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ARTICLE

Heterogeneous glycopeptide intermediate *Staphylococcus epidermidis* isolated from prosthetic joint infections

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Abstract Methicillin-resistant *Staphylococcus epidermidis* (MRSE) poses a major problem in prosthetic joint infections (PJIs). Vancomycin is often considered the drug of choice in the empirical treatment of staphylococcal PJIs. As recent decades have seen reports of heterogeneous glycopeptide intermediate *S. aureus* (hGISA), our aim was to examine the prevalence of heterogeneous glycopeptide intermediate *S. epidermidis* (hGISE) in PJIs. *S. epidermidis* isolates ($n = 122$) from 119 patients in three Swedish counties between 1993 and 2012 were included. All were isolated from perioperative tissue samples from revision surgery in clinically verified PJIs. Antimicrobial susceptibility testing against staphylococcal antibiotics was performed. The macromethod Etest (MME) and glycopeptide resistance detection (GRD) Etest were used to detect hGISE. Standard minimal inhibitory concentration (MIC) determination revealed no vancomycin-resistant isolates, while teicoplanin resistance was detected in 14 out of 122 isolates (11.5 %). hGISE was found in 95 out of 122 isolates (77.9 %), 64 out of 67 of isolates with teicoplanin MIC >2 mg/L (95.5 %) and 31 out of 55 of isolates with teicoplanin MIC ≤2 mg/L (56.4 %). Thus, the presence of hGISE cannot be ruled out by teicoplanin MIC ≤2 mg/L alone. Multidrug resistance was detected in 86 out of 95 hGISE isolates (90.5 %) and in 16 out of 27 isolates (59.3 %), where hGISE could not be detected. In conclusion, hGISE detected by MME or GRD was common in this material. However, hGISE is difficult to detect with standard laboratory diagnostic routines. Glycopeptide treatment may not be sufficient in many of these PJIs, even if standard MIC classifies the isolated *S. epidermidis* as susceptible.

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Introduction

The number of prosthetic joint replacements is steadily increasing in Sweden, with almost 16,000 hips and over 12,000 knees replaced annually (2011; Swedish hip arthroplasty registry; http://www.shpr.se/, Swedish knee arthroplasty registry; http://www.knee.nko.se/). Most patients experience improved quality of life including relief of pain and increased mobility. However, postoperative complications such as deep infections occur in 1–3 % of cases [1]. The majority of prosthetic joint infections (PJIs) are caused by staphylococci [2, 3], with *S. aureus* and *S.*

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epidermidis being of special interest. In Sweden, the incidence of methicillin-resistant *S. aureus* (MRSA) is generally low; less than 1 % [4]. However, in foreign-body infections such as PJIs, methicillin-resistance among coagulase-negative staphylococci (CoNS) such as *S. epidermidis* poses a major problem [5, 6]. In these infections, the empirical antibiotic therapy often consists of a glycopeptide antibiotic, usually vancomycin.

In recent decades, the emergence of glycopeptide-intermediate *S. aureus* (GISA) and heterogeneously glycopeptide-intermediate *S. aureus* (hGISA) has been recognised as a diagnostic and therapeutic challenge [7]. This reduced susceptibility of *S. aureus* is often linked to methicillin resistance [8]. The population analysis profile (PAP) is considered the gold standard method for the detection of hGISA/GISA. Less laborious methods such as the macromethod Etest (MME) and glycopeptide resistance detection (GRD) Etest have been evaluated for *S. aureus* [9–11], but not for CoNS. However, in a recent study [12] these methods were used to investigate the presence of heterogeneous glycopeptide-intermediate staphylococci (hGIS) in a material of 405 CoNS isolates obtained from patients with haematological malignancies.

We conducted a multicentre, observational, retrospective study including three counties (Värmland, Örebro and Östergötland) in central Sweden, representing 985 000 inhabitants. Our aim was to determine the presence of reduced susceptibility to the glycopeptides vancomycin and teicoplanin among *S. epidermidis* (GISE/hGISE) isolated from PJIs using standard Etest as well as the MME and GRD methods. In addition, we determined the antibiotic susceptibility patterns for other antibiotic groups that are potentially usable for the treatment of staphylococcal PJIs, and related these results to the presence of GISE/hGISE.

Materials and methods

Bacterial isolates

Coagulase-negative staphylococci (CoNS) isolated in ≥3 perioperative tissue samples (or in all if only two samples were taken) obtained from revision surgery for hip, knee or elbow arthroplasties due to PJI were included for further typing assessment. In the present study, 179 CoNS isolates obtained from 142 patients were evaluated. Isolates where further analyses showed that the PJI was caused by CoNS other than *S. epidermidis* were excluded, as were an additional two isolates owing to inappropriate handling and storage of the samples at the clinical laboratory.

If only one isolate from an individual patient had a divergent antimicrobial susceptibility pattern from the others, that isolate was considered a contaminant and thus excluded. If, however, two or more isolates with different antimicrobial susceptibility patterns appeared in multiples from the same perioperative session, this was considered a polymicrobial infection and one isolate from each phenotype was included. If the aforementioned criteria were fulfilled, the isolate was included, even if another potential pathogen was also isolated.

In total, 122 *S. epidermidis* isolates from 119 patients were included; 20 isolates from 19 patients between 2010 and 2012 at Centre 1, 50 isolates from 50 patients between 2000 and 2011 at Centre 2 and 52 isolates from 50 patients between 1993 and 2011 at Centre 3.

All isolates were stored at −70 °C at the clinical laboratory in each county. The bacterial isolates were subcultured at 35 °C overnight on GC agar (Acumedia, Lansing, MI, USA) plates containing soluble haemoglobin powder (Oxoid, Basingstoke, Hampshire, England).

rpoB sequencing

Species determination by rpoB sequencing was performed as previously described [13], and all isolates other than *S. epidermidis* were excluded. Further confirmation with MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) was also performed using a Microflex LT (Bruker Daltonik GmbH, Bremen, Germany) and MALDI Biotyper software (Bruker Daltonik).

Antibiotic susceptibility testing

Standard antibiotic susceptibility testing by disc diffusion test (DDT) was performed for cefoxitin (30 μg), fusidic acid (10 μg), erythromycin (15 μg), clindamycin (2 μg), tigecycline (15 μg), tobramycin (10 μg), gentamicin (10 μg), linezolid (10 μg), norfloxacin (10 μg), rifampin (5 μg) and vancomycin (5 μg), all antibiotic discs from Oxoid, with a 0.5 McFarland (McF) bacterial suspension in 0.85 % NaCl on Mueller–Hinton agar (MH agar, Oxoid). After 16–20 h incubation at 35 °C the zone diameters were measured and each isolate was evaluated according to EUCAST clinical zone diameter breakpoints (www.eucast.org, accessed 12 November 2012).

Standard MIC determination with Etest (bioMérieux, Marcy l'Etoile, France) was performed for vancomycin, teicoplanin and daptomycin on MH agar (Oxoid) with a bacterial suspension adjusted to 0.5 McF in 0.85 % NaCl. Results were determined after incubation for 24 h at 35 °C, and each isolate was evaluated according to EUCAST MIC breakpoints (www.eucast.org, accessed 12 November 2012).

S. epidermidis isolates resistant to ≥3 antibiotic groups tested were considered multidrug resistant (MDR).

The MME was performed as described by Walsh et al. [14], with the modification of plating only 100 μL bacterial suspension [15] with a turbidity of 2.0 McF in Mueller–Hinton broth (Becton Dickinson, Franklin Lakes, NJ, USA) on brain–heart infusion agar (BHI agar, Becton Dickinson). After approximately 10 min of drying, the Etest strips (vancomycin

and teicoplanin 0.016–256 mg/L respectively; bioMérieux, Marcy l'Etoile, France) were applied. Results were determined after 24 h and 48 h incubation at 35 °C.

For interpretation of the MME results, the previously described definitions for *S. aureus* [11, 14] were used; that is, an isolate was considered positive in the MME test if either vancomycin and teicoplanin macro-MIC were both ≥8 mg/L or teicoplanin macro-MIC was ≥12 mg/L.

The GRD Etest (0.5–32 mg/L, bioMérieux, Marcy l'Etoile, France) was performed by plating a 0.5 McF bacterial suspension in 0.85 % NaCl on MH agar (Oxoid) containing 5 % horse blood (Håtunalab, Uppsala, Sweden). Results were determined after incubation for 24 h and 48 h at 35 °C.

The results of the GRD Etest were also interpreted using previously described definitions for *S. aureus* [9, 10]. The test was considered positive when either the vancomycin or the teicoplanin MIC was ≥8 mg/L.

To separate GISE from hGISE, the same criteria were used as for *S. aureus*: a positive GRD or MME in combination with vancomycin standard MIC >4 mg/L was considered GISE while a positive GRD or MME in combination with vancomycin standard MIC≤4 mg/L was considered hGISE.

Statistics

Version 18 of the SPSS software package (IBM SPSS, Chicago, IL, USA) was used for statistical analysis. Fisher's exact test (two-tailed) was used to analyse the association between two binary variables, and the Kruskal–Wallis test was used to compare antibiotic susceptibility patterns between centres.

A p-value <0.05 was considered to be statistically significant.

Results

Standard MIC for glycopeptides determined by Etest

No *S. epidermidis* isolates were classified as vancomycin-resistant according to the EUCAST breakpoints (MIC >4 mg/L, Table 1). There were, however, four isolates with an MIC value of >2 mg/L. All these were hGISE according to both the MME and the GRD method. Teicoplanin resistance (MIC >4 mg/L) was found in 14 out of 122 (11.5 %) of isolates, with MIC values ranging from 6 to 96 mg/L. In total, 67 out of 122 isolates (54.9 %) displayed a MIC value >2 mg/L.

Detection of hGISE

The MME revealed hGISE among 84 out of 122 isolates (68.9 %), ranging from 59.6 % to 76.0 % for the three centres (Table 2).

Table 1 Antibiotic resistance in *S. epidermidis* in prosthetic joint infections determined by the disc diffusion test or Etest (MIC). Data are presented for all isolates in total and for non-hGISE and hGISE groups respectively

	Total (%=R) n=122	Non-hGISE (%=R) n=27	hGISE (%=R) n=95
Vancomycin (Etest)	0.0	0.0	0.0
Teicoplanin (Etest)	11.5	0.0	14.7
Cefoxitin	69.7	33.3	80.0
Fusidic acid	41.0	7.4	50.5
Erythromycin	62.3	40.7	68.4
Clindamycin	61.5	40.7	67.4
Tobramycin	80.3	70.4	83.2
Gentamicin	79.5	66.7	83.2
Norfloxacin	82.0	51.9	90.5
Rifampin	25.4	18.5	27.4
Linezolid	0.0	0.0	0.0
Tigecycline	0.0	0.0	0.0
Daptomycin (Etest)	0.0	0.0	0.0

The GRD Etest revealed hGISE in 78 out of 122 isolates (63.9 %), ranging from 55.0 % to 74.0 % for the three centres (Table 2). Of all hGISE isolates, 17 were positive in MME only and 11 in GRD only. We found no statistically significant difference between MME and GRD in the capacity to detect hGISE (p=0.50). When these two methods were combined, that is, when an isolate was considered positive regardless of whether the positive test was MME or GRD (or both), hGISE was detected in 95 out of 122 isolates (77.9 %).

Glycopeptide MIC vs hGISE

The relation between MIC for vancomycin or teicoplanin and the presence or absence of hGISE is shown in Tables 3 and 4.

hGISE was detected in 64 out of 67 isolates with teicoplanin MIC >2 mg/L (95.5 %), and 31 out of 55 isolates with teicoplanin MIC ≤2 mg/L (56.4 %; p<0.0001).

Notably, 14 out of 95 (14.7 %) of the hGISE isolates detected by MME and/or GRD were resistant to teicoplanin according to standard MIC determination with Etest (Table 1).

Antimicrobial susceptibility patterns for commonly used antibiotic groups in staphylococcal PJIs

Concerning the specific antibiotics (Table 1), the majority of the isolates were resistant to cefoxitin and fluoroquinolones (69.7 %. and 82.0 % respectively); the level of resistance to rifampin was lower (25.4 %).

As shown in Table 5, MDR was common; it was found in 103 out of 122 isolates (84.4 %), with figures for individual centres ranging from 73.1 % to 100 %.

Table 2 Prevalence of heterogeneous glycopeptide-intermediate *S. epidermidis* (hGISE) isolated from prosthetic joint infections detected by GRD Etest and/or macromethod Etest

	Total (%) $n=122$	Centre 1 (%) $n=20$	Centre 2 (%) $n=50$	Centre 3 (%) $n=52$	Centre 3 before 31 December 2007 (%) $n=20$	Centre 3 after 31 December 2007 (%) $n=32$
hGISE (MME)	84 (68.9)	15 (75.0)	38 (76.0)	31 (59.6)	11 (55.0)	20 (62.5)
hGISE (GRD)	78 (63.9)	11 (55.0)	37 (74.0)	30 (57.7)	12 (60.0)	18 (56.3)
hGISE (MME and/or GRD)	95 (77.9)	15 (75.0)	44 (88.0)	36 (69.2)	13 (65.0)	23 (71.9)

We found significant differences among the three centres regarding antimicrobial susceptibility patterns for erythromycin, clindamycin, tobramycin, gentamicin, and norfloxacin (Table 6).

Correlation between hGISE and multidrug resistance

As shown in Table 1, higher proportions of resistance were found among isolates of the hGISE group compared with the non-hGISE group. This was obvious for all antibiotic groups, not only among the glycopeptides. MDR was found in 87 out of 95 of the hGISE-group (91.6 %), compared with 16 out of 27 (59.3 %) among the non-hGISE isolates (Table 5; $p=0.0002$).

Discussion

In the early postoperative phase after performing revision surgery for PJI, administration of intravenous antibiotic therapy is recommended for 7–14 days [16]. Several factors influence the choice of antibiotic, including microbiological considerations ranging from an early educated guess, based on local epidemiology, to a definitive culture result including antimicrobial susceptibility patterns. In infections caused by methicillin-resistant staphylococci, glycopeptides have up to now been the drug of choice. Indications of poor outcome following treatment with glycopeptides in clinical infections with staphylococci [7, 17–19] raise concerns about present treatment strategies for methicillin-resistant staphylococci. The present study aimed to investigate the presence of hGISE among *S. epidermidis* isolated from PJIs, and supporting these concerns, we found a high proportion of hGISE.

As previously described in *S. aureus,* [8] hGIS is predominantly present at a low frequency ($\leq 10^{-5}$ to 10^{-6}): this contributes to sampling errors, and leads to false negative results. From the clinician's point of view, it is important to avoid false-negative results, since this might mislead the clinician into choosing inappropriate therapy. Therefore, in this study, we have chosen to combine the MME and GRD Etest methods to define the presence of hGISE.

When using the EUCAST breakpoints for MIC, nearly 85 % of the isolates displaying hGISE in the present study were classified as teicoplanin-sensitive and 100 % as vancomycin-sensitive; we rarely found MIC values for vancomycin exceeding 2 mg/L. hGISE was also present among isolates displaying teicoplanin MIC values as low as 0.094 mg/L. Conventional MIC determination thus failed to detect subpopulations with reduced susceptibility to glycopeptides.

The MIC value for teicoplanin seems to be a more reliable marker than vancomycin MIC for the presence of

Table 3 Vancomycin MIC distribution among hGISE and non-hGISE isolates respectively

	hGISE positive (%) ($n=95$)	hGISE negative (%) ($n=27$)	p
Vancomycin MIC≤1.5 mg/L ($n=64$)	45 (70.3)	19 (29.7)	0.048
Vancomycin MIC>1.5 mg/L ($n=58$)	50 (86.2)	8 (13.8)	0.048
Vancomycin MIC≤2 mg/L ($n=118$)	91 (77.1)	27 (22.9)	0.57
Vancomycin MIC>2 mg/L ($n=4$)	4 (100.0)	0 (0.0)	0.57

Table 4 Teicoplanin MIC distribution among hGISE and non-hGISE isolates respectively

	hGISE positive (%) ($n=95$)	hGISE negative (%) ($n=27$)	p
Teicoplanin MIC≤1.5 mg/L ($n=39$)	20 (51.3)	19 (48.7)	<0.0001
Teicoplanin MIC>1.5 mg/L ($n=83$)	75 (90.4)	8 (9.6)	<0.0001
Teicoplanin MIC≤2 mg/L ($n=55$)	31 (56.4)	24 (43.6)	<0.0001
Teicoplanin MIC>2 mg/L ($n=67$)	64 (95.5)	3 (4.5)	<0.0001

Table 5 Prevalence of multidrug resistance (MDR; ≥3 antibiotic classes =R determined by disc diffusion test or Etest). Data are presented for all isolates in total, divided by centres (including two time periods in Centre 3) and for hGISE and non-hGISE respectively

	MDR isolates (%)	*p*
Total (*n* = 122)	103 (84.4)	
Centre 1 (*n* = 20)	20 (100.0)	
Centre 2 (*n* = 50)	45 (90.0)	
Centre 3 (*n* = 52)	38 (73.1)	
non-hGISE (*n* = 27)	16 (59.3)	0.0002
hGISE (*n* = 95)	87 (91.6)	0.0002
Centre 3 before 31 December 2007 (*n* = 20)	13 (65.0)	0.35
Centre 3 after 31 December 2007 (*n* = 32)	25 (78.1)	0.35

heteroresistance, since 95.5 % of isolates with teicoplanin MIC >2 mg/L were hGISE-positive. We generally found lower MIC values for vancomycin than for teicoplanin; thus, the results were harder to interpret. Using teicoplanin MIC >2 mg/L as a breakpoint indicates a high risk of reduced susceptibility against both teicoplanin and vancomycin, while MIC values below 2 mg/L cannot be used to exclude the presence of hGISE. If the breakpoint is set at >1.5 mg/L, 90.4 % of isolates are hGISE-positive. Nevertheless, to verify the presence of hGISE in PJI, methods other than standard Etest are required.

The use of rifampin plays an important role in the oral follow-up treatment of orthopaedic staphylococcal biofilm infections. In our material, 25.4 % of the isolates were already rifampin-resistant. In rifampin-sensitive isolates, combination therapy with an additional antibiotic is crucial to prevent the emergence of further rifampin resistance, as one or two single-nucleotide polymorphisms in the *rpoB* gene are associated with resistance [6]. Previous inadequate rifampin use, including monotherapy, has been shown to be a risk factor associated with rifampin resistance [20]. The overall high levels of resistance against staphylococcal antibiotics (Table 1) highlight the importance of having access to representative perioperative tissue cultures before choosing antibiotic therapy. A study focusing on MRSA showed that fluoroquinolones, linezolid and high-dose daptomycin seemed to prevent the emergence of rifampin resistance in an animal model, while vancomycin offered no protection [21].

Table 6 Antibiotic resistance in *S. epidermidis* in prosthetic joint infections determined by disc diffusion test or Etest (MIC). Data divided by centres

	Centre 1 (%=R) *n* = 20	Centre 2 (%=R) *n* = 50	Centre 3 (%=R) *n* = 52	*p*
Vancomycin (Etest)	0.0	0.0	0.0	1.00
Teicoplanin (Etest)	15.0	8.0	13.5	0.695
Cefoxitin	80.0	70.0	65.4	0.473
Fusidic acid	55.0	34.0	42.3	0.284
Erythromycin	65.0	74.0	50.0	0.041
Clindamycin	65.0	74.0	48.1	0.027
Tobramycin	95.0	86.0	69.2	0.019
Gentamicin	100.0	80.0	71.2	0.021
Norfloxacin	95.0	90.0	69.2	0.006
Rifampin	20.0	36.0	17.3	0.085
Linezolid	0.0	0.0	0.0	1.00
Tigecycline	0.0	0.0	0.0	1.00
Daptomycin (Etest)	0.0	0.0	0.0	1.00

The high prevalence of hGISE in the present study further underscores the importance of choosing combination therapies other than rifampin and glycopeptides. It is crucial to have a highly effective combination to avoid the rapid emergence of rifampin resistance, and the current diagnostic procedures may be unreliable in the detection of hGISE.

In this study, the presence of hGISE also seems to be associated with resistance against other classes of antibiotics. This, together with the marked differences among our three different centres, poses the question of whether clonal spreading might be involved. Clonality among healthcare-associated *S. epidermidis* has been described in the USA and Australia [22, 23], and clonality among clinical PJI isolates has been reported in Sweden [24]. A recent study [25] points out an overrepresentation of sequence types ST2, ST5 and ST23 in glycopeptide-resistant *S. epidermidis* in bone and joint infections. As 20 different profiles were demonstrated (using multilocus variable-number tandem repeat analysis) among those sequence types, genetic diversity was suspected rather than the spread of a small number of clones. Further studies in this field are warranted.

This study has some limitations. It is not easy to evaluate the clinical importance of bacteria that can act as pathogens, but that are also commensal and thus potential contaminants. However, we tried to minimize this problem by selecting only *S. epidermidis* isolated perioperatively during revision surgery for PJI.

Another limitation might be the different time periods of sampling (1993–2012), especially as one centre only started to collect samples in 2010. However, further analysis of the 52 isolates from Centre 3, collected between 1993 and 2011, showed no significant differences regarding levels of multidrug resistance (Table 5) or presence of hGISE (Table 2) during the later period compared with the first. These results are also in accordance with a recent study from Centre 2 [12].

A final limitation is that only standard MIC has been validated on *S. epidermidis*; MME and GRD have only been evaluated on *S. aureus*.

In conclusion, the methods that are currently in routine clinical use are inadequate for detecting heteroresistance to

glycopeptides in *S. epidermidis*. As hGISE is obviously common among PJI isolates, there may be a reason to question both empirical antimicrobial strategies and standard diagnostic routines, to provide the clinician with better guidance in choosing an efficient therapy for PJIs caused by *S. epidermidis*. Determination of MIC values for teicoplanin may be better than using vancomycin MIC values, but neither is as sensitive as MME or GRD for revealing the presence of hGISE. Finally, the correlation between hGISE and multiresistance raises concerns about future treatment options such as optimal antibiotic combination strategies.

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Conflict of interest The authors declare that they have no conflict of interest.

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