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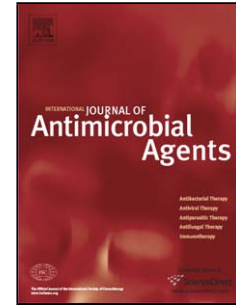


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**In vitro activity of ceftobiprole against *Acinetobacter baumannii*  
clinical isolates**

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**Abstract**

*Acinetobacter baumannii* is a multiresistant opportunistic nosocomial pathogen responsible for outbreaks worldwide. The main infection caused by this microorganism is nosocomial pneumonia, in particular ventilator-associated pneumonia in patients in Intensive Care Units. Treatment of these nosocomial infections is becoming problematic because the level of resistance to antimicrobial agents is rising. Ceftobiprole is a new cephalosporin with activity against Gram-positive and Gram-negative pathogens. This study evaluated the in vitro activity of ceftobiprole against a collection of 58 *A. baumannii* clinical isolates and showed that the activity of ceftobiprole was superior to ceftazidime and cefepime when the *bla*<sub>ADC</sub>-like gene was not expressed or was expressed at a low level.

## 1. Introduction

*Acinetobacter baumannii* is a nosocomial pathogen involved in a wide range of infections such as bacteraemia, secondary meningitis, pneumonia and urinary tract infections, and is currently one of the most important Gram-negative pathogen causing infections in immunocompromised patients [1]. *Acinetobacter baumannii* has been considered the paradigm of multiresistant bacteria because there are strains resistant to all antimicrobial agents [2].  $\beta$ -Lactam antibiotics, mainly carbapenems, were the first choice against these microorganisms. However, in the last decade resistance to these antimicrobial agents has appeared in hospitals worldwide owing to production of  $\beta$ -lactamases, changes in permeability, increase in efflux, and modification of the affinity of penicillin-binding proteins (PBPs) [2,3].

Ceftobiprole is a broad-spectrum cephalosporin that has successfully completed phase III clinical trials and is currently awaiting approval both in the USA and Europe [4]. Its bactericidal activity against certain  $\beta$ -lactam-resistant Gram-positive microorganisms is regarded as the main advantage of this antimicrobial agent over the older cephalosporins. Several studies have demonstrated that ceftobiprole has a strong affinity for PBP2 and PBP2x from staphylococci and pneumococci. However, this antimicrobial agent can also bind to other PBPs of resistant Gram-positive and Gram-negative bacteria [5,6]. For instance, in *Escherichia coli* ceftobiprole has a good affinity for PBP3 and PBP2, whilst in *Pseudomonas aeruginosa* the greatest affinity is for PBP1a and PBP3 [7]. In vitro studies suggested that ceftobiprole has a low potential for selection of

resistance; this conclusion was made after serial passages in the presence of subinhibitory concentrations of the antibiotic [4,5,8]. Previous studies have proposed that the activity of ceftobiprole against Gram-negative bacteria such as *P. aeruginosa* is comparable with the activity of other known antimicrobial agents such as ceftazidime and cefepime [5,6,9]. The purpose of this study was to evaluate the in vitro activity of ceftobiprole in a collection of *A. baumannii* clinical isolates.

## 2. Materials and methods

Fifty-eight epidemiologically unrelated *A. baumannii* clinical isolates were chosen for this study. Ceftobiprole was obtained from Johnson & Johnson Pharmaceutical Research and Development (Raritan, NJ); ceftazidime and cefepime were obtained from Sigma-Aldrich (Madrid, Spain). All drugs were prepared and dissolved as recommended by the manufacturer. Minimum inhibitory concentrations (MICs) were determined by the microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) [10]. The resistance breakpoint used for ceftazidime and cefepime was >8 mg/L. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has increased the susceptible breakpoint of cefepime and ceftazidime for *P. aeruginosa* to avoid dividing the MIC wild-type distribution. The breakpoint relates to a high dosage of both drugs, i.e. 2 g × 3. Since EUCAST does not define breakpoints for *Acinetobacter*, arbitrary breakpoints without any clinical relevance have been applied.

The *bla*<sub>ADC</sub>-like gene, the insertion sequence IS<sub>Aba1</sub> and the location of the IS in the promoter region of the *bla*<sub>ADC</sub>-like gene were detected by polymerase chain reaction (PCR) with the following primers: ADC1, 5'-CCG CGA CAG CAG GTG GAT A-3' and ADC2, 5'-TCG GCT GAT TTT CTT GGT T-3' for the *bla*<sub>ADC</sub>-like gene; and IS<sub>Aba1</sub>, 5'-CAT TGG CAT TAA ACT GAG GAG AAA-3' and IS<sub>Aba2</sub>, 5'-TTG GAA ATG GGG AAA ACG AA-3' for the IS element. Finally, for the location of IS<sub>Aba1</sub> upstream of the *bla*<sub>ADC</sub>-like gene, the primers ISADC1 (5'-GTT GCA CTT GGT CGA ATG AAA A-3') and ISADC2 (5'-ACG TCG CGA GTT GAA GTA AGT T-3') were used.

### 3. Results and discussion

Fifty-eight *A. baumannii* clinical isolates were separated into two groups depending on the presence or absence of IS<sub>Aba1</sub> in front of the *bla*<sub>ADC</sub>-like gene. The MICs for 50% and 90% of the organisms (MIC<sub>50</sub> and MIC<sub>90</sub> values, respectively) for ceftobiprole, ceftazidime and cefepime are shown in Table 1. The results show that in *A. baumannii* the overall resistance of the isolates to ceftobiprole (70.7%) is slightly lower than the resistance to ceftazidime (77.6%) or cefepime (75.9%). Although the MIC<sub>50</sub> is similar for the three antibiotics, the MIC<sub>90</sub> shows that the level of resistance to ceftazidime and cefepime is higher than the resistance to ceftobiprole. This is confirmed by the range of MICs obtained for the three antimicrobial agents.

Thirty-one of the clinical isolates expressed the *bla*<sub>ADC</sub>-like gene (Table 1). In this group, there was practically no difference between the activities of the three antibiotics. However, when the *bla*<sub>ADC</sub>-like gene is not expressed, resistance to

ceftobiprole (37%) is lower than resistance to ceftazidime (51.9%) and cefepime (51.9%) (Table 1). In this case, the range of MICs obtained for the three antimicrobial agents was wider for ceftobiprole than for ceftazidime and cefepime. In addition, the MIC<sub>50</sub> of ceftobiprole is the only sensitive value of the whole study. Three subpopulations can be defined according to our data. The first population (12 isolates) had a ceftobiprole MIC ranging from 0.06 mg/L to 0.5 mg/L and corresponds to those isolates without overexpression of the *bla*<sub>ADC</sub>-like gene. A second population did not overexpress this gene but had a ceftobiprole MIC between 4 mg/L and 64 mg/L (15 isolates). Six of these isolates showed an MIC of 32–64 mg/L and five of them presented OXA-37 (data not shown), which is an oxacillinase affecting third-generation cephalosporins [11]. Finally, the third population includes those isolates overexpressing the *bla*<sub>ADC</sub>-like gene, which had an MIC of 64 mg/L (Fig. 1).

Approximately one-half of the isolates used in this study (31) expressed the *bla*<sub>ADC</sub>-like gene because IS<sub>Aba1</sub> was located in the promoter region of the gene. The class C AmpC  $\beta$ -lactamase is an enzyme that hydrolyses the lactam ring in cephalosporins, conferring resistance to  $\beta$ -lactams. The presence of the insertion sequence IS<sub>Aba1</sub> in the promoter region of the *bla*<sub>ADC</sub>-like gene favours overexpression of this gene [12]. In a previous experiment with Gram-negative microorganisms, Queenan et al. [9] suggested that in *P. aeruginosa* strains producing high levels of AmpC the MICs for all the cephalosporins, including ceftobiprole, were >16 mg/L. Our results with *A. baumannii* corroborate these findings in *P. aeruginosa*. However, when the *bla*<sub>ADC</sub>-like gene was not expressed, the activity of ceftobiprole against *A. baumannii* was better than the

activity of ceftazidime and cefepime. Over 60% of the isolates had an MIC  $\leq$  8 mg/L for ceftobiprole, which is a good percentage in a multiresistant microorganism such as *A. baumannii*.

In summary, when the *bla*<sub>ADC</sub>-like gene was expressed, the activity of ceftobiprole was similar to that of ceftazidime and cefepime. However, based on the MIC<sub>50</sub> and MIC<sub>90</sub> values, ceftobiprole was the most active cephalosporin tested against *A. baumannii* clinical isolates when the *bla*<sub>ADC</sub>-like gene was repressed.

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**Competing interests:** None declared.

**Ethical approval:** Not required

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Fig. 1. Activity of ceftobiprole (CFB), cefepime (CFP) and ceftazidime (CFT) in *Acinetobacter baumannii* clinical isolates. MIC, minimum inhibitory concentration.

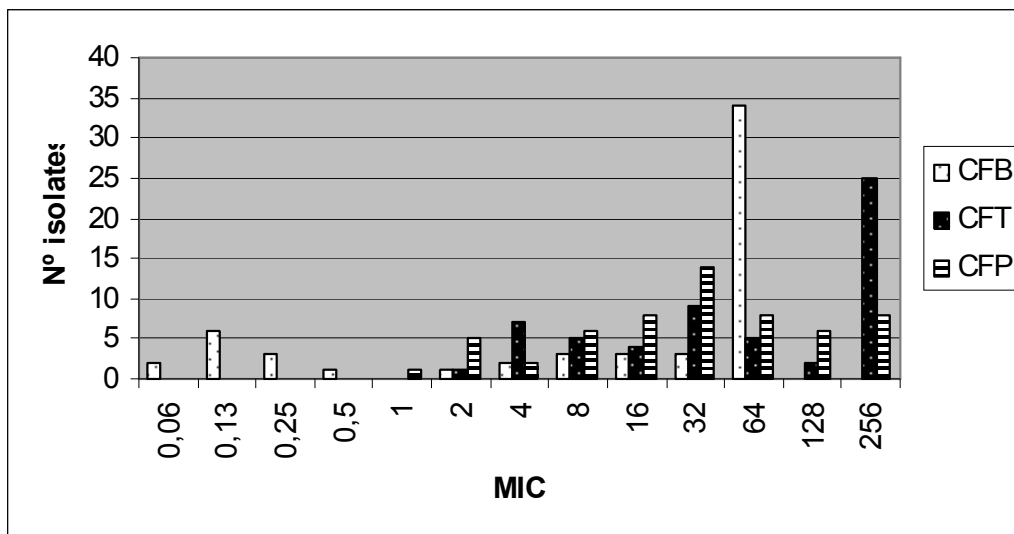
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Table 1

Activities of ceftobiprole, cefepime and ceftazidime in *Acinetobacter baumannii* clinical isolates ( $n = 58$ )

Clinical isolates	Antimicrobial agent	% resistance (>8 mg/L)	MIC (mg/L)		
			MIC <sub>50</sub>	MIC <sub>90</sub>	Range
All strains ( $n = 58$ )	Ceftazidime	77.6	64	256	2–256
	Cefepime	75.9	32	256	1–256
	Ceftobiprole	70.7	64	64	0.06–64
IS <sub>AmpC</sub> +ve ( $n = 31$ )	Ceftazidime	100	256	256	16–256
	Cefepime	96.8	64	256	8–256
	Ceftobiprole	100	64	64	32–64
IS <sub>AmpC</sub> –ve ( $n = 27$ )	Ceftazidime	51.9	16	256	2–256
	Cefepime	51.9	16	32	1–256
	Ceftobiprole	37	8	64	0.06–64

MIC, minimum inhibitory concentration; MIC<sub>50/90</sub>, MIC for 50% and 90% of the organisms, respectively; IS, insertion sequence.



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