JURNAL PHARMA BHAKTA

EFFECTIVENESS AND SAFETY OF CEFTAROLINE VS CEFTRIAXONE IN COMMUNITY ACQUIRED PNEUMONIA THERAPY: EVIDENCE FROM A DECADE OF RESEARCH

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ABSTRACT

Background: Community acquired pneumonia (CAP) remains a leading cause of morbidity and mortality among hospitalized adults. Appropriate selection of empirical antibiotics is crucial to prevent treatment failure and limit antimicrobial resistance. Ceftriaxone has long been the standard empirical therapy for moderate to severe CAP in many clinical guidelines. However, ceftaroline fosamil, a newer generation cephalosporin with activity against Streptococcus pneumoniae (including penicillin resistant strains), has emerged as a potential alternative. **Objective**: This review aims to evaluate randomized controlled trial (RCT) evidence published between 2015 and 2025 comparing the efficacy and safety of ceftaroline versus ceftriaxone in the treatment of CAP among hospitalized. **Methods**: A literature search was conducted in PubMed, ScienceDirect, and Scopus for RCTs published between 2015 and 2025 based on the checklist prism. **Results**: Evidence from RCTs (2015–2025) supports ceftaroline as an effective alternative to ceftriaxone for the management of CAP in hospitalized adults. Several pooled analyses suggest superiority of ceftaroline in terms of clinical cure, while no significant differences were observed in mortality outcomes. The safety profiles of both agents were generally comparable. **Conclusion**: This review supports ceftaroline as an effective empirical alternative to ceftriaxone for moderate to severe CAP, with evidence indicating potential advantages in clinical cure rates.

ABSTRAK

Latar belakang: Community acquired pneumonia (CAP) menjadi penyebab morbiditas dan mortalitas yang signifikan pada pasien dewasa yang dirawat di rumah sakit. Pemilihan antibiotik empiris yang tepat sangat penting untuk mencegah resistensi. Ceftriaxone sudah lama menjadi standar empiris untuk CAP sedang-berat di banyak pedoman dibandingkan secara klinis dengan Ceftaroline fosamil, sefalosporin generasi baru yang memiliki spektrum terhadap *Streptococcus pneumoniae* termasuk strain yang resisten terhadap penicillin. **Tujuan**: Kajian ini meninjau bukti RCT tahun 2015-2025 yang membandingkan efektivitas dan keamanan ceftaroline versus ceftriaxone untuk pengobatan CAP pada pasien dewasa yang dirawat di rumah sakit. **Metode**: Pencarian artikel dilakukan pada PubMed, ScienceDirect, dan Scopus (2015–2025) berdasarkan Prisma ceklis **Hasil**: Bukti RCT (2015–2025) mendukung bahwa ceftaroline

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merupakan alternatif efektif terhadap ceftriaxone untuk pengobatan CAP yang dirawat inap; beberapa analisis pooled menunjukkan keunggulan ceftaroline pada *clinical cure*, sementara mortalitas tidak berbeda bermakna. Profil keamanan kedua agen umumnya serupa. **Simpulan**: Kajian ini mendukung penggunaan ceftaroline sebagai alternatif empiris yang efektif untuk CAP sedang-berat, dengan beberapa bukti keunggulan dalam perbaikan klinis.

INTRODUCTION

Community acquired pneumonia (CAP) is a major cause of hospitalization and mortality worldwide (Anderson & Feldman, 2023; NICE, 2023). The incidence of CAP increases with age and the prevalence of comorbidities such as heart disease, diabetes, and chronic lung disease, making effective empirical therapy a clinical priority. Appropriate empiric antibiotic selection reduces the risk of treatment failure, length of hospital stay, and mortality (Malinis et al., 2024; NICE, 2023).

Ceftriaxone, a third generation, broad spectrum cephalosporin antibiotic, has long been the standard choice for empirical therapy of moderate to severe CAP. However, the emergence of *Streptococcus pneumoniae* strains with reduced susceptibility, the threat of *Staphylococcus aureus* (including Methicillin Resistant *S. aureus* [MRSA]), and the need for broader spectrum therapy have driven the development of newer antibiotics (Mahapatra et al., 2024; Metlay et al., 2019).

Ceftaroline fosamil, a prodrug converted into active ceftaroline, is a cephalosporin with affinity for several Penicillin Binding Proteins (PBPs) associated with resistance in *S. pneumoniae*, and has in vitro activity against certain *S. Aureus* strains, including MRSA (Bae & Stone, 2019; European Medicines Agency, 2019). This pharmacological profile makes ceftaroline a candidate for empirical therapy in CAP patients, particularly when suspected pathogens include less susceptible pneumococci or *S. aureus*. This potential has been evaluated in several phase III clinical trials and several regional studies (Bae & Stone, 2019; Kuraieva et al., 2023; Utt et al., 2023).

Phase III RCTs and recent studies (2015–2025) have compared ceftaroline with ceftriaxone. This review summarizes the latest evidence on their comparative clinical effectiveness and safety profiles to provide clinicians with an updated reference for selecting optimal empirical therapy for moderate to severe CAP.

METHOD

Articles included in this review were selected following PRISMA checklist (Figure 1). This review employed a systematic review method of randomized controlled trials (RCTs), aiming to comprehensively identify, evaluate, and synthesize evidence from RCTs comparing ceftaroline and ceftriaxone for the treatment of CAP. Literature searches were conducted in PubMed, ScienceDirect, and Scopus for RCTs published between 2015 and 2025, using the keywords: ceftaroline, ceftriaxone, community acquired pneumonia (CAP), effectiveness, and safety. This review aims to evaluate evidence from RCTs conducted between 2015 and 2025 that compared the efficacy and safety of ceftaroline versus ceftriaxone in the management of CAP among hospitalized patients.

Inclusion criteria included RCTs in adult patient populations with CAP, ceftaroline fosamil as the interventions, ceftriaxone as the comparator, and English language publications. Exclusion criteria included meta analyses, literature reviews, editorials, case reports, non RCTs, or trials without a ceftriaxone comparators, as well as studies on non CAP penumonia. From 750 identified articles, five met eligibility criteria and were analyzed. Initial selection was carried out by researchers based on the title and abstract, followed by full text assessment of relevant studies.

RESULT

A review of five research articles showed consistent findings regarding the effectiveness of ceftaroline fosamil compared with standard therapy (usually ceftriaxone, sometimes plus vancomycin) in the treatment of CAP in both adult and pediatric patients.

The study by Zhong et al. (2015) involving Asian adult patients with moderate to severe CAP (PORT III–IV) showed that ceftaroline fosamil had a higher clinical cure rate (84%) compared to ceftriaxone (74%). In terms of safety, the adverse event profile of ceftaroline was relatively similar to ceftriaxone, with most events being mild to moderate and no increase in serious adverse events. These findings indicate that ceftaroline can be safely used in adult populations with moderately severe pneumonia.

The study by Blumer et al. (2016) in pediatric patients with complicated CABP showed that ceftaroline provided a comparable clinical response rate to the combination of ceftriaxone plus vancomycin. However, a significant difference was observed in safety outcomes: only 40% of patients receiving ceftaroline experienced adverse events (generally mild to moderate), compared with 80% in the control group. This suggests that ceftaroline is more tolerable than the standard combination therapy involving vancomycin.

The study by Cannavino et al. (2016), which also examined pediatric patients with CAP, showed very high clinical cure rates in both groups, 88% for ceftaroline and 89% for ceftriaxone. Regarding safety, adverse events were similar between the two groups, with most being mild. No deaths or serious adverse events directly attributable to ceftaroline were reported. This study confirms the safety of ceftaroline in children, including those with resistant *S. aureus* infections.

A pooled analysis of six phase III clinical trials by Dryden et al. (2022) evaluated adult patients with CAP or cSSTI with secondary bacteremia. The results showed that ceftaroline achieved a clinical cure rate of 76.4% compared with 77.3% for the comparator, demonstrating comparable effectiveness. In terms of safety, adverse events in bacteremic patients were consistent with the previously established safety profile, including mild gastrointestinal reactions and transient elevations in liver enzymes. No new safety concerns were identified, nor was there an increased risk compared with standard therapy, indicating that ceftaroline is safe for use in complex systemic infections.

In a subset analysis of CAP patients in China, Zhuo et al. (2022) reported that ceftaroline fosamil achieved a significantly higher clinical cure rate (76.2%) compared with ceftriaxone (61.0%). The safety of ceftaroline was also confirmed, with most adverse events being mild to moderate, such as nausea and diarrhea, with no serious adverse events leading to treatment discontinuation. Thus, ceftaroline is considered safe and more effective than standard therapy in Asian populations.

Overall, all the reviewed studies demonstrated that ceftaroline fosamil is not only effective in the treatment of CAP but also has a consistent and well tolerated safety profile, often superior to standard therapy. These advantages establish ceftaroline as a viable therapeutic option for both adults and children, including those at high risk of complications.

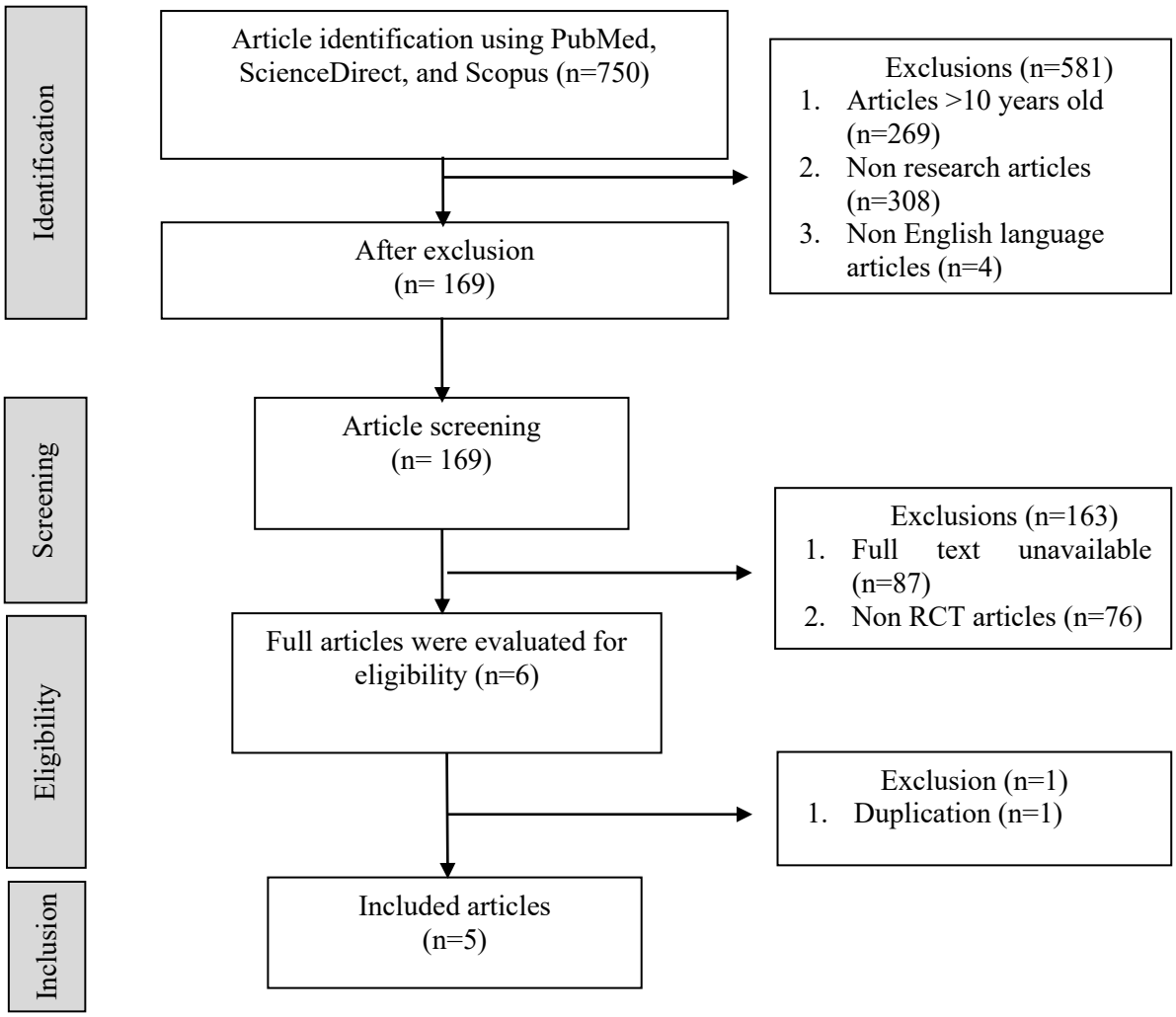

Figure 1. Publication Selection Process (PRISMA Flowchart)

DISCUSSION

The findings from the five reviewed studies indicate that ceftaroline fosamil is a new generation antibiotic with high effectiveness in the treatment of CAP in both adults

and children. The studies by Zhong et al. (2015) and Zhuo et al. (2022) in Asia showed that ceftaroline was superior to ceftriaxone in improving clinical symptoms and achieving higher cure rates in CAP patients. Furthermore, both groups had similar safety profiles, with no new safety signal identified. These findings are further reinforced by a real world study by Ferry et al. (2024), which confirmed the effectiveness of ceftaroline in adult patients across Europe and Latin America. In this setting, ceftaroline not only provided favorable clinical outcomes but also reduced the duration of hospitalization without introducing new safety concerns. Thus, evidence from RCT and real world practice supports and strengthens the role of ceftaroline as a therapeutic option for moderate to severe CAP.

In addition, ceftaroline has been shown to be effective against *S.aureus* infections, including *methicillinresistant strains*. Cannavino et al. (2016) and Blumer et al. (2016) demonstrated in pediatric populations that ceftaroline is safe and effective in treating infections involving MRSA. An in vitro study by Mohamed et al. (2024) further confirmed that ceftaroline remained active against MRSA and *S.pneumoniae* resistant to other antibiotics, demonstrating that ceftaroline's antibiotic activity is relevant amidst increasing global antibiotic resistance. In line with these findings, a systematic review by Torres et al. (2023) identified ceftaroline as a potential alternative to linezolid or vancomycin for the management of MRSA pneumonia, particularly in severe or complex cases. Moreover, real world evidence by Hammond et al. (2024) reinforced this by reporting that ceftaroline, either used alone or in combination with daptomycin or vancomycin, resulted in better clinical outcomes in patients with MRSA bacteremia, a condition known for its high mortality rate.

In the study by Blumer et al. (2016), the frequency of adverse events was lower in the ceftaroline group (40%) compared with ceftriaxone + vancomycin (80%). Meanwhile, Cannavino et al. (2016) reported Coombs seroconversion was found in 17%, but without evidence of hemolysis or other clinically significant effects. These data confirm that ceftaroline is well tolerated and represents a rational therapeutic option in children, including those at risk of MRSA infection. This evidence is further reinforced by Esposito et al. (2021), which confirmed the safety of ceftaroline in pediatric patients with pneumonia and complicated skin and soft tissue infections (cSSTI). Its safety profile remains consistent with other cephalosporin antibiotics, without introducing new potential safety concerns.

In adult patients with CAP and a higher risk of complications, the findings of Dryden et al. (2022) are particularly important because they analyzed six phase III trials (FOCUS 1–2, ASIA CAP, CANVAS 1–2, COVERS) and demonstrated that the clinical outcomes with ceftaroline in secondary bacteremia cases were comparable to the comparator without the emergence of new toxicity signals. This indicates that ceftaroline is able to maintain its effectiveness even when CAP progresses to systemic infection. Thus, the clinical relevance of ceftaroline is not limited to “inpatient CAP” but also includes “CAP complicated by systemic infection,” a condition commonly

observed in patients with high comorbidities. These results are further reinforced by real world data from Europe, Latin America reported by Ferry et al. (2024), which documented favorable clinical responses in adults with CAP, including severe cases, as well as a reduction in hospital length of stay without additional safety concerns. Furthermore, a recent systematic review by Torres et al. (2023) positioned ceftaroline as a competitive anti MRSA β lactam option for severe or high risk MRSA pneumonia, providing both biological rationale and clinical evidence to support its use in CAP with complications. Based on this accumulated evidence, it can be concluded that in adult patients with high risk CAP, including secondary bacteremia, ceftaroline provides effectiveness at least comparable to standard with a consistent safety profile, thereby making it a reasonable empirical choice for the management of severe and complex CAP cases.

From a structural perspective, ceftaroline retains the cephalosporin core (β lactam+dihydrothiazine) with side chain modifications at positions 3 and 7 that enhance its affinity for PBP2a (MRSA) and PBP2x (*S.pneumoniae*). This is the key to its antimicrobial spectrum, surpassing that of previous generation cephalosporins. Recent reviews and monographs have confirmed ceftaroline's high affinity for PBP2a and PBP2x as the basis of its clinical activity against MRSA and resistant pneumococci (Carcione et al., 2023). Ceftaroline differs from other β lactams by its ability to target the allosteric pocket of PBP2a in MRSA, a structural feature typically hidden and inaccessible to previous generation β lactam antibiotics. When ceftaroline binds to this allosteric pocket, it induces a conformational change that opens the active site of PBP2a, which is normally closed. This opening allows ceftaroline (or other β lactam) molecules to enter and inhibit transpeptidation activity, ultimately inactivating the enzyme and damaging the bacterial cell wall (Jiao et al., 2023; Rosado et al., 2025).

Table 1. Characteristics of included RCTs

Author	Year	Design	Treatment	N	Population	Duration	Main Outcome	Results	Source
Zhong et.al.	2015	*Randomized, double blind, active controlled, phase 3 non inferiority trial dengan nested superiority design*	Ceftaroline fosamil 600 mg IV every 12 hours versus Ceftriaxone 2 g IV every 24 hours	771	Asian adult patients with CAP (age ≥18 years)	5-7 days	Effectiveness (clinical cure on test of cure (TOC) in per-protocol (PP) population) and Safety (adverse events)	Clinical cure rate (PP): Ceftaroline: 91.6% (317/346) Ceftriaxone: 88.1% (310/352) Treatment difference: +3.5% (95% CI −1.6 to +8.7) Both groups had similar safety profiles.	(Zhong et al., 2015)
Blumer et.al.	2016	Multisenter, *randomized, observer blinded, active controlled trial*	Ceftaroline fosamil IV versus ceftriaxone + vancomycin IV	40	Pediatric patients aged 2 months to <18 years with CAP	Minimum ≥3 days	Effectiveness (clinical response and clinical stability) and safety (adverse events)	Clinical response (mITT): Ceftaroline 52% (15/29) vs Ceftriaxone 67% (6/9). Clinical stability on *Day-4*: Ceftaroline 21% (6/29) vs Ceftriaxone 22% (2/9). *Adverse events* (TEAEs): Occurred in 12/30 (40%) patients on ceftaroline vs 8/10 (80%) on ceftriaxone; most were mild–moderate.	(Blumer et al., 2016)
Cannavino et.al.	2016	*Randomized, active controlled, observer blinded clinical trial*	ceftaroline fosamil IV versus ceftriaxone IV; oral switch option for total	160	Pediatric patients with CAP	5–14 days (including oral switch option).	Effectiveness (clinical cure rate pada test of cure [TOC]) and Safety/ tolerability	Clinical cure in mITT in TOC: ceftaroline 94/107 (88%) vs ceftriaxone 32/36 (89%). The frequency of treatment emergent adverse events was similar (ceftaroline 55/121 [45%]	(Cannavino et al., 2016)

Author	Year	Design	Treatment	N	Population	Duration	Main Outcome	Results	Source
			duration of therapy.					vs. ceftriaxone 18/39 [46%]). Coombs test seroconversion occurred in 17% of ceftaroline patients, but without evidence of hemolytic anemia.	
Dryden et.al.	2022	*Six phase III randomized, prospective clinical trials were conducted with active comparators, three of which involved hospitalized adults with CAP.*	ceftaroline fosamil versus ceftriaxone	1976	Adult patients with CAP	5-7 days	Effectiveness (clinical cure dan microbial response rate) and Safety (adverse events)	Clinical cure rate (bacteremia): Ceftaroline vs Ceftriaxone: 55/72 (76.4%) vs 51/66 (77.3%) Clinical cure rate (non bacteremia): Ceftaroline vs Ceftriaxone: 822/966 (85.1%) vs 717/872 (82.2%) Microbiological response rate (bacteremia): Ceftaroline vs Ceftriaxone 56/72 (77.8%) vs 54/66 (81.8%) Microbiological response rate (non bacteremia): Ceftaroline vs Ceftriaxone: 825/966 (85.4%) vs 719/872 (82.5%) In patients with bacteremia, the observed adverse events aligned with the established safety profile of ceftaroline fosamil	(Dryden et al., 2022)
Zhuo et.al.	2022	*randomized, double blind, active controlled*	Ceftaroline fosamil 600 mg every 12 hours IV or	302	Adult patients hospitalize d in China	5-7 days	Effectiveness (clinical cure rate) and Safety	Clinical cure rate (TOC, CE population): Ceftaroline vs Ceftriaxone: 80/105 (76.2%) vs 61/100 (61.0%) Difference: +15.2%	(Zhuo et al., 2022)

Author	Year	Design	Treatment	N	Population	Duration	Main Outcome	Results	Source
			ceftriaxone 2 g every 24 hours IV		with CAP		(adverse events)	(95% CI: 2.5%–27.6%) The incidence of adverse events was consistent with the safety profile of the main study; no new threats were detected in the Chinese subset.	

The safety profile of ceftaroline is also influenced by its chemical structure. The absence of the N-methyl-thiotetrazole (NMTT) side chain at position 3, a structural feature in some previous generation cephalosporins that has been associated with hypoprothrombinemia or disulfiram like reactions, contributes to ceftaroline's improved safety profile. Recent reviews on cephalosporin safety have emphasized that NMTT related risks are restricted to specific agents and are not observed with ceftaroline (Park et al., 2019).

Overall, these findings indicate that ceftaroline fosamil is not only comparable or superior to ceftriaxone in the treatment of CAP, but also offers a distinct advantage in addressing resistant pathogens such as MRSA, in both adult and pediatric populations. The consistency of evidence from this study further reinforces the role of ceftaroline as an antibiotic with strong potential to serve as a first line option in the management of moderate to severe CAP, particularly in regions with high resistance prevalence and in patients at risk of serious complications.

CONCLUSION

Ceftaroline fosamil demonstrates clinical effectiveness comparable to or exceeding ceftriaxone in the treatment of Community Acquired Pneumonia (CAP), with a consistent and favorable safety profile. Evidence from adult, pediatric, and high risk populations, including cases with MRSA and secondary bacteremia, confirms its reliability across diverse settings. Its structural advantages and activity against resistant pathogens strengthen its role as an alternative or first line empirical therapy for moderate to severe CAP.

RECOMMENDATION

Future studies should further evaluate ceftaroline's role in special populations, including immunocompromised patients, the elderly with multiple comorbidities, and those with severe or recurrent CAP. Large scale, real world comparative studies are also warranted to confirm its effectiveness and safety beyond controlled trial settings, particularly in regions with high antimicrobial resistance rates. In addition, cost effectiveness analyses would be valuable to inform healthcare policy and antibiotic stewardship programs. Finally, mechanistic and pharmacokinetic investigations could provide deeper insights into optimizing dosing strategies and exploring combination therapies, especially for infections caused by multidrug resistant pathogens.

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