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Brief report

In vitro activity of ceftaroline in combination with other antimicrobials active against *Staphylococcus* spp.☆

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ABSTRACT

Introduction: We evaluated the *in vitro* activity of the combination of ceftaroline with daptomycin, linezolid and vancomycin against methicillin-resistant *Staphylococcus aureus* and coagulase-negative *Staphylococcus* (CNS).
Material and methods: We analysed 70 staphylococcal strains (31 *S. aureus* and 39 CNS) with the Etest using the MIC:MIC ratio method and calculation of fractional inhibitory concentration indexes.
Results: The combination of ceftaroline with daptomycin showed an additive effect (53.2%) and synergy (6.6%) against methicillin-susceptible *S. aureus,* and an additive effect (81.2%) against methicillin-resistant *S. aureus* (MRSA). This combination also showed an additive effect against 33% of linezolid-susceptible CNS and was not synergistic against linezolid-resistant CNS. The combination of ceftaroline with vancomycin was synergistic (87%) and ceftaroline with linezolid was additive (37%) against MRSA.
Conclusions: The combinations of ceftaroline with daptomycin, vancomycin or linezolid showed additive and/or synergistic effects against methicillin-resistant *Staphylococcus.*

Actividad *in vitro* de la combinación de ceftarolina con otros antimicrobianos activos frente a *Staphylococcus* spp.

Palabras clave:
Ceftarolina
Sinergias
Estafilococos

RESUMEN

Introducción: Evaluamos la actividad *in vitro* de la combinación de ceftarolina con daptomicina, linezolid y vancomicina frente a aislados de *Staphylococcus aureus (S. aureus)* y *Staphylococcus* coagulasa negativa (SCN) resistentes a meticilina.
Material y métodos: Se analizaron 70 cepas de estafilococos (31 *S. aureus* y 39 SCN) utilizando el método de CMI:CMI ratio con Etest y cálculo de los índices de concentración inhibitoria fraccionaria.
Resultados: La combinación de ceftarolina con daptomicina resultó aditiva (53,2%) y sinérgica (6,6%) frente a *S. aureus* sensibles a meticilina y aditiva (81,2%) frente a *S. aureus* resistentes a meticilina (SARM). También resultó aditiva frente al 33% de SCN sensibles a linezolid y no hubo sinergia frente a SCN resistentes a linezolid. Ceftarolina con vancomicina mostró sinergia (87%) y ceftarolina con linezolid adición (37%) frente a SAMR.
Conclusiones: Las combinaciones de ceftarolina con daptomicina, vancomicina o linezolid presentan efectos aditivos o sinérgicos frente a *Staphylococcus* resistentes a meticilina.

Introduction

Ceftaroline is a cephalosporin that has a broad spectrum of activity including gram-negative and gram-positive bacteria. For the latter, ceftaroline is characterised by its affinity for penicillin-binding proteins, such as methicillin-resistant *Staphylococcus aureus* (*S. aureus*) PBP2a and other PBPs present in other gram-positive ones, such as PBP2x, PBP2A and PBP3 of *Streptococcus pneumoniae.*[1]

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In many cases, combinations of antimicrobials can increase the spectrum and effectiveness of therapy, as well as decrease the chances of selecting resistant microorganisms.[2]

The objective of this study was to evaluate the *in vitro* activity of the combination of ceftaroline with daptomycin, linezolid and vancomycin against clinical isolates of *S. aureus*, and of different species of coagulase-negative staphylococci (CNS), using the Etest by the method of MIC:MIC ratio and its valuation by determining the fractional inhibitory concentration (FIC) indexes.[3]

Material and methods

Seventy strains of staphylococci were analysed retrospectively, including 31 strains of *S. aureus*, 16 MRSA and 15 methicillin-sensitive *S. aureus* (MSSA), and 39 strains of linezolid-sensitive methicillin-resistant CNS (LSCoNS) or linezolid-resistant methicillin-resistant CNS, of which 25 corresponded to *Staphylococcus epidermidis* and the remaining 14 to other CNS species. The strains were preserved at −70 °C and were subcultured in Columbia agar with sheep blood (bioMérieux, Marcy-l'Étoile, France) and incubated for 24 h at 37 °C. The isolates were identified again by mass spectrometry (MALDI-TOF, Vitek MS, bioMérieux, Marcy-l'Étoile, France).

The MIC determination of ceftaroline, daptomycin, linezolid and vancomycin, alone and in combination was performed using the gradient diffusion method, Etest (bioMérieux, France). The strains were classified as sensitive or resistant following interpretation criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The evaluation of the effects of the different combinations of the analysed antimicrobials (synergy, addition, indifference, antagonism) was performed using the Etest by the method of MIC:MIC ratio and the FIC indexes were calculated.[3] To do this, a strip of ceftaroline was placed on a Mueller-Hinton agar plate previously inoculated with a 0.5 McFarland suspension of each microorganism. After 1 h of incubation at room temperature, the strip was removed and the second antimicrobial strip was placed on the print of the first, matching the MIC values of the first antimicrobial with the MIC values of the second, and subsequently incubating for 24 h at 37 °C. To evaluate the effect of the combinations, the FIC was calculated, measuring the MIC values of each antibiotic separately (MICA and MICB) and combined (MICAB), according to the formula FIC = (MICAB/MICA) + (MICAB/MICB). The combinations were interpreted as synergistic (FIC ≤ 0.5), additive (FIC > 0.5 to ≤1), indifferent (FIC > 1 to ≤4) or antagonistic (FIC > 4).[3]

Results

The MIC_{50} values and the MIC ranges (mg/l) of ceftaroline, daptomycin, vancomycin and linezolid against the different microorganisms are indicated in Table 1.

Table 2 shows the values obtained with the combinations used of ceftaroline together with a second antimicrobial for the strains of *S. aureus* and CNS. The combination of ceftaroline with daptomycin had additive effects in 53.2% and synergistic effects in 6.6% of the MSSA. In the case of MRSA strains, no synergistic effects were observed, but 81.2% had additive effects. In no case was there an antagonistic effect with the combination.

Table 1
Ranges of MIC and MIC_{50} (mg/l) of ceftaroline, daptomycin, vancomycin and linezolid in 70 clinically significant isolates of *Staphylococcus* spp.

	Ceftaroline		Daptomycin		Vancomycin		Linezolid	
	Range	MIC_{50}	Range	MIC_{50}	Range	MIC_{50}	Range	MIC_{50}
MSSA (*n* = 15)	0.125–0.38	0.25	0.19–0.75	0.38	0.75–1.5	1	0.5–0.75	0.75
MRSA (*n* = 16)	0.5–2	1	0.12–0.75	0.19	1–2	1.5	0.5–2	0.75
LSCoNS (*n* = 21)	0.016–1.5	0.19	0.125–1	0.38	0.75–2	1.5	0.125–0.75	0.38
LRCoNS (*n* = 18)	0.25–1	0.38	0.19–0.5	0.25	0.75–2	2	≥256	≥256

MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; LRCoNS: Linezolid-resistant coagulase-negative *staphylococcus*; LSCoNS: Linezolid-sensitive coagulase-negative *staphylococcus*.

Table 2
Synergistic, additive and indifferent effects on ceftaroline combinations for 70 clinically significant strains of *Staphylococcus* spp.

	FIC			
	FIC ≤ 0.5 (synergistic)	FIC > 0.5 to ≤1 (additive)	FIC > 1 to ≤4 (indifferent)	FIC > 4 (antagonistic)
MSSA (n = 15)				
DPT + CFT	1 (6.6%)	8 (53.2)	6 (40%)	0
LNZ + CFT	1 (6.6%)	5 (33.3%)	9 (60.0%)	0
VAN + CFT	1 (6.6%)	7 (46.6%)	7 (46.6%)	0
MRSA (n = 16)				
DPT + CFT	0	13 (81.2%)	3 (18.8%)	0
LNZ + CFT	0	6 (37.5%)	10 (62.5%)	0
VAN + CFT	1 (6.2%)	13 (81.2%)	2 (12.5%)	0
LSCoNS (n = 21)				
DPT + CFT	2 (9.5%)	7 (33.3%)	12 (57.1%)	0
LNZ + CFT	0	5 (23.8%)	16 (76.9%)	0
VAN + CFT	1 (4.7%)	10 (52.6%)	10 (52.6%)	0
LRCoNS (n = 18)				
DPT + CFT	0	12 (66.6%)	6 (33.3%)	0
LNZ + CFT	4[a] (22.2%)	0	14 (77.7%)	0
VAN + CFT	0	12 (66.6%)	6 (33.3%)	0

CFT: ceftaroline; DPT: daptomycin; FIC: fractional inhibitory concentration indexes; LZD: linezolid; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; LRCoNS: Linezolid-resistant coagulase-negative *staphylococcus*; LSCoNS: Linezolid-sensitive coagulase-negative *staphylococcus*; VAN: vancomycin.

[a] Four strains of Staphylococcus hominis.

Discussion

The clinical experience published to date suggests that combinations of ceftaroline with other antistaphylococcal antibiotics such as linezolid, vancomycin or daptomycin offer advantages in terms of reducing the duration of bacteraemia,[2] as well as reducing the speed of resistance.[4]

In addition, it has been observed that the activity of beta-lactam, and especially that of ceftaroline, increases due to the seesaw effect as sensitivity to glycopeptides and lipopeptides decreases.[5] In our study, the combination of ceftaroline with daptomycin provided additive or synergistic effects for *S. aureus* similar to those previously published in the literature,[6] except in the case of MRSA, where we did not observe synergistic effects between daptomycin with ceftaroline in any case.

The combinations of ceftaroline with vancomycin and ceftaroline with linezolid were synergistic or additive in 87 and 37%, respectively, compared to the MRSA strains, so the latter seems to be the least effective combination, both against MRSA and against MSSA (Table 2).

Among the LSCoNS strains the combination of ceftaroline with daptomycin was synergistic against two strains and an additive effect was observed only against 33% of the strains, lower than the response obtained against *S. aureus* and similar to the responses obtained with combinations of cephalosporin with vancomycin or linezolid.

From the previous results it can be deduced that the combination of ceftaroline with daptomycin is not synergistic in most cases. However, additive phenomena do have a more valuable aspect. The limitations of the study include the use of a limited number of strains, so the results described would require confirmation with series that included a higher number of microorganisms. In addition, the methods used for the evaluation of synergy are not standardised, so the value of these tests in the clinical setting could be controversial.

In summary, the combination of ceftaroline with daptomycin, vancomycin and linezolid offers advantages due to the existence of additive or synergistic effects and its use *in vivo* could prevent the emergence of resistant strains. In our study, the least effective combination was that of ceftaroline with linezolid. None of the combinations was antagonistic in any case. Among the strains of MRSA, additive effects were observed more frequently than among those of MSSA. As for the CNSs, in general, the phenomena of addition were less frequent than in the case of *S. aureus*.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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