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REVIEW

Ceftobiprole: drug evaluation and place in therapy

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ABSTRACT

Introduction: Ceftobiprole is a fifth-generation cephalosporin with a broad spectrum of antimicrobial activity, including also methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftobiprole is approved for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia, in several European and non-European countries.

Areas covered: In this narrative review, we discuss the current place in therapy of ceftobiprole, both within and outside approved indications. An inductive MEDLINE/PubMed search of the available literature was conducted.

Expert opinion: There are three main reasons which render ceftobiprole an attractive option for the empirical and targeted treatment of CAP and HAP: (*i*) its broad spectrum of activity; (*ii*) its activity against MRSA; (*iii*) its good safety profile. For these indications, ceftobiprole should be employed thoughtfully, in those scenarios in which its intrinsic advantages could be maximized. The use of ceftobiprole outside approved indications could be justified in specific scenarios, such as when other approved alternatives are ineffective, when the risk of toxicity due to other agents is unacceptable, and for salvage therapy. In the near future, ongoing phase 3 studies and further observational experiences could both enlarge the current panel of approved indications and enrich our knowledge on the use of ceftobiprole for off-label indications.

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Ceftobiprole; CAP; HAP; MRSA; *Staphylococcus aureus*

1. Introduction

Ceftobiprole is a fifth-generation cephalosporin with a wide spectrum of antimicrobial activity, including various Gram-positive and Gram-negative bacteria [1,2]. One of the preeminent features of ceftobiprole is its activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [3], a peculiarity of a very few β-lactams, that could represent an important advantage in specific scenarios.

Ceftobiprole is approved for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP), in several European and non-European countries [4–6]. In this narrative review, we discuss its current place in therapy in light of the available literature, both within and outside approved indications.

2. Methods

During a remote meeting on December 2018, the structure of the present narrative review was decided, and divided in the following main chapters: (*i*) antimicrobial properties of ceftobiprole; (*ii*) pharmacological properties of ceftobiprole; (*iii*) use of ceftobiprole for pneumonia; (*iv*) use of ceftobiprole for other indications; (*v*) safety and tolerability of ceftobiprole. Subsequently, an inductive MEDLINE/PubMed search for relevant publications was conducted, using various combinations of dedicated keywords for each topic. Then, different teams of authors produced separated drafts addressing the different topics, that were later merged in a final manuscript reviewed and approved by all authors.

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Article highlights

- Ceftobiprole is a fifth-generation cephalosporin with a broad spectrum of antimicrobial activity, including also MRSA, and is approved for the treatment of CAP and HAP, excluding VAP, in several European and non-European countries.
- On the basis of the high-level evidence provided by RCT, ceftobiprole is an effective β-lactam option for the treatment of patients with CAP or HAP, with the notable advantage of anti-MRSA activity.
- In the literature, the use of ceftobiprole for indications other than pneumonia has been reported in patients with skin and soft tissue infections, bloodstream infections, infective endocarditis, mediastinitis, and osteomyelitis.

In the near future, ongoing RCT and further observational experiences could both enlarge the current panel of approved indications and enrich our knowledge on its use for off-label indications...

3. Antimicrobial properties of ceftobiprole

Ceftobiprole is an expanded-spectrum cephalosporin which, like other β-lactams, exerts its antibacterial activity by inhibition of the transpeptidase moiety of the penicillin binding proteins (PBPs). It exhibits tight binding to several different PBPs of Gram-positive and Gram-negative pathogens, and a most notable feature is the ability to inhibit also the PBPs that are resistant or poorly susceptible to conventional β-lactams, including PBP2a of methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP2x of penicillin-resistant pneumococci (PRP) [1–3].

Concerning β-lactamases, ceftobiprole is stable to the PC1 staphylococcal penicillinase, to the class A broad-spectrum β-lactamases of the TEM type (less so to those of the SHV type and to the K1 β-lactamase of *Klebsiella oxytoca*), and to the chromosomal AmpC-type β-lactamases of *Enterobacterales* and *P. aeruginosa*. Similar to third- and fourth generation cephalosporins, ceftobiprole is degraded by class A extended-spectrum β-lactamases (ESBLs) (e. g. CTX-M-15) and by carbapenemases (both serine-carbapenemases, such as KPC-2, and metallo-carbapenemases, such as IMP-1 and VIM-2), and is also degraded by some class D enzymes (e. g. OXA-10) [7].

Altogether, these features account for a broad spectrum of antimicrobial activity which covers staphylococci (including methicillin-resistant strains of *S. aureus* and of coagulase-negative staphylococci), streptococci (including PRP strains), *Haemophilus influenzae, Moraxella catarrhalis*, most members of the order *Enterobacterales*, and also *P. aeruginosa* and *Enterococcus faecalis*. On the other hand, ceftobiprole has reduced or no activity against *Enterococcus faecium, Acinetobacter baumannii, Burkholderia cepacia* complex, *Stenotrophomonas maltophilia, Proteus vulgaris*, most Gram-negative anaerobes (e. g. *Bacteroides fragilis* group and *Prevotella* spp.), and strains of *Enterobacterales* producing acquired ESBLs or carbapenemases [2,8–10]. The activity against methicillin-resistant staphylococci and PRP, which is outstanding compared to that of conventional β-lactams, has led to classification of ceftobiprole among the fifth generation of cephalosporins [11].

Large surveillance studies carried out during the past decade on clinical isolates from different geographic regions have shown a remarkable activity of ceftobiprole against staphylococci and pneumococci, including methicillin-resistant and penicillin-resistant isolates, respectively. In particular, for MRSA and pneumococci, MIC_{90} values of 2 and 0.5 mg/L, respectively, have been reported, with susceptibility rates consistently exceeding 95% and 99%, respectively (Table 1). Strains of MRSA resistant to ceftobiprole are uncommon, and usually exhibit an MIC of 4 mg/L, i. e. only two-fold higher than the EUCAST breakpoint for susceptibility (European Committee on Antimicrobial Susceptibility Testing [EUCAST] clinical breakpoint tables, version 9.0, 2019; http://www.eucast.org) [12–16]. Against *Enterobacterales*, MIC_{90} values ≥16 mg/L have been reported, with variable susceptibility rates (Table 1) [12–18], depending on the prevalence of ESBL and carbapenemase producers. No clinical breakpoints are yet available for CoNS, streptococci other than pneumococci, *E. faecalis, H. influenzae, M. catarrhalis*, and *P. aeruginosa*. However, considering the EUCAST PK/PD breakpoint for susceptibility of 4 mg/L and the MIC_{90} values of these pathogens (Table 1) [12–18], also these species could be considered among the potential targets for this antibiotic.

In vitro studies have shown that ceftobiprole can be synergistic with daptomycin against MSSA, MRSA and methicillin-resistant *Staphylococcus epidermidis* strains [19,20] and with amikacin and levofloxacin against *P. aeruginosa* [21].

Table 1. Ceftobiprole activity against clinical isolates of various bacterial species, from large surveillance studies.

Pathogen	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptible (%)[a]	References
S. aureus	0.5	1 – 2	99.2 – 100	[12–17]
MRSA	1 – 2	2	96.5 – 100	[12–17]
CoNS	0.5 – 1	1 – 2	n. a. (>90 – 100)	[12–14,17]
MR-CoNS	1	1 – 4	n. a. (>90 – 100)	[12–15,17]
S. pneumoniae	≤0.06–0.25	0.06–0.5	99.3–99.8	[12–17]
β-hemolytic streptococci	≤0.06	≤0.06	n. a. (100)	[12–14]
viridans group streptococci	≤0.06	0.25	n. a. (>90 – 100)	[12–15]
E. faecalis	0.5	2-4	n. a. (95.9–100)	[12–14]
H. influenzae	≤0.06	≤0.06–0.25	n. a. (>90 – 100)	[12–14,16]
M. catarrhalis	≤0.06–0.12	0.12 – >4	n. a. (>90 – 100)	[12–14,16]
Enterobacterales	≤0.06	16 – >16	73.8 – 87	[12–17]
P. aeruginosa	2 – 4	8 – >16	n. a. (61.8–86)	[12–18]

CoNS, coagulase-negative staphylococci; MIC, minimum inhibitory concentration; MR-CoNS, methicillin-resistant CoNS; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]susceptibility rates calculated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints, version 9.0, 2019 (www.eucast.org), from references where the value was reported or could be calculated from the reported MIC data; n.a., not applicable, due to the lack of clinical breakpoints. Values in parentheses are susceptibility rates considering the EUCAST PK/PD breakpoint for susceptibility of 4 mg/L (www.eucast.org).

Ceftobiprole was also shown to have notable activity against methicillin-susceptible and methicillin-resistant strains of *S. aureus* and *S. epidermidis* grown as biofilms, alone and in combination with rifampin or vancomycin [22], suggesting potential activity against infections associated with biofilm growth (e.g. infections of devices). Indeed, ceftobiprole showed remarkable activity against staphylococcal isolates from foreign body-associated infections and prosthetic joint infections [23,24].

4. Pharmacological properties of ceftobiprole

Ceftobiprole is the active moiety of the water-soluble prodrug ceftobiprole medocaril, which is rapidly activated in plasma by type A esterases [25,26].

Similar to other cephalosporins, ceftobiprole exhibits time-dependent antibacterial activity. It has been shown in experimental infection models that maintenance of plasma concentrations above the MIC for 30% to 60% of the dosing interval (t> MIC) may guarantee effective bactericidal activity, in terms of >2–3 $\log_{10}$ decrease in CFU over 24 h, against *S. aureus, S. pneumoniae* and wild-type *Enterobacterales* [27]. Noteworthy, the pharmacodynamic target of ceftobiprole against *S. aureus* in experimental pneumonia models was very similar (t> MIC of 40%) among phenotypically diverse strains (methicillin-susceptible *S. aureus*, community-associated (CA)-MRSA and healthcare-acquired (HA)-MRSA) [28].

Ceftobiprole is administered intravenously at the dosage of 500 mg q8h infused over 2 h. The pharmacokinetic parameters of ceftobiprole in healthy volunteers are summarized in Table 2 [25,29]. Similar to several other beta-lactams, ceftobiprole is poorly bound to plasma protein (16%) and has a Vd which is similar to the extracellular compartment. Penetration of ceftobiprole was evaluated into the epithelial lining fluid (ELF) and into soft tissues of healthy volunteers. Mean penetration (calculated as tissue-to-plasma AUCs ratio) was 25.5% into the ELF [30], 69% and 49% into skeletal muscle and adipose tissue, respectively [31]. Ceftobiprole has a low potential for drug–drug interaction, a short elimination half-life and is excreted almost completely as unmodified moiety by the renal route. Dosage adjustments are needed in patients with renal impairment (500 mg q12h over 2 h, 250 mg q12h over 2 h, 250 q24h over 2 h in presence of CLCr 30–50 mL/min, <30 mL/min and end stage renal disease or intermittent hemodialysis, respectively) [32]. A recent PK analysis carried out in a single case of critically ill patient undergoing continuous-veno-venous-hemodiafiltration (CVVHDF) suggested that a ceftobiprole dosage of 250 mg q12h over 2 h may allow appropriate target attainment in terms of maintenance of 100% t> MIC [33]. In patients with augmented renal clearance (>130 mL/min/1.73 m^2), the infusion time of ceftobiprole must be extended up to 4 h for optimizing drug exposure [29,32].

Table 2. Pharmacokinetic (PK) parameters of ceftobiprole after single 500 mg intravenous dose over 2 h infusion in healthy volunteers [25,29].

PK parameter	
C_{max} (mg/L)	29.2 ± 5.52
Protein binding (%)	16.0
Vd (L)	21.7 ± 3.3
$t_{1/2}$ (h)	3.1 ± 0.3
$AUC_{0-\infty}$ (mg·h/L)	104.0 ± 13.9
CL_T (L/h)	4.89 ± 0.69
CL_R (L/h)	4.08 ± 0.72
Urinary excretion (%)	83.1 ± 9.1

The relationship between ceftobiprole exposure and microbiological and/or clinical outcomes was analyzed in patients with nosocomial pneumonia by using data from a randomized double-blind phase 3 clinical trial [34]. Multiple logistic regression analysis showed a strong correlation, and CART analysis determined that the percentage of t> MIC needed for obtaining favorable clinical outcome was of 51% of the dosing interval, a value which is in line with those found in preclinical models [34]. A Monte Carlo simulation showed that at this percentage of t> MIC, pharmacokinetic data coming from phase 1 study in healthy volunteers accurately predicted the actual clinical exposure to ceftobiprole in patients who were enrolled in the phase 3 nosocomial pneumonia study, the difference being very small (3.5% for PK-sampled patients) [35].

A recent population pharmacokinetic/pharmacodynamic analysis demonstrated that at the standard ceftobiprole dose of 500 mg every 8 h as a 2-h infusion no pharmacokinetic or pharmacodynamic differences existed between Asian and non-Asian subjects, considering that, at a pharmacodynamic target of 60% t> MIC of the dosing interval, more than 90% of the population was adequately exposed in both subgroups [36].

5. Use of ceftobiprole in patients with pneumonia

Within in-label indications, ceftobiprole is an important option for the empirical treatment of patients with CAP and HAP, given its activity against MRSA, *Enterobacterales*, and *P. aeruginosa*.

The approval of ceftobiprole for CAP and HAP is based on two phase 3 randomized controlled trials (RCT) [37,38]. The first one, published in 2011, was a non-inferiority, double-blind RCT comparing ceftobiprole vs. ceftriaxone (plus optional linezolid, based on investigators' suspicion of MRSA involvement) for the treatment of severe CAP requiring hospitalization and intravenous treatment [38]. Ceftobiprole was administered q8h at 500 mg over a 120-min infusion, whereas ceftriaxone was administered once-daily at 2 g over a 30-min infusion. The minimum target duration of therapy was 7 days in both arms, with optional step-down to oral cefuroxime at day 3 in case of significant improvement. The primary efficacy endpoint was clinical cure (defined either as resolution of signs and symptoms of infection or as sufficient improvement rendering continuation of antibacterial therapy unnecessary) at the test-of-cure (TOC) visit (7–14 days after the end of treatment) in the intention-to-treat (ITT) and the clinically evaluable (CE) populations. Overall, 706 patients were enrolled, 638 of whom were included in the ITT population. The CE population consisted of 469 patients. Clinical cure was achieved in 76.4% (240/314) and 79.3% (257/324) of ITT patients treated with ceftobiprole and with ceftriaxone ± linezolid, respectively (difference −2.9%, 95% confidence interval [CI] −9.3 to 3.6), and in 86.6% (200/231) and 87.4% (208/238) of CE patients treated with ceftobiprole and with ceftriaxone ± linezolid, respectively (difference −0.8%, 95% CI −6.9 to 5.3), meeting non-inferiority in both populations according to the pre-fixed 10% non-inferiority margin [38].

The second registrative study, published in 2014, was a non-inferiority, double-blind, RCT comparing ceftobiprole vs. ceftazidime plus linezolid for the treatment of HAP and VAP [37]. Ceftobiprole was administered q8h at 500 mg over a 120-min infusion, ceftazidime was administered q8h at 2 g over a 120-min infusion, and linezolid was administered q12h at 600 mg over a 60-min infusion. The planned treatment duration was 7 days, with a maximum of 14 days. The primary efficacy endpoint was clinical cure (defined either as resolution of signs and symptoms of infection or as sufficient improvement rendering continuation of antibacterial therapy unnecessary) at the TOC visit (7–14 days after the end of treatment) in the ITT and in the CE populations. The ITT and CE populations consisted of 781 (571 HAP and 210 VAP) and 495 (383 HAP and 112 VAP) patients, respectively. Clinical cure was achieved in 59.6% (171/287) and 58.8% (167/284) of ITT patients with HAP treated with ceftobiprole and with ceftazidime plus linezolid, respectively (difference 0.8%, 95% CI −7.3 to 8.8), and in 77.8% (154/198) and 76.2% (141/185) of CE patients treated with ceftobiprole and with ceftazidime plus linezolid, respectively (difference 1.6, 95% CI −6.9 to 10.0), meeting non-inferiority in both populations according to the pre-fixed 15% non-inferiority margin. Of note, in the CE population HAP patients treated with ceftobiprole showed a higher rate of early improvement (assessed at day 4 after the onset of therapy) than HAP patients treated with ceftazidime plus linezolid (86.9% [172/198] vs. 78.4% [145/185], respectively, difference 8.5%, 95% CI 0.9 to 16.1), with the largest difference being observed in patients with MRSA-positive cultures at baseline (94.7% [18/19] vs. 52.6% [10/19], respectively, difference 42.1%, 95% CI 17.5 to 66.7) [37].

With regard to VAP patients, clinical cure rates were 23.1% (24/104) and 36.8% (39/106) in ITT patients treated with ceftobiprole and with ceftazidime plus linezolid, respectively (difference −13.7%, 95% CI −26.0 to −1.0), and in 37.7% (20/53) and 55.9% (33/59) in CE patients treated with ceftobiprole and with ceftazidime plus linezolid, respectively (difference −18.2%, 95% CI −36.4 to 0.0), failing to demonstrate non-inferiority [37].

The reasons underlying failure in demonstrating non-inferiority of ceftobiprole vs. ceftazidime plus linezolid in patients with VAP are not perfectly clear. A possible unfavorable effect due to the presence biofilm-embedded organisms has been hypothesized, which is nonetheless in contrast with the higher rates of clinical cure observed in ceftobiprole-treated patients than in ceftazidime plus linezolid-treated patients in the subgroup of mechanically ventilated HAP (30.4% [21/69] vs. 27.1% [19/70] in the ITT population, difference 3.3%, 95% CI −11.8 to 18.3, and 55.3% [21/38] vs. 40.5% [15/37] in the CE population, difference 14.7%, 95% CI −7.6 to 37.1) [37]. In addition, ceftobiprole demonstrated activity in an experimental model of foreign-body infection [39]. An alternative explanation is the possibly insufficient attainment of therapeutic concentrations of ceftobiprole in patients with CLCr ≥150 ml/min, a condition encountered in as many as 29% of ceftobiprole-treated patients with VAP, and that might require higher dosages and prolonged infusions to achieve adequate therapeutic levels [29,32].

As regards post-hoc analyzes of patients with CAP or HAP in the two major trials, higher rates of early clinical improvement in patients treated with ceftobiprole than in those treated with comparators were observed overall and especially in CAP patients aged ≥75 years (difference 16.3%, 95% CI 1.8 to 30.8), CAP patients with chronic obstructive pulmonary disease (difference 20.1%, 95% CI 8.8 to 31.1), HAP patients considered to be at higher risk of poor outcomes according to previous literature (difference 12.5%, 95% CI 3.5 to 21.4), and HAP patients with >10 baseline comorbidities (difference 15.3%, 95% CI 0.3 to 30.4) [40].

The main findings of the two registrative studies are also summarized in Table 3. Overall, on the basis of the high-level evidence provided by RCT, ceftobiprole is an effective β-lactam option for the treatment of patients with CAP or HAP, with the notable advantage of anti-MRSA and anti-PRP activity [41]. Conversely, without further high-level evidence from dedicated RCT, the use of ceftobiprole for VAP cannot be supported.

6. Use of ceftobiprole for other indications

The use of ceftobiprole outside approved indications could be justified in specific, non-mutually exclusive scenarios: (i) when other approved alternatives are ineffective (e.g. resistance); (ii) when the risk of toxicity or allergic reactions is unacceptable; (iii) for salvage therapy. In the literature, the use of ceftobiprole for indications other than pneumonia has been reported in patients with skin and soft tissue infections, bloodstream infections, infective endocarditis, mediastinitis, and osteomyelitis [42–47].

6.1. Skin and soft tissue infections

In a mouse subcutaneous abscess model, ceftobiprole showed a more potent activity than vancomycin or linezolid against MRSA and VISA [2]. In healthy volunteers, *in vivo* microdialysis techniques have evidenced adequate penetration of ceftobiprole in soft tissues, with prediction of optimal activity against organisms with MIC up to 2 mg/L [31].

From 2004 to 2005, a phase 3, non-inferiority, double-blind RCT was conducted in 129 sites worldwide, in patients with suspected or documented Gram-positive complicated skin and soft tissue infections (cSSTI) [46]. Patients were randomized to receive either ceftobiprole at 500 mg q12h or vancomycin at 1 g q12h. The duration of treatment was 7–14 days. Diabetic foot infections, bite wound infection, and osteomyelitis were excluded. The primary endpoint was clinical cure at the TOC visit (7–14 days after the end of treatment). The non-inferiority margin was set at 10%. In the ITT population, clinical cure was achieved in 77.8% (309/397) and 77.5% (300/387) of patients treated with ceftobiprole and vancomycin, respectively (difference 0.3%, 95% CI −5.5 to 6.1). In the CE population, clinical cure was achieved in 93.3% (263/282) and 93.5% (259/277) of patients treated with ceftobiprole and vancomycin, respectively (difference −0.2%, 95% CI −4.4 to 3.9) [46].

From 2005 to 2006 another phase 3, double-blind, RCT was conducted in patients with cSSTI caused by either Gram-positive or Gram-negative bacteria, comparing ceftobiprole vs. vancomycin plus ceftazidime [45]. Ceftobiprole was administered at 500 mg q8h, vancomycin was administered at 1 g q12h, and ceftazidime was administered at 1 g q8h. The primary endpoint was clinical cure at the TOC visit (7–14 days after the end of treatment). The

Table 3. Efficacy data from phase 3, non-inferiority, randomized clinical trials in patients with CAP and HAP/VAP.

Study	Reference	Investigational drugs (dosage)	Comparator/s (dosage)	Primary endpoint	Study population	Cure rates (cured/treated)	% difference (95% CI)
CAP, 2012	[38]	Ceftobiprole (500 mg q8h)	Ceftriaxone* (2 g q24h)	*Clinical cure* (either resolution of signs and symptoms of infection or sufficient improvement rendering continuation of antibacterial therapy unnecessary)	CAP		
					ITT population		
					Ceftobiprole	76.4% (240/314)	−2.9 (−9.3 to +3.6)
					Ceftriaxone	79.3% (257/324)	Reference
					CE population		
					Ceftobiprole	86.6% (200/231)	-0.8 (−6.9 to +5.3)
					Ceftriaxone	87.4% (208/238)	Reference
HAP/VAP, 2014	[37]	Ceftobiprole (500 mg q8h)	Ceftazidime (2 g q8h) plus Linezolid (600 mg q 12h)	*Clinical cure* (either resolution of signs and symptoms of infection or sufficient improvement rendering continuation of antibacterial therapy unnecessary)	HAP excluding VAP		
					ITT population		
					Ceftobiprole	59.6% (171/287)	+0.8 (−7.3 to +8.8)
					Ceftazidime plus linezolid	58.8% (167/284)	Reference
					CE population		
					Ceftobiprole	77.8% (154/198)	+1.6 (−6.9 to +10.0)
					Ceftazidime plus linezolid	76.2% (141/185)	Reference
					VAP		
					ITT population		
					Ceftobiprole	23.1% (24/104)	-13.7 (−26.0 to −1.0)
					Ceftazidime plus linezolid	36.8% (39/106)	Reference
					CE population		
					Ceftobiprole	37.7% (20/53)	-18.2 (−36.4 to +0.0)
					Ceftazidime plus linezolid	55.9% (33/59)	Reference

CAP, community-acquired pneumonia; CE, clinically evaluable; HAP, hospital-acquired pneumonia; ITT, intention-to-teat; VAP, ventilator-associated pneumonia.
*plus optional linezolid

non-inferiority margin was set at 10%. In the ITT population, clinical cure was achieved in 81.9% (448/547) and 80.8% (227/281) of patients treated with ceftobiprole and vancomycin plus ceftazidime, respectively (difference 1.1%, 95% CI −4.5 to 6.7). In the CE population, clinical cure was achieved in 90.5% (439/485) and 90.2% (220/244) of patients treated with ceftobiprole and vancomycin plus ceftazidime, respectively (difference 0.3%, 95% CI −4.2 to 4.9) [45].

However, despite the results of these two RCT suggested that ceftobiprole was beneficial to patients, it should be noted that authorization for SSTI was ultimately not granted. This decision was based on the lack of compliance with good clinical practice (GCP) recommendations registered in some participating sites in the United States [48]. A novel phase 3, non-inferiority, double-blind RCT comparing ceftobiprole vs. vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections (ABSSSI) has been initiated and is currently ongoing (NCT03137173).

6.2. Bacteremia, endocarditis, and mediastinitis

The interest in using ceftobiprole for the treatment of bacteremia and endocarditis is increased by the results of rat and rabbit models of infective endocarditis (IE) due to MRSA, which showed a bactericidal effect possibly higher than that of linezolid and daptomycin [49,50]. Therapy with ceftobiprole was also successful in a rat model of mediastinitis, induced by the injection of MRSA into the sternal bone [51]. A higher reduction in MRSA load after 5 days of therapy was observed in rats receiving ceftobiprole in comparison with rats receiving vancomycin. At day 14 of treatment, there was evidence of complete/most complete MRSA sternal clearance in both ceftobiprole-treated and vancomycin-treated rats [51].

Regarding the available evidence in humans, some information about the efficacy of ceftobiprole for the treatment of staphylococcal bacteremia can be extrapolated from existent RCT. In a post-hoc pooled analysis of four phase 3 double-blind RCT (two in patients with cSSTI, one in patients with CAP, and one in patients with HAP/VAP) [37,38,45,46], which was presented at the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) congress in 2016, clinical cure rates and 30-day all-cause mortality were compared between patients with staphylococcal bacteremia treated with ceftobiprole and patients with staphylococcal bacteremia treated with the different comparators (vancomycin and vancomycin plus ceftazidime in cSSTI trials, ceftriaxone ± linezolid in the CAP trial, and ceftazidime plus linezolid in the HAP/VAP trial) [52]. Cumulatively, 95 patients had staphylococcal bacteremia in the four RCT. With the limitation of the small sample size, both clinical cure rates and 30-day all-cause mortality were similar between patients treated with ceftobiprole and patients treated with the comparators (for clinical cure, 48.9% [22/45] vs. 44.0% [22/50], respectively, difference 4.9%, 95% CI −12.2 to 25.0; for 30-day all-cause mortality, 8.9% [4/45] vs. 16.0% [8/50], respectively, difference −7.1%, 95% CI −20.2 to 6.0). Of note, a trend toward higher rates of favorable outcomes was observed in ceftobiprole-treated vs. comparator/s-treated patients in the subgroup of patients with MRSA bacteremia, although the very small denominator (n = 18) precludes generalization (for clinical cure, 55.6% [5/9] vs. 22.2% [2/9], respectively, difference 33.3%, 95% CI −9.0 to 77.7; for 30-day all-cause mortality, 0.0% [0/9] vs. 22.2% [2/9], respectively, difference −22.2%, 95% CI −49.4 to 4.9) [52].

No evidence from RCT is available regarding the efficacy of ceftobiprole for the treatment of infective endocarditis.

However, a non-inferiority, double-blind, RCT comparing ceftobiprole vs. daptomycin for the treatment of *S. aureus* bacteremia, including right-sided infective endocarditis, is currently being conducted in adult patients (NCT03138733), and could open the door to the future approval of ceftobiprole for these indications should non-inferiority be demonstrated.

With regard to observational studies, 10 episodes of severe MRSA infection treated with ceftobiprole (of which 7/10 were bacteremia and 3/10 were pneumonia) were reported in a single-center retrospective case series in Canada [42]. Microbiological eradication was observed in 9/10 patients treated with ceftobiprole, including two bacteremic cases of salvage therapy following previous treatment failure with vancomycin, and one bacteremic case of salvage therapy following previous treatment failure with linezolid. Of note, breakthrough bacteremia was observed in a patient in whom ceftobiprole was underdosed due to a medication error. Overall, a favorable outcome was observed in 8/10 episodes (80%) [42].

Two case reports describing the successful treatment with ceftobiprole of patients with IE have also been published [43,47]. The first case involved a patient with severe pancytopenia after autologous hematopoietic stem cells transplantation (HSCT) for Burkitt lymphoma and recurrent bacteremia due to methicillin-resistant *Staphylococcus epidermidis* (MRSE) in presence of a prosthetic endovascular infection of the aortic valve and the ascending aorta, which responded favorably to ceftobiprole monotherapy [43]. After blood cultures turned negative, the patient underwent halogenic HSCT without episodes of breakthrough bacteremia in the postoperative period. Ceftobiprole was discontinued 3 months after allogeneic HSCT, and no radiological or clinical signs of infection were detected during a 1-year follow-up [43].

The second case involved a patient with renal insufficiency and aortic valve replacement complicated by MRSA mediastinitis [47]. After several failed courses of antimicrobials, a combination regimen of daptomycin plus ceftobiprole was initiated, with favorable response (the patient became afebrile) and subsequent valve surgery [47]. The use of combination therapy (ceftobiprole plus daptomycin) was in line with *in vitro* studies reporting a potent synergy between ceftobiprole and daptomycin [19,20]. This is an intriguing possibility to be further investigated in clinical studies, since it could represent an important option for salvage therapy of MRSA bacteremia and/or endocarditis. Of note, synergy between ceftobiprole and daptomycin has also been demonstrated against enterococci, including vancomycin-resistant isolates [20,53]. However, the related evidence is currently limited to *in vitro* studies, and further evidence from either animal models or clinical studies is needed regarding the possible use of ceftobiprole/daptomycin combinations for severe enterococcal infections in humans.

6.3. Osteomyelitis

Ceftobiprole showed potent activity against MRSA and methicillin-resistant coagulase-negative staphylococci isolates from bone and joint infections in an *in vitro* study, as well as in a rabbit model of CA-MRSA osteomyelitis [54,55]. The interest in using ceftobiprole for osteomyelitis and prosthetic joint infections also relies of its synergy with rifampin observed against biofilms [22].

An experience about the use of ceftobiprole for osteomyelitis was reported in 2010 [44]. A diabetic patient with a septic arthritis and bone destruction, with MRSA and *Peptostreptococcus prevotii* isolation and involving both the second and third metatarsophalangeal joints at the right foot, was initially treated with vancomycin and piperacillin/tazobactam, later replaced by ceftobiprole monotherapy due to kidney failure [44]. The patient underwent excision of the second and third metatarsal heads and was successfully treated with intravenous ceftobiprole for a total duration of 42 days including the postoperative period, with no evidence of relapsed osteomyelitis after a 1-year follow-up [44]. However, there could have been a major role of infected tissue removal in favorably influencing clinical cure, thus more supportive clinical evidence is warranted.

7. Safety and tolerability of ceftobiprole

Safety and tolerability of ceftobiprole were first assessed in phase 1 trials [26,56]. In a single dose-increasing study, caramel-like dysgeusia, attributable to a diacetyl product of conversion, was the only relevant mild adverse event (AE) observed [26]. In two subsequent phase 1 trials, nausea, vomiting and headache were reported as dose-related events [57].

Data from phase 2 and phase 3 studies involved a total of 3037 patients (1668 receiving ceftobiprole and 1369 receiving the comparator/s) [58]. Pooled data from pneumonia studies included a total of 1404 patients (696 receiving ceftobiprole and 708 the comparator/s). Ceftobiprole was generally well tolerated with a low discontinuation rate due to AE drug-related, similar to that observed with the comparator/s (10.3% vs. 7.3% for ceftobiprole vs. comparator/s, overall; 14.0% vs. 10.4% in the HAP/VAP phase 3 trial and 5.8% vs. 3.7% in the CAP phase 3 trials). Most patients reported at least one AE (74.1% in the ceftobiprole and 71.8% comparator arm, respectively), with rates being 77.5% in the ceftobiprole arm vs. 77.7% in the comparators arm in the HAP/VAP trial, and 70.0% in the ceftobiprole arm vs. 64.6% in the comparator/s arm in the CAP trial [58].

Overall, the most common AEs (≥3% of patients) reported with ceftobiprole from the pooled analysis of HAP, CAP or cSSTI studies were nausea, vomiting, diarrhea, infusion site reactions, dysgeusia and drug-related hypersensitivity (urticaria, pruritus, and rash) [58].

In the phase 3 CAP RCT, the overall AE rate was 36% in the ceftobiprole group vs. 26% in the ceftriaxone ± linezolid comparator group [38]. This difference was mainly related to higher occurrence of nausea (7% vs. 2%) and vomiting (5% vs. 2%) in the ceftobiprole group, whereas occurrence of injection-site AEs (7% vs. 5%), hyponatremia (1% vs. 3%) and hepatic AEs (7% vs. 7%) were similar in both groups.

In the phase 3 HAP/VAP RCT the overall AE rate was 24.9% in the ceftobiprole group vs. 25.4% in the ceftazidime plus linezolid group [37]. Diarrhea was less frequently reported in the ceftobiprole arm (3.1% and 6.5%), whereas hyponatremia was more frequent in patients treated with ceftobiprole than in those receiving the comparators (4.4% and 2.6%, respectively). In patients treated with ceftobiprole, dysgeusia occurred only in 1.3% of cases. No other clinically relevant differences in laboratory values, vital signs, physical

examinations, or electrocardiograms were observed between the treatment arms.

Overall, *Clostridioides difficile* colitis was rare in ceftobiprole-treated patients in RCT. This is possibly related to the valid inhibitory activity that ceftobiprole exhibits against *C. difficile* [59]. This hypothesis is supported by the fact that ceftobiprole was shown to have no significant ecological impact on the human intestinal microflora of healthy volunteers [60]. Additionally, in experimental models, ceftobiprole did not promote neither growth of nor toxin production by *C. difficile* in mouse cecal contents, differently from what occurred with other cephalosporins (ceftazidime, cefoxitin, ceftriaxone, cefotaxime) and with carbapenems (ertapenem) [59].

8. Conclusion

Ceftobiprole is an important option for the treatment of CAP and HAP when MRSA is suspected or involved. In the near future, ongoing RCT and further observational experiences could both enlarge the current panel of approved indications and enrich our knowledge on its use for off-label indications.

9. Expert opinion

There are three main and non-mutually exclusive reasons which render ceftobiprole an attractive option for the empirical and targeted treatment of CAP and HAP: (*i*) its broad spectrum of activity; (*ii*) its activity against MRSA; (*iii*) its good safety profile. For example, these advantages should be taken into account when dealing with HAP in hospitalized patients with multiple comorbidities and at risk both of MRSA infection and of adverse events due non-β-lactam anti-MRSA agents. Another suitable scenario for ceftobiprole therapy could be that of severe CAP complicating influenza, in which empirical coverage of CA-MRSA should be guaranteed [61]. On the other hand, costs and antimicrobial stewardship principles (which dictate against the use of anti-MRSA agents in absence of substantial risk, in order to avoid useless selective pressure) indicate that ceftobiprole should not be overused, but rather employed thoughtfully in those scenarios in which its intrinsic advantages could be maximized. Based on these premises, a potential treatment algorithm for guiding clinicians' decisions regarding the use of ceftobiprole in CAP and HAP is depicted in Figure 1.

Another framework in which ceftobiprole could represent a reasonable choice at the present time is the salvage therapy of bacteremia and endocarditis (despite not approved) due to MRSA after failure of vancomycin or daptomycin therapy. In such a case, the possible advantage of a salvage combination of ceftobiprole plus either daptomycin or vancomycin lies in the synergy observed *in vitro* studies [11], for which several possible mechanisms have been described. Amongst others are the reduced expression of the *mecA* gene and the inhibitory effect on the early stages of the peptidoglycan synthesis by daptomycin [62], the reduction in the cell surface charge by β-lactams that might favor daptomycin binding [63], and the seesaw effect enhancing activity of β-lactams in case of isolates with increased daptomycin or vancomycin MIC [11,64]. It should nonetheless be noted that, despite the use this strategy could be considered after failure of standard therapy, the related evidence from clinical studies remains limited, and further experience is thus warranted to determine its true efficacy. Notably, also the use of ceftobiprole monotherapy may be considered in the future for the treatment of MRSA bacteremia, not only as salvage therapy but also possibly as a primary therapeutic approach, in case of favorable results from ongoing RCT (NCT03138733). The possible synergistic activity of ceftobiprole and daptomycin against some strains of

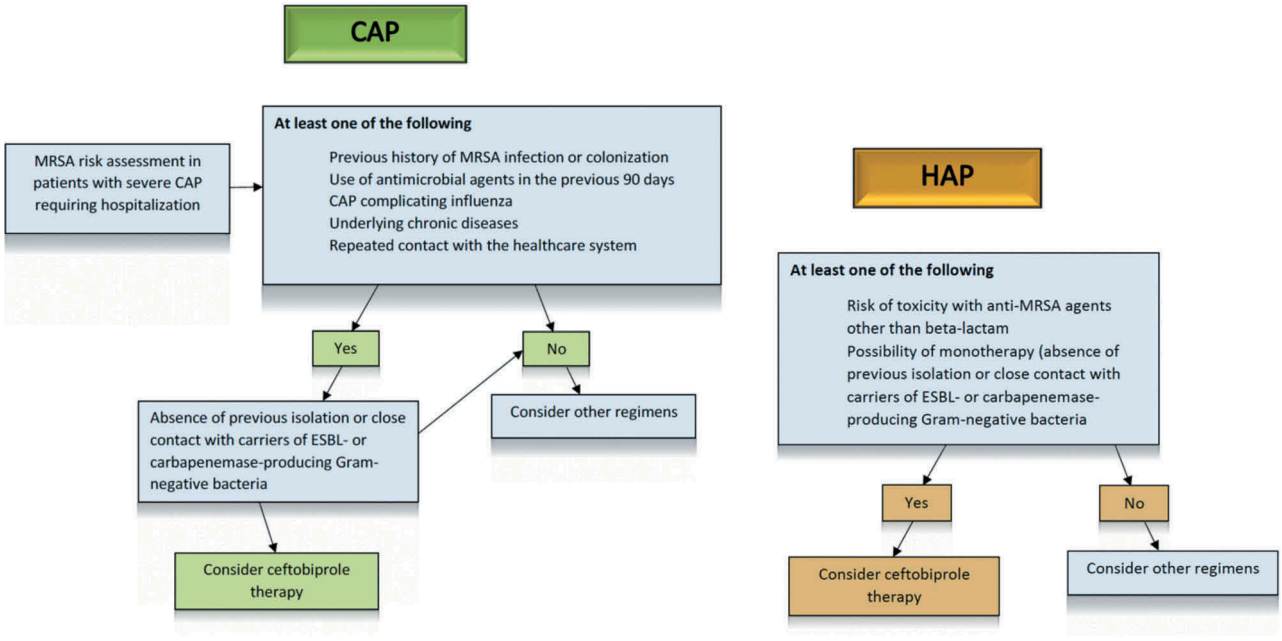

Figure 1. Algorithm illustrating the possible use of ceftobiprole for empirical therapy in patients with CAP and HAP (non-VAP).

CAP, community-acquired pneumonia; ESBL, extended-spectrum β-lactamases; HAP, hospital-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

vancomycin-resistant enterococci, suggested in a preliminary *in vitro* study, deserves further investigation [65].

In the next five years, we expect to witness an increasing number of observational studies and case reports about the use of ceftobiprole for currently off-label indications such as bacteremia, endocarditis, osteomyelitis, and mediastinitis. In addition, results of phase 3 RCT on ABSSSI and *S. aureus* bacteremia (NCT03137173 and NCT03138733) are much awaited and may provide important high-evidence efficacy data regarding the use of ceftobiprole for these potential, additional indications.

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Declaration of interest

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