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REVIEW

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Current role of ceftobiprole in the treatment of hospital-acquired and community-acquired pneumonia: expert opinion based on literature and real-life experiences

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ABSTRACT

Introduction: Community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) are major global health challenges, with high morbidity and mortality rates. The increasing prevalence of multidrug-resistant (MDR) bacteria may diminish the effectiveness of standard empirical antibiotics, highlighting the need for broader-spectrum agents that target also MDR organisms.

Areas covered: This review summarizes findings from a PubMed search on the use of ceftobiprole in CAP and HAP. It highlights key features of ceftobiprole, including its mechanism of action and broad spectrum of activity against multiple MDR pathogens. Clinical data from randomized controlled trials and real-world studies underscore its non-inferiority to standard treatments, with favorable safety profile and high clinical cure rates even in challenging cases.

Expert opinion: Ceftobiprole represents a valid option for the patients with CAP and HAP. Its main advantages include its broad spectrum of activity, making it a valuable therapeutic choice for treating polymicrobial infections, and its favorable safety profile, which makes it a good candidate in elderly patients with multiple comorbidities and polypharmacy. Caution is advised in patients at high risk of ESBL-producing organisms or MDR *Pseudomonas aeruginosa* infections, where combination therapy is recommended. Moreover, therapeutic drug monitoring is recommended to improve outcomes, particularly in complex clinical conditions.

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Ceftobiprole; community-acquired pneumonia; hospital-acquired pneumonia; multidrug-resistant bacteria; therapeutic drug monitoring; real-life evidence; expert opinion

1. Introduction

Despite medical advances, bacterial pneumonia remains a major health concern with high morbidity and mortality worldwide [1–3]. The two most common forms of this disease are community-acquired pneumonia (CAP), contracted outside of healthcare settings [4], and hospital-acquired pneumonia (HAP), which develops 48 hours or more after hospital admission [5]. Both conditions are associated with high mortality rates, especially among young children, the elderly, and immunocompromised individuals [5–7]. Moreover, these diseases pose a significant burden on patients, leading to frequent hospitalizations, intensive care unit (ICU) admissions, and extended hospital stays, as well as high healthcare costs [6,8].

The empirical treatment for hospitalized CAP patients without risk factors for infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa (P. aeruginosa)*, typically includes a beta-lactam combined with a macrolide or, alternatively, monotherapy with a respiratory fluoroquinolone [9,10]. When MRSA or *P. aeruginosa* infection is suspected, vancomycin or linezolid should be included for MRSA, while *P. aeruginosa* coverage requires a traditional anti-pseudomonal beta-lactam, a beta-lactam/beta-lactamase inhibitor combination or carbapenem [9]. Regarding HAP, an initial empirical regimen should include a beta-lactam with activity against *P. aeruginosa*, other Gram-negative bacteria and methicillin-susceptible *Staphylococcus aureus* (MSSA) [11]. In the presence of risk factors for multidrug-resistant (MDR) Gram-negative bacteria, newer beta-lactam/beta-lactamase inhibitor combinations – such as ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam,

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Article highlights

- The increasing prevalence of multidrug-resistant pathogens poses significant challenges in treating bacterial CAP and HAP. This prompts the use of broad-spectrum antibiotics and tailored therapies for patients at high risk of MDR infections.
- Ceftobiprole is a fifth-generation cephalosporin with broad-spectrum activity. It is effective against a wide range of Gram-positive and Gram-negative pathogens, including MRSA and *Streptococcus pneumoniae*, but lacks activity against MDR *Pseudomonas aeruginosa* and ESBL-producing *Enterobacterales*.
- Ceftobiprole has a short half-life and renal elimination, thus requiring dose adjustments in patients with renal impairment. Therapeutic drug monitoring is recommended to optimize the bactericidal activity while mitigating the risk of overexposure.
- Phase 3 RCTs demonstrated ceftobiprole's non-inferiority to standard treatments for CAP and HAP, with comparable safety profiles. Post-hoc analyses further highlighted its efficacy in high-risk populations, including elderly patients and those with comorbidities.
- Observational studies report high clinical cure rates (up to 85%) in CAP and HAP, a positive safety profile, and effectiveness both in monotherapy and combination therapy. Ceftobiprole shows activity in polymicrobial infections and against selected MDR pathogens, offering advantages as a carbapenem-sparing agent to reduce reliance on more toxic antibiotics.
- In conclusion, literature supports ceftobiprole as a safe and effective option for CAP and HAP due to its broad-spectrum activity and favorable safety profile. Experts recommend caution in patients at high risk for MDR *Pseudomonas aeruginosa* and ESBL-producing *Enterobacterales*, and suggest the use of TDM to improve clinical outcomes.

or cefiderocol – may be considered [12]. If risk factors for MRSA are present, the addition of vancomycin or linezolid should be considered [11]. For both CAP and HAP, the antimicrobial regimen should be tailored based on the results of antimicrobial susceptibility testing (AST) once available.

Despite the availability of multiple empirical treatment options, the burden of CAP and HAP has been increasing in recent decades due to the aging population, with concomitant increases in the rates of comorbidities and in the prevalence of MDR bacteria [6,13,14]. Bacteria such as MRSA, penicillin and ceftriaxone-resistant *Streptococcus pneumoniae* [15] as well as extended-spectrum β-lactamases (ESBLs) and carbapenemase-producing *Enterobacterales* have rendered many first-line treatments for lower respiratory infections ineffective in patients at risk of infection by MDR organisms [16]. As a result, the empirical treatments currently in use may be insufficient in some cases, and antibiotic coverage also for MDR organisms may be needed. It is especially important to identify patients at higher risk of infection from MDR pathogens to avoid increased mortality due to inappropriate initial antibiotic therapy [17,18]. Many factors are acknowledged to be associated with drug-resistant pathogens. With regard to CAP, prior hospitalization, immunosuppression, previous antibiotic use and non-ambulatory status stand out among the numerous risk factors [19]. Regarding HAP, established risk factors for resistant pathogens include residence in a nursing home, intravenous antibiotic use within the previous 90 days, septic shock and need for intubation [17,20]. In this context, a useful tool to identify high-risk patients is the PES score, a recently validated scale which has shown to effectively predict the risk of infections from *P. aeruginosa*, ESBL-producing Enterobacterales and MRSA. The score was particularly effective in ruling out patients at risk, while also helping to identify those who may benefit from more thorough diagnostic testing and broader-spectrum antibiotic therapy [21,22].

Among the new antimicrobial agents, ceftobiprole is a fifth-generation cephalosporin that offers broad-spectrum activity against various respiratory pathogens, including MRSA [23]. Its safety and non-inferiority to standard treatments were confirmed through two randomized clinical trials, leading to its approval for treating CAP and HAP by both EMA and FDA [24,25]. Additionally, observational studies have demonstrated its favorable cure rates and safety profile in real-world patients, as well as potential advantages in its use, including its broad bactericidal activity, its role as a sparing agent and its use in complex patients with multiple comorbidities [26–34].

This review outlines the main characteristics of ceftobiprole that makes it an effective agent in the treatment of CAP and HAP, including its mechanism of action, *in vitro* activity and pharmacological properties. Moreover, the review provides an updated overview of the main results of phase-3 randomized controlled trials and real-life experiences on the outcomes of ceftobiprole use in the treatment of CAP and HAP. Additionally, this review integrates the opinion of experts in infectious diseases to offer a comprehensive perspective on ceftobiprole's efficacy, safety, and role in clinical practice, highlighting its potential advantages and considerations for use.

2. Methods

A group of infectious disease experts conducted a systematic literature review to evaluate the use of ceftobiprole in community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). The search was performed in the PubMed database using the following keywords: 'ceftobiprole,' 'CAP,' 'HAP,' 'pneumonia,' 'comparator,' 'real-life,' and 'real-world.' The search was restricted to articles published in English and limited to the following publication types: Observational Studies, Reviews, Systematic Reviews, Clinical Trials, Clinical Studies, Case Reports, Meta-Analyses, Classical Articles, and Letters. The search period covered articles published between 2014 and 2024, with the inclusion of key registrational studies published prior to 2014.

A total of 146 articles were identified; these were manually reviewed to remove duplicates, and titles and abstracts were screened for relevance to the study objectives. Articles focusing exclusively on the off-label use of ceftobiprole were excluded. Relevant articles were further reviewed and discussed by the experts to summarize key findings on the clinical use of ceftobiprole. Notably, information on the off-label use of ceftobiprole was excluded from the discussion and the manuscript.

3. Antimicrobial properties and in vitro evidence

Ceftobiprole exhibits its antibacterial activity by inhibiting the transpeptidase moiety of penicillin-binding proteins (PBPs), thus blocking cell wall synthesis in Gram-positive and Gram-negative bacteria. It is effective also against PBPs that are resistant or poorly susceptible to traditional β-lactams, including PBP2a in MRSA and PBP2b and PBP2× in *S. pneumoniae*.

Moreover, compared to other cephalosporins, it exhibits stronger affinity for PBPs [35,36].

Ceftobiprole is resistant to degradation by several β-lactamases, including the staphylococcal PC1 penicillinase, class A broad-spectrum β-lactamases of the TEM type, and chromosomal AmpC-type β-lactamases found in *Enterobacterales* and *P. aeruginosa*. Conversely it is degraded by class B, class D enzymes, and class A ESBLs [35,37].

Altogether, these characteristics contribute to ceftobiprole's broad spectrum of activity, which effectively targets a wide range of Gram-positive and Gram-negative pathogens. Large surveillance studies conducted in Europe and the United States have demonstrated ceftobiprole's activity against clinical isolates from various infections [38–41].

Specifically, ceftobiprole exhibited potent *in vitro* activity against nearly 100% of tested *S. aureus* strains, including up to 99.6% of MRSA with a reduced susceptibility to levofloxacin, clindamycin, and erythromycin [38,40,41]. It also demonstrated significant *in vitro* activity against *S. pneumoniae* (up to 98.4% of isolates) [41], coagulase-negative staphylococci, beta-hemolytic streptococci, and *Enterococcus faecalis*. Additionally, non-ESBL *Enterobacterales* were susceptible to ceftobiprole, with rates ranging from 77.4% [41] to 84.8% [39]. Up to 74.4% of *P. aeruginosa* strains tested were also susceptible to ceftobiprole [39]. However, ceftobiprole has a low activity against the MDR phenotype of *P. aeruginosa* and its susceptibility should be tested prior to use it for targeted treatment. Therefore, in case of empirical treatment for patients having risk factors for MDR *P. aeruginosa*, in settings where MDR strains are highly prevalent, it may be recommended to use ceftobiprole in combination with other potentially active antipseudomonal agents, such as amikacin and levofloxacin, which have demonstrated synergistic activity with ceftobiprole in *in vitro* studies [35,42].

Lastly, ceftobiprole has demonstrated notable activity against MSSA/MSRA and methicillin-sensitive and resistant *Staphylococcus epidermidis* (MSSE/MRSE) grown as biofilms, both alone and in combination with rifampin or vancomycin [43].

Notably, the reference method recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for the determination of the minimum inhibitory concentration (MIC) is the broth microdilution method [44,45]. The EUCAST clinical breakpoints for susceptibility to ceftobiprole are ≤2 mg/L for *S. aureus*, ≤ 0.5 mg/L for *Streptococcus pneumoniae*, ≤ 0.25 mg/L for *Enterobacterales*, while there is insufficient evidence to determine susceptibility breakpoints for *Streptococcus* groups A, B, C, G, *Haemophilus influenzae, Moraxella catarrhalis* and *P. aeruginosa* [44].

4. Pharmacological and pharmacokinetic properties

Like other beta-lactam antibiotics, ceftobiprole is a hydrophilic molecule, it has low plasma protein binding (16%), a short elimination half-life of approximately 3 hours, minimal potential for drug-drug interactions, and is completely eliminated as an unmodified moiety through the kidneys [46].

Its pharmacokinetic/pharmacodynamic (PK/PD) profile reflects time-dependent antibacterial activity, and higher drug exposure strongly correlates with both microbiological eradication and clinical cure [47]. A percentage of the dosing interval above the minimum inhibitory concentration ($t > MIC$) > 51% is required to achieved favorable clinical outcome, while a percentage > 62.2% is needed for microbiological eradication [47]. However, literature evidence suggests that more aggressive PK/PD targets may be used to minimize the risks of microbiological failure and resistance, especially in critically ill patients or in difficult-to-treat infections [46,48]. Moreover, it is important to consider the concentration-time profile required at the primary infection site, which in case of ceftobiprole is the epithelial lining fluid (ELF) [46]. Median ELF penetration of ceftobiprole was 69% in a murine pneumonia model and 25.5% in healthy volunteers; although it remains unclear whether higher dosages may increase the ELF penetration of ceftobiprole [46,49].

Based on its PK/PD characteristics, the current recommended dosage of ceftobiprole for pneumonia is 500 mg intravenously over 2 hours every 8 hours, though adjustments are needed for patients with renal impairment or those undergoing hemodialysis. Patients with augmented renal clearance (ARC) should receive a prolonged 4-hour infusion to optimize exposure [42,50].

Due to significant variability in individual PK/PD responses, and the importance of obtaining an optimal drug exposure, therapeutic drug monitoring (TDM) is recommended to improve patients' outcomes and reduce the risk of side effects [51]. A retrospective study showed a 96.7% eradication rate among patients with staphylococcal infections who underwent TDM while being treated with ceftobiprole [46]. According to the authors, intensified dosages administered as continuous infusion are recommended against MRSA in patients with impaired renal function and ARC [46]. On the other hand, TDM is critical to preventing overexposure and mitigating the risk of neurotoxicity, particularly in elderly patients or those on continuous infusions [48,52].

Despite its advantages, TDM is not commonly implemented in clinical practice due to several challenges that hinder its widespread use. These include the existence of variable methodologies and differing laboratory protocols, the absence of validated therapeutic ranges for many antibiotics, and practical aspects such as the complexity of sampling, the need for costly equipment and the lack of specialized expertise [51]. However, experts believe that establishing a functional TDM platform could significantly improve the management of patients with CAP or HAP treated with ceftobiprole.

5. Ceftobiprole cure rate and safety profile: evidence from phase-3 randomized controlled trials and post-hoc analyses

Ceftobiprole is approved for the treatment of patients with CAP or HAP based on two key phase 3 randomized, controlled, non-inferiority trials that demonstrated its safety profile and non-inferiority compared to standard treatments [24,25].

In the first study, a multicenter, double-blind trial involving 706 patients with CAP requiring hospitalization, ceftobiprole (500 mg q8h) was compared 1:1 to ceftriaxone (2 g/

day), with optional linezolid for suspected MRSA infections. The primary endpoint, clinical cure at the test-of-cure (TOC) visit, showed that ceftobiprole was non-inferior to ceftriaxone in both the intention-to-treat (ITT) and clinically evaluable (CE) populations. Clinical cure rates for ceftobiprole were 76.4% in the ITT population and 86.6% in the CE population, compared to 79.3% and 87.4% for ceftriaxone ± linezolid, thus meeting the predefined margin of 10% for non-inferiority. Both drugs were well tolerated, with adverse events requiring premature discontinuation being rare (6% vs 4% for ceftobiprole vs comparator) and slightly higher rates of mild nausea (7% vs 2%) and vomiting (5% vs 2%) in the ceftobiprole group [24,35].

The second trial, conducted by Awad et al. focused on patients with HAP and confirmed the non-inferiority of ceftobiprole (500 mg q8h) when compared to ceftazidime (2 g q8h) combined with linezolid (600 mg q12h). In this study, involving 781 patients, the cure rates for ceftobiprole and the ceftazidime/linezolid combination were similar, namely 59.6% vs 58.8%, respectively, in the ITT population, and 77.8% vs 76.2% in the CE population, thus meeting the 15% non-inferiority margin. Importantly, ceftobiprole showed an advantage in early improvement compared to the comparator (86.9% vs. 78.4%), particularly in patients with MRSA-positive cultures (94.7% vs. 52.6%). The safety profile of ceftobiprole was comparable to that of ceftazidime/linezolid, with treatment-related adverse events occurring at similar rates in both groups (24.9% vs 25.4%) [25,35]. Possible explanations for the study results are that ceftobiprole, in addition to its anti-MRSA activity, demonstrates activity against *Enterobacterales* and *P. aeruginosa* similar to that of advanced-generation cephalosporins such as ceftazidime and cefepime [53–57]. Additionally, ceftobiprole exhibits lower MICs against class C AmpC beta-lactamase-producing *Enterobacterales*, particularly AmpC-overexpressing *Enterobacter cloacae*, compared to ceftazidime [37]. This may be attributed to its relative resistance to hydrolysis by AmpC beta-lactamases and its rapid penetration into the periplasm of Gram negative bacteria [37]. Post-hoc analyses provided additional insights into the impact of ceftobiprole, particularly in high-risk [58] and older patients [59]. Scheeren et al. analyzed data from patients with CAP ($n = 398$) and HAP ($n = 307$, excluding ventilator-associated pneumonia (VAP)) focusing on high-risk groups such as older individuals, those treated in an ICU, and those with comorbidities like chronic obstructive pulmonary disease (COPD) or bacteremia. Ceftobiprole demonstrated higher early clinical improvement rates in these high-risk populations, particularly among patients aged ≥75 years (16.3% difference vs comparator), those with COPD (20.1%), all high-risk HAP patients (12.5%) and HAP patients with multiple baseline comorbidities (15.3%), highlighting its potential benefits in critically ill patients [58].

Further supporting its role in elderly patients, Welte et al. conducted a post-hoc analysis of three randomized trials, including patients with CAP and HAP. The study found that ceftobiprole was as effective as comparator treatments across all age groups, although with differences < 10% (CAP, 2.5%; and HAP, 8.5%). However, in the CAP subgroup, ceftobiprole showed a statistically improved clinical outcome in patients aged ≥65 years (11.8%) and ≥75 years (16.3%). In HAP, while ceftobiprole's benefit was less pronounced, it still showed consistent results across age groups, with a favorable safety profile [59].

6. Real life evidence and emerging properties of ceftobiprole

Several observational studies have further confirmed in real life the positive safety profile and effective action of ceftobiprole in patients with CAP and HAP, with high cure rates and broad spectrum of activity [26–29]. Moreover, these studies highlight the possible use of ceftobiprole in both monotherapy and combination treatments [26] and its potential advantages as a sparing agent to avoid more toxic therapeutic options, even in more severe or complex patients with multiple comorbidities [28,29,32–34].

Gentile et al. conducted a retrospective analysis of 195 patients treated with ceftobiprole in a real-world setting across 10 Italian centers. The median age of patients was 67 years and median Charlson Comorbidity Index (CCI) was 5; most of the patients were treated for pneumonia (77%), especially HAP. Ceftobiprole was usually an empiric choice (65%), it was frequently administered as second-line therapy (58%), often in combination with other drugs, notably meropenem (31%). A causative agent was identified in 39% of the cases (mainly MRSA 38%, MRNSA 21%, and MSSA 11%) while 25% of infections were polymicrobial. In patients with pneumonia the study reported a clinical cure rate of 85%, with an all-cause mortality rate of 18%. Thirty-five patients were treated for a bloodstream infection with a success rate of 74%. Moreover, pooling the 45 cases of methicillin resistant staphylococci isolates (both aureus and non-aureus), the success rate was 89% with a mortality of 9%. Predictors of better outcomes included male gender, presence of pneumonia, and identification of the causative pathogen. From a safety point of view the drug was well tolerated with adverse events reported in only 3% of cases [26]. In a post-hoc analysis comparing ceftobiprole used as monotherapy or in combination, controlling for confounding by inverse probability of treatment weighting, no differences in terms of clinical success and all-cause mortality were detected [26].

In a separate analysis by Hidalgo-Tenorio, ceftobiprole was assessed in 249 patients with infections from 12 Spanish centers. The mean age of patients was 66.6 years, mean age-adjusted CCI was 4 and 49.4% of the patients had cardiovascular risk factors. Respiratory infections were the most common type (55.8%), including CAP (24.1%) and HAP (24.9%). Ceftobiprole was used empirically in 67.9% of cases, proving appropriate in 82.8% of these. It was administered either as monotherapy (53.8%) or in combination with other drugs (46.2%), mainly metronidazole, azithromycin and levofloxacin. Mortality rates varied by infection type, being 16.7% for CAP and 14.5% for HAP, and infections due to MRSA (20.8%) and *P. aeruginosa* (16.1%). Microbiological cultures were polymicrobial in 40.6% of patients, and all isolated pathogens were susceptible to ceftobiprole, highlighting its broad spectrum of activity. Adverse effects were minimal, with only 3.2% experiencing mild or moderate events, and no patient discontinuing treatment due to side effects [27].

Corcione et al. investigated the outcomes of patients treated with ceftobiprole for CAP and HAP in a single-center Italian study involving 159 individuals [28]. The median age was 70 years, and many patients had significant comorbidities, as shown by a CCI of 5. Ceftobiprole was given as a first-line therapy in 26% of cases, and as a second-line treatment in 74%, primarily for carbapenem-sparing purposes. This is notably different from the study by Gentile et al. [26], where carbapenem was the most frequently administered drugs. Ceftobiprole was administered either as monotherapy (23%) or in combination treatment (77%), mainly with levofloxacin or azithromycin. The mortality rate was 25%, with no difference between shorter (<7 days) and longer (≥7 days) treatment durations, suggesting the rapid onset of ceftobiprole's action [28].

Crapis et al. further reported on the use of ceftobiprole, documenting outcomes in 48 ceftobiprole-treated patients with severe pneumonia hospitalized in an emergency department, including approximately 30% of over 75 years old. Ceftobiprole was used primarily as an empirical therapy (45.8%), as second-line option (27.1%), as de-escalation from previous combination treatment (18.5%) or as targeted therapy (8.3%). The study reported an overall clinical cure rate of 85.4%, with 95.8% of patients showing early clinical improvement within 72 hours, accompanied by a reduction in inflammatory markers such as C-reactive protein and procalcitonin. Moreover, ceftobiprole was well tolerated, with only one patient discontinuing treatment due to side effects [29].

In a French observational study, Bellut et al. focused on ceftobiprole's use in critically ill patients with multiple infected sites. Among 47 patients enrolled, 51% were treated for pneumonia, and 72% had concurrent bacteremia. Ceftobiprole was mainly used to treat polymicrobial infections caused by both Gram-negative and Gram-positive bacteria, or as a single-agent alternative to piperacillin/tazobactam. Notably, combination therapy was employed in nearly 25% of cases, and over 50% of patients received higher doses compared to those recommended for non-severe infection. The study showed that ceftobiprole achieved a clinical cure in over 80% of patients, with an in-hospital mortality of 32% [32].

Durante-Mangoni et al. analyzed ceftobiprole's use in older patients with multiple comorbidities. In this cohort of 29 patients, the average age was 70.5 years, median CCI was 7 and comorbidities such as heart disease, kidney dysfunction and COPD were common. Most patients (58.6%) were treated for pneumonia (HAP 81.2%, CAP 18.8%). Ceftobiprole was used alone in 37.9% of cases and combined with other drugs in 62.1%; it was mostly used as target therapy (69%) rather than as empirical treatment (31%). A favorable clinical outcome was seen in 68.9% of patients, and the 30-day mortality rate was 27.5%, though none of the deaths occurred during ceftobiprole treatment. Although the outcomes were slightly lower than those observed in previous studies [33,60], ceftobiprole still proved to be beneficial in elderly subjects with a high burden of comorbidities. The drug was generally well tolerated, although 10% of the patients experienced a ceftobiprole-related event, including myoclonus and skin rash [33].

Oliva et al. also confirmed that ceftobiprole is a valuable option for patients with HAP, particularly in older subjects with complex medical conditions. The study included 25 patients with non-VAP HAP treated with ceftobiprole. Median age was 71 years, CCI was 5 and patients presented at least one (88%) or two or more (68%) comorbidities. Ceftobiprole clinical cure rate was 80%, while the mortality rate was 16%. Comparable outcomes were reported in patients with COPD (80%) and those with at least two comorbidities (82%), while slightly reduced rates were noted in patients aged ≥75 years (72.7%), immunosuppressed subjects (71.4%) and those with a CCI > 5 (70%). The safety profile was acceptable, with only two patients experiencing mild skin rashes, and one patient discontinuing treatment [34].

6.1. Comparative studies vs. other cephalosporins

Some observational studies and meta-analysis have investigated the use of ceftobiprole compared to other cephalosporins, such as ceftaroline [30,31] and ceftriaxone [61].

Arnés García et al. compared the real-world outcomes of ceftobiprole and ceftaroline in 439 hospitalized patients with various infections. The study included 212 patients treated with ceftobiprole and 227 with ceftaroline. Ceftaroline was prescribed less frequently for respiratory infections compared to ceftobiprole (45.4% vs. 66%) and was typically administered at higher doses (11.7 vs 11 g), for longer durations (8 vs 7 days), and in combination with other therapies (89% vs 45.8%). Ceftobiprole was more commonly used for polymicrobial infections (38.1% vs 14.0%), Gram-negative bacteria (19.7% vs 6.0%), and HAP (33% vs 10.6%). Both antibiotics were found to be safe and effective, with no significant difference in overall health outcomes. Mortality rate was higher in the ceftaroline group (33.9% vs. 21.2%), though no significant difference was found at 14 or 28 days. Adverse effects were minimal, with similar drop-out rates for both ceftaroline and ceftobiprole (2.2% vs 0.9%) [30].

Zampino et al. also conducted a retrospective study comparing ceftaroline and ceftobiprole in 138 patients. Notably, patients in the ceftobiprole group ($n = 63$) had more comorbidities and a higher prevalence of multiple site infections compared to those in the ceftaroline group ($n = 75$). Ceftobiprole was also more frequently used empirically and as first-line therapy. Both drugs showed similar results in terms of hospital mortality, length of stay, and clinical cure rates. Specifically, no difference was observed between the two drugs in terms of clinical cure or improvement in lower respiratory tract infections (32% vs 35% lower for ceftaroline vs ceftobiprole). No significant adverse events or treatment discontinuation were noted in either group [31].

Finally, a systemic review and meta-analysis compared the clinical efficacy of ceftriaxone vs fifth generation cephalosporins (ceftaroline and ceftobiprole) in treating CAP caused by MSSA. The analysis included five randomized controlled trials, four on ceftaroline and one on ceftobiprole. The results showed that clinical cure rates were significantly lower with

ceftriaxone compared to the two fifth-generation cephalosporins, supporting increased effectiveness of both ceftobiprole and ceftaroline vs. ceftriaxone in patients with CAP caused by MSSA [61].

7. Conclusion

In conclusion, literature evidence supports the use of ceftobiprole as a safe and effective option for both CAP and HAP. Its broad-spectrum activity against both Gram-positive and Gram-negative bacteria, makes it a valuable therapeutic choice, especially in cases of risk of MRSA infection. Real-world evidence and comparative studies against ceftaroline have shown its non-inferiority to standard treatments, with high clinical cure rates and a favorable safety profile.

In real-world practice, ceftobiprole has further confirmed its broad spectrum of activity, rapid onset of action, and ease of use both as monotherapy and in combination with other drugs. Moreover, the good tolerability profile and favorable cure rates reported in elderly subjects make it a valuable tool for older patients with complex clinical conditions and in challenging-to-treat infections.

Given the importance of achieving an optimal drug exposure and considering the individual variability in PK/PD parameters, TDM remains crucial for optimizing dosing while administering ceftobiprole, particularly in vulnerable populations such as the elderly or those with impaired renal function.

8. Expert opinion section

Evidence from preclinical and *in vitro* studies, along with results from registrational trials and real-world experiences, highlights that ceftobiprole is a valid option for the empirical and targeted treatment of patients with CAP and HAP.

One of ceftobiprole's primary strengths is its broad bactericidal activity. This feature makes it a valid empirical treatment option for patients at heightened risk of inappropriate therapy and mortality due to MDR pathogens or MRSA. This agent may be used in targeted therapy for *S. aureus* infections, as well as in case of infections from other Gram-positive bacteria. Interestingly, ceftobiprole (500 mg every 6 hours for 8 days) seems to be a good therapeutic option for the treatment of bacteremic CAP and HAP caused by *S. aureus*, including MRSA, having met non-inferiority to daptomycin in a highly anticipated trial [62].

Due to its broad spectrum of activity ceftobiprole can be used as monotherapy for treating polymicrobial infections. This feature allows ceftobiprole to potentially provide equivalent antibacterial coverage as multiple antibiotics, possibly reducing the use of more toxic agents such as oxazolidinones or glycopeptides. A recent systematic review and meta-analysis of randomized controlled trials showed that ceftobiprole used in monotherapy is both effective and safe for treating severe infections, with outcomes comparable to other combination or non-combination antibiotic regimen [63]. However, caution about the use of ceftobiprole monotherapy is required in settings where the prevalence of ESBL-producing *Enterobacterales* is high.

Another significant advantage of ceftobiprole is its favorable tolerability and safety profile, characterized by minimal adverse events and drug interactions. This makes it particularly suitable for elderly patients and those with multiple comorbidities and polypharmacy, who may be more susceptible to adverse effects or drug-drug interactions. Ceftobiprole appears to be more tolerable and easier to use than other non-beta-lactams antibiotics. Indeed, compared to linezolid, ceftobiprole is a safer option, especially in older patients at risk of bone marrow depression and thrombocytopenia, and in whom polypharmacy is quite common [64,65]. Moreover, ceftobiprole exhibits a better safety profile than vancomycin, which may be associated with nephrotoxicity, particularly in patients with preexisting renal impairment [65]. Importantly, ceftobiprole also offers comparable lung penetration to other beta-lactams, which is significantly higher than that of vancomycin [42], and is a critical factor for enhancing its activity in treating respiratory infections.

Another important safety aspect of ceftobiprole is its limited impact on intestinal microflora. Most antibiotics, especially broad-spectrum cephalosporins, can disrupt the indigenous flora of the colon, leading to *Clostridioides difficile* infections (CDI). Research, including *in vivo* studies and trials on healthy volunteers, suggests that ceftobiprole does not promote the growth of or toxin production by *C. difficile*, thereby minimizing the risk of CDI. This relatively low propensity is attributed to ceftobiprole's inhibitory activity against *C. difficile* while sparing anaerobic microflora [66,67]. This feature may be important for populations at high risk of CDI, including elderly patients and solid organ transplant recipients [68,69].

Despite its numerous advantages, some limitations to the use of ceftobiprole exist. Although this agent has a broad spectrum of activity, it is not effective against ESLB-producing organism and MDR *P. aeruginosa*, therefore, careful consideration should be given when using ceftobiprole monotherapy empirically in patients at high risk for these infections. In addition, many physicians remain unfamiliar with its favorable activity and safety profile and may lack awareness of its effectiveness in critically ill patients. Additionally, the limited availability of TDM poses challenges to an optimized use of ceftobiprole. The absence of standardized methods and protocols, combined with constraints such as time, resources, and personnel, limits the widespread implementation of this technique, that would be crucial for ensuring optimal drug exposure, improving microbiological eradication and clinical outcomes in patients with CAP and HAP treated with ceftobiprole.

Future research on the use of ceftobiprole should focus on areas of unmet need in patients with difficult to treat infections. One key area is the evaluation of ceftobiprole in the treatment of primary *S. aureus* bacteremia, particularly in cases involving MRSA. Additionally, the potential synergistic effects of combining ceftobiprole with daptomycin in treating *S. aureus* bacteremia warrant further investigation. Another interesting avenue for future studies is the role of ceftobiprole in managing pneumonias caused by strains producing Panton-Valentine leukocidin (PVL). Although PVL-producing *S. aureus* infections are rare, they are often associated with severe clinical outcomes, and the rapid bactericidal action of ceftobiprole may be particularly beneficial in these cases. Research in these

areas could provide important insights into optimizing ceftobiprole's use in critically ill patients.

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