indications included community-acquired pneumonia, sepsis, febrile neutropenia, complicated urinary tract infections, meningitis, and surgical prophylaxis. Standard dosing ranged from 1-2 g intravenously every 24 hours [2,8], with shorter treatment durations demonstrating comparable efficacy to prolonged regimens [9]. Evidence indicates that ceftriaxone remains effective when resistance risk is low, however, routine overuse is strongly associated with resistance. A multicenter surveillance study reported approximately 28% resistance among Enterobacterales isolates [3]. Higher dosing (2 g) rarely improves outcomes compared to 1 g in most infections [8,7], except in selected critically ill patients. Antimicrobial stewardship strategies, including restriction policies, de-escalation, and IV-to-oral conversion, have demonstrated effectiveness in reducing inappropriate use [12]. Current evidence supports reserving empiric ceftriaxone for well-defined indications and avoiding its use when local resistance exceeds 10-20% [13].

*Keywords:* Ceftriaxone; Empiric therapy; Antimicrobial resistance; Dosing strategies; Clinical outcomes.

## Introduction

Ceftriaxone, a third-generation cephalosporin with broad-spectrum antimicrobial activity, is widely used as empiric therapy for a range of serious bacterial infections, including community-acquired pneumonia, sepsis of unknown origin, pyelonephritis, meningitis, and gonorrhea [1,2]. Its clinical utility is largely explained by favorable pharmacokinetic properties, including excellent tissue penetration and the convenience of once-daily dosing [2]. In addition, its activity against common pathogens such as Enterobacterales and Streptococcus pneumoniae has established ceftriaxone as a first-line agent in multiple clinical guidelines [10]. These characteristics make it a practical and effective option in situations where rapid initiation of therapy is required before microbiological confirmation is available [1,10].

However, the effectiveness of ceftriaxone is increasingly challenged by the global rise in antimicrobial resistance. The emergence of extended-spectrum β-lactamase (ESBL)-producing organisms, AmpC β-lactamase producers, and resistant strains of Neisseria gonorrhoeae has

significantly reduced its reliability in certain settings [3,4]. Moreover, ceftriaxone lacks activity against specific clinically relevant pathogens such as Pseudomonas aeruginosa and Enterococci, further limiting its empirical applicability in high-risk populations [10]. Importantly, inappropriate use of broad-spectrum antibiotics, such as prescribing ceftriaxone for viral infections or extending prophylactic use beyond recommended durations, has accelerated resistance development and undermined its long-term effectiveness [5–7].

Given these concerns, the rational use of ceftriaxone in empiric therapy has become a critical issue in contemporary clinical practice. This review examines the patterns of ceftriaxone use and evaluates its impact on bacterial resistance and clinical outcomes. Specifically, it explores epidemiological trends, common clinical indications, dosing and duration strategies, and the role of antimicrobial stewardship interventions in optimizing its use [12,13].

The objectives of this research paper are :

[1]. describe current patterns of empiric ceftriaxone use and related stewardship recommendations;
[2]. summarize evidence on optimal dosing and treatment duration in terms of efficacy and safety;
[3]. analyze current resistance trends, including ESBL and AmpC prevalence as well as gonococcal resistance;
[4]. compare findings from key clinical studies;
[5]. discuss implications for clinical practice and health policy. Through this structured analysis, the paper aims to clarify the appropriate role of ceftriaxone in empiric therapy and to identify strategies to preserve its clinical effectiveness.

## Methods

We conducted a narrative literature review using PubMed, Scopus, and Google Scholar, covering publications up to April 2026. The search strategy included the following keywords and their combinations: “ceftriaxone,” “empiric therapy,” “antibiotic resistance,” “third-generation cephalosporin,” “extended-spectrum β-lactamase,” “antimicrobial stewardship,” as well as infection-specific terms such as “community-acquired pneumonia,” “urinary tract infection,” “typhoid fever,” and “gonorrhea.”

Priority was given to recent systematic reviews, high-quality original research articles, international clinical guidelines (IDSA, ATS/IDSA, ESCMID), and authoritative surveillance reports, including WHO GLASS, CDC, and ECDC data. Studies were included if they specifically addressed empiric ceftriaxone use, dosing strategies, treatment duration, or the impact of resistance on clinical effectiveness. Studies focusing exclusively on pediatric or veterinary populations were excluded unless they provided findings of broader clinical relevance to human medicine.

Data extraction focused on reported clinical outcomes, dosing regimens, resistance patterns, and stewardship-related outcomes.

## Results

*Epidemiology of ceftriaxone use:* Ceftriaxone is among the most frequently prescribed broad-spectrum antibiotics in hospital settings worldwide [14]. Utilization studies indicate that its use accounts for approximately 30–60% of inpatient antibiotic exposure, depending on the clinical

and geographical context. High empirical utilization is particularly evident in low-resource settings.

In a tertiary hospital in Ethiopia, ceftriaxone was used in 59% of hospitalized patients, with 79.5% administered empirically [5]. The mean duration of therapy was 11.5 days (range 1–52 days), reflecting substantial deviation from guideline-recommended treatment durations [5].

A systematic review and meta-analysis reported a pooled prevalence of inappropriate ceftriaxone use of approximately 55% [6]. The main drivers included lack of microbiological confirmation, incorrect dosing intervals, and unnecessarily prolonged therapy. Similar patterns have been described across multiple regions, indicating a global issue in empirical antibiotic stewardship.

Common empirical indications include community-acquired pneumonia, sepsis of unknown origin, complicated urinary tract infections, meningitis, surgical prophylaxis, and sexually transmitted infections [1,10–12].

In European settings, ceftriaxone use remains high, alongside increasing third-generation cephalosporin resistance trends reported by surveillance systems [13].

*Dosing regimens and treatment duration:* Ceftriaxone is typically administered at 1–2 g intravenously once daily, consistent with its pharmacokinetic and pharmacodynamic profile [2]. The 2 g dose is generally reserved for severe infections or conditions requiring enhanced tissue penetration.

Evidence does not demonstrate a consistent clinical advantage of higher dosing. A meta-analysis found no significant differences between 1 g and higher doses in terms of clinical cure, mortality, or length of hospital stay [7]. These findings support the use of 1 g daily as standard therapy in most non-severe infections.

Shorter treatment durations have shown comparable efficacy to prolonged regimens. In uncomplicated urinary tract infections, a 3-day intravenous ceftriaxone regimen was non-inferior to longer courses [8]. These data support early de-escalation strategies and transition to oral therapy when clinically appropriate.

*Antimicrobial stewardship and prescribing optimization*: Ceftriaxone is a key target for antimicrobial stewardship interventions due to its frequent overuse and broad-spectrum activity. Effective strategies include formulary restriction, audit and feedback, dose optimization, and intravenous-to-oral switch protocols.

Stewardship interventions have been shown to reduce inappropriate use without negatively affecting clinical outcomes [9]. International guidelines emphasize reassessment of empiric therapy once microbiological results become available, with de-escalation to narrower-spectrum agents when possible [10,11].

The Infectious Diseases Society of America recommends that empiric ceftriaxone use should be guided by local resistance patterns, particularly avoiding use when resistance exceeds 10–20% or when risk factors for extended-spectrum beta-lactamase producing organisms are present [10,11].

*Bacterial resistance trends and mechanisms:*

*Enterobacterales:* Resistance to third-generation cephalosporins among Enterobacterales is increasing globally. A longitudinal surveillance study reported a ceftriaxone resistance rate of 28.2% in intra-abdominal and urinary tract infections [3].
The main resistance mechanisms include extended-spectrum beta-lactamases and AmpC beta-lactamases. Among resistant isolates, 44% carried AmpC genes and 38.8% carried ESBL determinants [3]. Similar trends have been reported in Europe, where resistance rates in invasive Klebsiella pneumoniae exceed 30% in many regions [13].

*Neisseria gonorrhoeae:* Ceftriaxone resistance in Neisseria gonorrhoeae is an emerging global concern. In China, resistance increased from 2.9% in 2017 to 8.1% in 2022 [4], largely associated with dissemination of the FC428 clone [4]. European surveillance reports lower but concerning levels of reduced susceptibility [12].
Resistance is primarily mediated by mosaic alterations in the penA gene, which reduce binding affinity of beta-lactam antibiotics [12].

*Salmonella enterica serovar Typhi:* Ceftriaxone-resistant Salmonella Typhi has recently emerged in South Asia. A 2024 outbreak in Bangladesh was caused by an ESBL-producing CTX-M-15 strain, indicating selective pressure from widespread empirical ceftriaxone use [14]. This highlights the risk of resistance emergence in high-burden infectious disease regions.

*Other pathogens:* Ceftriaxone has intrinsic inactivity against Pseudomonas aeruginosa and Enterococcus species, limiting its empirical utility in high-risk infections. Resistance in Haemophilus influenzae is mainly mediated by beta-lactamase production, although ceftriaxone retains activity in most cases [10].

*Safety and adverse effects:* Ceftriaxone is generally well tolerated and associated with a favorable safety profile [9]. The most common adverse effects include gastrointestinal symptoms and local infusion site reactions.
Large observational studies indicate a low incidence of Clostridioides difficile infection, with minimal differences between dosing strategies [7]. Severe hypersensitivity reactions are rare but clinically significant.
Biliary pseudolithiasis is a recognized complication, particularly in prolonged treatment courses, and is typically reversible after discontinuation [9]. Overall, the major clinical concern related to ceftriaxone is not toxicity but its contribution to antimicrobial resistance due to widespread overuse.

## 3. Discussion

Ceftriaxone remains one of the most extensively utilized third-generation cephalosporins in contemporary clinical practice, owing to its broad antimicrobial spectrum, favorable pharmacokinetic profile, once-daily dosing, and consistent efficacy across multiple infectious syndromes. Its established role in community-acquired pneumonia, pyelonephritis, complicated urinary tract infections (UTIs), intra-abdominal infections, gonorrhea, and sepsis has rendered it a cornerstone of empiric inpatient therapy [1,2]. Nevertheless, the very

attributes that make ceftriaxone clinically valuable have also contributed to widespread overuse, inappropriate empiricism, and prolonged treatment courses, thereby intensifying selective pressure for antimicrobial resistance.

Available evidence indicates that ceftriaxone achieves high rates of clinical success when prescribed in settings with preserved pathogen susceptibility and when aligned with syndrome-specific treatment principles. In hospitalized patients with uncomplicated UTIs, short-course regimens (e.g., three days) have demonstrated outcomes comparable to longer treatment durations, suggesting that extended intravenous therapy is frequently unnecessary [8]. Comparable observations have emerged in respiratory infections, where standard-dose regimens often provide equivalent clinical resolution to intensified dosing strategies in non-critically ill populations [7].

These findings reinforce a central antimicrobial stewardship principle: therapeutic effectiveness is determined less by maximal exposure than by appropriate indication, adequate source control, and pathogen susceptibility. Escalation of dose or prolongation of therapy in clinically stable patients rarely confers additional benefit and may instead increase adverse drug events, catheter-associated complications, costs, and ecological disruption of the microbiome [7,9].

Despite its therapeutic utility, ceftriaxone is frequently prescribed outside evidence-based indications. Studies from low- and middle-income settings have reported substantial rates of irrational prescribing, including unnecessary empiric initiation, continuation despite negative cultures, and excessive duration of therapy. A systematic review from Ethiopia estimated inappropriate ceftriaxone use at approximately 80%, highlighting the scale of stewardship failure in some health systems [6]. Prospective ward-based evaluations similarly identified frequent discordance between prescribing practice and guideline standards [5].

Such misuse is not a benign systems inefficiency; it directly contributes to the expansion of resistant Enterobacterales, Clostridioides difficile risk, and increased hospital antimicrobial consumption. Repeated exposure to third-generation cephalosporins is a recognized ecological driver of extended-spectrum beta-lactamase (ESBL)-producing organisms and AmpC-mediated resistance, particularly among Escherichia coli and Klebsiella pneumoniae.

Recent data further demonstrate the clinical consequences of indiscriminate empiric ceftriaxone use. In community-onset healthcare-associated UTIs, ceftriaxone-based empiric therapy was associated with elevated rates of inappropriate empiric antimicrobial treatment (IEAT), particularly in patients harboring resistant pathogens [1]. This has direct relevance for early sepsis management, where delays in active therapy correlate with poorer outcomes.

Accordingly, empiric ceftriaxone should not be considered a universal default agent. Risk stratification prior to prescription is essential. Factors consistently associated with resistance include:

[1] prior colonization or infection with ESBL-producing organisms;
[2] recent cephalosporin or fluoroquinolone exposure;
[3] residence in long-term care facilities;
[4] recurrent healthcare contact or recent hospitalization;
[5] indwelling urinary devices;
[6] recent international travel to high-resistance regions.

Where these factors are present, broader initial coverage (e.g., carbapenems or advanced β-lactam/β-lactamase inhibitor combinations) may be more appropriate pending microbiological confirmation [11].

The expanding resistance landscape represents the greatest threat to ceftriaxone's future utility. Longitudinal SMART surveillance from Taiwan documented substantial ceftriaxone resistance among Enterobacterales causing intra-abdominal and urinary infections, with rates approaching or exceeding thresholds at which empiric reliability becomes questionable [3]. Similar trends are reflected in European surveillance datasets, where cephalosporin resistance among invasive Gram-negative pathogens continues to rise heterogeneously across member states [13].

Equally concerning is the emergence of ceftriaxone-resistant Neisseria gonorrhoeae. Reports from China and national surveillance systems such as GRASP in the United Kingdom indicate increasing reduced susceptibility and resistant isolates, challenging one of the last dependable therapies for gonorrhea [4,12]. In parallel, outbreaks of ceftriaxone-resistant Salmonella Typhi underscore the capacity for resistance determinants to spread beyond hospital pathogens into major community-acquired infections [14].

Collectively, these developments signal a broader epidemiologic transition: ceftriaxone can no longer be assumed reliably active across many regions or syndromes without local resistance intelligence.

Given these realities, ceftriaxone stewardship should be operationalized through six integrated strategies:

[1] Restrictive indication-based prescribing
Reserve ceftriaxone for clinical scenarios where spectrum, tissue penetration, and parenteral administration are clearly justified. Narrower agents should be preferred whenever microbiologically and clinically appropriate.

[2] Resistance-informed empiricism
Empiric selection should incorporate illness severity, prior microbiology, healthcare exposure, host factors, and current institutional antibiograms.

[3] Dose optimization
For many non-severe infections, 1 g daily remains sufficient. Higher doses should be reserved for severe sepsis, obesity, meningitis protocols, or deep-seated infection when pharmacodynamic rationale exists [7].

[4] Duration minimization
Use the shortest effective treatment course, with early switch to oral therapy when clinically feasible. Evidence increasingly supports abbreviated regimens in selected UTIs and respiratory infections [8].

[5] Culture acquisition and de-escalation
Microbiological samples should precede antibiotic initiation whenever possible. Therapy should then be narrowed, discontinued, or redirected once susceptibility results become available.

[6] Audit, feedback, and surveillance systems
Institutional review mechanisms, prescribing dashboards, and national AMR surveillance platforms remain among the most effective tools for reducing unnecessary ceftriaxone exposure [6,12,13].

*Table 1. Comparative Analysis of Key Studies on Empirical Ceftriaxone Use and Bacterial Resistance*

| Study (Year) | Design & Population | Setting / Patients | Intervention & Comparison | Key Outcomes and Findings | Resistance / Clinical Implications |
|---|---|---|---|---|---|
| **Madrazo et al., J Clin Med 2025 [1]** | Prospective cohort; 235 adults with community-onset healthcare-associated UTI | Spanish tertiary hospital; median age 79 years | Empiric ceftriaxone monotherapy vs alternative antibiotics | Inappropriate empiric antimicrobial therapy (IEAT) was higher with ceftriaxone (36.4% vs 17.1%; *p*=0.001). Thirty-day mortality was similar (~11%). Median hospital stay was shorter with ceftriaxone (5 vs 6 days; *p*=0.037). | Resistant pathogens identified in 27.2% of ceftriaxone recipients, including ESBL/AmpC producers. Highlights need for risk-based empiric selection. |
| **Elajouz et al., 2022 [8]** | Retrospective cohort; 145 adults with uncomplicated UTI | Two US hospitals | Three-day IV ceftriaxone vs longer IV β-lactam regimens | Three-day ceftriaxone was non-inferior to longer regimens for clinical cure. Supports abbreviated treatment strategies. | Suggests shorter exposure may reduce selective pressure and hospital resource use. |
| **Aso et al., 2025 [2]** | Retrospective nationwide cohort; ~472,000 hospitalized CAP patients | Japanese national inpatient database | Ceftriaxone 2 g/day vs 1 g/day during first 2 treatment days | Thirty-day mortality was similar (4.5% vs 4.6%). In ventilated patients, 2 g/day showed lower mortality. Slightly higher *C. difficile* incidence with 2 g/day. | Routine dose escalation may be unnecessary outside critical illness. |
| **Brust-Sisti et al., Meta-analysis 2026 [7]** | Meta-analysis of 8 studies (5,145 patients) | Adults with non-CNS infections | High-dose (≥2 g/day) vs low-dose (1 g/day) | No significant difference in cure, mortality, or length of stay. | Supports 1 g/day as adequate for many routine infections. |

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| | | | ceftriaxone | | |
| **Ayele et al., Pharmacol Res Perspect 2018 [5]** | Prospective cross-sectional; 390 adult inpatients receiving ceftriaxone | Gondar University Hospital, Ethiopia | Drug utilization study | Point prevalence of ceftriaxone use was 59%; 79.5% prescribed empirically. Mean duration 11.47 days. Large proportion considered inappropriate. | Demonstrates excessive empiric use and prolonged exposure as stewardship concerns. |
| **Mulatu et al., Sci Rep 2024 [6]** | Systematic review/meta-analysis; 17 Ethiopian studies | National pooled prescribing data | Observational pooled analysis | Pooled inappropriate ceftriaxone use was 55.2% (95% CI 42.2–68.3%). Empiric prescribing strongly associated with misuse. | Confirms persistent inappropriate utilization at system level. |
| **Li et al., SMART Taiwan 2025 [3]** | Prospective surveillance (2009–2019); 31,611 Enterobacterales isolates | Intra-abdominal and urinary infections, Taiwan | Molecular epidemiology of 2,614 ceftriaxone-resistant isolates | Overall ceftriaxone resistance rate was 28.2%. Most common resistant isolates were *E. coli* and *K. pneumoniae*. | Resistance driven by AmpC and ESBL mechanisms; empiric ceftriaxone reliability reduced in high-burden settings. |
| **Zhu et al., MMWR 2024 [4]** | National surveillance report (2017–2022) | Gonococcal isolates from 13 provinces, China | Observational surveillance | Ceftriaxone resistance increased from 2.9% to 8.1%; five provinces exceeded 10%. | Signals emerging threat to first-line gonorrhea treatment. |
| **CDC / Hooda et al., Emerg Infect Dis 2025 [14]** | Passive surveillance / outbreak case-series | Bloodstream *Salmonella Typhi* isolates, Bangladesh | Outbreak investigation | Forty-seven ceftriaxone-resistant typhoid cases detected. | ESBL-mediated typhoid strains threaten standard therapy and require surveillance response. |
| **Real-world Safety** | Observational stewardship study | Hospitalized adults | Safety outcomes | Ceftriaxone-associated adverse events | Reinforces that stewardship protects both |

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| **Evaluation, ASHE [9]** | | receiving ceftriaxone | during routine use | included biliary complications, hypersensitivity, and *C. difficile*-related harms. | efficacy and patient safety. |

## Conclusions

Ceftriaxone remains a cornerstone of empiric antimicrobial therapy in the management of severe bacterial infections, primarily due to its broad antibacterial spectrum, favorable pharmacokinetic profile, and reliable once-daily dosing regimen. Its established efficacy across a wide range of clinical syndromes has secured its position in contemporary treatment algorithms. However, its sustained clinical value is increasingly constrained by cumulative prescribing pressure, inappropriate empiric initiation, prolonged treatment courses, and the progressive expansion of antimicrobial resistance among key bacterial pathogens.

Current evidence consistently demonstrates that ceftriaxone achieves maximal therapeutic benefit when its use is guided by a structured assessment of infection probability, patient-specific risk stratification, and up-to-date local susceptibility data. In environments with low resistance prevalence, it continues to serve as an effective first-line empiric agent, enabling timely intervention while maintaining favorable clinical outcomes. In contrast, in settings where resistance among relevant pathogens approaches or exceeds clinically significant thresholds, routine empiric reliance becomes progressively less justifiable and necessitates early reconsideration of alternative regimens or prompt de-escalation once microbiological data are available.

Optimization of dosing and duration is a critical determinant of both efficacy and resistance containment. Standard dosing of 1 g once daily is sufficient for most non-severe infections, whereas higher doses should be reserved for selected high-acuity conditions characterized by increased tissue penetration requirements or severe systemic involvement. In parallel, treatment duration should be strictly aligned with syndrome-specific evidence, favoring shorter courses and early transition to oral therapy whenever clinical stability permits.

From a population health perspective, the preservation of ceftriaxone efficacy is inseparable from the strength of antimicrobial stewardship systems. Effective control strategies require systematic reassessment of empiric therapy within 48 to 72 hours, mandatory culture acquisition prior to treatment initiation when feasible, routine de-escalation based on microbiological results, and continuous integration of local and international resistance surveillance data. These measures are increasingly urgent in the context of expanding resistance among Enterobacterales, Salmonella enterica serovar Typhi, and Neisseria gonorrhoeae, which collectively signal a narrowing therapeutic window for third-generation cephalosporins.

Ultimately, ceftriaxone should be viewed not as a universally applicable empiric solution, but as a highly effective intervention whose utility depends entirely on precision of use. Its future clinical relevance will be determined by whether prescribing practices evolve from empirical convenience toward microbiologically informed restraint. In this sense, ceftriaxone functions as a sensitive indicator of antimicrobial discipline within healthcare systems: its continued effectiveness reflects stewardship success, whereas its loss of reliability reflects systemic overuse.

A rational, evidence-driven approach remains the decisive factor in preserving its value. The imperative is therefore clear: ceftriaxone must be used with greater selectivity, accountability, and integration of diagnostic data. Only through such disciplined practice can its role as a life-saving empiric agent be sustained for future clinical generations.

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