

The antimicrobial activity of ceftobiprole against Methicillin-resistant *Staphylococcus aureus* and multi-drug resistant *Pseudomonas aeruginosa*

A large tertiary care university hospital experience in Riyadh, Saudi Arabia

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ABSTRACT

الأهداف: تقييم فعالية السفتوبيبرول (ceftobiprole) ضد بكتيريا المكورات العنقودية الذهبية المقاومة للميثيسيلين (MRSA) والزائفة الزنجارية (MDR *P. aeruginosa*) ذات المقاومة المتعددة للأدوية باستخدام أنواع مختلفة من العينات وأنماط مختلفة من المقاومة.

المنهجية: عزلنا ما مجموعه 49 عينة من المكورات العنقودية الذهبية المقاومة للميثيسيلين (MRSA) و99 عينة من الزائفة الزنجارية ذات المقاومة المتعددة للأدوية (MDR *P. aeruginosa*) في مختبر الأحياء الدقيقة في المدينة الطبية بجامعة الملك سعود، الرياض، المملكة العربية السعودية خلال عامي 2018م و2019م. تم اختيار عينات عشوائية من مصادر مختلفة من الجسم وتم تحديد الحد الأدنى لتركيز التثبيط (MIC) من السفتوبيبرول بواسطة اختبار الاستعداد المناعي للمضادات الحيوية. كما تم تقييم حساسية المضادات الحيوية باستخدام معايير اللجنة الأوروبية لاختبار حساسية مضادات الميكروبات (EUCAST).

النتائج: وجدنا 100% من عينات المكورات العنقودية الذهبية المقاومة للميثيسيلين MRSA كانت حساسة للسفتوبيبرول (MIC 50/90: 1/1.5 mg/L) بينما 69.8% من عينات الزائفة الزنجارية ذات المقاومة المتعددة للأدوية (MDR *P. aeruginosa*) كانت مقاومة للسفتوبيبرول (MIC 50/90: 16/32 mg/L).

الخلاصة: سيكون للنشاط الممتاز للسفتوبيبرول ضد MRSA أثر كبير في علاج المرضى المصابين بعدوى خطيرة، كعلاج تجريبي أو بديل للفانكومايسين. أظهر السفتوبيبرول نشاطاً منخفضاً جداً ضد MDR *P. aeruginosa*، ويجب اختبار مدى حساسيته قبل استخدامه للعلاج.

Objectives: To assess the antibacterial activity of ceftobiprole against Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (*P. aeruginosa*) from various body specimen types and different patterns of resistance.

Methods: A retrospective cohort study with a total of 49 MRSA and 99 *P. aeruginosa* isolated in the Microbiology Laboratory at King Saud University Medical City, Riyadh, Saudi Arabia, between 2018-2019, were used. Isolates were randomly selected from various specimen types. The minimum inhibition concentration (MIC) of ceftobiprole was

determined by E-test. Breakpoints carried out by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used to assess antibiotic susceptibility.

Results: Approximately 100% of the MRSA isolates were susceptible with MIC_{50/90} value of 1/1.5 mg/L while 69.8% of multi-drug resistant (MDR) *P. aeruginosa* isolates were resistant with MIC_{50/90} value of 16/32 mg/L.

Conclusion: The excellent activity of ceftobiprole against MRSA would have major implications in management of the patients with serious infections, as an empirical treatment or alternative to vancomycin. Ceftobiprole has a very low activity against MDR *P. aeruginosa*, and its susceptibility should be tested prior to use for treatment.

Keywords: ceftobiprole, MRSA, MDR *P. aeruginosa*, tertiary care

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The recent rise in Methicillin-resistant *S. aureus* (MRSA) and multi-drug resistant *Pseudomonas aeruginosa* (MDR *P. aeruginosa*) infections in hospitals and community settings is a serious issue worldwide.^{1,2} Due to the remarkable resistance to several commonly used antibiotics, eradication and treatment of bacterial infections has become a challenge.^{1,2} Many reports from Saudi Arabia showed a significant increase in MRSA and *P. aeruginosa* resistance during the previous decade.³

Only a few antibiotics have been approved for the treatment of MRSA and MDR *P. aeruginosa*. Vancomycin with individual dosing is an acceptable treatment option.^{4,5} Inadequate vancomycin doses and extended therapy, on the other hand, can result in an increase in the minimum inhibitory concentration (MIC), which can lead to therapeutic failure and toxicity.⁶ Linezolid and daptomycin have been used, but resistance was reported only after 5 years, which led to the need for new antibiotics.⁷ Cefazolin is an antibiotic that can be used to treat a variety of Gram-positive and Gram-negative infections, including MRSA and MDR *P. aeruginosa*, and has a broad spectrum of activity.⁸ Cefazolin was approved as a clinical and microbiological cure, but there was limited evidence of its usage in pediatric, pregnant or breastfeeding patients, and it is contraindicated in those with severe beta-lactams hypersensitivity.⁸

Ceftobiprole is a novel fifth-generation cephalosporin with a broad-spectrum antimicrobial activity against various bacteria such as MRSA and MDR *P. aeruginosa*.⁹⁻¹¹ A total of 17 European countries and 8 non-European countries have authorized ceftobiprole for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), except ventilator-associated pneumonia, caused by Gram-positive and Gram-negative infections.^{12,13} Ceftobiprole is recommended as a parenteral therapy for the empirical treatment of hospitalized CAP patients who have risk factors for MRSA or *P. aeruginosa*.¹⁴ Moreover, it exhibits good activity against *Staphylococcus aureus* (*S. aureus*) isolated from HAP.^{15,16}

Ceftobiprole has been proven to have a low possibility of causing antibiotic resistance.^{17,18} In addition, it has a high binding sensitivity for penicillin-binding protein 2a, a special transpeptidase that is not inhibited with β -lactam antibiotics, which

increases its bactericidal efficacy against almost all MRSA strains.¹⁹

The objective of this study was to assess the antibacterial activity of ceftobiprole against MRSA and *P. aeruginosa* from various body specimen types and different patterns of resistance.

Methods. A retrospective cohort study with a total of 49 MRSA and 99 MDR *P. aeruginosa* isolated in the Microbiology Laboratory at King Saud University Medical City, Riyadh, Saudi Arabia, from January 2018 until December 2019 were included in the study.

Isolates were randomly selected from various specimen types, including body fluids, sputum, endotracheal secretions, blood, wound swabs, and urine. Isolates were refrigerated at -80°C in skimmed milk, and each sample was rolled for at least 20 seconds on sheep blood agar (SBA) to guarantee that all sides of the specimen encountered the culture media. The SBA plates were incubated for 24 hours in an atmosphere containing 5% CO_2 at 35°C . Definitive identification of methicillin-sensitive *S. aureus* and MRSA was carried out using automated identification and susceptibility testing. MicroScan Combo Panel (Vitek2 AST-N292 Microscan [Negative breakpoint combo 50]) was used for *Pseudomonas*. Acquired non-susceptibility of MDR organisms was defined as resistance to at least one agent from 3 or more antimicrobial categories.²⁰

Susceptibility testing was carried out according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.²¹ The E-test (BioMérieux, France) was used to determine the MIC of ceftobiprole on Mueller-Hinton agar (Saudi Prepared Media [SPM.co]). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints and M100-S28 were used for ceftobiprole susceptibility interpretations, *S. aureus* (susceptible: $\leq 2\text{g/ml}$; resistant: $> 2\text{g/ml}$) and non-species-specific breakpoints (susceptible: $\leq 4\text{g/ml}$; resistant: $> 4\text{g/ml}$).²²

Quality control criteria for ceftobiprole $5\mu\text{g}$ were carried out for *S. aureus* American Type Culture Collection ATCC 29213 and *P. aeruginosa* ATCC 27853 according to EUCAST SOP 9.0.²¹

Ethical approval was obtained from the Institutional Review Board of King Saud University, Riyadh, Saudi Arabia.

Statistical analysis. Minimum inhibitory concentration ranges (MIC₅₀, MIC₉₀) were presented by pathogen or pathogen group. There were no statistical analyses in this descriptive study.

Results. A total of 49 MRSA isolates were collected. Most isolates were from male patients

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between 20-39 years. **Table 1** summarizes the pathogen distribution based on central laboratory identification and reflects the collection design. Isolates from the intensive care unit (ICU) accounted for 2.1% of the sample. Most of the samples were cultured from wounds.

Minimum inhibitory concentration and E-test results of ceftobiprole against MRSA are shown in **Table 2**. All 49 (100%) tested isolates were susceptible (MIC: ≤ 2 mg/L) with MIC50/90 value of 1/1.5mg/L.

A total of 99 MDR *P. aeruginosa* isolates were collected. The majority were from male patients aged 70-79 years. **Table 3** shows the distribution of pathogens using central laboratory identification and reflects the collection design. A total of 15.2% of the isolates were from patients in the ICU. Most samples were cultured from respiratory sources.

Table 1 - Methicillin-resistant *Staphylococcus aureus* isolate and patient characteristics.

Characteristics	n (%)
Total number of isolates	49
Male gender	33 (67.3)
<i>Age, years</i>	
0-4	8 (16.3)
5-19	6 (12.3)
20-39	16 (32.7)
40-49	6 (12.3)
50-59	2 (4.1)
60-69	7 (14.3)
70-79	3 (6.1)
≥ 80	1 (2.0)
<i>Source</i>	
Respiratory	7 (14.3)
Blood	5 (10.2)
Urine	2 (4.1)
Wound	27 (55.1)
Body fluid	2 (4.1)
Tissue	1 (2.1)
Swab	5 (10.2)
<i>Infection type</i>	
ICU	1 (2.1)

ICU: intensive care unit

Table 2 - Distribution of ceftobiprole MIC by E-test of 49 isolates of MRSA.

MIC (mg/L)	No. of isolates	Percentage	MIC50	MIC90	MIC50/90
0.75	8	16.3			
1	23	46.9	1	1.5	0.7
1.5	15	30.6			
2	3	6.1			

MIC: minimum inhibitory concentration, No: number, MRSA: Methicillin-resistant *Staphylococcus aureus*

Table 4 presents the E-test results and MIC of ceftobiprole against MDR *P. aeruginosa*. Of the 99 tested isolates, 30 (30.2%) were susceptible (MIC: ≤ 4 μ g/mL), while 69 (69.8%) were resistant (MIC: ≥ 4 μ g/mL) with MIC50/90 value of 16/32mg/L.

Table 5 shows the antimicrobial resistance patterns of MDR *P. aeruginosa* isolates. Nearly 50% of the isolates are

Table 3 - Multi-drug resistant *P. aeruginosa* isolate and patient's characteristics.

Characteristics	n (%)
Total number of isolates	99
Male gender	54 (54.5)
<i>Age, years</i>	
0-4	12 (12.1)
5-19	7 (7.1)
20-39	18 (18.2)
40-49	2 (2.0)
50-59	16 (16.2)
60-69	13 (13.1)
70-79	19 (19.2)
≥ 80	12 (12.1)
<i>Source</i>	
Respiratory	42 (42.4)
Blood	0 (0.0)
Urine	24 (24.2)
Wound	22 (22.2)
Body fluid	7 (7.1)
Tissue	3 (3.0)
Swab	1 (1.0)
<i>Infection type</i>	
ICU	15 (15.2)

P. aeruginosa: *Pseudomonas aeruginosa*, ICU: intensive care unit

Table 4 - Distribution of ceftobiprole MIC by E-test of 99 isolates of MDR *P. aeruginosa*.

MIC (mg/L)	No. of isolates	Percentage	MIC50	MIC90	MIC50/90
0.047	1	1.01			
0.094	1	1.01			
1	3	3.03			
1.5	2	2.02			
2	2	2.02			
3	10	10.10			
4	11	11.11	16	32	0.5
6	4	4.04			
8	4	4.04			
12	6	6.06			
16	4	4.04			
32	46	46.46			
>32	5	5.05			

MIC: minimum inhibitory concentration, MDR: multi-drug resistant, No: number, *P. aeruginosa*: *Pseudomonas aeruginosa*

Table 5 - Antibiotic susceptibility patterns of tested MDR *P. aeruginosa* (N=99).

Antibiotic suitability pattern	Total tested	MDR <i>P. aeruginosa</i>	
		Susceptible	Resistant
Ceftazidime	81	56 (56.6)	25 (25.6)
Piperacillin/tazobactam	67	51 (51.5)	16 (16.2)
Imipenem	50	11(11.1)	39 (39.4)
Meropenem	47	10 (10.1)	37 (37.4)
Gentamicin	80	50 (50.5)	30 (30.3)
Tobramycin	63	50 (50.5)	13 (13.1)
Amikacin	57	45 (45.5)	12 (12.1)
Ciprofloxacin	81	55 (55.6)	26 (26.3)

MDR *P. aeruginosa*: Multi-drug resistant *Pseudomonas aeruginosa*

non-susceptible to ceftazidime, piperacillin/tazobactam, aminoglycoside, and ciprofloxacin, while only 10% are resistant to carbapenem.

American Type Culture Collection microbial reference strains were used to provide high quality control. Quality control criteria for ceftobiprole 5 µg were carried out for *S. aureus* ATCC 29213 and *P. aeruginosa* ATCC 27853. The E-test was carried out to detect the MIC for both *S. aureus* 29213 and *P. aeruginosa* 27853. The results were 0.38mg/L (susceptible) in *S. aureus* 29213 and 4mg/L (susceptible) in *P. aeruginosa* 27853.

Discussion. Methicillin-resistant *S. aureus* infections are common medical problems that cause major consequences and have a higher morbidity and mortality rate than other bacterial infections.³ Clinical trials have led to the use of ceftobiprole for the empirical regimen and tailored therapy of CAP and HAP due to its activity against MRSA, favorable safety profile, and broad-spectrum activity.^{12,23}

A recently published case series described a clinical trial treating MRSA bacteremia with ceftobiprole in combination with vancomycin. Results were promising, and clinical outcomes were excellent even when the patient had endocarditis and was immunocompromised.²⁴ However, there is limited evidence for ceftobiprole use in Saudi Arabia. Also, there is a lack of studies that investigate the in vitro activity of ceftobiprole against MRSA and *P. aeruginosa* in Saudi Arabia or the Middle East.

In this study, 49 (100%) of the MRSA isolates were susceptible to ceftobiprole with MIC_{50/90}: 1/1.5mg/L. Our results are compatible with previous studies that reported susceptibility percentages. A study in Italy found only a 12% resistance rate to ceftobiprole (12/102 isolates; MIC: ≥4mg/L).²⁵ A similar susceptibility rate was reported in Europe and Turkey

(98.3% susceptible).²⁶ Susceptibility of approximately 99.3% was reported in the United States (US).¹⁰ Thus, ceftobiprole had a significant in vitro activity against MRSA.

Infection with MDR *P. aeruginosa* strains has become more common in recent years, posing a threat to public health. These strains cause serious infection, especially in hospital settings and in immuno-compromised patients.²⁷ Ceftobiprole shows potent activity and great coverage of Gram-positive pathogens, such as MRSA. It has a range of action against Gram-negative *bacilli* such as MDR *P. aeruginosa*.^{10,27} However, there are no Saudi clinical trials to assess the effect of ceftobiprole against *P. aeruginosa*.

In our study, we found that only 30 (30.2%) of MDR *P. aeruginosa* isolates were susceptible (MIC: ≤4µg/mL) while 69 (69.8%) of the isolates were resistant with MIC_{50/90} value of 16/32mg/L. Previous studies have identified ceftobiprole's activity against MDR *P. aeruginosa* at a variety of susceptibility levels. A study in the Middle East, reported 62.4% susceptibility for ceftobiprole against *P. aeruginosa*.²⁸ The potential of ceftobiprole against *P. aeruginosa* (MIC_{50/90} value of 2/>8µg/ml; 64.6% at MIC value of ≤4µg/ml) was reported in a European and Turkish study.²⁶ A US study reported that approximately 72.7% of the *P. aeruginosa* isolates were susceptible to ceftobiprole.¹⁰ The notable discrepancy in the reported susceptibility percentages was likely multifactorial and might be due to the difference in sample sizes or sources.

A Turkish study compared the antimicrobial activity of fifth-generation cephalosporin, ceftaroline (both of which have recently received approval from the US Food and Drug Administration for therapeutic purposes), and ceftobiprole. The MIC₅₀ and MIC₉₀ values of all ceftaroline and ceftobiprole isolates were comparable to each other and defined as 0.50µg/ml

and 1 µg/ml. For both antibiotics, the in vitro activities against MRSA indicated that they should be effective therapeutic options.²⁹

Study limitations. The collected data was from a single center rather than multiple sites, and the sample size was small. The findings were not compared to the microdilution which is the gold standard way of measuring an antimicrobial agent's in vitro activity against a bacterial isolate. Nonetheless, this study provides useful preliminary data regarding the in vitro antibacterial activity of ceftobiprole in Saudi Arabia and the surrounding regions.

In conclusion, based on the E-test results, we found that ceftobiprole provides comprehensive coverage of MRSA and has limited activity against MDR *P. aeruginosa*. Although the clinical effectiveness of ceftobiprole for MRSA and MDR *P. aeruginosa* have been reported in some international studies, we recommend a larger multi-center clinical and laboratory study, together with local studies, to confirm ceftobiprole efficacy against MRSA and MDR *P. aeruginosa* strains.

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