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Update on activity of dalbavancin and comparators against clinical isolates of Gram-positive pathogens from Europe and Russia (2017–2018), and on clonal distribution of MRSA

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ABSTRACT

Background: Gram-positive pathogens remain a major cause of healthcare- and community-associated infections. In particular, the dissemination of methicillin-resistant staphylococci, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), have significantly reduced the therapeutic options, making the management of these infections even more challenging. Dalbavancin is a second-generation lipoglycopeptide approved for the treatment of moderate to severe acute bacterial skin and skin structure infections (ABSSSIs) caused by Gram-positive organisms, showing a bactericidal effect and a low propensity towards the selection of resistance over time.
Aim: To evaluate the antimicrobial activity of dalbavancin and other comparators against recent clinical isolates of Gram-positive pathogens obtained from different sources and from several European countries, including countries of Southern and Eastern Europe, and Russia, where resistance rates are typically high. This study also aimed to describe the clonal relationship of MRSA strains circulating in Southern and Eastern Europe and Russia.
Results: In total, 1478 isolates were collected. Study results demonstrated the excellent and stable activity of dalbavancin against Gram-positive microorganisms, including MRSA. Interestingly, dalbavancin has retained unaltered minimum inhibitory concentration (MIC_{50} and MIC_{90}) values over the years, and seems to have a low propensity towards the selection of resistance.
Conclusions: These data support the potential efficacy of dalbavancin against Gram-positive bacteria and uncommon Gram-positive pathogens in patients with ABSSSIs. Of note, few coagulase-negative staphylococci (CoNS) isolates were resistant to dalbavancin and susceptible to vancomycin, highlighting the importance of testing for susceptibility to dalbavancin before its administration for CoNS infections.

1. Background

Gram-positive pathogens, particularly staphylococci, enterococci and streptococci, remain a major cause of healthcare- and community-associated infections. *Staphylococcus aureus* is one of the most common causes of infection, associated with a wide range of diseases including mild skin infections, more severe skin and skin structure infections, and life-threatening diseases such as pneumonia and bacteraemia [1]. *S. aureus* and other staphylococci are among the most common causes of biofilm-related infections, such as catheter-related bloodstream infections, prosthetic joint infections and other device infections. Staphylococcal infections have a significant clinical and economic burden in both the community and the hospital setting [2–4]. In addition, enterococci are pathogens of major concern due to their capability to persist in the hospital environment and their propensity to cause serious infections (i.e. bacteraemia, endocarditis, urinary tract infections, sur-

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Table 1
Inclusion criteria for the isolates collection based on the different infection sources of interest.

Species	Source						
	SSTI	BJI	BSI	CRBSI	UTI	URTI	LRTI
Staphylococcus aureus	Yes	Yes	Yes	Yes	No	No	Yes
Coagulase-negative staphylococci	No	Yes	Yes	Yes	No	No	No
β-haemolytic streptococci	Yes	Yes	Yes	Yes	No	Yes	Yes
Other streptococci	Yes	Yes	Yes	Yes	No	No	Yes
Enterococcus spp.	Yes	Yes	Yes	Yes	Yes	No	No
Uncommon Gram-positive	Yes	Yes	Yes	Yes	Yes	No	Yes

SSTI, skin and soft tissue infections (including acute bacterial skin and skin structure infections, diabetic foot and surgical site infections); BJI, bone and joint infections; BSI, bloodstream infections; CRBSI, catheter-related BSI; UTI, urinary tract infections; LRTI, lower respiratory tract infections; URTI, upper respiratory tract infections.

gical wound infections, intra-abdominal infections and intra-pelvic infections) [5].

The worldwide emergence and dissemination of methicillin-resistant staphylococci, particularly methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE), have significantly reduced the therapeutic options, making the management of these infections even more challenging, and associated with significantly increased morbidity, mortality and healthcare costs [4,6].

Dalbavancin is a second-generation lipoglycopeptide approved in the USA (2014) and Europe (2015) for the treatment of moderate to severe acute bacterial skin and skin structure infections (ABSSSIs) caused by Gram-positive organisms in adults [2]. Since its discovery, dalbavancin has demonstrated potent antimicrobial activity against Gram-positive pathogens (including MRSA) that are responsible for ABSSSIs, showing a bactericidal effect and a low propensity towards the selection of resistance over time [7]. These features, along with a favourable pharmacokinetic profile characterized by good tissue distribution and an extremely long elimination half-life, which allows for single- or two-dose regimens, and a favourable safety profile make dalbavancin an option for the treatment of ABSSSIs in adult patients [8–10].

The available surveillance data, which cover isolates collected over a decade from different geographical locations, did not reveal relevant geographical differences in susceptibility patterns of dalbavancin, nor trends for emerging resistance. Recent global large-scale surveillance data confirmed the excellent *in vitro* activity of dalbavancin against isolates from different types of infection. However, in many surveys, only specific Gram-positive species were considered [11–15].

This study aimed to evaluate the antimicrobial activity of dalbavancin and other comparators against recent clinical isolates of Gram-positive pathogens obtained from different sources and from several European countries, including countries of Southern and Eastern Europe, and Russia, where resistance rates are typically high. This study also aimed to describe the clonal relationship of MRSA strains circulating in Southern and Eastern Europe and Russia.

2. Methods

2.1. Study design and sample collection

A total of 37 laboratories (henceforth, 'local collecting centres' [LCC]) from 12 countries participated in this study: Austria (n=1), Bulgaria (n=1), Czech Republic (n=3), France (n=1), Greece (n=2), Hungary (n=4), Italy (n=5), Poland (n=3), Portugal (n=3), Romania (n=4), Russia (n=6, one main site coordinated five satellite sites) and Spain (n=4).

Each LCC collected 24–40 non-replicate isolates of Gram-positive pathogens from hospitalized adult patients (aged ≥18 years) following their local standard operational procedures over a maximum of 4 months between May 2017 and March 2018.

S. aureus, coagulase-negative staphylococci (CoNS), β-haemolytic *Streptococcus* spp., other streptococci (including *S. pneumoniae*), *Enterococcus* spp. and other uncommon Gram-positive pathogens considered of clinical significance were collected from different infection sources, such as skin and soft tissue infections; bone and joint infections; bloodstream infections (BSIs), including catheter-related BSIs; urinary tract infections; and lower and upper respiratory tract infections. In particular, all bacterial species isolated from bone and joint infections, BSIs, catheter-related BSIs, skin and soft tissue infections (except for CoNS), and lower upper respiratory tract infections (except for CoNS and *Enterococcus* spp.) were included, while only *Enterococcus* spp. and uncommon Gram-positive bacteria were collected from urinary tract infections, and β-haemolytic streptococci were the sole species collected from upper respiratory tract infections (Table 1).

The isolates were collected according to the following distribution: *S. aureus* (n=15–20), CoNS (n=3–6), *Streptococcus* spp. (n=3–6), *Enterococcus* spp. (n=3–6), and other Gram-positive bacteria of clinical interest (n=0–2). Where only one site per country was selected, the site could collect up to a maximum of 40 additional isolates according to the original distribution. Samples were collected avoiding any reference to the patient's data. At the end of the collection period, all isolates were sent to the Microbiology and Virology Unit of the University Hospital of Careggi (Florence, Italy; henceforth 'central laboratory' (CL)] where identification was confirmed using a matrix-assisted laser desorption/ionization-time of flight mass spectrometry system (bioMérieux, Marcy l'Etoile, France). The isolates were sent using swabs with a transport medium. A duplicate of each collected isolate was stored at the LCC for retesting purposes if needed.

To ensure the quality and integrity of research, this study was conducted following the applicable Principles of Good Laboratory Practices, the recommendations of the Clinical and Laboratory Standards Institute, and the regulations for the transport of infectious substances among the participating countries [16–18].

The European Regulation on personal data protection was taken into consideration during design of the present study and preparation of the relevant study protocol.

2.2. Antimicrobial susceptibility testing

Bacterial isolates were tested by the CL for susceptibility to dalbavancin and several comparators (vancomycin, teicoplanin, erythromycin, daptomycin, penicillin G, ceftaroline, cefoxitin, ceftriaxone, gentamicin, trimethoprim-sulfamethoxazole, tigecycline, rifampin, linezolid and levofloxacin) by calculating the minimal inhibitory concentration (MIC) using custom commercial lyophilized microdilution panels manufactured by Thermo Fisher Scientific Inc.

(Milan, Italy). In the case of fastidious organisms, cation-adjusted Mueller–Hinton broth was supplemented with lysed horse blood (2.5–5% v/v) as recommended by ISO 20776-1:2019. Antibiotic susceptibility tests were interpreted according to EUCAST breakpoints (www.eucast.org v 11.0). In particular, the categorization of dalbavancin MIC values for staphylococci; β-haemolytic streptococci belonging to Lancefield's groups A, B, C and G; and viridans streptococci in the *S. anginosus* group was done using the susceptibility breakpoint of $\leq$0.125 mg/L and the resistance breakpoint of $>$0.125 mg/L. Only dalbavancin MIC values were reported for enterococci and other uncommon Gram-positive pathogens, for which breakpoints are not provided (www.eucast.org v 11.0). Quality control was performed using the following reference strains: *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212.

2.3. Molecular characterization

Reduced susceptibility to cefoxitin was used as a specific marker of *mecA*/*mecC*-mediated methicillin resistance, as recommended by EUCAST [19]. All *S. aureus* isolates with reduced susceptibility to cefoxitin were therefore investigated for the presence of *mecA* and *mecC* genes, and all vancomycin-resistant enterococci were screened for *vanA* and *vanB* genes, as described previously [20,21].

To investigate the possible clonal relationship between MRSA strains circulating in Europe and Russia, all *S. aureus* isolates harbouring *mec* genes were subjected to genotyping analysis by staphylococcal protein A (*spa*) typing, following the protocol proposed by Harmsen *et al.* [22].

3. Results

In total, 1478 isolates were collected by the 37 LCCs, and 1470 were evaluated (eight isolates were excluded because they were not viable or did not meet the inclusion criteria).

3.1. Antimicrobial activity and molecular characterization

Among 1470 isolates studied for susceptibility to dalbavancin and other comparator antimicrobials, 756 were *S. aureus* [MRSA: 224 (29.6%); MSSA: 532 (70.4%)], 218 were CoNS, 227 were *Enterococcus* spp. [*E. faecalis*: 151 (20.0%); *E. faecium*: 74 (9.8%); *E. avium*: 2 (0.8%)], 222 were *Streptococcus* spp. [*S. pneumoniae:* 19 (8.6%); viridans streptococci*:* 53 (23.9%); β-haemolytic streptococci belonging to Lancefield's groups A, B, C and G: 150 (67.5%)] and 47 belonged to other uncommon Gram-positive species of clinical interest (Table 2).

The activity of dalbavancin and comparator agents against Gram-positive species included in the collection study are reported in Table 3.

Dalbavancin demonstrated excellent activity against *S. aureus* with all isolates being susceptible and showing MIC_{50} and MIC_{90} values of 0.03 mg/L and 0.06 mg/L, respectively, regardless of methicillin susceptibility. The same uniform activity was observed for vancomycin and linezolid with MIC_{50} values of 1 mg/L and 2 mg/L, and MIC_{90} values of 1 mg/L and 4 mg/L, respectively. Regarding the other comparator agents, teicoplanin, cotrimoxazole, ceftaroline, daptomycin, gentamicin, rifampin and tigecycline revealed overall good activity with susceptibility rates $>$90%, irrespective of methicillin susceptibility, while lower susceptibility rates were observed with the other antibiotics, especially in the case of MRSA, which showed low susceptibility to levofloxacin (23.2%) and erythromycin (29.0%).

Molecular characterization of MRSA isolates showed that all harboured the *mecA* gene.

Table 2
Gram-positive species and their distribution in the collection study.

Gram-positive species	Isolates (*n*)
***Staphylococcus* spp.**	
Staphylococcus aureus	**756**
MRSA	224
MSSA	532
Coagulase-negative staphylococci	**218**
S. epidermidis	131
S. hominis	31
S. haemolyticus	30
S. capitis	9
S. warneri	6
S. lugdunensis	4
S. saprophyticus	3
S. simulans	2
S. cohnii	1
S. pasteuri	1
Total	**974**
***Enterococcus* spp.**	
***Enterococcus* spp.**	**227**
E. faecalis	151
E. faecium	74
E. avium	2
Total	**227**
***Streptococcus* spp.**	
Streptococcus pneumoniae	**19**
Viridan *Streptococcus* spp.	**53**
S. anginosus	15
S. mitis	10
S. gallolyticus	5
S. parasanguinis	4
S. constellatus	4
S. oralis	3
S. sanguinis	3
S. cristatus	2
S. gordonii	2
S. salivarius	2
S. vestibularis	2
S. mutans	1
Streptococcus groups A, B, C and G	**150**
S. pyogenes	75
S. agalactiae	57
S. dysgalactiae	16
S. β-haemolyticus	2
Total	**222**
Other	
Other Gram-positive bacteria	**47**
Corynebacterium striatum	11
Listeria monocytogenes	9
Bacillus cereus	5
Actinomyces viscosus	2
Aerococcus viridans	2
Bacillus clausii	2
Corynebacterium amycolatum	2
Corynebacterium jeikeium	2
Actinomyces neuii	1
Bacillus altitudinis	1
Clostridium tertium	1
Corynebacterium coyleae	1
Corynebacterium pseudodiphtheriticum	1
Gemella morbillorum	1
Janibacter hoylei	1
Lactobacillus plantarum	1
Lactococcus lactis	1
Nocardia farcinica	1
Rothia amarae	1
Trueperella bernardiae	1
Total	**47**

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 3
Activity of dalbavancin and comparator agents against Gram-positive species included in the study.

Organism group	Susceptible isolates (%) EUCAST[b]	MIC (μg/mL) 50%	90%	Range
***Staphylococcus aureus* (*n*=756)**				
Ceftaroline	99.3	0.25	1	≤0.12–4
Dalbavancin	100	0.03	0.06	≤0.015–0.12
Daptomycin	99.5	0.5	0.5	≤0.25–4
Erythromycin	65.7	0.25	>16	≤0.12–>16
Gentamicin	91	≤0.5	1	≤0.5–>2
Levofloxacin	75.3	≤0.25	>8	≤0.25–>8
Linezolid	100	2	4	1–4
Rifampin	96.2	≤0.03	≤0.03	≤0.03–>8
Teicoplanin	99.7	0.5	1	≤0.25–4
Tigecycline	99.6	0.25	0.5	≤0.12–1
Cotrimoxazole	99.9	0.06	0.12	≤0.015–4
Vancomycin	100	1	1	0.5–2
MRSA (*n*=224)				
Ceftaroline	97.8	1	1	0.25–4
Dalbavancin	100	0.03	0.06	≤0.015–0.12
Daptomycin	98.7	0.5	0.5	≤0.25–4
Erythromycin	29	>16	>16	0.25–>16
Gentamicin	75	≤0.5	>2	≤0.5–>2
Levofloxacin	23.2	>8	>8	≤0.25–>8
Linezolid	100	2	4	1–4
Rifampin	90.6	≤0.03	≤0.03	≤0.03–>8
Teicoplanin	99.1	0.5	2	≤0.25-4
Tigecycline	98.7	0.25	0.5	≤0.12–1
Cotrimoxazole	100	0.06	0.25	0.03–2
Vancomycin	100	1	1	0.5–2
Coagulase-negative staphylococci (*n*=218)				
Ceftaroline	–	0.5	2	≤0.12–>4
Dalbavancin	97.2	0.03	0.12	≤0.015–1
Daptomycin	98.6	0.5	1	≤0.25–4
Erythromycin	28.9	>16	>16	≤0.12–>16
Gentamicin	44.5	>2	>2	≤0.5–>2
Levofloxacin	40.8	4	>8	≤0.25–>8
Linezolid	98.2	1	2	≤0.5–>8
Rifampin	80.3	≤0.03	>8	≤0.03–>8
Teicoplanin	79.4	2	8	≤0.25–>8
Tigecycline	99.1	0.25	0.5	≤0.12–1
Cotrimoxazole	62.4	0.5	>8	≤0.015–>8
Vancomycin	100	1	2	≤0.25-4
***Enterococcus faecalis* (*n*=150[a])**				
Dalbavancin	–	0.06	0.06	≤0.015–>2
Levofloxacin	56.7	2	>8	0.5–>8
Linezolid	100	2	2	≤0.5–4
Teicoplanin	98.7	≤0.25	≤0.25	≤0.25–>8
Tigecycline	100	0.25	0.25	≤0.12–0.25
Vancomycin	98	1	2	0.5–>8
***Enterococcus faecium* (*n*=74)**				
Dalbavancin	-	0.12	>2	≤0.015–>2
Levofloxacin	4	>8	>8	2–>8
Linezolid	97.3	2	4	1–>8
Teicoplanin	74.3	0.5	>8	≤0.25–>8
Tigecycline	98.6	c	0.25	≤0.12–8
Vancomycin	70.3	1	>8	1–>8
***Enterococcus avium* (*n*=2)**				
Dalbavancin	–	0.03	0.03	0.03
Levofloxacin	100	1	2	1–2
Linezolid	100	1	2	1–2
Teicoplanin	100	≤0.25	≤0.25	≤0.25
Tigecycline	–	≤0.12	≤0.12	≤0.12
Vancomycin	100	0.5	0.5	0.5
***Streptococcus* spp. (*n*=222)**				
Dalbavancin	–	≤0.015	0.06	≤0.015–0.12
***Streptococcus pneumoniae* (*n*=19)**				
Dalbavancin	–	≤0.015	≤0.015	≤0.015–0.03
Viridans (*n*=34)				
Dalbavancin	–	≤0.015	≤0.03	≤0.015–0.12
Group ABCG, *Streptococcus anginosus, Streptococcus constellatus* (*n*=169)				
Dalbavancin	100	≤0.015	≤0.06	≤0.015–0.12
Other uncommon Gram-positive bacteria (*n*=40)				
Dalbavancin	–	0.06	0.12	≤0.015–0.12

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] One of the 151 *E. faecalis* was excluded from the susceptibility testing because it did not grow in the broth medium supplied by Thermo Fisher Scientific Inc.
[b] In case of the absence of EUCAST breakpoints, percentage susceptibility is not expressed.

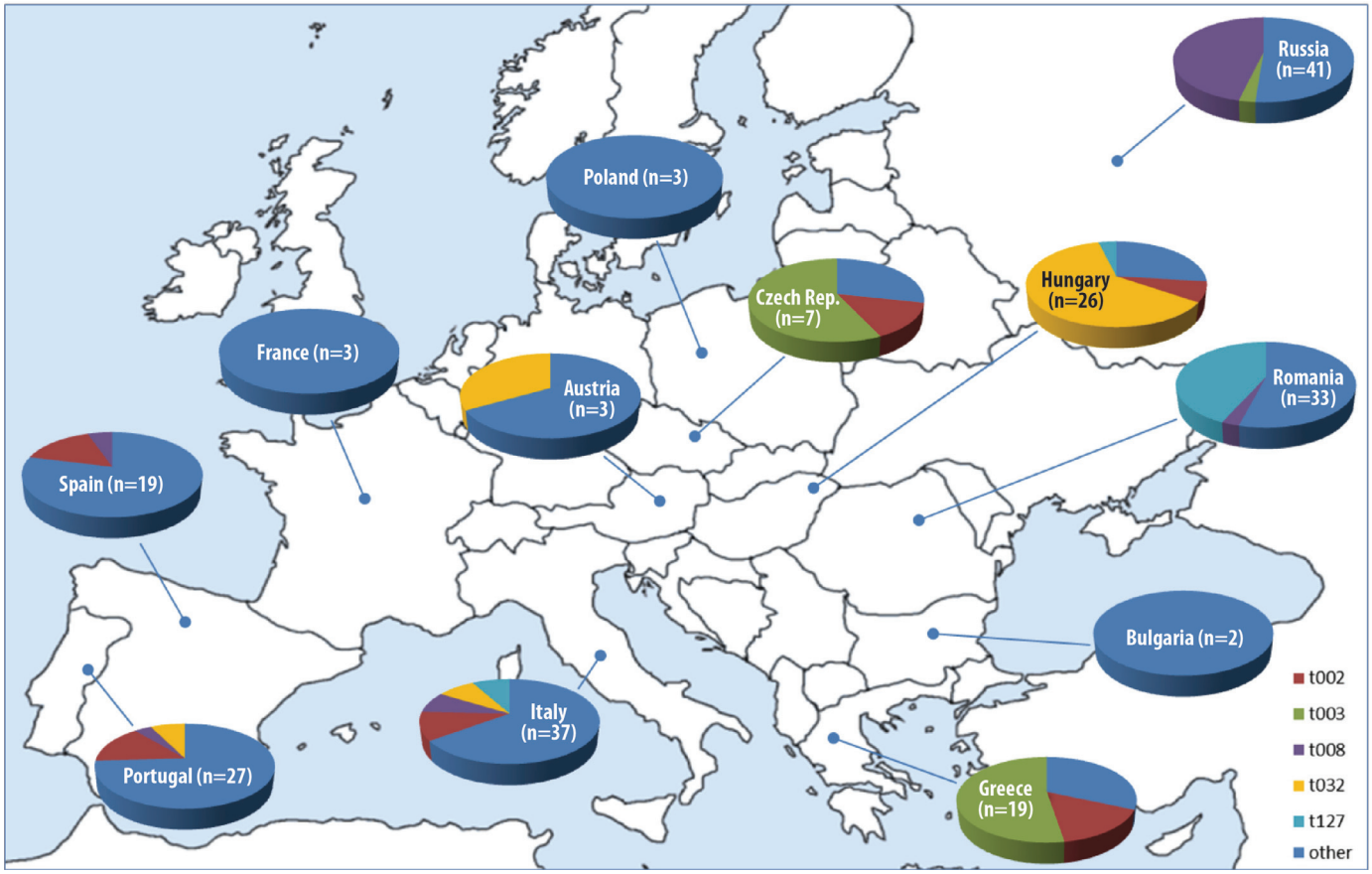

Figure 1. Geographic distribution of methicillin-resistant *Staphylococcus aureus spa* types circulating in Europe and Russia.

The vast majority (97.2%) of CoNS isolates were susceptible to dalbavancin (MIC_{50} 0.03 mg/L and MIC_{90} 0.12 mg/L), while six isolates (including three *S. epidermidis*, two *S. haemolyticus* and one *S. saprophyticus*) were resistant (MIC range 0.25–1 mg/L). In particular, the sole *S. saprophyticus* strain and one of the *S. epidermidis* strains had MIC values of 0.5 mg/L and 1 mg/L, respectively, while two *S. epidermidis* (one was linezolid-resistant) and two *S. haemolyticus* isolates had MIC values of 0.25 mg/L, confirmed in triplicate. All CoNS were susceptible to vancomycin (MIC_{50} 1 mg/L and MIC_{90} 2 mg/L), while 79.4% were susceptible to teicoplanin alone.

Among the *Enterococcus* spp., 88.9% were susceptible to vancomycin and the remaining 11.1% were VRE. The majority (n=21, 84%) of VRE isolates carried *vanA* gene (n=2 *E. faecalis* and n=19 *E. faecium*), while 12% (n=3 *E. faecium*) were positive for *vanB* gene, and a single isolate of *E. faecalis* was negative for both *vanA* and *vanB* genes. All vancomycin-susceptible isolates were inhibited by dalbavancin within a MIC range of ≤0.015–0.25 mg/L. In particular, *E. faecalis* and *E. faecium* showed MIC_{50} values of 0.03 mg/L and 0.06 mg/L and MIC_{90} values of 0.06 mg/L and 0.12 mg/L, respectively (data not shown). Among the VRE isolates, dalbavancin showed low MIC values towards those isolates harbouring *vanB* gene and the sole *vanA/B*-negative *E. faecalis* (MIC_{50} and MIC_{90} 0.06 mg/L), while isolates harbouring *vanA* gene were uniformly resistant to dalbavancin (MIC_{50} and MIC_{90} >2 mg/L, data not shown).

The activity of dalbavancin was excellent for all *Streptococcus* spp. isolates, with groups A, B, C, G and *S. anginosus* and *S. constellatus* being susceptible, and other viridans species and *S. pneumoniae* showing MIC_{50} ≤0.015 mg/L and MIC_{90} of ≤0.03 mg/L and ≤0.015 mg/L, respectively (Table 3).

Regarding the other uncommon Gram-positive bacteria, which included *Corynebacterium* spp. (n=17), *Listeria monocytogenes* (n=9), *Bacillus* spp. (n=8), *Actinomyces* spp. (n=3), *Aerococcus viridans* (n=2), *Clostridium tertium* (n=1), *Gemella morbillorum* (n=1), *Janibacter hoylei* (n=1), *Lactobacillus plantarum* (n=1), *Lactococcus lactis* (n=1), *Nocardia farcinica* (n=1), *Rothia amarae* (n=1) and *Trueperella bernardiae* (n=1), dalbavancin had MIC_{50} of 0.06 mg/L and MIC_{90} of 0.12 mg/L overall (Table 3). To the best of the authors' knowledge, this is the first study to test dalbavancin against some of these uncommon species (e.g. *J. hoylei, T. bernardiae, R. amarae*).

3.2. MRSA circulating in Europe

The clonal analysis performed on MRSA isolates revealed considerable heterogeneity among those circulating inside and between countries, with 223/224 isolates belonging to 75 different known *spa* types and one isolate from Spain that has been assigned a new *spa* type (t18469). The most common *spa* types were t008 (n=25), t032 (n=22), t127 (n=20), t002 (n=17) and t003 (n=15), geographically distributed as represented in Figure 1. All the other *spa* types were reported in no more than 10 MRSA isolates each.

4. Discussion

Dalbavancin has demonstrated high *in vitro* activity against Gram-positive clinical isolates collected as part of global, US, Canadian and European surveillance studies [11,13–15,23–27].

The available surveillance data, covering isolates collected over a couple of decades from different geographical locations, did not reveal relevant geographical differences in dalbavancin

susceptibility patterns, nor trends for emerging resistance over time, and report an overall high susceptibility rate (>99%) in *S. aureus* (including MRSA), CoNS, streptococci and vancomycin-susceptible *Enterococcus* spp. [11,13–15,23–27]. On the other hand, among VRE isolates, very low (4.2%) and moderate (81.8%) activity has been reported recently for *vanA* and *vanB* isolates, respectively [25].

This study aimed to expand knowledge of dalbavancin activity in a collection of several species of Gram-positive pathogens, including a collection of uncommon species, isolated from different body sites and different countries in Europe and Russia. Data obtained demonstrated that dalbavancin, linezolid and vancomycin retained potent *in vitro* activity against *S. aureus* isolates (including MRSA).

This microbiological study reported lower susceptibility of CoNS to dalbavancin (97.2%) compared with vancomycin (100%), and higher susceptibility compared with teicoplanin (79.4%), with two isolates characterized by a phenotype of resistance to dalbavancin and susceptibility to both vancomycin and teicoplanin, and four isolates showing a phenotype of resistance to both dalbavancin and teicoplanin and susceptibility to vancomycin. These findings suggest that caution is needed when using susceptibility to vancomycin as a proxy to infer susceptibility to other glycopeptides and lipoglycopeptides in CoNS, and highlight the importance of including dalbavancin in the panel of drugs to be tested.

The finding of teicoplanin resistance and vancomycin-susceptible CoNS is consistent with data reported previously, where this phenomenon is described especially in *S. epidermidis* and *S. haemolyticus* with resistance rates ranging from 20% to 26% for teicoplanin and up to 0.1% for vancomycin [28–34]. Even if the exact mechanism of glycopeptide resistance in CoNS has not been clarified to date, some differences between resistant and susceptible strains have been observed with respect to cell wall composition and synthesis, and binding to glycopeptides [30,31,35].

The higher susceptibility of CoNS to dalbavancin compared with teicoplanin, which showed the lowest performance among glycopeptides tested, is also in agreement with previously reported data [32–34]. Interestingly, three of four linezolid-resistant CoNS were susceptible to dalbavancin, and this phenomenon has been reported increasingly worldwide [36]. The molecular basis of resistance to lipoglycopeptides, such as dalbavancin, is still unclear and needs to be further investigated. However, Kussmann *et al.* recently identified, in a dalbavancin non-susceptible/teicoplanin-resistant, but vancomycin- and daptomycin-susceptible *S. aureus* strain, some genetic mutations affecting the biosynthesis and metabolism of the cell wall, which could probably be implicated in dalbavancin resistance [37].

Regarding *Enterococcus* spp., dalbavancin exhibited excellent activity against all the vancomycin-susceptible isolates, but showed variable activity against VRE, being active against *vanB*-harbouring strains and inactive against *vanA*-harbouring strains, as described previously [25,38–40]. The mechanism underling this phenomenon could be the same as that observed for teicoplanin which induces the *vanA* operon, but not *vanB*, thus maintaining activity against *vanB Enterococcus* spp. alone [40,41].

Dalbavancin was active against all streptococci belonging to the ABCG group and the *S. anginosus* group, and showed low MIC values for *S. pneumoniae*, viridans streptococci and other uncommon Gram-positive bacteria for which clinical breakpoints are not currently available.

The clonal relationship study performed on MRSA strains revealed considerable heterogeneity among isolates circulating in European countries and Russia, with t008, t032, t127, t002 and t003 being the most common *spa* types, in agreement with the current literature [42,43].

5. Conclusion

The study results gave a significant update on dalbavancin, confirming its known excellent and stable activity against Gram-positive microorganisms, including MRSA. Interestingly, dalbavancin has retained unaltered MIC_{50} and MIC_{90} values over the years, and seems to have a low propensity towards the selection of resistance. These data support the potential efficacy of dalbavancin against Gram-positive bacteria, including MRSA and other species and uncommon Gram-positive pathogens in patients with ABSSSIs.

Despite these favourable findings, this study reported few CoNS isolates resistant to dalbavancin and susceptible to vancomycin, which highlights the importance of testing susceptibility to dalbavancin before its administration for CoNS infections, raising concerns about the use of vancomycin as a proxy to infer susceptibility to dalbavancin, at least in the case of CoNS. This issue suggests that further surveillance studies are needed to monitor this phenomenon.

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Competing interests

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Availability of data and material

Data may be made available upon reasonable request.

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