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Methicillin-Resistant *Staphylococcus aureus* and Negative Coagulase Staphylococcal Bacteremia: National Epidemiology of Antibiotic Resistance in 2011-2012

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INTRODUCTION AND PURPOSE

Methicillin-resistant *Staphylococcus aureus* (MRSA) and negative coagulase staphylococci (CoNS) are a leading cause of hospital-diagnosed bacteremia. They are increasingly involved in infective endocarditis. Antibiotic treatment is a real problem for clinicians and bacteriologists because of the diffusion of multiresistant strains all around the world. Four molecules with an anti-Gram positive cocci activity are particularly monitored : the glycopeptids : vancomycin and teicoplanin, whose resistance has emerged in 1997 with Glycopeptide Intermediary *S. aureus* (GISA) and hetero-GISA strains; daptomycin (lipopeptid family) whose staphylococcal isolates with MIC values above the susceptible beakpoint are very rare and linezolid (an oxazolidinone) of which resistance has been detected among staphylococcus. The following of the prevalence of the resistance to antibiotics is essential to detect new emergent resistance phenomenon and to adapt therapeutic and prophylactic therapies.
This study aimed to assess the epidemiology of antibiotic resistance of MRSA and CoNS isolates responsible for bacteremia in French hospitals.

METHODS

This study, called MICROBS (Novartis pharmaceuticals) is a national, prospective study of staphylococcal invasive infections. The microbiological laboratories of 37 hospitals in France over a five-months period between October 2011 and February 2012 with strain centralization in the coordination laboratory (Antoine Beclere hospital). Each center included the 5 first strains of MRSA and the 10 first strains of CoNS isolated from clinically revelant bacteremia according to the recommendations of the CDC (≥ 2 blood cultures for CoNS). This study excluded *S. aureus* susceptible to methicillin. All the species of CoNS were identified by mass spectrometry (Vitek MS, Biomérieux). MICs of nine antibiotics : vancomycin, teicoplanin, linezolid, daptomycin, rifampicin, tigecyclin, acid fusidic, levofloxacin and gentamicin, were determined by broth microdilution method (BMD, Biocentric) and interpreted in accordance with EUCAST recommendations (2013). A calcium supplement (50mg/l final concentration) was used for testing daptomycin. *S.aureus* ATCC29213 was used as a control strain in every set of tests; Screening for hGISA was performed using the Etest® macromethod (vancomycin and teicoplanin), Mueller Hinton agar with 5 mg/L of teicoplanin, as recommended by CASFM (2012) and brain heart infusion agar with 3 mg/L of vancomycin.

RESULTS

MRSA: During the study period, we included 197 MRSA isolates from the 37 participating hospitals. Bacteremia were related to central (15,2%) and peripheral (11,2%) catheters. And were nosocomial in 73% of cases. Hetero-GISA were suspected for 20 positive cases of MRSA with at least one of the 3 screening methods. Susceptibility to antibiotics and details of vancomycin, teicoplanin, linezolid and daptomycin MICs were as follows in the tables 1 and 2.

CoNS: We included 446 CoNS isolates from bloodstream infections. The origin mainly implicated in bacteremia was central catheters (65.9%) and peripheral catheters (13.5%). *S. epidermidis* accounts for 74.2% of CoNS. The percentage of the others species of CoNS were : *S. haemolyticus* (9,3%), *S. hominis* (6,3%), *S. capitis* (4.0%), *S. lugdunensis* (2.3%), *S. cohnii* (0.5%), *S. warneri* (0.5%), *S. xylosus* (0.2%), *S. pasteuri* (0.2%), *S. saprophyticus* (0.2%), *S. schleiferi* (0.2%), *S. sciuri* (0.2%), *S. simulans* (0.2%). The percentage of methicillin resistance was 77.8% (center data). Susceptibility to antibiotics and vancomycin, teicoplanin, linezolid and daptomycin MICs were as follows in Table 1 and 3.

Table 1. Percentage of MRSA and CoNS strains susceptible to antibiotics by BMD

Antibiotic	vancomycin	teicoplanin	linezolid	daptomycin	fusidic acid	levofloxacin	gentamicin	tigecyclin	rifampicin
MRSA	100%	99.5%	100%	100%	86.3%	15.2%	86.8%	100%	94.9%
CoNS	100%	74.0%	98.4%	99.7%	42.4%	37;0%	41.5%	99.3%	82.1%

Table 2. Activities of vancomycin, teicoplanin, linezolid and daptomycin against 197 MRSA bloodstream isolates

	Breakpoint (EUCAST 2013)	range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
vancomycin	2	[0.5-2]	1	1
teicoplanin	2	[0.25-4]	0,5	1
linezolid	4	[0.25-4]	2	4
daptomycin	1	[0.25-1]	0.5	0.5

Table 3. Activities of vancomycin, teicoplanin, linezolid and daptomycin against 446 CoNS bloodstream isolates

	Breakpoint (EUCAST 2013)	range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
vancomycin	4	[0.5 – 4]	2	2
teicoplanin	4	[0.12 – 64]	4	8
linezolid	4	[0.12 – > 32]	1	2
daptomycin	1	[0.06 – 2]	0.5	1

CONCLUSION

The results of the susceptibility study showed that several agents were active against the isolates tested. MRSA strains isolated from bloodstream infections in France are very susceptible to vancomycin, teicoplanin, linezolid and daptomycin, four anti-Gram positive antibiotics used by intravenously. Hetero-GISA strains seem to have disappeared, in relation with emergence of the gentamicin-susceptible MRSA clone. This study brings recent and quantitatively important data on CoNS resistance to antibiotics in France. Linezolid resistance of CoNS is limited (1.6%).The good in vitro activity of daptomycin in the present study, together with its potent bactericidal activity suggests that this agent represents a useful therapeutic option in the treatment of staphylococcal bacteremia. These national data must be taken into consideration when selecting empirical treatments. Even if the susceptibility of many antibiotics is preserved today, we have to stay vigilant regarding the emergence of resistance in staphylococcal strains.

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