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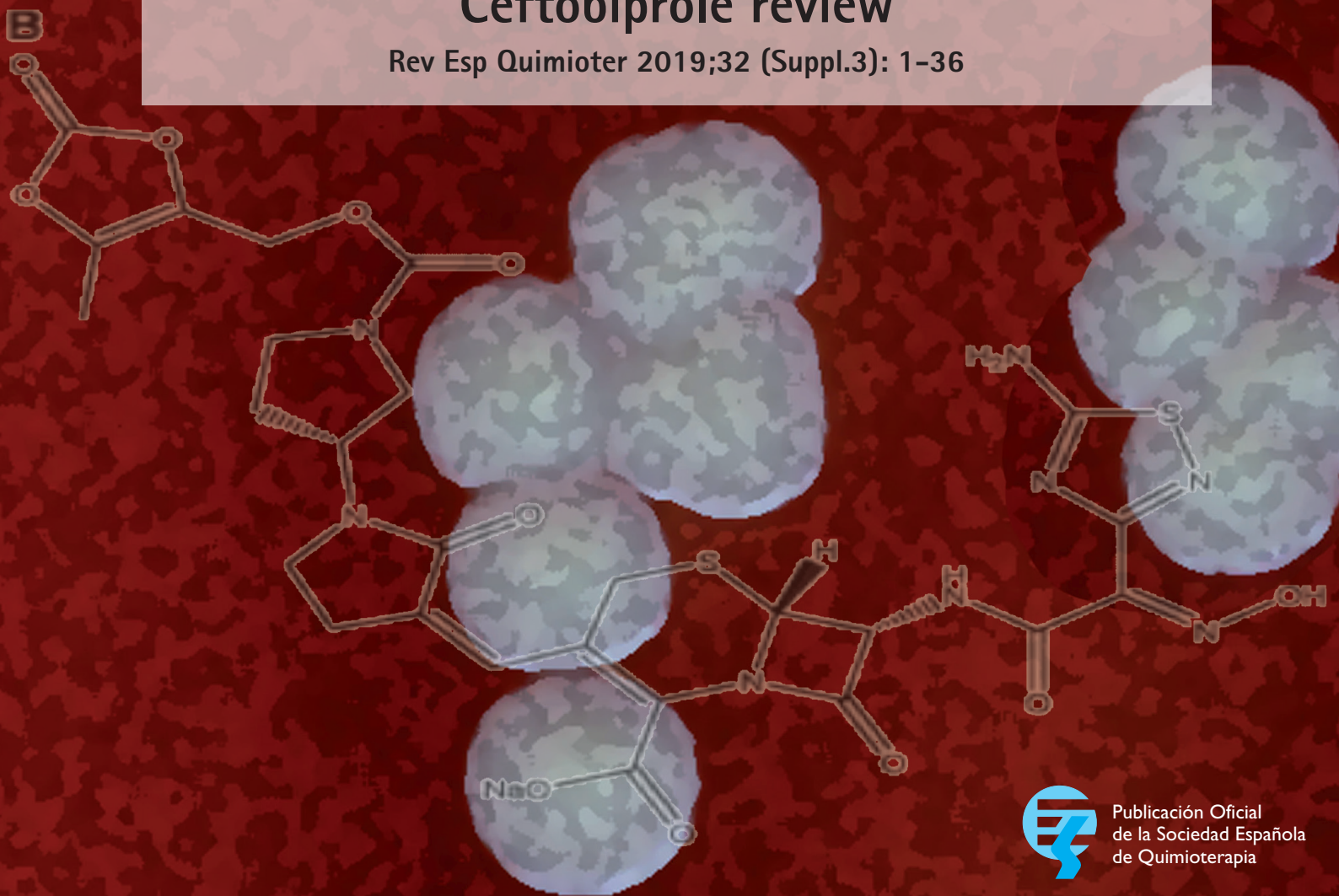

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Ceftobiprole review

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Ceftobiprole review

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Introduction

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The increase in resistance to antibiotics has been a concerning matter in recent years. Controlling the spread, the rational use of antibiotics and the search for new agents are among the most effective measures for controlling the progression of resistance. Fortunately, after a long period of time when antibiotic development was very limited, in the last few years new active molecules have appeared against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA) (oxazolidinones, daptomycin, dalbavancin) and multi-resistant Gram-negative bacilli such as ESBL/carbapenemase-producing Enterobacteriaceae and/or *Pseudomonas aeruginosa* (tigecycline, ceftolozane-tazobactam, and ceftazidime-avibactam). However, in the majority of clinical situations, these antibiotics cannot be used as monotherapy in empirical treatment regimens because, despite their elevated intrinsic activity, their antibacterial spectrum is limited.

Recently, two new cephalosporins have been included in the antibiotic treatment armamentarium: ceftobiprole and ceftaroline. These are the first two cephalosporins with activity against both MRSA and non-ESBL-producing *Enterobacteriaceae*. In the case of ceftobiprole, its activity also extends to *P. aeruginosa* and a large number of *Enterococcus faecalis*. A beta-lactam with the antibiotic spectrum of ceftobiprole certainly constitutes an interesting option for empirical treatment as monotherapy as well as in combination with a variety of molecules if is needed to have the widest coverage for many nosocomial infections.

This monograph reviews the most significant characteristics of ceftobiprole, marketed in Spain since the end of 2018 by Correvio under the commercial name Zevtera.

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From a microbiological point of view, Dr Cantón, Dr Morosini and Dr Aguilar present the mechanisms of action and the antimicrobial activity of ceftobiprole. As outlined above, ceftobiprole is a 5th generation (last generation) cephalosporin with rapid bactericidal activity against a wide range of Gram-positive and Gram-negative bacteria, including methicillin-susceptible and resistant *Staphylococcus aureus* (MSSA, MRSA) and susceptible *Pseudomonas* spp.

Dr Azanza and Dr Sábada review the pharmacokinetic and pharmacodynamic (PK/PD) aspects of the molecule. Ceftobiprole has linear pharmacokinetics with no absorption via the oral route. It is well distributed in the extracellular liquid compartment at its normal dosage of 500 mg iv every 8 hrs. The majority of the administered drug is excreted via the kidneys: for this reason, dose or timing adjustments are required according to renal clearance in patients with moderate to severe kidney failure. However, no dose adjustments are required according to weight or age, even in patients with mild to moderate liver failure. Upon augmented renal clearance or when external clearance techniques are used, an increase in infusion time is required, and increased dosage might also be required for critically ill patients in the Intensive Care Unit (augmented renal clearance). The 2-hour intravenous infusion, along with the excretion half-life greater than 3 hours, allows for an optimal time T>MIC PK/PD parameter to be easily reached when the MIC is ≤4 mg/l. In critically ill patients with hyperdynamic circulation and creatinine clearance >150 ml/min, the infusion may be extended to 4 hours to achieve an adequate therapeutic concentration.

Dr Cillóniz, Dr Dominedo, Dr Garcia-Vidal, and Dr Torres present their experience with ceftobiprole in pneumonia, the antibiotic is approved in major European countries) for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) excluding patients with Ventilator Acquired Pneumonia (VAP). In a phase-3 trial performed on patients with CAP, in which ceftobiprole was compared with ceftriaxone, with the possibility of adding linezolid upon

suspicion or confirmation of MRSA, no significant differences were found in clinical efficacy. Similarly, ceftobiprole was non-inferior in clinical efficacy compared with linezolid associated with ceftazidime in a phase-3 trial in HAP patients (excluding VAP). Patients who received ceftobiprole had an earlier clinical response, including cases with positive MRSA cultures. However, non-inferiority of ceftobiprole has not been demonstrated in the VAP subgroup of patients.

The authors believe that ceftobiprole may be used in patients with CAP and suspected involvement of MSSA or MRSA; such as in the case of post-influenza pneumonia during flu epidemics, and in patients with HAP who do not require mechanical ventilation.

Dr Soriano and Dr Morata will discuss some interesting aspects of the drug, such as the experience with ceftobiprole in staphylococcus bacteraemia. It has powerful activity against both methicillin-sensitive and resistant *S. aureus* as well as coagulase-negative *Staphylococcus,* isolated in episodes of bacteraemia. Its capacity for synergy with other antibiotics, especially daptomycin, suggests that this combination may be an option in the treatment of endovascular staphylococcal infections. On the other hand, ceftobiprole's activity against other clinically relevant pathogens, such as *E. faecalis* and enterobacteria as well as *P. aeruginosa*, positions it as a possibility in the empirical treatment of catheter-related bacteraemia.

Dr Barberán discusses other possible indications for ceftobiprole. Due to its extended-spectrum coverage, which includes MRSA, ceftobiprole may be considered in the treatment of complicated skin and soft tissue infections in special situations. In two comparative studies, one with vancomycin and another with vancomycin and ceftazidime, no significant differences were found. The same applies for diabetic foot infection, where in one clinical study the therapeutic response to ceftobiprole was faster than with the comparator. The author also believes that due to the drug's extended-spectrum antibiotic qualities, ceftobiprole may be an option for the empirical treatment of fever with no apparent focus in hospitalised patients without septic shock or severe immunosuppression, and for infections suspected to originate from vascular catheters.

Lastly, Dr Grau provides us with information concerning the safety and tolerability of ceftobiprole. In phase-3 studies, no significant differences have been observed against its comparators. On the other hand, and in contrast to other cephalosporins, ceftobiprole presents a low risk of infection due to *Clostridium difficile* and, in comparison with ceftaroline, neutropenia has not been reported to present any significant issues.

Official journal of the Spanish Society of Chemotherapy

María-Isabel Morosini
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Mechanisms of action and antimicrobial activity of ceftobiprole

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ABSTRACT

Ceftobiprole, a novel last generation parenteral cephalosporin, has an extended spectrum of activity, notably against methicillin-resistant *Staphylococcus aureus* (MRSA), ampicillin-susceptible enterococci, penicillin-resistant pneumococci, *Enterobacterales* and susceptible *Pseudomonas aeruginosa*. It exerts an inhibitory action on essential peptidoglycan transpeptidases, interfering with cell wall synthesis. The inhibitory action of ceftobiprole through binding to abnormal PBPs like PBP2a in methicillin-resistant staphylococci and PBP2b and PBP2x in the case of β-lactam-resistant pneumococci, ultimately leads to rapid bacterial cell death. In the case of *Enterobacterales*, ceftobiprole retains activity against narrow spectrum β-lactamases but is hydrolysed by their extended-spectrum counterparts, overexpressed Amp C, and carbapenemases. It is also affected by certain efflux pumps from *P. aeruginosa*. For anaerobic bacteria, ceftobiprole is active against Gram-positive *Clostridioides difficile* and *Peptococcus* spp. and Gram-negative *Fusobacterium nucleatum* but not against *Bacteroides* group or other anaerobic Gram-negatives. In *in vitro* studies, a low propensity to select for resistant subpopulations has been demonstrated. Currently, ceftobiprole is approved for the treatment of community-acquired pneumonia and hospital-acquired pneumonia with the exception of ventilator-associated pneumonia. Ceftobiprole's place in therapy appears to lie mainly in its combined activity against Gram-positive organisms, such as *S. aureus* and *S. pneumoniae* alongside that against Gram-negative organisms such as *P. aeruginosa*.

Key words: Ceftobiprole, methicillin-resistant *Staphylococcus aureus*; penicillin-resistant *Streptococcus pneumoniae*; *Pseudomonas aeruginosa*

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INTRODUCTION

Staphylococcus aureus is responsible for serious skin, soft tissue and bone infections as well as pneumonia, and is one of the leading causes of bloodstream infections in Europe, particularly within intensive care units [1]. However, the emergence of methicillin-resistant *S. aureus* (MRSA) in the 1960's as a result of the widespread use of penicillin stifled the use of subsequent promising molecules e.g isoxazolyl-penicillins [2].

Methicillin resistance in *S. aureus* and other staphylococci is due to the acquisition and expression of the *mecA* or less frequently, the *mecC* gene. These genes code for a PBP2a variant of the penicillin binding protein (PBP) PBP2 which exhibits low affinity for nearly all β-lactams thus preventing the inhibition of cell wall synthesis by these antimicrobials [3]. According to the 2017 report of the European Antimicrobial Resistance Surveillance Network (EARS-net, www.ecdc.europa.eu) the EU/EEA population-weighted mean MRSA percentage (in invasive isolates from blood stream and cerebrospinal fluid) was 16.9% (ranging from 1.0% to 44.4%, 25.8% in Spain). According to ECDC, this figure reaches 23.1% in ICUs in Europe [1].

The limited number of approved antimicrobials with activity against MRSA led to a strong demand for new agents to overcome this resistance. The fifth generation cephalosporins, ceftaroline and ceftobiprole, were the first β-lactams specifically designed to have activity against MRSA [4]. Ceftaroline was approved by European Medicines Agency in 2010, followed by ceftobiprole in 2013 in major European countries.

Ceftobiprole is a bactericidal cephalosporin with an extended-spectrum of activity against both Gram-positive cocci and Gram-negative bacilli. Ceftobiprole demonstrates potent binding to PBPs from Gram-positive bacteria, including those with decreased β-lactam sensitivity, such as PBP2a in MRSA and PBP2x in penicillin-resistant *Streptococcus pneumoniae* (PRSP), the latter, in contrast to ceftriaxone. In *Escherichia coli*, ceftobiprole also exhibits strong binding to the essential PBP2 and PBP3.

Unlike ceftaroline, ceftobiprole also exhibits a binding profile similar to that of cefepime and ceftazidime to PBPs in *P. aeruginosa* but with enhanced binding to PBP2. These properties explain the extended-spectrum activity of ceftobiprole and its indication in nosocomial pneumonia in which *P. aeruginosa* is a common pathogen [4-6]. In addition, in single-step and serial passage *in vitro* resistance development studies, ceftobiprole demonstrates a low propensity to select for resistance [6].

In this article we review the mechanism of action of ceftobiprole as well as its antimicrobial activity in international surveillance studies.

MECHANISM OF ACTION AND ANTIMICROBIAL PROFILE

Ceftobiprole is a parenteral pyrrolidinone-3-ylidene-methyl cephalosporin (figure 1) with an extended-spectrum of activity against MRSA, other Gram-positive bacteria (*S. pneumoniae* and *Enterococcus faecalis*) and Gram-negative bacteria (*Enterobacterales* and *P. aeruginosa*) exerted through the inhibition of essential peptidoglycan transpeptidases. Like other cephalosporins, the binding of ceftobiprole to PBPs interferes with cell wall synthesis, inhibiting cell growth and ultimately leading to bacterial cell death. Ceftobiprole exhibits a rapid bactericidal mode of action on an extended spectrum of clinically important Gram-positive and Gram-negative pathogens [5].

The bactericidal activity of ceftobiprole against MRSA sets it apart from other cephalosporins (with the exception of ceftaroline). Their efficacy as anti-MRSA is due to a successful inhibitory interaction with the extended narrow groove of the PBP2a active site coded by *mec* genes, favouring its acylation, inhibiting cell growth and, ultimately, leading to bacterial cell death. The molecular structures of first to fourth generation cephalosporins do not lead to suitable binding to PBP2a. The presence of a large hydrophobic side chain at C3 in the ceftobiprole molecule facilitates a conformational change in PBP2a leading to a stronger and energetically more favourable interaction with the PBP2a site groove and the formation of a stable acyl-enzyme complex. This interaction along with ceftobiprole's affinity for a range of other staphylococcal PBPS such as PBP1, PBP3, and PBP4 explains its high activity against staphylococci, including coagulase-negative isolates [7] Figure 2 comparatively includes the interaction of ceftobiprole and other beta-lactams with PBPs from different microorganisms [8-12].

Ceftobiprole demonstrates potent binding to PBPs in other Gram-positive bacteria, including those resistant to other β-lactam antibiotics, such as is the case of penicillin-intermediate and-resistant *S. pneumoniae* isolates. In these resistant strains, ceftobiprole exerts higher binding affinity to PBP2b and PBP2x than ceftriaxone [13].

The bactericidal activity against *E. faecalis* is a unique characteristic of ceftobiprole among the cephalosporins and is attributed to the high affinity for the enterococcal penicillin binding proteins. However, ceftobiprole does not bind to PBP5 in *E. faecium* although, in the minority of *E. faecium* isolates that are ampicillin sensitive, ceftobiprole appears to be active [7-13, 14]. This effect has been shown to be much lower with ceftaroline, being this one 4-fold less effective on *E. faecalis* versus ceftobiprole [15].

Against Gram-negative bacteria, ceftobiprole exhibits high affinity for PBPs in *Enterobacterales*. However, ceftobiprole is inactive against *Enterobacterales* expressing Ambler's Class A β-lactamases including ESBLs, overexpressed AmpC β-lactamase types, and all carbapenemases. *P. aeruginosa*, when grown in the presence of ceftobiprole, produces filamentation, suggesting that PBP3 is the site of action [9]. Ceftobiprole is ineffective against *P. aeruginosa* expressing Ambler's Class A β-lactamases including ESBLs and all carbapenemases, as class A (PSE-type, GES and others), metallo-carbapenemases (IMP and VIM) and D (OXA-10). Ceftobiprole is partially and slowly hydrolysed by AmpC and interestingly, unlike ceftazidime and cefepime, did not select AmpC derepressed mutants [16]. In a similar fashion, ceftobiprole, and ceftaroline display limited activity against *Acinetobacter* spp., *Burkholderia cepacia* and *Stenotrophomonas maltophilia* [14, 17].

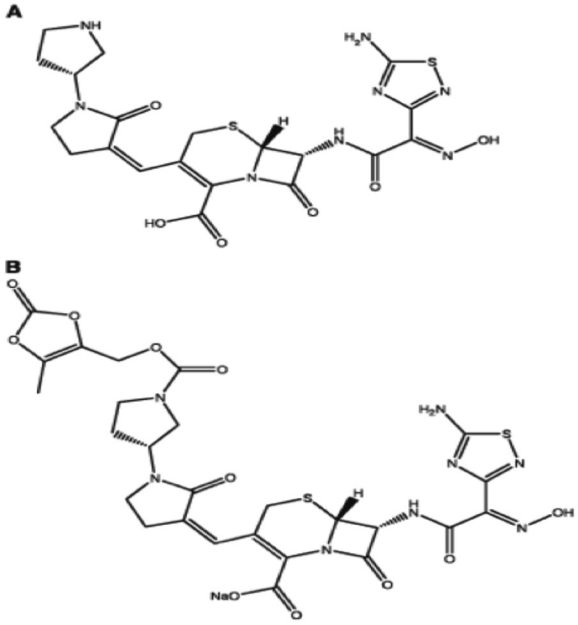

Figure 1 | **A: Ceftobiprole, the active cephalosporin. B: Ceftobiprole medocaril, the water-soluble prodrug. Substitution at position 7 of the cephem by an oxyimino aminothiazolyl confers remarkable betalactamase stability and substitution at position 3 with a vinylpyrrolidinone moiety facilitates the association of the molecule with PBP2a and hence facilitates the subsequent acylation reaction.**

Table 1 **Ceftobiprole and ceftaroline breakpoints and ECOFF values of bacterial species and groups, according to EUCAST-2019.**

Microorganism	Ceftobiprole			Ceftaroline		
	Clinical breakpoints (mg/L)		ECOFF (mg/L)	Clinical breakpoints (mg/l)		ECOFF (mg/L)
	Susceptible (≤)	Resistant (>)		Susceptible (≤)	Resistant (>)	
S. aureus (including MRSA)	2	2	1	1*	1** 2***	0.5
S. pneumoniae (including PNS[a])	0.5	0.5	0.03	0.25	0.25	0.03
E. faecalis	-[b]	-	ND[c]	-	-	ND
Enterobacterales	0.25	0.25	0.12-0.25	0.5	0.5	0.12-0.25
P. aeruginosa	IE[d]	IE	8	-	-	ND
H. influenzae	IE	IE	0.25	0.03	0.03	0.03
M. catarrhalis	IE	IE	ND	IE	IE	ND
Non-species related[e]	4[f]	4	-	0.5	0.5	-

*Including pneumonia; **Pneumonia isolates; *** Other isolates than pneumonia; [a]Penicillin-non-susceptible; [b]-: no breakpoint; [c]ND: not determined; [d]IE: insufficient evidence; [e]PK-PD breakpoints; [f]Based on PK-PD target for Gram-negative organisms.

Ceftobiprole is active against both non- and β-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis*, and against *Neisseria* spp.

For anaerobic bacteria, ceftobiprole is active against Gram-positive *Clostridioides difficile*, *Peptococcus* spp. and *Fusobacterium nucleatum* but not against the *Bacteroides* group and other anaerobic Gram-negatives [18]. Ceftobiprole has limited activity against Gram-negative anaerobes such as *Bacteroides fragilis* and *Bacteroides* spp. β-lactamase negative anaerobes are more susceptible to ceftobiprole than β-lactamase-positive isolates, suggesting that ceftobiprole is hydrolysed by most β-lactamases found in these bacteria. Ceftobiprole is also active against *Cutibacterium acnes*, *Peptostreptococcus* spp., *Clostridium innocuum*, *Finegoldia magna*, and many strains of *Porphyromonas* spp. It demonstrates lower MICs for *Clostridium perfringes* and *Clostridiums difficile* than other cephalosporins, and has been shown to be less active *in vitro* than ceftriaxone against isolates of *Fusobacterium* spp., *Prevotella* spp. and *Veillonella* spp. [19].

CLINICAL BREAKPOINTS AND *IN VITRO* ACTIVITY

Ceftobiprole clinical breakpoints and ECOFF values (EUCAST, 2019. www.eucast.org) for Gram-positive and Gram-negative species in comparison with those defined for ceftaroline are shown in table 1. EUCAST has not yet established ECOFF values for all the targeted species, however, where ECOFF values are defined for both for ceftobiprole and ceftaroline, they are similar. However, it should be noted that PK/PD breakpoints are higher for ceftobiprole than for ceftaroline. This situation reflects the favourable T>MIC PK/PD index for ceftobiprole associated with its administration schedule, 500 mg every 8 h with an extended 2 h IV infusion [20-24]. For ceftaroline, the regular schedule is 600 mg every 12 h with 1 h IV infusion, although recently, a higher posology of 600 mg every 8 h with an extended 2 h IV infusion has been approved for cSSTI due to *S. aureus* [25]. This higher dosing regimen might assure coverage of MRSA isolates displaying at least a ceftaroline MICs of 2 mg/l, but this posology is not approved for community acquired pneumonia by the EMA. For ceftobiprole, the higher breakpoints ascertain coverage is achieved without increasing the standard dose.

Apart from its affinity against altered PBP2a in methicillin-resistant staphylococci and PBPs involved in penicillin (PBP2b) and ceftriaxone (PBP2x) resistance in *S. pneumoniae*, the extended-spectrum of ceftobiprole activity is due to its ability to withstand hydrolysis by many β-lactamases, like PC1 from *S. aureus*, the narrow spectrum TEM and SHV β-lactamases from *Escherichia coli* and *Klebsiella pneumoniae*, respectively, among other *Enterobacterales*. However, as indicated above, ceftobiprole is susceptible to the hydrolysis by the extended-spectrum β-lactamases (ESBLs), all molecular types of carbapenemases (A, B and D) and overexpressed or derepressed AmpC β-lactamase types from both *Enterobacterales* and *P. aeruginosa*. In addition, overexpression of certain efflux pumps like MexXY from this latter organism also diminishes ceftobiprole activity [18, 26]. All of these resistance mechanisms equally affect ceftaroline.

In a recent surveillance study that included key target pathogens [27], ceftobiprole exhibited potent activity against *S. aureus* isolates (including MRSA isolates, which were 99.3% susceptible), coagulase-negative staphylococci (100% susceptible), *E. faecalis* (100% susceptible), and *S. pneumoniae* (99.7% susceptible). Likewise, ceftobiprole was highly active against enterobacterial isolates that did not exhibit an ESBL phenotype, including *E. coli* (99.8% susceptible) and *K. pneu-*

Table 2 | **Summary of activities of ceftobiprole against Gram-positive and Gram-negative species (Adapted from reference [20])**

Species	Antimicrobial	MIC (mg/L)			% Susceptibility*
		MIC_{50}	MIC_{90}	MIC range	
S. aureus	Ceftobiprole	0.5	2	≤0.03-4	99.7
	Ceftaroline	0.25	2	≤0.06-4	98.5
MRSA	Ceftobiprole	1	2	0.25-4	99.3
	Ceftaroline	0.5	1	0.25-4	96.4
CoNS[a]	Ceftobiprole	0.5	1	≤0.03-4	100.0
	Ceftaroline	0.25	0.5	≤0.06-2	-[c]
MRCoNS[b]	Ceftobiprole	1	1	0.12-4	100.0
	Ceftaroline	0.25	0.5	≤0.06-2	-[c]
S. pneumoniae	Ceftobiprole	0.015	0.5	0.002-1	99.7
	Ceftaroline	≤0.008	0.12	≤0.008-0.5	99.7
E. faecalis	Ceftobiprole	0.5	2	≤0.03-4	100.0
	Ceftaroline	2	8	≤0.06->8	-[c]
E. coli	Ceftobiprole	0.03	>16	0.015->16	82.5
	Ceftaroline	0.12	>32	≤0.015->32	78.5
K. pneumoniae	Ceftobiprole	0.03	>16	0.015->16	83.4
	Ceftaroline	0.12	>32	≤0.015->32	80.4
P. aeruginosa	Ceftobiprole	2	16	0.12->16	72.7
	Ceftaroline	16	>32	0.25->32	-[c]
H. influenzae	Ceftobiprole	0.06	0.12	0.015->1	92.0
	Ceftaroline	0.015	0.03	0.002-2	92.0
M. catarrhalis	Ceftobiprole	0.12	0.25	≤0.008->1	-[c]
	Ceftaroline	0.12	0.25	0.002-2	-[c]

***EUCAST criteria; [a]coagulase-negative staphylococci; [b]methicillin-resistant coagulase-negative staphylococci, [c]breakpoints have not been established**

moniae (99.6% susceptible) isolates. A total of 99.6% of all *H. influenzae* and *M. catarrhalis* isolates were inhibited by 1 mg/L of ceftobiprole, and 72.7% of the *P. aeruginosa* isolates were susceptible to ceftobiprole (table 2). In this study, susceptibility values were established using EUCAST breakpoints. The corresponding values for ceftaroline are also included in table 2. With the exception of *E. faecalis* and *P. aeruginosa*, in which ceftobiprole displayed a clearly higher intrinsic activity, the activity of both cephalosporins were within one-fold dilution of each other. Nevertheless, rates of ceftobiprole susceptible MRSA isolates were higher than for ceftaroline.

The high coverage of ceftobiprole in key pathogens, including *S. aureus*, *S. pneumoniae* and *P. aeruginosa* with relevant resistance mechanisms is shown in figure 3. Data were obtained for a large multicentric study in different European countries over a five-year period [28]. In the case of *S. aureus*, all methicillin susceptible isolates were susceptible to ceftaroline and only 1.7% of MRSA isolates were considered non-susceptible to ceftobiprole. Ceftobiprole displayed a high intrinsic activity against *S. pneumoniae*, although MIC increased with the decrease of penicillin susceptibility. Overall, only 0.15% of *S. pneumoniae* were considered resistant. For *P. aeruginosa* and using the EUCAST non-species-specific PK/PD breakpoints (susceptible ≤4 mg/L; resistant >4 mg/L), 78.4% of the ceftazidime-susceptible isolates were also susceptible to ceftobiprole but this percentage decrease to 22.7% in ceftazidime-resistant isolates. MIC distributions of all these isolates is summarised in figure 3.

ANTIMICROBIAL RESISTANCE

To date, ceftobiprole has demonstrated a low potential to select for resistance. Although staphylococci have a proven ability to develop resistance to most antibiotics in clinical use, results from *in vitro* studies indicate that the potential for MRSA to become resistant to ceftobiprole appears to be low [29]. Different studies using laboratory strains submitted either to serially growing concentrations or to continuous challenge with

Staphylococcus spp.					
	PBP1	PBP2	PBP2a	PBP3	PBP4
Ceftobiprole	✔	✔	✔	✔	✔
Ceftaroline	✔	✔	✔	✔	✘
Ceftriaxone	✔	✔	✘	✔	✘
Meropenem	✔	✔	✘	✔	✔
Piperacillin	✔	✔	✘	✔	✔

Escherichia coli							
	PBP1a	PBP1b	PBP2	PBP3	PBP4	PBP5	PBP6
Ceftobiprole	✔	Some	✔	✔	✔	✘	✔
Ceftazidime	✔	✔	Some	✔	✘	✘	✘
Cefepime	✔	Some	✔	✔	✘	✘	✘
Imipenem	✔	✔	✔	✘	✔	✔	✔
Piperacillin	✔	Some	✔	✔	✔	✘	✘
Ceftolozane	✘	✔	✘	✔	✘	✘	✘

Pseudomonas aeruginosa						
	PBP1a	PBP1b	PBP2	PBP3	PBP4	PBP5/6
Ceftobiprole	✔	✔	✔	✔	✔	✘
Ceftazidime	✔	✔	✘	✔	✔	✘
Cefepime	✔	✔	Some	✔	✔	✘
Imipenem	✔	✔	✔	✔	✔	✔
Piperacillin	✔	✔	✔	✔	✔	✘
Ceftolozane	✘	✔	✔	✔	✔	✘

Figure 2 | **Ceftobiprole binding to PBPs of different microorganisms in comparison with other beta-lactam compounds [7-12]**

✘: not biologically relevant; PBP, penicillin-binding protein

subinhibitory levels of the antibiotic, demonstrated that the most frequent changes leading to *in vitro* resistance are due to: i) Mutations in the *mecA* gene that result in amino acid changes within the transpeptidase domain of PBP2a together with changes in the non-penicillin-binding domain, ii) Non *mecA*-mediated mechanisms of resistance resulting from mutations in different PBPs, PBP4 (a non-essential, low-molecular weight PBP of *S. aureus*) being the most frequently involved. Mutations in PBP4 occurred in the structural coding gene and/or in its promoter region. It should also be noted that those modifications in *pbp4* gene and its promoter produce a highly crosslinked cell wall peptidoglycan, indicative of increased transpeptidase activity associated with greatly increased amounts of membrane PBP4 [30]. Moreover, additional mutations in other genes such as ClpX endopeptidase, PP2C protein phosphatase, transcription terminator Rho, and GdpP phosphodiesterase, have all been involved in fifth-generation cephalosporins resistance development [31].

At present, few studies describe the presence of ceftobiprole resistance among clinical isolates. In a study conducted in France with 440 *S. aureus* (MSSA and MRSA) isolates from bronchopulmonary infections, only one ceftobiprole resistant strain (MIC 4 mg/L) was detected among the MRSA (n=115) subpopulation [32]. This strain (clonal complex, CC8) was a PVL-negative MRSA strain isolated from a tracheal aspirate, presenting a mutation in PBP2a previously associated with low-level resistance to ceftobiprole and ceftaroline. The strain was resistant to both ceftobiprole and ceftaroline, but remained susceptible to vancomycin, daptomycin, and linezolid. The authors noted that the MRSA subpopulation displayed higher ceftobiprole MIC_{50} and MIC_{90} (1 mg/L), and interestingly, that the genetic background of *S. aureus* strains (*agr* group and CC) may slightly impact the strain susceptibility to ceftobiprole [32].

During a one-year surveillance study in an Italian Hospital, 12% of ceftobiprole resistance (12/102 isolates; MIC, 4 mg/L) among the MRSA population (only *mecA* producers) was found. After epidemiological characterization, isolates belonged to different clones, as well as substitutions in all PBPs and with a novel insertion in PBP2a [26]. It is worth mentioning that ceftobiprole became available at the hospital only one year before the study took place thus selective pressure for this situation can be excluded [33].

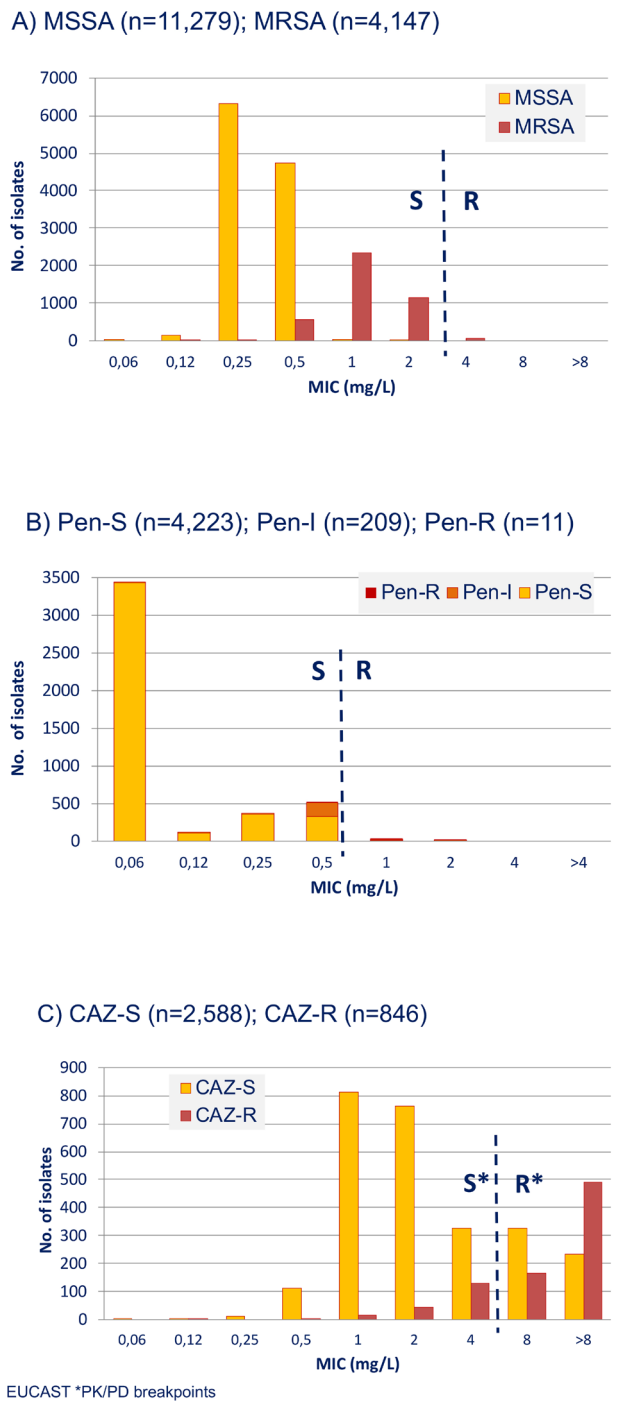

Figure 3 MIC distributions of methicillin-susceptible and resistant *S. aureus* (A), penicillin-susceptible, -intermediate and -resistant *S. pneumoniae* (B) and ceftazidime-susceptible and -resistant *P. aeruginosa* (C) isolates recovered from European surveillance studies (data obtained from reference [21])

Though the presence of resistant isolates in the clinical setting is at present scarcely observed, ceftobiprole susceptibility screening is essential to avoid therapeutic failure and the spread of resistant strains. Close microbiological monitoring of isolates should be maintained to prevent resistant strains diffusion by early detection of changes in susceptibility pattern. In a recent surveillance study monitoring ceftobiprole susceptibility performed in USA with blood isolates, only 0.3% (4 isolates over 558 tested isolates) of MRSA were non-susceptible to ceftobiprole [34].

CONCLUSIONS

Ceftobiprole is a novel parenteral extended-spectrum cephalosporin covering resistant Gram-positive and Gram-negative organisms due to its inhibition of abnormal PBP2a in MRSA and PBP2b and PBP2x in the case of β-lactam-resistant pneumococci. Moreover, it is also effective against *Enterobacterales* not producing extended-spectrum β-lactamases, AmpC overproducers or carbapenemases, and susceptible *P. aeruginosa*. This activity and results from clinical trials positions this cephalosporin for the treatment of community-acquired pneumonia and hospital-acquired pneumonia with the exception of ventilator-associated pneumonia in patients who require a broad-spectrum treatment with the highest safety due to the novel broad spectrum of coverage that has been shown as cephalosporin.

CONFLICTS OF INTERESTS

RC has participated in educational programs sponsored by Pfizer.

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Ceftobiprole: pharmacokinetics and PK/PD profile

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ABSTRACT

Ceftobiprole shows many similar pharmacokinetic properties to other cephalosporins, except for not being orally bioactive, and that it is administered by IV infusion as the prodrug ceftobiprole medocaril, which is subsequently hydrolyzed in the blood into the active molecule. Distribution focus in extracellular fluid and active antibiotic concentration has been proven in different corporal tissues using dosing regimen of 500 mg intravenous infusion over 2 h every 8 h. Ceftobiprole is eliminated exclusively into the urine, thus the reason why dose adjustment is required for patients with moderate or severe renal impairment, or increased creatinine clearance. However, there is no need for dose adjustments related with other comorbidities and patients' conditions such as age, body weight. Although considering distribution features, molecular weight and dose fraction, increase dosing regimen might be necessary in patients using renal replacement therapy. The half-life of ceftobiprole is more than 3 h, allowing to easily reach optimal PK/PD parameters with the infusion time of 2 h, using the usual dosing regimen.

Keywords: Ceftobiprole, clinical pharmacokinetics, PK/PD relationships

INTRODUCTION

The on-going and rapid development of antibiotic resistance of different pathogens is now a growing concern leading to potential risks for patients. The specific case of Gram-positive bacteria is not impervious to this situation, for which reason the availability of a new drug that allows for specifically directed treatment toward resistant forms is welcome.

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Ceftobiprole, a beta-lactam antibiotic belonging to the cephalosporin group, is the latest inclusion into the select group of active drugs against these types of bacteria, hence the interest in practically describing the primary pharmacokinetic and pharmacokinetic/pharmacodynamic (PK/PD) characteristics in order to achieve more efficient use of this drug.

PHARMACOKINETICS

General Information. Ceftobiprole is a cephalosporin that is administered in the form of the prodrug ceftobiprole medocaril, which is rapidly converted in the plasma, likely through esterases, to its active fraction; ceftobiprole. The approved dose is 500 mg every 8 hours administered intravenously as a 120 minute infusion. This cephalosporin presents linear pharmacokinetics after a single dose and multiple doses between 125 and 1,000 mg [1-3]; furthermore, the pharmacokinetics are independent of the duration of administration [4]. The state of equilibrium is achieved during the first day [5], there is no drug accumulation when administered every 8 h in patients with normal kidney function [4], which is fully justified considering the elimination half-life of about 3 h. Table 1 [6] shows the pharmacokinetic parameters obtained after administration of the approved dose of 500 mg in a 2-hour infusion to healthy volunteers.

Systemic exposure defined by the area under the curve during the dosing interval ($AUC_{0-\tau}$), and maximum plasma concentration (Cmax) reached on day 5 were similar to those determined on day 1 (AUC 102 ± 11.9 and 90 ± 12.4 mg h/l, respectively; Cmax, 33 ± 4.83 and 29.2 ± 5.52 mg/l, respectively).

The renal clearance and systemic clearance values did not change either in relation to the day of administration, kidney clearance for the first day being 4.28 ± 0.57, and 4.08 ± 0.72 l/h on day 5, resulting in total clearance on these same days of 4.98 ± 0.58 and 4.89 ± 0.69 l/h, respectively.

Table 1 Single dose ceftobiprole. Pharmacokinetic parameters [2, 4, 6]

Dose (mg)	500
Perfusion time (hours)	2
Cmax (mg/l)	29.2 ± 5.5
AUC0-∞ (mg h/l)	104 ± 13
t½ (h)	3.1 ± 0.3
Vd (l)	21.7 ± 3.3
Plasma protein binding (%)	16
Cl_t (l/h)	4.8 ± 0.7
Cl_r (l/h)	4.1 ± 0.7
Active urinary excretion (%)	83.1 ± 9.1

Cmax: maximum plasma concentration
$AUC_{0-\infty}$: extrapolated area under the curve
t½: excretion half-life
Vd: volume of distribution
Cl_t: total clearance
Cl_r: kidney clearance

The drug elimination half-life was 3.3 ± 0.3 h the first day and 3.1 ± 0.3 h on day 5 [4, 6].

Distribution. A volume of distribution of 21.7 ± 3.3 l and 15.5 ± 2.33 l on day 1 and day 5, respectively, has been reported. This volume of distribution is similar to extracellular volume for an adult patient, information consistent with that of the vast majority of beta-lactam antibiotics in general and cephalosporins in particular [6]. The plasma protein binding of ceftobiprole is very low, only 16% of it is albumin-bound [5], which facilities this drug's penetration of several body tissues.

Ceftobiprole's penetration of soft tissues, including adipose, and bone tissue, has been studied, following the administration of a single dose of 500 mg of ceftobiprole over a 2-h infusion in healthy volunteers, using microdialysis measures. Striated muscle penetration of 69% and adipose tissue penetration of 49% were determined [7]. In adult patients who received 500 mg ceftobiprole in an IV infusion before undergoing hip prosthesis surgery, ceftobiprole exposure in cortical bone was 3.5 times higher than what was determined for spongy bone [8]. The ratio between tissue and plasma concentrations was 0.22 for cortical bone and 0.06 for spongy bone (0.15-0.3) [9]. The PK/PD study performed using the collected data confirmed that the likelihood of reaching a value of T > MIC of 30-40% was >90% in all tissues evaluated when MIC was 2 mg/l [10].

The clinical relevance of this PK/PD profile has been shown in relation to the differences evaluated in a rabbit tibia infection model in which the administration of this drug for 4 weeks reduced the bacterial count to below detectable limit in all animals treated, while it was reduced by 73% in animals treated with vancomycin or linezolid [11].

The penetration of ceftobiprole was evaluated in bronchoalveolar lavage (BAL) fluid in healthy subjects following the administration of 4 conventional doses of ceftobiprole [12], verifying that the BAL concentration was lower than in plasma 8h after starting the infusion, reporting a value of 25.5% in relation to BAL/plasma concentration.

Excretion. Ceftobiprole is predominantly excreted in the urine [4, 6] as indicated by total clearance values, which coincide with kidney clearance. Approximately 80-90% of the drug administered may be recovered unaltered in the urine [1, 4]. Excretion occurs primarily through glomerular filtration and it appears that active tubular secretion is not involved [4], therefore, no interactions are expected in the kidney excretion of the drug [13]. This circumstance justifies the fact that the pharmacokinetics of ceftobiprole are modified in patients with kidney failure [14]. At the same time, it justifies the limited presence of ceftobiprole in the intestinal lumen, which explains why active drug concentrations have not been detected in the faeces of healthy subjects who received IV infusions of 500 mg/8 h ceftobiprole for 7 days. This characteristic may account for the rare incidence of effects on the intestinal flora, as well as not detecting *C. difficile* or its toxin in ceftobiprole-treated patients [15].

PHARMACOKINETICS IN SPECIAL SITUATIONS

Patients with kidney failure. Ceftobiprole is almost entirely passively excreted unchanged through glomerular filtration, it is therefore important to know the impact that the presence of kidney failure could have on pharmacokinetics and the corresponding dose adjustment.

To that end, a study was conducted in which the pharmacokinetic parameters of administering a single 250-mg dose in one 30-minute infusion in healthy volunteers and subjects with different degrees altered kidney function were compared [14, 16].

As shown in table 2, kidney clearance for ceftobiprole was reduced in a significant manner in patients with moderate to severe kidney failure (80% and 91%, respectively) when compared with normal kidney function. Systemic clearance and kidney clearance showed a linear relationship with patients' creatinine clearance (CrCl) (correlation coefficient of 0.98 in both cases), confirming that required dose adjustment according to kidney function may be predicted based on creatinine clearance [14].

A study conducted on patients with terminal kidney failure requiring dialysis [14] demonstrated that systemic exposure expressed as a value of area under the curve between 0 and infinity ($AUC_{0-\infty}$), was 3.2 times higher in subjects with altered kidney function than in healthy subjects when analysed pre-dialysis, and approximately 7 times higher when analysed post-dialysis. This finding is explained through the reduction of systemic clearance with subsequent increase in half-life. It has been estimated that ceftobiprole extraction during a 4-h

Table 2 **Ceftobiprole. Pharmacokinetic parameters (mean ± standard deviation) in patients with kidney failure [14, 16]**

Degree of kidney failure. Creatinine Clearance (CrCl ml/min). Dose: 250 mg IV, in 30 minutes.

	Cmax (mg/l)	AUC_{0-last} (mg-h/L)	t½ (h)	V_{SS} (L)	CL_T (L/h)	CL_R (L/h)	U (%)
Normal CrCl>80 ml/min	20.6 ± 2.0	52.4 ± 6.9	3.4 ± 0.3	15.8 ± 1.8	4.8 ± 0.6	4.3 ± 0.5	91.6 ± 6.5
Mild (CrCl 50-80 ml/min)	20.1 ± 1.4	72.7 ± 13.9	4.7 ± 0.8	18 ± 0.7	3.4 ± 0.7	2.4 ± 0.6	71.1 ± 7.3
Moderate (CrCl 30-50 ml/min)	24.4 ± 1.65	139 ± 15.7	6.8 ± 1.1	14.2 ± 0.8	1.6 ± 0.2	0.8 ± 0.2	51.9 ± 9.9
Severe (CrCl <30 ml/min)	22.8 ± 3.4	174 ± 44.5	11.1 ± 1.9	16.9 ± 2.39	1.2 ± 0.3	0.4 ± 0.2	31.5 ± 9.6

Dialysis. Dose: 250 mg IV, in 120 minutes.

	Cmax (mg/l)	AUC_{0-last} (mg-h/L)	t½ (h)	V_{SS} (L)	CL_T (L/h)	CL_R (L/h)	U (%)
Healthy subjects	11.1 ± 1.7	44.3 ± 7.1	3.0 ± 0.4	24.4 ± 3.6	5.6 ± 0.7	5.1 ± 0.8	88.6 ± 4.06
Pre-dialysis	13.3 ± 2.3	118 ± 8.73	20.7 ± 1.83	52.5 ± 5.2	1.7 ± 0.10	N/A	N/A
Post-dialysis	21.1 ± 14.7	249 ± 49.0	20.5 ± 5.33	23.9 ± 5.1	0.8 ± 0.2	N/A	N/A

Cmax: maximum plasma concentration; AUC_{0-last}: area under the curve between zero and last plasma concentration; t½: excretion half-life; V_{ss}: volume of distribution in state of equilibrium; Cl_r: kidney clearance; Cl_t: total clearance; U: percentage of drug actively excreted by urine.

dialysis session is 68% and average dialysis clearance is 7.91 l/h [16].

A population pharmacokinetic (PK) study assessing the need for dose adjustment, demonstrated that kidney function expressed in the form of creatinine clearance was the only patient characteristic s with impact on ceftobiprole PK [17].

These data justify use of conventional doses in patients who present with mild kidney failure (CrCl between 50 and 80 ml/min), but recommending the administration of 500 mg every 12 hours via intravenous perfusion for a period of 2 hours when kidney failure is moderate (CrCl 30 - <50 ml/min), and reducing the dose 250 mg administered every 12 hours for a period of 2 h for patients with severe kidney failure (CrCl <30 ml/min). In the event that intermittent dialysis is needed, the recommended dose is 250 mg administered once every 24 hours [5].

Critically ill patients. The impact on the pharmacokinetic parameters of ceftobiprole on the presence of hyperdynamic circulation characterised by elevated creatinine clearance, typical of some critically ill patients, has been assessed in a multicenter, open-label, parallel-group, non-randomized study [18]. Thirty-three adult subjects hospitalised in the Intensive Care Unit were evaluated, who received 1000 mg of ceftobiprole as a 4-h perfusion. Systemic clearance of ceftobiprole was significantly higher in patients with creatinine clearance above 150 ml/min compared to those with normal clearance or reduced creatinine clearance (table 3).

In patients which presented elevated creatinine clearance the drug is excreted from the plasma faster but at the same time there is greater distribution, preventing changes to the excretion half-life but leading to lower plasma concentrations. The authors indicated that ceftobiprole administered in a 4-hour infusion time was able to reach and maintain a plasma concentration of the free drug that exceeded MIC throughout the dosing interval. At a dose of 500 mg, the T>MIC value was 91%, demonstrating that the conventional dose administered in a 4-h infusion also provided therapeutic concentrations [18].

Therefore, prolonging the infusion to 4 hours may optimise drug exposure with a standard dose of ceftobiprole of 500 mg/8 h administered to patients with creatinine clearance above 150 ml/min [5].

Paediatric patients. The pharmacokinetic properties of ceftobiprole have been evaluated in 55 children aged 3 months to 18 years requiring systemic antibiotic therapy [19]. The drug was administered in a 2-hour infusion with doses adjusted to 15 mg/kg for patients aged 3 months to 6 years, 10 mg/kg when aged 6 to 12 years, and 7 mg/kg in patients aged 12 to 18 years. Ceftobiprole exposure, expressed in Cmax and $AUC_{0-\infty}$, was 20% and 40% below that of adults for patients under 12

Table 3 **Ceftobiprole. Pharmacokinetic parameters (mean ± standard deviation) in patients with elevated creatinine clearance (CrCl) [18]**

	Cmax (mg/l)	AUC_{0-last} (mg-h/L)	t½ (h)	V_{SS} (L)	CL_T (L/h)	F (%)
Reduced[a] CrCl 50-79 ml/min (N=5)	51.6 ± 11.2	405 ± 93.2	4.5 ± 1.0	23.7 ± 6.6	3.8 ± 0.6	19.1 ± 4.4
Normal[b] CrCl 80-150 ml/min (N= 20)	37.8 ± 7.3	269 ± 116	3.8 ± 1.6	23.1 ± 6.3	5.2 ± 1.2	20.5 ± 7.3
Elevated[b] CrCl >150 ml/min. (N= 6)	27.6 ± 7.3	180 ± 75.3	3.8 ± 1.2	29.4 ± 7.5	7.4 ± 1.5	21.6 ± 3.5

N: number of subjects. Cmax: maximum plasma concentration; AUC_{0-last}: area under the curve between zero and last plasma concentration; t½: excretion half-life; V_{ss}: volume of distribution at steady state; Cl_t: total clearance; F: percentage of binding to plasma proteins.

[a]Ceftobiprole 1000 mg administered in 4 h. of infusion every 12 h.

[b]Ceftobiprole 1000 mg administered in 4 h. of infusion every 8 h.

years old and those aged 12-18 years, respectively. When the dose was adjusted by body weight, the volume of distribution and total clearance decreased in relation to increased age, while kidney clearance and excretion half-life remained unchanged. The lowest detected exposure in children aged 12 to 18 years should be considered when establishing the most appropriate dosing regimen. However, in this age sub-group, in the PK/PD study, the ceftobiprole concentration remained higher than the MIC of 4 mg/l for 66.5-75.3% of the 8-hour dosing interval and the drug was also well tolerated [19].

Obese patients. A pharmacokinetic study was conducted in 13 morbidly obese adult patients (BMI >40 kg/m^2) administered a single 500-mg dose of ceftobiprole in 2-hours and compared to PK in subjects who were not obese [20]. A lower Cmax was reported in obese patients (21.4 ± 3.0 versus 30.2 ± 4.3 mg/l), lower $AUC_{0-\infty}$ (91.0 ± 11.7 vs. 110 ± 20.1 mg h/l), higher volume of distribution (27.2 ± 3.9 vs. 21.6 ± 5.1 l), and higher total clearance (5.6 ± 0.7 vs. 4.7 ± 0.7), although with similar half-life values (3.4 ± 0.3 vs. 3.2 ± 0.5). Despite these changes in pharmacokinetic parameters, the plasma concentration of ceftobiprole not bound to proteins remained above an MIC of 4 mg/l for 76.6 and 79.7% of the 8-hour interval, respectively, for both obese and non-obese subjects. Therefore, although in obese subjects the volume of distribution and clearance are greater and the AUC lower, the therapeutic objective is reached in a manner similar with the conventional dose, thus a dose adjustment is not needed in this type of patient.

Other situations

Other external clearance techniques. No studies have reported on the effect of different external clearance techniques, hemofiltration, etc. on the pharmacokinetic behaviour of ceftobiprole. However, it should be considered that it has a molecular weight of 534.56 g/mol, binds to proteins in lower proportion (<20%) and its volume of distribution indicates that the drug remains in accessible areas, characteristics which require one to consider the necessity of using higher than recommended doses according to the patient's kidney function, without a specific amount being needed.

Liver failure. The pharmacokinetics of ceftobiprole in patients with liver failure has not been established. Since ceftobiprole endures minimal liver metabolism and is essentially excreted unaltered in the urine, liver failure is not expected to affect ceftobiprole clearance.

Elderly patients. Population Pharmacokinetic data has demonstrated that age as an independent parameter has no effect on the pharmacokinetics of ceftobiprole. Dose adjustment is not believed to be required in elderly patients with normal kidney function.

Gender. Systemic exposure to ceftobiprole was higher in women than in men; 21% for Cmax and 15% for AUC in one study, and 32% and 21%, respectively, in another study. However, the parameter of % T > MIC was similar in both sexes. Therefore, dose adjustment is not believed to be necessary based on gender [16].

Race. Pharmacokinetic population assays (including groups of Caucasians, black patients, and others) and a specific pharmacokinetics study on healthy Japanese subjects showed that race had no effect on the pharmacokinetics of ceftobiprole. Therefore, dose adjustment is not believed to be necessary based on race [16].

PHARMACOKINETICS/PHARMACODYNAMICS

For beta-lactam antibiotics, the concentration exposure time above the MIC value (T>MIC) is the pharmacokinetic/pharmacodynamic index (PK/PD) shown to be most related to therapeutic efficacy [21], hence it is the parameter evaluated when establishing the dose to be used for a drug in this group [22-23].

Studies conducted on laboratory animals have demonstrated an important relationship between the efficacy of ceftobiprole and the T > MIC value. Ceftobiprole demonstrated time-dependent killing; its in vivo postantibiotic effects varied from 3.8 h to 4.8 h for MRSA and from 0 to 0.8 h for penicillin-resistant *Streptococcus pneumoniae*, a bacteriostatic effect was already associated with a T > MIC value of 36-45% in the case of *Enterobacteriaceae,* 14–28% for *S. aureus* and 15–22% for *S. pneumoniae*. In this study, the T > MIC for the 2-log kill dose for strains of *Enterobacteriaceae* (64.5% ± 25.1% of the dosing interval) was also significantly longer than those for the strains of *S. pneumoniae* and *S. aureus* (25.8% ± 4.8% and 29.3% ± 4.6%, respectively) [24].

Based on the findings of *in vivo* models for mice with pneumonia and mouse thigh infection, the doses that produced a T > MIC of 30% were selected for documented gram positive bacteria and 50% in the case of infections due to mixed flora, Gram-positive bacteria, and Gram-negative bacteria. A T> MIC of 50% was used to determine the PK/PD breakpoint of 4 mg/l (EUCAST), with which it is expected to reduce 1-2 $\log_{10}$ the number of bacterial colony-forming units (CFU) [4, 25, 26].

In another study, the activity of ceftobiprole on mice with pneumonia caused by *S. aureus* was explored, demonstrating that T > MIC of ceftobiprole on BAL to cause a reduction in colony-forming units of 1 and 2 $\log_{10}$, was 13 and 24%, respectively. Based on a Monte Carlo simulation and using the concentrations described for the administration of 500 mg/8 h ceftobiprole in a 2-h infusion, and the distribution of MICs from 4950 strains of methicillin-resistant *S. aureus,* an accumulated response fraction of 85.6% was expected to reduce by 1 $\log_{10}$ the number of CFU/g and 79.7% to reduce bacterial load by 2 $\log_{10}$ [12].

In a Monte Carlo simulation conducted with the data collected during phase I trials using pharmacokinetic population models [27], different dosing regimens of ceftobiprole were studied to reach a therapeutic target of T > MIC of 30-60% for MIC values of 1-16 mg/l. Ceftobiprole 500 mg/8 h demonstrated a likelihood to reach a therapeutic target of 100% for T > MIC 30 and 40% and 99% for T > MIC of 50% for an MIC of 4 mg/l and a likelihood of 100% for T > CMI of 50-60% for an MIC of 2 mg/l [25].

In another Monte Carlo simulation performed using pharmacokinetic data from 150 subjects enrolled in phase I and phase II studies, the probability of target attainment (PTA) for ceftobiprole 500 mg/8 h, administered over 30 minutes, 1 or 2 h of infusion, was determined to achieve T > MIC values of 30-60% with different MICs (0.25–8 mg/l). The likelihood of reaching T > MIC of 40-60% with the proposed dosing regimen was greater than 90% for MICs of 3 to 4 mg/l [28].

Considering all reported results, the Monte Carlo simulations, and some other publications [29-31], the dose of 500 mg infused in 2 h., administered every 8 h, is optimal for achieving the proposed T> MIC values when the MIC is ≤4 mg/l; that is, at the non-species-specific sensitivity breakpoint.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in the creation of this article.

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Ceftobiprole for the treatment of pneumonia

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ABSTRACT

Ceftobiprole is a fifth-generation cephalosporin with potent antimicrobial activity against Gram positive and Gram-negative bacteria. It has been approved in major European countries for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP). Ceftobiprole is currently in a phase 3 clinical program for registration in the U.S. In 2015, it was designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA. The efficacy of ceftobiprole in pneumonia has been demonstrated in two-phase III clinical trials conducted in patients with CAP and HAP. The recommended dose in the adult with pneumonia is 500 mg every 8 h infused in 2 h; in case of renal failure, the regimen of administration must be adjusted according to the patient's renal function. It is not necessary to adjust the dose according to gender, age, body weight or liver failure. In case of hyperfiltration, an extension to 4 h infusion of the 500mg TID is required.

INTRODUCTION

Pneumonia is a serious health problem and a significant cause of morbidity and mortality around the world despite advances in clinical treatment and antibiotic therapy [1]. Community-acquired pneumonia (CAP) is associated with elevated health costs and is a common cause of emergency care and hospital admissions, especially in elderly patients and those with multiple comorbidities, whose mortality rate (which is approximately 10%) may reach 40% in cases of severe CAP that requires treatment in the intensive care unit (ICU) [2–5]. Hospital-acquired pneumonia (HAP) represents more than 25% of all infections in the ICU; hospital stays and health costs are very high, with a mortality rate between 27% and 50% [6]. The microbiological diagnosis is generally difficult to establish, including when complex and invasive diagnostic methods are used. In fact, microbiological confirmation is achieved in less than half of the cases and the initial antibiotic regimen must be empirically chosen to prevent delays in establishing an appropriate treatment, which is associated with elevated mortality [7–10].

Streptococcus pneumoniae (pneumococcus) continues to be the most common cause of CAP in all patient treatment settings (outpatient, hospitalized and patients admitted into intensive care units), age groups, and regardless of the patient's comorbidities [11].

However, it is reported that approximately 6% of CAP is caused by antibiotic-resistant pathogens, with *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) being the most common [12].

In cases of pneumonia due to influenza virus, pneumococcus is the most commonly identified pathogen in patients with bacterial co-infection. However, other pathogens such as *S. aureus* (methicillin-susceptible or resistant), *Haemophilus influenzae* and non-fermenting Gram-negative bacilli such as *P. aeruginosa* have also been reported. In patients with severe CAP, *P. aeruginosa* has been identified in 8.3% of patients, with a mortality rate of up to 100% [9, 13]

In HAP, the most common infecting bacteria are members of the *Enterobacteriaceae* family (such as *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp.), *S. aureus*, *P. aeruginosa*, and *Acinetobacter baumannii*, the majority of these microorganisms being multi-drug resistant, highlighting their importance in the current challenge of antibiotic resistance [14].

Ceftobiprole, a fifth-generation (last generation) extended-spectrum cephalosporin, shows potent *in vitro* activity against several Gram-positive pathogens, including methi-

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cillin-susceptible *S. aureus* (MSSA), MRSA with reduced susceptibility to linezolid, daptomycin or vancomycin, methicillin-resistant coagulase-negative staphylococci (MR-CoNS), penicillin- and ceftriaxone-resistant *S. pneumoniae,* along with *in vitro* activity Gram-negative pathogens including *P. aeruginosa* and non-extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae* [15] (table 1). Ceftobiprole has shown to have a time-dependent bactericidal activity, as expected by this class of molecules. It exerts its action by blocking the transpeptidase activity in penicillin-binding proteins (PBP) both in Gram-positive and Gram-negative pathogens. As a result, peptidoglycan synthesis decreases and the bacteria die due to the osmotic effects or by autolytic enzyme digestion [16].

CLINICAL EFFICACY IN PATIENTS WITH PNEUMONIA

The safety and efficacy of ceftobiprole medocaril has been investigated in two phase-III clinical trials in patients with CAP and HAP [17, 18].

Clinical trial on CAP. This was a multi-centre, double-blind, randomised study on 638 patients with CAP who required hospitalization, ceftobiprole (500 mg/8h) was compared to ceftriaxone (2g/day) with or without linezolid (if suspected MRSA infection, 600 mg/12h). Linezolid was administered in patients with suspected MRSA or ceftriaxone-resistant *S. pneumoniae*. Patients were stratified according to severity measured by the Pneumonia Severity Index (PSI) and by need for adding linezolid. Primary endpoint was the clinical cure rate at the TOC visit on the intent-to-treat (ITT) and clinically evaluable (CE) population. The secondary efficacy criteria were microbiological eradication rate at TOC visit, the rate of clinical recovery according to the baseline PSI in ITT and CE populations, and specific mortality due to pneumonia after 30 days in ITT and CE populations. The pre-defined non-inferiority margin of 10% (95% CI) was set for all endpoints.

The study demonstrated that ceftobiprole (500 mg/8 h infused in 2 h) was not inferior to ceftriaxone (2 g/24 h), whether as monotherapy or combined with linezolid (600 mg/12 h). No difference was found in the overall clinical and microbiological analyses, as well as in predefined high-risk subgroups or other subgroups of interest (including those treated with antistaphylococcal agents). For all 469 clinically evaluable patients, the recovery rates were 86.6% versus 87.4%, respectively; in the intent-to-treat (IIT) analysis of 638 patients with CAP, the recovery rate was 76% versus 79%, respectively [17] (figure 1).

For the secondary criterion of microbiological eradication, non-inferiority between ceftobiprole and the comparator was established. Specific mortality due to pneumonia in the first 30 days was very low, both for the ceftobiprole group and the ceftriaxone ± linezolid (1 versus 3 patients in the ITT population and 0 versus 2 patients in the CE population).

Clinical trial on HAP. Similar to the first study, the second was a phase-III , multi-national, randomised, double-blind study that compared ceftobiprole against the combination of ceftazidime plus linezolid in 781 adults with HAP (defined as a pneumonia arising after >72 h of hospitalization or stay in a

Table 1 | **Ceftobiprole's antibiotic activity**

ACTIVE
Gram-positive bacteria
Streptococcus pneumoniae (including the strains resistant to benzylpenicillin and ceftriaxone)
Staphylococcus aureus
Methicillin-resistant *Staphylococcus aureus*
Gram-negative bacteria
Haemophilus influenzae (including clinical isolates resistant to ampicillin)
Pseudomonas aeruginosa
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis Non-extended-spectrum beta-lactamase (ESBL)-producing
INACTIVE
Strains of *Enterobacteriaceae* that express Amber class A beta lactamases, especially TEM, SHV and CTX-M types, as well as KPC-type carbapenemases; it is also inactive against Amber class B, C (high levels of expression) and D, particularly the ESBL variants and OXA-48 carbapenemases.
Strains of beta-lactamase-producing *Pseudomonas aeruginosa* from classes A (PSE-1), B (IMP-1, VIM-1, VIM-2) and D (OXA-10).
Strains of beta-lactamase-producing *Acinetobacter* spp. from classes A (VEB-1), B (IMP-1, IMP-4) and D (OXA-25, OXA-26)

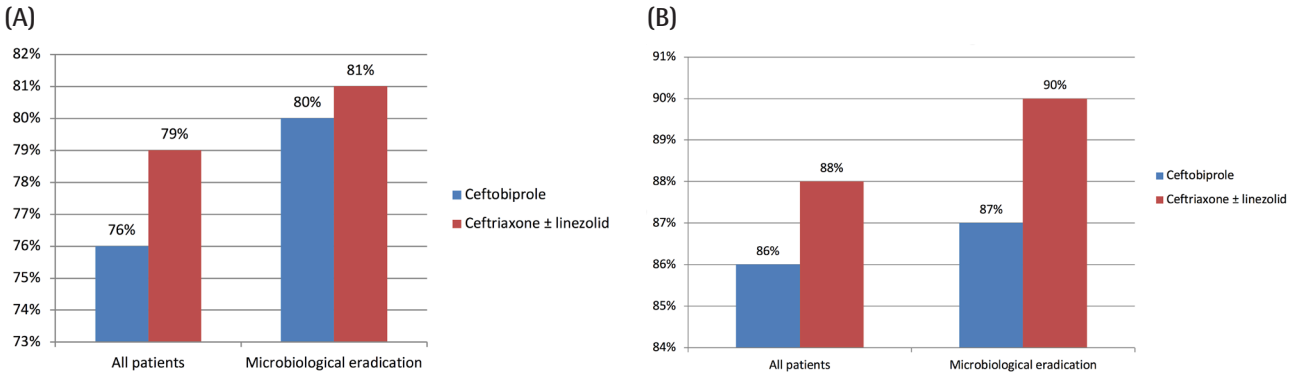
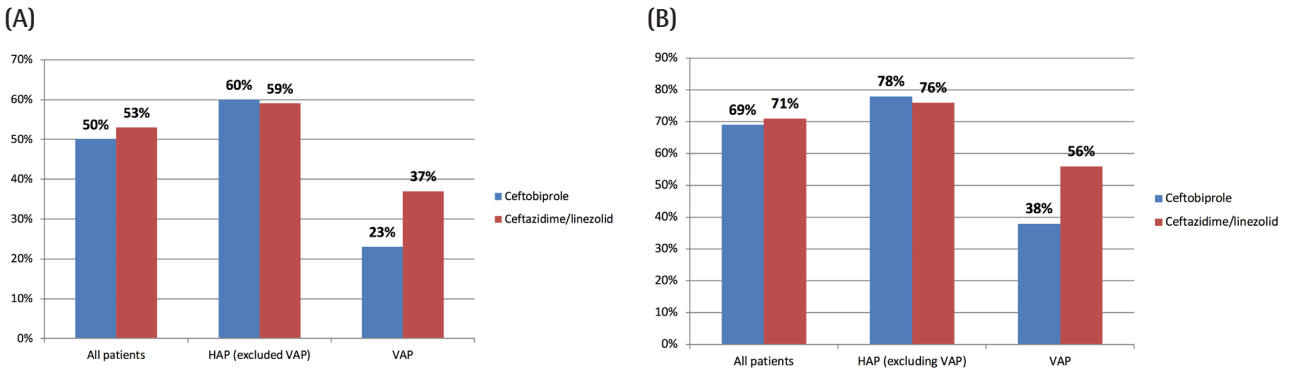


Figure 1 CAP: Percentage of clinical efficacy in the population by intention to treat (A) and in clinically evaluable population (B)



Differences between groups -2.9% (-10.0–4.1) 0.8% (-7.3–8.8) -13.7% (-26.0 to -1.5) IC 95%

Differences between groups -2.0% (-10.0–6.1) 1.6% (-6.9–10.0) -18.2% (-36.4 to -0.0) IC 95%

Figure 2 HAP: Percentage of patients with clinical cure visit of cure test in the population by intention to treat (A) and in clinically evaluable population (B)

long-term care unit). The inclusion criteria were: clinical signs and symptoms of pneumonia (at least two including purulent respiratory secretion, tachypnoea, or hypoxemia); fever or leukocytosis/leukopenia; new or persistent radiographic infiltrates; and an APACHE II score of 8-25. The exclusion criteria were: severe kidney or liver failure; evidence of infection due to ceftobiprole or ceftazidime-resistant pathogens; clinical conditions that could interfere with the efficacy evaluation (for example, sustained shock, active tuberculosis, pulmonary abscess, and post-obstructive pneumonia); and systemic antibiotic treatment for >24 h in the 48 h prior to inclusion. Patients were stratified for treatment according to presence of VAP (pneumonia arising after >48 h after the start of mechanical ventilation) and APACHE II score (8–19/20–25); VAP patients were stratified according to length of mechanical ventilation (</≥5 days).

The primary efficacy endpoint was the clinical cure rate at the TOC visit (7 to 14 days after the last dose of the study drug or early termination) in the ITT and clinically evaluable (CE) populations; non-inferiority was defined using a margin of 15% for the 95% CIs. The secondary criteria were microbiological eradication at the TOC visit in ITT and microbiologically evaluable populations with a valid pathogen at baseline, 30-day all-cause mortality in the ITT population, as well as safety and tolerability.

For the primary efficacy criteria, the study demonstrated that treatment with ceftobiprole monotherapy (500 mg/8 h infused in 2 h) was non-inferior to a combined treatment that included ceftazidime (2 g/8 h) plus linezolid (600 mg/12 h) for patients with HAP, excluding patients with VAP. In the CE population, 86.9% of patients with HAP (excluding patients with VAP) in the ceftobiprole group demonstrated early improvement (4 days after beginning therapy); compared to 78.4% in the ceftazidime plus linezolid group (difference 8.5 [CI of 95%, 0.9–16.1]). A major numerical difference was observed in the subgroup of patients with microbiological evidence of MRSA infection (94.7% in the ceftobiprole group vs. 52.6% in the ceftazidime group plus linezolid (difference, 42.1 [CI 95%, 17.5–66.7]). For the secondary efficacy criteria, the microbio-

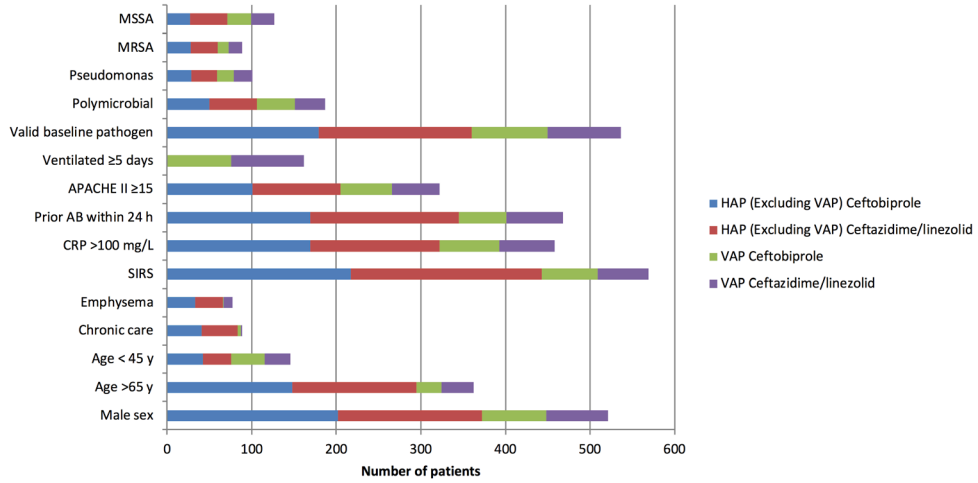


Figure 3 | **Clinical characteristics between groups: HAP (excluding VAP) ceftobiprole, HAP (excluding VAP) ceftazidime/linezolid, VAP ceftobiprole, VAP ceftazidima/linezolid**

logical eradication rates at the completion of treatment (CT) visit in patients with HAP (excluding VAP) were similar in the ceftobiprole and ceftazidime/linezolid groups in the ITT (49% versus 54%; difference 5.0; CI 95%: 15.3–5.3) and microbiologically evaluable groups (63% vs. 68%; difference -4.6; CI 95%: -16.7–7.6) (figure 2A). In addition, clinical recovery and rates of microbiological eradication of pathogens in patients with HAP (excluding VAP) were similar for Gram-positive and the majority of Gram-negative microorganisms.

In the overall population, the recovery rates in clinically evaluable patients for ceftobiprole compared to ceftazidime/linezolid were 69.3% vs. 71.3%, respectively. Ceftobiprole noninferiority was not demonstrated in the subgroup of patients with VAP patients with recovery rates in the clinically evaluable cases of VAP of 37.7% vs. 55.9% [18], respectively (figure 2B).

Interestingly, in patients with HAP requiring mechanical ventilation for less than 48 h, thus not defined as VAP, clinical outcomes favoured ceftobiprole, suggesting that mechanical ventilation itself may not be associated with poor outcomes, whereby ceftobiprole may be administered in patients with HAP requiring mechanical ventilation. There are different explanations for ceftobiprole outcomes observed in the VAP subgroup of patients: the small sample size and considerable heterogeneity of baseline clinical characteristics in the VAP subgroup may have contributed to the difference in outcomes (figure 3) [19].

Furthermore, out of the 16 (62.5%) patients ≤45 years with VAP and cranial trauma who were randomized into the ceftobiprole group, 12 (17.6%) were characterized as treatment failures compared to two out of four assigned to the ceftazidime/linezolid group.

The pharmacokinetics (PK) of ceftobiprole in patients with VAP was different from patients without VAP, which may be attributed to increased cardiac output, augmented glomerular filtration rate, and increased volume of distribution associated with critical illness. For this reason, it is unlikely that ceftobiprole will meet the desired PD objectives when the PK parameters are altered. Indeed, for patients hospitalized in the ICU with creatinine clearance (CrCl) >150 ml/min, extending the ceftobiprole infusion time to 4 h contributes to keep plasma levels above the minimum inhibitory concentration (MIC) (4 mg/L). As such, for patients with increased kidney function (CrCl>150 ml/min), increasing the duration of ceftobiprole infusion is recommended (500 mg for 4 h/8 h), according to linear PK and low protein binding [19].

The inferior outcome of ceftobiprole in VAP may have been the result of suboptimal concentrations of ceftobiprole at the infection site as a result of the change in volume of distribution due to mechanical ventilation capillary filtration.

Ceftobiprole has so far demonstrated a good safety profile in preliminary studies, with a tolerance similar to that of comparators. The most commonly observed adverse events with ceftobiprole include headache and gastrointestinal disorders. Ceftobiprole is the first cephalosporin monotherapy that has been approved in Europe for the treatment of CAP and HAP, excluding VAP. Ceftobiprole is not approved by the Food and Drug Administration (FDA); however in 2015 it was designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA [20]. There is an ongoing phase III study at this time to compare the safety and efficacy of ceftobiprole medocaril versus vancomycin plus aztreonam in the treatment of patients with acute bacterial skin and skin structure infections. BARDA program https://clinicaltrials.gov/ct2/show/NCT03137173?term=Ceftobiprole&draw=3&rank=11

DOSING ROUTES IN PNEUMONIA

Ceftobiprole should be administered at a dose of 500 mg every 8 h, infused over 2 h, in patients with normal kidney function. Ceftobiprole should be reconstituted with 10 ml sterile saline or 5% dextrose. It is further diluted in 250 ml of 0.9% sodium chloride, 5% dextrose, or lactated ringers solution prior to intravenous infusion.

Dosing in Special Patient Populations

• **Patients with Kidney Failure:** it is recommended to adjust the dose of ceftobiprole in patients with moderate to severe kidney failure. For patients with moderate deterioration (CrCl 30 to <50 ml/min), the recommended dose is 500 mg administered as intravenous infusion for 2 h every 12 h, while for those with severe deterioration (CrCl <30 ml/min), the recommended dose is 250 mg administered as intravenous infusion for 2 h every 12 h. For patients with terminal stage kidney disease, the recommended dose is 250 mg once every 24 h, regardless of whether or not they are undergoing haemodialysis.

• **Treatment of Critically Ill Patients:** antibiotics are among the most important and commonly prescribed medicines in the treatment of critically ill patients and β-lactams are the most widely used class of antibiotic. Pathophysiological factors in critically ill patients lead to altered pharmacokinetics and pharmacodynamics of β-lactams. In critically ill patients, capillary leak and oedema, fluid therapy, pleural effusion, ascites, permanent post-surgical drainage and hypo-albuminaemia may all increase the volume of distribution and cause dilution of antibiotics in plasma and extracellular fluids. Some pathophysiological factors may also improve (hyperdynamic condition in early stage sepsis, the use of haemodynamically active drugs) or reduce (kidney failure, bedridden patients) the concentrations of the antibiotic in plasma and extracellular fluid (with implications for MIC over time), prompting high intra and inter-patient variability and promoting the risk of antibiotic overdose. Extra-corporeal support techniques also contribute to the variability of antibiotic concentration [19, 21]. There are very few studies that have investigated β-lactam PK/PD issues in critically ill patients with pneumonia. Rodvolt et al. [22] conducted a prospective, observational, pre-clinical murine model of pneumonia due to MRSA and a clinical study with 24 healthy volunteers who received ceftobiprole 500 mg over 2 h, every 8 h. Its conclusions were that for critically ill patients, particularly in the ICU, higher doses or longer infusion times (to prolong T>MIC), or both, will be required to guarantee adequate achievement of objectives for 90% of critically ill patients with pneumonia due to MRSA.

• **Obese Patients:** the physiological changes that obese patients present may influence the pharmacokinetics of antibiotics. One study compared the pharmacokinetics of a single intravenous infusion of ceftobiprole 500 mg for 2 h in obese adults [body mass index (BMI)] [40 kg/m^2] and those who were not obese (BMI 18-30 kg/m^2)[24]. The average BMI was 45.5 kg/m^2 in the group with severe obesity (n = 12) compared to 24.0 kg/m^2 in the non-obese group (n = 13); other baseline characteristics were similar in both groups. The volume of distribution and total clearance of ceftobiprole were 25.9 and 19.1% higher, respectively, in those who were severely obese compared to non-obese individuals; exposure to ceftobiprole was lower in adults who were severely obese than in those who were not. Plasma concentrations of unbound ceftobiprole remained above the MIC objective of 4 mg/L (fT >MIC) for 76.6 and 79.7% of an 8 h. dose interval in severely obese and non-obese individuals, respectively. Although the volume of distribution and total clearance were higher and exposure was lower in adults with severe obesity compared to non-obese individuals after a ceftobiprole infusion, the % fT >MIC was similar in both groups, which indicates that it's not necessary to adjust the dose of ceftobiprole in patients with severe obesity [24].

TOLERABILITY

With respect to the tolerability of ceftobiprole, one potential benefit of kidney excretion is that it may limit exposure to antibiotics in the intestine, although to date there are no studies that specifically address this topic. Only one study published in 2010 investigated the effect of the administration of ceftobiprole on the normal intestinal microflora of 12 healthy subjects aged 20 to 31 years who received ceftobiprole 500 mg via intravenous infusion every 8 h for 7 days. This study showed that ceftobiprole achieves low levels of intestinal exposure, with only minor effects on the intestinal microbiota. In fact, no measurable concentrations of ceftobiprole were detected in faeces following intravenous administration in healthy volunteers and no *Clostridium difficile* strains or toxins were found. Also, one study on mice showed that ceftobiprole did not promote the growth of *C. difficile* in faecal content and was not associated with toxin production.

Ceftobiprole in CAP and HAP (excluding VAP). Due to its safety profile and good antibiotic activity against an extended spectrum of pathogens in CAP, especially penicillin- and ceftriaxone-resistant *S. pneumoniae,* as well as *S. aureus* especially MRSA, ceftobiprole may be a very good therapeutic option for patients with risk factors for infection caused by these pathogens. Also, ceftobiprole appears to be very promising in patients with CAP due to influenza with suspected or confirmed co-infection with *S. pneumoniae* or *S. aureus* (MSSA or MRSA). Furthermore, a *post hoc* retrospective analysis of the subgroups of high-risk patients with CAP (n= 398) (PORT risk score >III, age >75 years, sepsis, COPD, bacteraemia, need for ICU) and HAP (n=307) (need for mechanical ventilation, APACHE score >15, age >75 years, bacteraemia, treatment in ICU, COPD, >10 comorbidities) from both of the aforementioned phase-III clinical trials has evaluated early clinical response (3rd day in CAP and 4th day in HAP) for ceftobiprole versus the active comparator regimes, yielding overall similar results, with a trend towards better outcomes in the ceftobiprole treated arm (numerical superiority assessed by 10% difference or CI not crossing 0). For this reason, high-risk patients with CAP and HAP (excluding VAP) may show earlier improvement upon ceftobiprole administration [25]. Case series presented at ECCMID 2019 on 57 patients with important

contraindications: 18 months of real-life use of ceftobiprole: clinical experience in an internal medicine ward. Giuseppe Russo et al. https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=68737

Lastly, considering that ceftobiprole shows potent in vitro activity against the pathogens most commonly associated with HAP, above all *S. aureus*, non-ESBL *Enterobacteriaceae*, and *P. aeruginosa*, it has the potential to simplify empirical combination treatment with two antibiotics in a monotherapy regimen for HAP (excluding VAP).

REGISTRATIONS

Ceftobiprole medocaril has been approved in major European countries for the treatment of CAP and HAP, excluding VAP [26, 27]. Ceftobiprole is currently in a phase 3 clinical program for registration in the U.S. In 2015 it was designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA [20]. This year ceftobiprole has been launched in Argentina [28].

CONCLUSIONS

One of the main challenges in the treatment of pneumonia (CAP and HAP) is overcoming the problems of resistance, which have become so important and common in recent years. Ceftobiproles potent activity as a new-generation cephalosporin against broad spectrum of Gram-positive and Gram-negative bacteria has been demonstrated in two clinical trials, one on CAP and the other on HAP (excluding ventilation-associated pneumonia). Ceftobiprole is approved in major European countries as therapy for CAP and HAP (excluding VAP), and is designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA.

Ceftobiprole may be used in patients with CAP with suspected or confirmed *Staphylococcus aureus* (MSSA or MRSA) as is the case with pneumonia due to the influenza virus in which *S. pneumoniae* may also be involved, and in patients with HAP to cover *S. aureus,* susceptible *Pseudomonas aeruginosa* and non-ESBL *Enterobacteriaceae*.

Extended-spectrum coverage with ceftobiprole monotherapy may simplify empirical treatment in relation to combined therapies against MRSA.

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Ceftobripole: Experience in staphylococcal bacteremia

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ABSTRACT

Ceftobiprole is a new cephalosporin with an extended spectrum activity against the majority of microorganisms isolated in bacteremia including methicillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA). This antibiotic has demonstrated a potent activity against MRSA in animal models of endocarditis in monotherapy but particularly in combination with daptomycin, suggesting that this combination could be a future option to improve the outcome of staphylococcal endovascular infections. In addition, the extended-spectrum ceftobiprole activity, including coagulase-negative staphylococci, *Enterococcus faecalis*, *Enterobacteriaceae* and *Pseudomonas aeruginosa* represents an advantage for use as empirical therapy in bacteremia potentially caused by a broad spectrum of microorganisms, such as in catheter-related bacteremia.

INTRODUCTION

Staphylococcus aureus is one of the leading causes of bloodstream infections [1] and in the recent years the most common microorganism causing endocarditis [2]. Despite therapeutic advances, a recent study on 3395 consecutive adult patients with *S. aureus* bacteremia (SAB) from 20 care centers in Europe and the United States reported a crude 14 and 90-day mortality rate of 14.6% and 29.2%, respectively [3]. Source control (catheter removal, abscess drainage) and early administration of an adequate antibiotic treatment are factors independently associated with success [4], however, randomized control trials to determine the best antibiotic treatment in SAB are scarce and new data mainly arise from observational studies. The major advances can be summarized as follows:

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1) The *in vitro* synergy between beta-lactams and aminoglycosides has not been translated into a clinical benefit probably due to the unacceptable risk of nephrotoxicity [5] and it is no longer recommended [6].

2) Vancomycin is associated with a higher failure rate than beta-lactams against methicillin-susceptible *S. aureus* (MSSA), even when vancomycin is given empirically and switched to a beta-lactam within 72h after the first blood culture [7].

3) For the treatment of methicillin-resistant *S. aureus* (MRSA) bacteremia, vancomycin should be dosed to achieve an AUC/MIC≥400. To obtain this goal, a minimum serum concentration of 15-20 mg/L is necessary, and the recommended dose is 15-20 mg/kg/12h. In critically ill patients, a loading dose of 30-35 mg/kg is suggested to early achieve the pharmacodynamic goal [8].

4) Vancomycin MIC of 2 mg/L has been associated with a higher mortality rate in MRSA bacteremia probably due to the low probability to attain the pharmacodynamic target [9, 10], and the higher prevalence of hetero-resistance to vancomycin in those strains with a MIC≥2 mg/L [11].

5) The therapeutic range of vancomycin (serum concentration between 15 and 20 mg/L) overlaps with the nephrotoxic range [12].

6) A randomized clinical trial in *S. aureus* bacteremia comparing daptomycin vs. anti-staphylococcal penicillin (for MSSA) or vancomycin (for MRSA) plus gentamicin for the first 4 days showed that daptomycin is a suitable alternative but still associated with a high failure rate for high-inoculum infections like left-sided endocarditis because of a risk of selecting strains with reduced susceptibility [13]. In addition, a loss of daptomycin susceptibility in the absence of any administered antibiotic has been recently observed in an experimental model of prosthetic joint infection, probably as a result of *in vivo* selection pressure from cationic host peptides [14, 15].

In the last guidelines from the Infectious Diseases Society of America (IDSA) [6], vancomycin is still the first line choice

but daptomycin is considered an alternative. Recent recommendations from Spanish experts support the use of high dose daptomycin (8-10 mg/kg/24h), and for high-inoculum infections, combination therapy with a second active antibiotic [16, 17]. These findings clearly point out 1) the need of alternative treatments for *S. aureus* bacteremia and 2) the major efficacy issues of beta-lactams over any alternative.

Table 1 **Cure rate at test of cure and 30-day mortality of patients with bacteremia in the 4 pivotal studies of ceftobiprole and comparators.**

Outcome	Ceftobiprole, n/N (%)	Comparator, n/N (%)
Clinical cure rate at test of cure		
Any staphylococcal bacteremia	22/45 (48.9)	22/50 (44)
Coagulase-negative staphylococci	10/22 (45.5)	10/22 (45.5)
S. aureus	12/23 (52.2)	12/28 (42.9)
MSSA	4/9 (44.4)	7/15 (46.7)
MRSA	5/9 (55.6)	2/9 (22.2)
30-day all cause mortality		
Any staphylococcal bacteremia	4/45 (8.9)	8/50 (16)
Coagulase-negative staphylococci	1/22 (4.5)	2/22 (9.1)
S. aureus	3/23 (13)	6/28 (21.4)
MSSA	1/9 (11.1)	2/15 (13.3)
MRSA	0/9	2/9 (22.2)

ACTIVITY OF CEFTOBIPROLE AGAINST STAPHYLOCOCCI

Ceftobiprole medocaril is a new cephalosporin with *in vitro* activity against *S. aureus* and coagulase-negative staphylococci (CoNS). In a recent study, 99.5% of 15.426 *S. aureus* isolates were susceptible to ceftobiprole at the EUCAST breakpoint of 2 mg/L. The minimum inhibitory concentrations of 90% (MIC_{90}) for methicillin susceptible and resistant isolates were 0.5 and 2 mg/L, respectively. Against CoNS, the ceftobiprole MIC_{90} was 0.25 and 2 mg/L against methicillin susceptible and -resistant isolates, respectively [18]. Ceftobiprole's activity was not affected by vancomycin MIC and it remained active against isolates with an elevated vancomycin MIC (2 mg/L). Ceftobiprole has a time-dependent bactericidal activity that is optimal at 2 to 8 times the MIC [19]. In the rabbit endocarditis model using MRSA strains with a MIC of 2 mg/L, ceftobiprole was as effective as vancomycin [20, 21] and even superior to vancomycin, daptomycin and linezolid using the same model but a different strain with a ceftobiprole MIC of 4 mg/L [22]. In a rat model of endocarditis the efficacy of a continuous infusion of ceftobiprole to maintain serum concentrations about 6, 12 or 25 mg/L was evaluated [23]. The highest concentration sterilized 100% of the vegetations and the other two >90%, supporting the *in vitro* pharmacodynamic models showing a bactericidal activity against MRSA when T>MIC is 100% [24]. In these animal models, no selection of ceftobiprole resistant strains was detected in line with *in vitro* data showing very low frequency of resistance development after single-passage selection [19]. These studies also demonstrated a high stability of ceftobiprole, after 24h exposure to a high inoculum (10^9 CFU) of a penicillinase-producing *S. aureus* strain, being even more stable than methicillin. This is of interest since a high failure rate in high inoculum infections (endocarditis) has been observed with cephalosporins like cefazolin when the causative strain is producing type A beta-lactamase [25]. The activity of ceftobiprole against type A, B, and C beta-lactamase producing MSSA has been tested and a slight increase in the MIC was documented when comparing standard and high inoculum of type A, B and C producing MSSA beta-lactamase positive strains but the MIC remained ≤2 mg/L in all cases [26].

CLINICAL EXPERIENCE WITH CEFTOBIPROLE IN BACTERAEMIC PATIENTS

The clinical experience is scarce but there were bacteraemic patients within the 4 pivotal phase 3 clinical trials comparing ceftobiprole with other alternatives for community (CAP), hospital (HAP) acquired pneumonia, and for complicated skin and soft tissue infections (cSSTI) [27-30]. A pooled analysis of these 4 trials assessed the efficacy of ceftobiprole and comparators against staphylococcal bacteraemia in cSSTI, CAP, and HAP. Comparators included vancomycin (cSSTI), vancomycin plus ceftadizime (cSSTI), ceftriaxone (with linezolid in cases of suspected MRSA) (CAP) and ceftazidime plus linezolid (HAP) (Rello J, Rahav, Scheeren T, Saulay M, Engelhardt M, Welte T. Pooled analysis of clinical cure and mortality with ceftobiprole medocaril versus comparators in staphylococcal bacteremia in complicated skin infections, community- and hospital-acquired pneumonia. ECCMID 2016: O-318). The outcomes showed that clinical responses were similar with ceftobiprole and standard-of-care comparators (table 1). In patients with MRSA, there was a trend towards improved clinical cure rates at test of cure (55.6% vs. 22.2%) and all-cause mortality at day 30 (0 vs. 22.2%) with ceftobiprole compared with other regimens (table 1). A double-blind, randomised, non-inferiority study to compare ceftobiprole (500 mg/8h) and daptomycin (6 mg/kg/24h) in adult patients with *S. aureus* bacteraemia, including right-sided infective endocarditis, is ongoing (https://clinicaltrials.gov/ct2/show/NCT03138733).

The high mortality associated with particular pathologies such as endovascular infections deserves a particular attention since several *in vitro* antibiotic combinations have shown synergism but clinical trials to test these new therapeutic alternatives are scarce [3]. For instance, beta-lactams have shown *in vitro* synergy with vancomycin against MRSA [31-34] and a subsequent clinical trial randomized 60 patients with MRSA bacteremia to receive vancomycin alone or in combination with flucloxacillin for 7 days [35]. The mean time to resolution of bacteremia in the combination group was 1.94 days compared with 3 days in the vancomycin group (P = 0.06). In line with this, ceftobiprole has also demonstrated *in vitro* synergism with vancomycin and in a rat model

of endocarditis, the combination of sub-therapeutic dose of ceftobiprole and vancomycin was as effective as monotherapy with standard ceftobiprole dose against MRSA and VISA strains [36, 37]. However, the combination with vancomycin does not avoid the potential risk of nephrotoxicity, therefore, other alternatives are required. The most promising approach is the association of daptomycin with a beta-lactam since 1) the *in vitro* synergy has been described [38-41], 2) the ability of beta-lactams to avoid the selection of daptomycin resistant mutants, 3) the dual effect of beta-lactams, potentiating the activity of cationic host peptides against MSSA and MRSA [42], and 4) two retrospective case series exist showing good clinical results [43, 44]. Sub-inhibitory concentrations of ceftobiprole reduced daptomycin MICs >4-fold which was confirmed in time-kill studies [45]. Interestingly, a recent case report of a patient with a prosthetic valve endocarditis due to MRSA; who failed on daptomycin monotherapy and to daptomycin plus piperacillin-tazobactam, was switched to daptomycin plus ceftobiprole due to persistent bacteremia and fever. After 48h, under the new combination, the patient became afebrile and he was operated with good outcome afterwards [46].

A potential concern is the adequate dose of ceftobiprole for bacteremia and endocarditis. The pharmacodynamic target derived from skin and soft tissue infections is a free concentration over the MIC for 50% of the interval between 2 consecutive doses (>50% *f*T>MIC). The probability of achieving this target, with the current approved dose (500 mg/8h in 2h infusion), is >90% for MIC≤4 mg/L [47]. However, a higher exposure (100% *f*T>MIC) is associated with a potent bactericidal activity [24] and it would be the preferred target for severe and high inoculum infections. Using the current dose, the probability of obtaining a 100% of *f*T>MIC for MRSA strains is lower but it can be significantly improved by giving 500 mg/6h or 1 g/8h both infused in 4h or any dose in continuous infusion. A recent open-label study carried out in 33 adults treated in the ICU examined the pharmacokinetics of high-dose ceftobiprole administered over a longer infusion period (1000 mg over 4 h/12h for patients with a CrCl 50-79 mL/min and /8h for CrCl≥80 mL/min) for 1 day [48]. Ceftobiprole was well tolerated and a 100% of *f*T>MIC of 4 mg/L was obtained regardless of the CrCl.

On the other hand, catheters are the leading cause of nosocomial bacteremia and according to recent experience; although Gram-positives are still the most frequent microorganisms, Gram-negative pathogens including *Enterobacteriaceae* and *P. aeruginosa* are significantly increasing [49, 50]. The extended-spectrum activity, including methicillin-resistant coagulase-negative staphylococci, *Enterococcus faecalis* and Gram-negatives including *P. aeruginosa,* of ceftobiprole is an advantage for a monotherapy as empirical treatment for catheter related bacteremia.

In conclusion, ceftobiprole is a new anti-MRSA beta-lactam with a time-dependent bactericidal activity and strong data in animal models of endocarditis showing that this monotherapy is more effective than vancomycin and that the combination with daptomycin has a potent synergistic activity. Therefore, ceftobiprole should be considered as a potential empirical option when MRSA bacteremia is suspected and in combination with daptomycin for the treatment of endovascular infections as a primary option or as a salvage therapy. In the future, it is necessary to collect more clinical experience with this antibiotic and to evaluate the most adequate dosage particularly for more severe infections.

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Possible clinical indications of ceftobiprole

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ABSTRACT

Ceftobiprole is a fifth-generation cephalosporin approved for the treatment of adult community-acquired pneumonia and non-ventilator associated hospital-acquired pneumonia. However, its microbiological and pharmacokinetic profile is very attractive as armamentarium for empirical monotherapy treatment in other infections too. Among these, the following scenarios could be considered complicated skin and soft tissue infections, moderate-severe diabetic foot infections without bone involvement, vascular-catheter-associated-bloodstream infections, and fever without apparent focus in the hospitalized patient without septic shock or profound immunosuppression.

Key words: ceftobiprole, skin soft tissue infections, diabetic foot infections, vascular-catheter-associated-bloodstream infections and fever without apparent focus.

INTRODUCTION

Ceftobiprole is a fifth-generation cephalosporin currently approved in major European countries for the treatment of adult community-acquired (CAP) and Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP) [1]. However, the safety profile of this molecule as demonstrated in clinical trials, along with its antimicrobial and pharmacokinetic profile [2, 3], makes it a very attractive treatment option as monotherapy for empirical treatment of infections in which many patients could benefit from this potential alternative, despite the lack of data from clinical trials and observational studies.

Ceftobiprole is an extended-spectrum cephalosporin with demonstrated *in vitro* activity on the majority of Gram-positive cocci and aerobic Gram-negative bacilli of clinical relevance. On the former, it has heightened bactericidal action and includes: 1) *Staphylococcus* spp., both methicillin- and vancomycin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, 2) *Streptococcus* spp., including *Streptococcus pneumoniae* resistant to penicillins and third-generation cephalosporins, and 3) *Enterococcus faecalis*, as it is the first and only cephalosporin here with demonstrated activity. With regard to Gram-negative bacilli, its spectrum includes the majority of non-extended spectrum beta-lactamase (ESBL)-producing enterobacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, *Proteus mirabilis*), with activity similar to that of cefotaxime and ceftriaxone, and *Pseudomonas aeruginosa*, with similar activities to ceftazidime and cefepime [2].

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OTHER POSSIBLE MONOTHERAPY INDICATIONS

The unique antibiotic spectrum of ceftobiprole, which for the first time combines activity against methicillin-resistant *Staphylococcus* spp. and *P. aeruginosa*, along with non-ESBL-producing enterobacteria, *Streptococcus* spp and *E. faecalis*, makes it a very attractive and advantageous monotherapy alternative compared to antibiotic combinations commonly used for empirical treatment of infections (table 1), which may be caused by one or several of the aforementioned microorganisms.

1. Complicated skin and soft tissue infections (cSSTIs)

According to data from a pharmacovigilance study conducted in Europe over the course of 7 years, *S. aureus* was the primary agent in SSTIs (37.5%), of which 22.8% were MRSA. This was followed by *P. aeruginosa* (12%), *E. coli* (10.8%), and *Enterococcus* spp. (6.1%). Considering the polymicrobial aetiology and mechanisms of resistance that these microorganisms

Table 1 Possible indications of ceftobiprole

1. Community-acquired pneumonia, non-ventilator-associated hospital-acquired pneumonia
2. Complicated skin and soft tissue infections
   a) Infections in areas with high prevalence of methicillin-resistant *S. aureus*
      - Severe and extensive, which may be life-threatening
      - Elderly patient with significant comorbidity (Child B or C cirrhosis of the liver or haemodialysis)
      - Immunosuppressed patient
   b) Manipulated or previously treated chronic ulcers with signs of infection
   c) Surgical or traumatic wound infections
3. Moderate or severe diabetic foot infections without bone involvement
4. Infection originating from a vascular catheter
5. Fever with no apparent focus in hospitalised patient without septic shock or severe immunosuppression

can express, an initial extended-spectrum empirical treatment appears as an obvious choice, where ceftobiprole may have great potential [4].

In this regard, within the vast group of SSTIs, the use of ceftobiprole should be considered in a) infections in areas with large prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), which are severe and extensive and may be life-threatening, b) elderly patients with significant comorbidities (Child B or C cirrhosis of the liver, haemodialysis) or immunosuppression c) manipulated or previously treated chronic ulcers with signs of infection, and d) surgical or trauma wound infections [5].

The factors to bear in mind when selecting empirical treatment for these infections are the following: severity, history of infection/colonisation by resistant microorganisms, previous antibiotic treatment and local sensitivity patterns [6]. Recently, a prospective, observational Spanish study analysed bacteraemia's associated with pressure ulcers. The microorganisms most commonly isolated from blood were the following: *S. aureus* 17 (30%), *Proteus* spp. 16 (28%), *Bacteroides* spp. 13 (23%), *E. coli* 8 (14%) and *P. aeruginosa* 4 (7%). In 25% of cases, the infection was polymicrobial. Bacteraemia-related mortality was 21% and was independently associated with nosocomial origin and polymicrobial aetiology [7].

Published data on experiences with ceftobiprole in this context is already available. In an experimental murine model of MRSA and *P. aeruginosa* infections, ceftobiprole achieved a significantly greater reduction in lesion volume and bacterial load than linezolid and vancomycin (in MRSA) and cefepime (in *P. aeruginosa*) [8].

The concentration of ceftobiprole (free drug) in subcutaneous cellular and musculoskeletal tissue, following a dose of 500 mg IV and determined *in vivo* by microdialysis, remains above 2 mg/L for at least 40% of the 8-hour interval between consecutive doses [9]. The cut-off points established by EUCAST, which determine the sensitivity of ceftobiprole, are as follows: *S. aureus* ≤2 mg/L, *S. pneumoniae* ≤0.5 mg/L, and *Enterobacteriacea* ≤0.25 mg/L [10].

The efficacy and safety of ceftobiprole in cSSTI was also assessed in two multi-centre, non-inferiority, phase-III, double-blind, and randomised clinical studies with over 1600 patients [11, 12]. In one study, ceftobiprole (500 mg/12 h. IV) (n= 397) was compared to vancomycin (1000 mg/12 h IV) (n= 387) (1:1 ratio) for the duration of 7-14 days in infections due to Gram-positive microorganisms. Approximately 50% of the infections were abscesses, 30% wounds (surgical, traumatic and burns), and 20% cellulitis. Around 80% of infections were caused by *S. aureus* (1/3 MRSA). The clinical recovery rate was similar in clinically evaluable patients (>90%) and in the intent-to-treat analysis (77%). The same was observed in the rate of microbiological eradication (>90%). There were no differences in tolerability. The most common side effects of ceftobiprole were nausea (14%) and changes in taste (8%) [11].

The second study included Gram-positive and Gram-negative infections. Ceftobiprole (500 mg/8 h IV administered over a two-hour infusion) (n= 547) was compared with the combination of vancomycin (1000 mg/12 h. IV) and ceftazidime 1000 mg/8 h IV) (n=281) (2:1 ratio). The most common infections were: diabetic foot abscesses and infections (30%), wounds (surgical, traumatic, and burns), and cellulitis 20%. *S. aureus* was the most common causative microorganism (64%, 1/3 MRSA), followed by *E. coli* (10.7%) and *P. aeruginosa* (6.6%). The clinical recovery rate in clinically evaluable patients and in the intent-to-treat was similar (90.5% vs. 90.2% and 81.9% vs. 80.8%, respectively). There were neither differences observed in patients who experienced bacteraemia in infections with severity criteria (CRP >50 mg/L, fascia or muscle involvement, with systemic inflammatory response syndrome or Panton-Valentine toxin-producing MRSA infection), nor by type of microorganism (Gram-positive 91.8% vs. 90.3%,

Gram-negative 87.9% vs. 89.7%, respectively). In the ceftobiprole group, it is noteworthy that in cases with isolation of *P. aeruginosa* only, failure occurred when the MIC_{90} was >8 mg/L. Tolerability was equivalent, and nausea was the most common adverse effect of ceftobiprole [12]. Despite the favourable results of these studies, the FDA (*Food and Drug Administration*) and the EMA (*European Medicines Agency*) have not approved the use of ceftobiprole in cSSTIs due to a lack of inspections and audits in one-third of patients [13, 14]. For this reason it is being carried out a new phase 3 clinical trial in the treatment of patients with acute bacterial skin and skin structure infections, to establish the efficacy and safety of ceftobiprole compared with vancomycin plus aztreonam [15].

2. Moderate or severe diabetic foot infections without bone involvement

In Spain, the aetiology of diabetic foot infections has been well documented in recent studies. *S. aureus* (>30% MRSA) remains the most common agent, followed by Gram-negative bacilli (enterobacteria and *P. aeruginosa*) [16, 17].

The experience with ceftobiprole in diabetic foot infections has been analysed in detail. One three-year study examined the *in vitro* activity of ceftobiprole against 443 isolates (251 aerobic and 192 anaerobic) of complicated diabetic foot infections, in which it was demonstrated to be active against a wide range of aerobic and anaerobic Gram-positive and Gram-negative microorganisms. Ceftobiprole's activity was also compared with other antibiotics. In the case of aerobic Gram-positive cocci (*S. aureus*, including MRSA, *Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae* and other streptococci) ceftobiprole was more active than cefepime, ceftazidime, cefotaxime, cefoxitin, levofloxacin, linezolid, daptomycin and vancomycin [18]. Furthermore, in a multi-centre, double-blind, randomised clinical study on cSSTIs, in which ceftobiprole (500 mg/8 h) was compared to vancomycin (100 mg/12 h) plus ceftazidime (1000 mg/8 h), approximately one-third of the cases included were diabetic foot infections (n=257, 72% of these considered to be moderate or severe). The most frequently isolated microorganisms were: Methicillin-sensitive *S. aureus* (MSSA) 38%, MRSA 18%, *Enterobacter cloacae* 9%, *Streptococcus agalactiae* 9%, *P. aeruginosa* 8%, and *Proteus mirabilis* 7%. In this sub-population, the clinical recovery rates were as follows: 125/145, 86.2% for ceftobiprole and 63/77, 81.8% for vancomycin plus ceftazidime (mild infection 97.6% vs. 100% and severe infection 70.6% vs. 53.8%, respectively). However, the average duration of treatment was significantly shorter with ceftobiprole (8.7 vs. 9.5 days, respectively, $p < 0.05$), suggesting a faster response to treatment when ceftobiprole is used [19].

3. Infections originating from vascular catheters

S. aureus (MRSA: 9.5-26.6%) and coagulase-negative staphylococci (methicillin-resistant: 53.4%) are the most common causative organisms of infections associated with venous catheters (central and peripheral) in our country [18-20]. However, in recent years a significant increase in Gram-negative bacilli has been reported, most notably *P. aeruginosa*, *E. coli* and *Klebsiella* spp., which have been associated to a significant degree with solid organ transplant, post-surgery, prior use of beta-lactams, prolonged hospital stay (>7-11 days), and more than 3 days post-catheter insertion [21, 22].

In this context, choosing ceftobiprole as monotherapy may replace the usual combinations of a glycopeptide with a beta-lactam, preferentially active against *P. aeruginosa*. Experience with ceftobiprole in the treatment of bacteraemia, although favourable, is still limited. In the first cSSTI study due to Gram-positive cocci, three episodes of staphylococcal bacteraemia (2 due to MRSA) treated with ceftobiprole resolved without complication [11]. In the other cSSTI study, 13 cases of bacteraemia were reported in the ceftobiprole group, 11 of which (84.6%) resolved. In the control group, 8 cases of bacteraemia were observed with favourable outcome in 62.5% (5/8) [12]. In the hospital-acquired pneumonia study, 41 cases of bacteraemia were identified in the ceftobiprole arm and 45 in the comparator group. The authors do not comment on the aetiology or clinical and microbiological outcomes in this sub-group [23]. In the community-acquired pneumonia clinical trial, several cases of bacteraemia are described with no mention of causal agents. The recovery rate in this subpopulation does not differ between treatment groups or in comparison to treated cases without bacteraemia (ceftobiprole 6/7, 85.7%, comparator 12/14, 85.7%) [24]. Also at this time there is a phase III ongoing study in *S. aureus* bacteremia. The purpose of this study is to compare the efficacy and safety of ceftobiprole medocaril versus daptomicyn in the treatment of patients with complicated *S. aureus* bacteremia [25].

4. Fever with no apparent focus in hospitalised patients

The first point to consider in this patient type is to determine whether the origin of the fever is infectious, thus evaluating the clinical, biological and imaging data that may suggest infection. The second aspect is taking culture samples prior to starting treatment. The third decision involves choosing the empirical antibiotic treatment, clouded by a lack of focality [26]. In a large number of patients, the origin may be the venous catheter. In any case, one must always consider the most prevalent microorganisms as a cause of infection in hospitalised patients (*S.* aureus, coagulase-negative staphylococci, *Enterococcus* spp., and Gram-negative bacteria (enterobacteria and *P. aeruginosa*) which depend on the comorbidity, the invasive diagnostic or therapeutic procedures performed, and local epidemiology [27]. Furthermore, one must consider the risk of resistance, which is closely related to prior use of antibiotics, loss of colonisation immunity and colonisation pressure [28]. In patients without significant immunosuppression or septic shock, ceftobiprole may be used empirically as monotherapy with the goal of addressing the possible role of methicillin-resistant *Staphylococcus* spp., *E. faecalis*, *P. aeruginosa* and non-ESBL-producing enterobacteria.

CONCLUSIONS

Ceftobiprole may be a good therapeutic alternative for the empirical treatment of cSSTIs, including those involving diabetic foot, vascular catheter, and fever with no apparent infectious origin, which require hospitalisation and have risk factors for MRSA and *P. aeruginosa*. Always within the treatment protocols established at each hospital.

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Safety and tolerability of ceftobiprole

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ABSTRACT

Ceftobiprole is a fifth generation cephalosporin with a series of characteristics differentiating it from other beta-lactams, including its antibacterial activity, mainly against methicillin-resistant *Staphylococcus aureus*, resistant *Streptococcus pneumoniae* and also Gram-negative microorganisms such as *Pseudomonas aeruginosa*. This antibiotic has been subjected to various clinical trials and the results of these have led to its approval in Spain for the treatment of nosocomial pneumonia, excluding that associated with mechanical ventilation, and community-acquired pneumonia. The results of various ceftobiprole clinical studies provide consistent information on efficacy and tolerability. Ceftobiprole as monotherapy has been shown to be non-inferior to comparator antibiotics in different settings. Information is available on its compatibility with other drugs in Y-site administration, important from the point of view of the intravenous treatment of patients who present venous access limitation. On the other hand, and in contrast to other cephalosporins, ceftobiprole presents a low risk of infection due to *Clostridium difficile* and, in comparison with ceftaroline, neutropenia has not been reported to present any significant issues.

Keywords: ceftobiprole, tolerability, safety, Y-site administration

INTRODUCTION

Ceftobiprole is a cephalosporin that has as a number of differences compared to most other compounds of this family of beta-lactams, its activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae* resistant to third-generation cephalosporins and penicillin [1]. Ceftobiprole is excreted mainly in the urine in an unaltered form and with a high recovery of the administered dose of the drug [2]. The information from the clinical trials evaluating the pharmacokinetics of ceftobiprole shows that the AUC and C_{max} values are proportional to the doses that were used. Likewise, using data from the participants in these trials the degree of dose modification required based on alterations in renal function has been established (table 1) [3]. In the following, we describe the tolerability and safety of ceftobiprole.

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Table 1 Ceftobiprole dose adjustment according to renal function[a]

Normal renal function	500 mg/8h
CrCl 50-80 mL/min	500 mg/8h
CrCl 30-49 mL/min	500 mg/12h
CrCl < 30 mL/min	250 mg/12h

[a]The proposed adjustment is based on the Cockcroft-Gault formula and a standard dose of 500 mg / 8h intravenously. The dose is based on a 2-hour infusion.

SAFETY AND TOLERABILITY OF CEFTOBIPROLE IN CLINICAL TRIALS

A phase I study in which a single dose ranging from 125 mg to 1,000 mg was administered aimed at analysing the pharmacokinetics and safety of ceftobiprole. One study objective was to establish the duration of time with ceftobiprole concentration maintained above the MIC, since, as a beta-lactam antibiotic, its efficacy is related to the pharmacokinetic-pharmacodynamic index of T> MIC [4]. The safety of the drug was assessed in 40 patients, eight (20%) of whose presented a total of 10 adverse effects. Only 3 adverse events of moderate importance were recorded (nausea and vomiting), with taste changes

observed in the remaining 7 cases. No serious adverse effects were detected. When the study was extended to multiple doses in 16 healthy male volunteers, 5 patients had at least one adverse effect in the 500 mg group versus 6 in the 750 mg group compared to 3 in the placebo group. The number of adverse events was higher in patients receiving the highest dose, with a total of 22 mild and 5 moderate events, and reversible taste alteration again predominating [5]. A network meta-analysis compared the efficacy and safety of ceftobiprole versus 8 other antibiotics for the treatment of Hospital-acquired pneumonia [6]. The results showed no significant differences in the adverse effects of this cephalosporin against the rest of the comparator agents. A double-blind, randomized, multinational clinical trial compared the efficacy and safety of ceftobiprole versus vancomycin in the treatment of skin and soft tissue infections caused by gram-positive organisms [7]. A total of 784 patients were included in the study. Adverse effects and concomitant diseases were the main reasons for patient discontinuation in the study. A total of 52% of the patients presented at least one adverse event in the ceftobiprole group compared to 51% in the vancomycin group. Serious side effects were observed in 6% of patients in each group, 4% and 6% of patients discontinuated the study drug in the ceftobiprole and the vancomycin group, respectively. Nausea and vomiting were the most frequent adverse effects, reaching 21% in the ceftobiprole group versus 12% in the vancomycin group. In the vancomycin group 3 deaths were recorded compared to none in the ceftobiprole group. None of the deaths were attributed to antibiotic treatment. Similar results were observed in another phase III clinical trial in this same indication with 56% patients presenting adverse events in the ceftobiprole arm compared to 57% in the comparator group, which in this case was the combination of vancomycin associated with ceftazidime. Four percent of patients discontinued treatment in both groups [8].

One study evaluated the efficacy and safety of ceftobiprole vs ceftriaxone with or without linezolid in patients with community-acquired pneumonia who required hospital admission [9].

A total of 638 patients were included in the analysis. A total of 6% patients discontinued the treatment early in the ceftobiprole group compared to 4% in the comparator group. The incidence of adverse events was 36% in the ceftobiprole group versus 26% with the comparator, the differences being mainly due to the occurrence of nausea and vomiting.

A phase III study analyzed the efficacy of ceftobiprole versus ceftazidime with or without linezolid in the treatment of nosocomial pneumonia, including pneumonia associated with mechanical ventilation (VAP) [10]. A total of 781 patients were randomized, 176 of whom had VAP. A total of 24.9% patients presented some adverse events in the ceftobiprole group compared to 25.4% in the comparator group. Patients in the ceftobiprole group had a lower incidence of diarrhea than those in the ceftazidime plus linezolid group, 3.1% versus 6.5%, respectively. A total of 4.4% patients in the ceftobiprole arm versus 2.6% of patients treated in the comparator group (ceftazidime plus linezolid) developed hyponatremia. Dysgeusia was only observed in the ceftobiprole group, in 1.3% of patients. There were 15 cases of serious adverse events, 3.9% in the ceftobiprole group compared to 3.1% in the comparator.

SAFETY AND TOLERABILITY OF CEFTOBIPROLE IN OTHER STUDIES

One study was conducted to analyse possible modifications of the intestinal microflora produced by the 7-day exposure to treatment with ceftobiprole [11]. A total of 12 healthy volunteers of both genders were included. No fecal excretion of ceftobiprole was observed and only a minimal effect on the fecal flora was reported. Unlike other cephalosporins, ceftobiprole is considered an antibiotic associated with a lower risk of *Clostridium difficile* infection. In a subsequent study in mice, it has been proposed that ceftobiprole has an inhibitory effect on *C. difficile* activity and a moderate effect on the anaerobic microflora [12].

Agranulocytosis associated with prolonged treatment with ceftobiprole, related to a mechanism related to T-cells has been described [13].

Although the understanding of the impact of the inoculum effect in cephalosporins observed *in vitro* is limited, in a study conducted on strains of methicillin-susceptible *S. aureus,* ceftobiprole had the lowest MICs at a high inoculum when compared to other cephalosporins [14]. The significance of these results should be considered alongside the findings of subsequent *in vivo* studies.

A review of the literature analysing the neurological effects attributable to treatment with beta-lactams has been published [15]. This review highlighted renal failure as the main risk factor for production of neurological adverse effects attributable to beta-lactams. Unlike what was observed with other cephalosporins, no case of neurological alterations related to ceftobiprole could be identified in that review.

A case report of combination therapy with daptomycin and ceftobiprole in the treatment of a methicillin-resistant *S. aureus* endocarditis in prosthetic valve has been described [16]. The patient was treated with a dose of 500 mg/8h of ceftobiprole for 11 weeks, with resulting good antibiotic tolerability.

COMPATIBILITY OF CEFTOBIPROLE IN Y-SITE ADMINISTRATION

Patients who require treatment with more than one drug administered intravenously, and have limited venous access, have a higher risk of receiving ineffective treatment when one drug is administered simultaneously with another in Y-site administration [17]. One study aimed to analyze the compatibility of ceftobiprole with other drugs, through visual observation, measurement of turbidity and the appearance of possible particles as a result of Y-site administration. The initial solution of ceftobiprole was diluted as per the product specifications resulted in a turbid-free mixture, without particles. Table 2 shows the compatibility of ceftobiprole with other antimicrobials included in the study.

Table 2 **Antimicrobials compatible with ceftobiprole in 5% glucose solution, saline solution and ringer lactate solution for injection[a].**

Antimicrobial	Concentration (mg/mL)
Acyclovir	7
Azithromycin	2
Clindamycin phosphate	10
Fluconazole	2
Metronidazole	5
Trimethoprim/sulfamethoxazole	0.8/4
Voriconazole	4

[a]The information contained in this table is only valid for the specific brands used in the referenced study [16] and at the concentrations indicated.

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