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Could ceftaroline be an alternative therapy for linezolid resistant *Staphylococcus epidermidis* infections in Intensive Care Medicine?

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ABSTRACT

Introduction. Coagulase negative *Staphylococcus* continues generating interest in critically ill patients, due to their infections in extended admissions, in instrumented patients and due to their described multidrug resistance, which include glycopeptide heterorresistance and the increase in oxazolidinone resistance. Ceftaroline is a new cephalosporin with activity against resistant gram-positives, which, being betalactam, may provide adequate safety profile in the critical ill patient. The aim of this study was to determine the activity of ceftaroline and other antimicrobial agents against methicillin and linezolid-resistant *Staphylococcus epidermidis*.

Material and methods. We studied susceptibility of ceftaroline, tigecycline, daptomycin and vancomycin in a total of sixty-eight methicillin and linezolid-resistant *S. epidermidis* isolates with clinical significance from an Intensive Care Unit, using E-test.

Results. All strains were susceptible to the four antimicrobial agents, regardless of the level of resistance to linezolid.

Conclusion. Ceftaroline could be an alternative in the treatment of methicillin and linezolid-resistant *S. epidermidis* infections in critically ill patients.

Key words: *Staphylococcus epidermidis*, Linezolid resistance, ceftaroline

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¿Podría ceftarolina ser una alternativa terapéutica frente a las infecciones por *Staphylococcus epidermidis* en el paciente crítico?

RESUMEN

Introduction. *Staphylococcus* coagulasa negativo sigue generando interés en los pacientes críticos, debido a sus infecciones en los ingresos prolongados, en pacientes instrumentados y, debido a su resistencia a múltiples fármacos descrito, que incluyen la heterorresistencia a glicopéptidos y el aumento de la resistencia oxazolidinonas. Ceftarolina es una nueva cefalosporina con actividad frente a grampositivos resistentes, que, por ser un betalactámico, podría proporcionar un perfil de seguridad adecuado en el paciente crítico. El objetivo de este estudio fue determinar la actividad de ceftarolina y otros agentes antimicrobianos frente a cepas de *Staphylococcus epidermidis* resistente a meticilina y linezolid.

Material y métodos. Estudiamos la sensibilidad de ceftarolina, tigeciclina, daptomicina y vancomicina en un total de sesenta y ocho aislamientos con significación clínica de *S. epidermidis* resistente a meticilina y linezolid en una Unidad de Cuidados Intensivos, usando E-test.

Resultados. Todas las cepas fueron sensibles a los cuatro agentes antimicrobianos, con independencia del nivel de resistencia a linezolid.

Conclusión. Ceftarolina podría ser una alternativa en el tratamiento de infecciones por *S. epidermidis* resistente a meticilina y linezolid en el paciente crítico.

Palabras clave: *Staphylococcus epidermidis*, Linezolid resistance, ceftaroline

INTRODUCTION

Infection by coagulase-negative *Staphylococcus* (CNS) is generating increasing interest in intensive care units (ICU) because these microorganisms to attach to devices and are frequently multidrug resistant. Recently, heteroresistance to vancomycin has slightly increased, and linezolid resistance among CNS isolates in Spanish ICUs has reached 20%[1]. Ceftaroline is

a new cephalosporin with activity against multidrug resistant *Staphylococci*. The objective of this pilot study was to determine the *in vitro* activity of ceftaroline and other antimicrobial agents among methicillin and linezolid-resistant *Staphylococcus epidermidis* (MLRSE) obtained from clinical samples over a 4 year period in order to optimize antimicrobial therapy.

MATERIAL AND METHODS

From 2008–2011, MLRSE with clinical significance were collected in the 50-bed ICU of a 1000-bed teaching hospital in downtown Madrid. We determined minimum inhibitory concentrations (MICs) for linezolid, vancomycin, daptomycin, and tigecycline using VITEK panels (bioMérieux SA, Marcy l´Etoile, France) or the WIDER system (Francisco Soria Melguizo SA, Madrid, Spain). Linezolid MICs were confirmed and ceftaroline MICs determined using the E-test (AB BIODISK, Solna, Sweden). Following Clinical Laboratory Standards Institute guidelines, we considered strains ceftaroline-susceptible when the MICs were ≤1 mg/L and resistant when MICs were >1 mg/L[3, 4].

RESULTS AND DISCUSION

Sixty eight MLRSE strains were obtained; 29 from hemocultures, 24 from infected catheters, and 9 from corporal fluids (6 pleural, 2 peritoneal, and 1 cerebrospinal fluid). The remaining 6 were obtained from surgical site infection exudates. All strains were susceptible to ceftaroline (29 had MIC of 0.5 mg/L and 39 had MIC of 1 mg/L) independent of their level of resistance to linezolid. All 68 strains where tested with other antimicrobial agents and all were susceptible to vancomycin (MIC_{50} 2 mg/L, MIC_{90} 4 mg/L), daptomycin (MIC_{50} 0.5 mg/L, MIC_{90} 0.5 mg/L), and tigecycline (MIC_{50} 0.125 mg/L, MIC_{90} 0.5 mg/L) (table 1).

Ceftaroline is a fifth generation cephalosporin with activity against Gram-negative and Gram-positive organisms, including those resistant to methicillin. It has better lung diffusion than daptomycin or vancomycin, and higher plasma concentrations than linezolid can be achieved[5]. Thus, the bactericidal activity of ceftaroline is more rapid than vancomycin and linezolid (minimum bactericidal concentration against *S. aureus* of 1, 2, and >64 mg/L, respectively)[6,7]. Against linezolid-resistant CNS, ceftaroline has MIC_{50}/MIC_{90} values of 0.5 and 0.5 mg/L, respectively. In daptomycin non-susceptible strains, it has a MIC range of 0.03 mg/L to 0.12 mg/L[8,9]. In our study, 4 of the 8 MLRSE strains with a vancomycin MIC of 4 mg/L were susceptible to ceftaroline, with a MIC of 0.5 mg/L. The other 4 strains had MICs of 1 mg/L. All 8 strains were treated with vancomycin or daptomycin with good evolution.

Most of our MLRSE isolates were isolated from blood cultures and vascular catheters. Bacteraemia is the third most common cause of infection in ICUs in Spain after ventilator-associated pneumonia and urinary tract infections in patients with urinary catheters. Over one third of these are related to vascular catheters and *S. epidermidis* is the most frequently isolated pathogen. Vancomycin and daptomycin, after catheter removal, are frequently used to treat this type of infection[1]. Ceftaroline has not been used for MLRSE bacteraemia; however, about 120 cases are reported in the treatment of methicillin-resistant *Staphylococcus aureus* bacteraemic infections. The main indications for use (alone or in combination) were vancomycin MIC >2 mg/L, daptomycin MIC >1 mg/L, poor clinical response after treatment with any of the above, recurrent or persistent bacteraemia, and toxicity[10,11]. The success rate was >50% and the drug was generally well tolerated[10]. Therefore, we believe that ceftaroline could represent an alternative treatment for MLRSE infections.

Table 1 **Ceftaroline, daptomycin, vancomycin, and tigecycline susceptibility among MLRSE strains, grouped by the origin of the clinical sample.**

Source (N = 68)	Ceftaroline MIC	Linezolid MIC		Daptomycin MIC		Vancomycin MIC		Tigecycline MIC	
		Low level resistance ≤ 32 mg/L (*cfr* gene, G2576T, G125S alone)*	High level resistance ≥ 32 mg/L (combination among *cfr* gene, G2576T, G125S)*	< 1 mg/L	= 1 mg/L	≤ 2 mg/L	≥ 4 mg/L	< 0.5 mg/L	≥ 0.5 mg/L
Hemoculture (n=29)	0.5 mg/L	5	7	10	2	9	2	11	1
	1 mg/L	9	8	17	-	16	2	17	-
Catheter (n=24)	0.5 mg/L	5	4	9	-	7	2	8	1
	1 mg/L	2	13	15	-	14	1	9	6
Corporal fluid (n=9)	0.5 mg/L	-	4	4	-	4	-	3	1
	1 mg/L	1	4	5	-	4	1	5	-
Exudate (n=6)	0.5 mg/L	2	2	3	2	4	-	3	1
	1 mg/L	1	1	1	-	2	-	1	1

MLRSE= Methicillin- and linezolid-resistant *Staphylococcus epidermidis*; MIC = minimal inhibitory concentration.

* (Linezolid resistance characterization from reference 2).

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CONFLICTS OF INTEREST

The authors have no conflicts of interests to declare.

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