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Activity of Daptomycin Against Multiresistant Clinical Isolates of *Staphylococcus aureus* and *Streptococcus agalactiae*

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The activity of daptomycin against 141 *Staphylococcus aureus* and 63 *Streptococcus agalactiae* isolates was assessed. The isolates were previously characterized and showed resistance to the antibiotics normally used against gram-positive cocci. Daptomycin was active against 100% of the isolates (minimum inhibitory concentration [MIC_{90}] = 0.5 μg/ml, for both species). This antibiotic shows good *in vitro* activity; therefore, it is an excellent therapeutic alternative against these isolates.

Daptomycin is an antibiotic derived from *Streptomyces roseosporus* whose structure confers on it a mechanism of action that is different from that of other drugs. It binds with the bacterial cytoplasmic membrane by means of a calcium-dependent mechanism but without actually penetrating the bacterial cell. Its insertion in cytoplasmatic membranes causes rapid depolarization of the bacterial cell, leading to a loss of potential, the elimination of potassium, and the inhibition of protein and nucleic acid synthesis. This results in bacterial cell death without cell lysis.[8]

It is active against both bacterial growth and stationary phases and exercises a bactericidal effect against gram-positive pathogens, including resistant microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate or vancomycin-resistant *S. aureus*, vancomycin-resistant enterococci, gram-positive bacteria with reduced susceptibility to linezolid and quinupristin-dalfopristin, and penicillin- and macrolide-resistant streptococci.[6,7] It is also active against anaerobic microorganisms such as *Clostridium* spp. and *Propionibacterium* spp., among others.[16] However, it is not effective against gram-negative bacteria due to its inability to penetrate the outer membrane.

It was approved for clinical use in the USA by the U.S. Food and Drug Administration in 2003 and in Europe by the European Medicines Agency (EMEA) in 2006 for the treatment of complicated skin and soft-tissue infections caused by multiresistant gram-positive microorganisms.[1] In 2006, the treatment of bacteremia and right-side infectious endocarditis caused by *S. aureus* (including MRSA) was included by both U.S. Food and Drug Administration and EMEA.

Because it has recently been included as anti–gram-positive antibiotic, studies are now necessary to evaluate its efficacy, both *in vitro* and *in vivo*, against the microorganisms susceptible to this molecule. The aim of this paper was to evaluate the activity of daptomycin against clinical *S. aureus* and *Streptococcus agalactiae* isolates that are resistant to various antibiotics normally used against gram-positive cocci.

This study was conducted using 141 *S. aureus* and 63 *S. agalactiae* clinical isolates whose susceptibility to various antibiotics was first characterized by our team.[14] The principal characteristic was that these isolates were resistant to one or more of the antibiotics normally used to treat gram-positive cocci infections. In that study, 51.1% of the 141 *S. aureus* isolates were resistant to oxacillin, 33.3% to gentamicin, 63.8% to levofloxacin, 38.3% to telithromycin, 80.9% to erythromycin, 53.9% to clindamycin, and 8.5% to cotrimoxazole. Only vancomycin, teicoplanin, linezolid, and tigecycline were active against 100% of the *S. aureus* isolates (Table 1). In the case of *S. agalactiae*, 6.3% of the 63 isolates were resistant to levofloxacin, 92.1% to erythromycin, and 88.9% to clindamycin. The glycopeptides, linezolid, tigecycline, ampicillin, and cefotaxime were active against 100% of the isolates of this species (Table 1).

The daptomycin susceptibility testing of the 204 isolates was performed using a microdilution technique in which the Mueller-Hinton II broth (Becton Dickinson, Madrid, Spain) with a defined Ca^{++} content was adjusted to contain physiological levels of calcium (50 μg/ml), following Clinical and Laboratory Standards Institute[2] recommendations. A range of dilutions between 0.001 and 2 μg/ml was tested, in both species. The performance of the medium was checked by the use of control strains of *S. aureus* (ATCC 29213) and *Enterococcus faecalis* (ATCC 29212) as recommended by the manufacturer.

The minimum inhibitory concentration (MIC) was defined as the lowest antibiotic concentration to completely inhibit

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Table 1. MIC_{50} and MIC_{90} Values (in μg/ml) of 141 *Staphylococcus aureus* and 63 *Streptococcus agalactiae* Isolates, According to a Previous Study[14]

	S. aureus		S. agalactiae	
Antibiotics	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Daptomycin	0.25	0.5	0.125	0.5
Vancomycin	0.25	1	1	1
Teicoplanin	0.125	1	≤0.004	≤0.004
Linezolid	2	4	1	2
Tigecycline	0.125	0.25	0.125	0.25
Ampicillin	—	—	0.06	0.125
Cefotaxime	—	—	0.03	0.06

MIC, minimum inhibitory concentration.

bacterial growth. A daptomycin-susceptible breakpoint of ≤1 μg/ml was used for staphylococci and streptococci, according to the recommendations of the CLSI.

After conducting the microdilution test, daptomycin was active against 100% of the isolates, both in the case of *S. aureus* (range: 0.03–1 μg/ml; $MIC_{50} = 0.25$ μg/ml and $MIC_{90} = 0.5$ μg/ml) and of *S. agalactiae* (range: 0.004–1 μg/ml; $MIC_{50} = 0.125$ μg/ml and $MIC_{90} = 0.5$ μg/ml).

In comparison with the study previously published by our team,[14] the activity of daptomycin in this study was higher than that of glycopeptide and linezolid, and comparable to that of tigecycline. However, daptomycin has some notable advantages over these antibiotics. Namely, it has a rapid bactericidal effect on bacteria, both in the rest and growth phase; the daily treatment cost is less than that of linezolid, teicoplanin, and tigecycline, but greater than that of vancomycin; and it has less side effects, particularly in view of the neurotoxicity and nephrotoxicity of vancomycin.[8]

Various studies indicate that the current MICs of daptomycin against MRSA isolates do not exceed 0.5 or 0.75 μg/ml.[5,9] However, some authors have demonstrated that there is an increase in the daptomycin MIC values in *S. aureus* isolates with reduced glycopeptide susceptibility where values ≥2 μg/ml are reached. According to current criteria, these may be considered as isolates with reduced susceptibility to daptomycin.[4,10] This may be caused by the thickening of the bacterial cell wall, which blocks vancomycin penetration as well as hindering the action of daptomycin.[4] In our study (in which there was no isolate with reduced glycopeptide susceptibility), 8 of the 141 isolates (all MRSA) presented an MIC value of 1 μg/ml, which, although greater than the values obtained in other studies, it is nonetheless within the susceptibility limit determined by the CLSI.

In the case of *S. agalactiae*, daptomycin also presents excellent activity, with MIC_{90} values of around 0.25 μg/ml in various studies,[3,15] irrespective of whether or not the isolates presented resistance to macrolides or fluoroquinolones.

The real incidence of daptomycin resistance in these species remains very low. In a multicenter European study, only 2 of the 4842 *S. aureus* isolates were found to have reduced sensitivity to daptomycin ($MIC = 2$ μg/ml) and none of the 660 *S. agalactiae* isolates ($MIC_{90} = 0.25$ μg/ml).[13] Similar results were found in American studies.[11,12]

In conclusion, daptomycin presents good *in vitro* activity against *S. aureus* and *S. agalactiae* clinical isolates resistant to other antibiotic groups, making it an excellent therapeutic alternative.

Disclosure Statement

No competing financial interests exist.

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