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ARTICLE

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Characterisation of Coagulase-Negative Staphylococci Isolated from Blood Infections: Incidence, Susceptibility to Glycopeptides, and Molecular Epidemiology

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Abstract The purpose of this study was to determine incidence of coagulase-negative staphylococci (CNS) bacteraemia and to characterise the epidemiology of isolates with reduced susceptibility to glycopeptides. CNS isolates from bloodstream infections were collected and characterised by determination of the species, analysis of antibiotic susceptibility, and restriction fragment length polymorphism using pulsed-field gel electrophoresis. The medical records of patients with positive cultures and the trends in glycopeptide use were reviewed to determine the effect of previous antibiotic treatment on the susceptibility profile of these organisms. The incidence of bacteraemia caused by CNS was 0.26 per 100 patients or 0.36 per 1,000 days of hospitalisation. According to genomic fingerprinting typing, 41 (67.2%) cases of bacteraemia were caused by a unique strain of CNS and 20 were caused by several strains. Nineteen of the 61 cases of bacteraemia studied were caused by an isolate with decreased susceptibility to teicoplanin. Genomic DNA analysis of the 90 CNS isolates recovered from the 61 cases of bacteraemia generated 50 unique profiles (1 isolate per major PFGE pattern) and 13 multiple profiles (several isolates per major PFGE pattern). Neither decreased susceptibility of an isolate to teicoplanin nor hospital acquisition was associated with a multiple profile. There was a significant correlation between the incidence of bacteraemia caused by CNS with decreased susceptibility to teicoplanin and glycopeptide use at the unit level but not in individual patients. Cross-transmission did not play an important role in the dissemination of CNS with decreased susceptibility to teicoplanin, thus strains probably become resistant as a result of antibiotic pressure. Prudent use of glycopeptides is necessary to minimise the spread of resistance to these agents.

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Introduction

Coagulase-negative staphylococci (CNS) are among the most frequently isolated microorganisms in clinical microbiology laboratories. CNS have gradually become true pathogens rather than just culture contaminants [1, 2]. Their role as major pathogens has been well established, particularly in bloodstream infections in immunocompromised patients following surgery and/or as a result of foreign body colonisation [1, 2]. In addition, a large proportion of nosocomial CNS isolates are resistant to a number of antibiotics, including penicillinase-resistant penicillins [3]. Given the high frequency of these isolates, glycopeptides are recommended for the empirical treatment of CNS infections [1, 3, 4]. Some CNS are resistant to glycopeptides; while this usually only results in the decreased efficiency of teicoplanin against *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* [5, 6, 7, 8], other species of CNS are resistant to these agents [9]. The level of glycopeptide resistance among CNS has been assessed in a number of countries: in the UK in 1991, in the Slovak Republic in 1996, and in the USA in 1999 [10, 11, 12, 13]. The conclusion of these studies was that the resistance of CNS to these agents should be actively monitored.

We recently detected the emergence of CNS with decreased susceptibility to teicoplanin (CNS-DST) in our hospital. Our aim was to determine the incidence of bacteraemia caused by CNS, to characterise the isolates with reduced susceptibility to glycopeptides, and to describe the epidemiology of these isolates.

Materials and Methods

Setting

Besançon Hospital is a university-affiliated public hospital with 1,228 acute-care beds. The hospital comprises three intensive care units (ICUs), 33 medical units, and 21 surgical units. Kidney, liver, and bone marrow transplantations are performed regularly.

Study Design

Blood cultures were monitored prospectively from 21 May 2001 through 21 September 2001. All patients who had blood cultures positive for CNS were identified and included in the study. Blood cultures were taken according to the sampling policy of each unit.

The medical records of selected patients were reviewed, and the following information was recorded: demographic characteristics (age, sex, underlying conditions, hospitalisation ward, length of hospitalisation), clinical signs, the presence of a possible source of CNS blood infection (intravascular catheter or peripheral venipuncture), antibiotic therapy administered, and other identifiable infections. We also recorded data concerning the wards: the number of patients admitted to each ward and the number of days of hospitalisation.

Definitions

Bacteraemia caused by CNS was defined according to the recommendations of the Centers for Disease Control and Prevention [14]. Cases of bacteraemia were assessed according to the presence of fever (>38°C) or hypothermia (<36°C), chills, hypotension, and any of the following: isolation of CNS from two (or more) blood cultures collected on separate occasions, isolation of CNS from a single blood culture collected with an intravascular device, and the initiation of appropriate antimicrobial therapy (vancomycin or teicoplanin) by the physician. An episode of bacteraemia was defined as when all blood cultures taken within a 96 h period were positive. A positive blood culture occurring more than 96 h after the initial positive culture was considered to be a separate episode of bacteraemia, unless the same organism was repeatedly isolated from a given patient and the patient had received appropriate antimicrobial therapy. Bacteraemia was considered to be community-acquired if the first positive blood culture was obtained within 48 h of hospitalisation in patients who had not been hospitalised during the previous 48 h; otherwise, the bacteraemia was considered to be nosocomial.

Microbiological Processing

Blood cultures were analysed with the BACTEC 9240 System (Becton Dickinson, France). Positive blood cultures were isolated on Columbia broth agar supplemented with 5% horse blood, and the plate was incubated at 37°C for 24 h. CNS were identified based on colony morphology, Gram staining and the absence of coagulase activity. Antibiotic susceptibility was determined by the disk diffusion method on cation-adjusted Mueller-Hinton agar (Bio-Rad, France). Isolates were classified as being susceptible, intermediate, or resistant according to the recommendations of the French Antibiogram Committee [15].

Resistance to methicillin was detected by incubating the plates with disks containing 5 µg oxacillin at 30°C and 37°C for 48 h. Decreased susceptibility to teicoplanin was screened by spotting 10 µl of a suspension containing 10^6 cfu/ml on Mueller-Hinton agar (Bio-Rad) plates containing 4 and 16 mg/l of teicoplanin. The MICs of teicoplanin and vancomycin were determined for each isolate that grew on the medium containing teicoplanin. This determination was performed by the E test method (BMD, France) using Mueller-Hinton agar (Bio-Rad) in accordance with the manufacturer's instructions. Decreased susceptibility to teicoplanin and vancomycin was defined by an MIC of >4 mg/l. When a positive blood culture exhibited different antibiotypes, we performed further investigations on each colony type. We used the API Staph assay (bioMérieux, France) to identify the isolates to the species level.

Genotyping

We analysed the genotypes of all the CNS isolated from blood infections. We typed all of the CNS isolates from single cases of bacteraemia (including CNS with various phenotypes from different blood cultures from a single patient and CNS with various phenotypes from single blood cultures). The macrorestriction pattern of total DNA was determined by pulsed-field gel electrophoresis (PFGE) (CHEF DRIII, Bio-Rad) using *SmaI* as previously described by Prevost et al. [16]. We used the Gel Compar software (Applied Maths, Belgium) to establish a DNA similarity matrix based on the Dice coefficient (2×2 strains comparisons). A dendrogram was constructed using the unweighted pair group method of arithmetic averages clustering method with the Dice coefficient [17]. We ensured that the gels were comparable by including *Staphylococcus aureus* NCTC 8325 as a reference. Isolates with indistinguishable PFGE patterns were assigned to the same pulsotype and subtype. Isolates that differed by ≤3 bands were considered to belong to different subtypes, and isolates differing by >3 bands were considered to belong to different pulsotypes [18, 19]. Pulsotypes are designated by letters, and subtypes are designated by a number in suffix. Major pulsotypes observed in a single patient were considered to be unique patterns, and major pulsotypes observed in several patients were considered to be multiple patterns.

Glycopeptide Use

Monthly quantities and courses of glycopeptides delivered to each unit during the study period were recorded from the pharmacy information system. The defined daily dose (DDD) of vancomycin for adult patients was 2 g when administered via the parenteral route and 1 g when administered via the oral route. The DDD of vancomycin was 0.5 g for children for parenteral administration. The DDD of teicoplanin was 400 mg for adult patients and 5 mg/kg for children [20].

Statistical Analysis

Percentage data were compared using the chi-square test. Potential risk factors for the development of decreased susceptibility to glycopeptides were analysed by the use of univariate methods in order to identify differences between patients who did and did not develop bacteraemia caused by CNS-DST. A *P* value of below 0.05 was considered to be significant. These analyses were performed using the Epi-Info (Centers for Disease Control, Atlanta, USA) and BMDP (BMDP Statistical Sofware, Los Angeles, USA) software packages.

The correlation between glycopeptide use in each hospital unit and decreased susceptibility to teicoplanin was assessed using the nonparametric Spearman Rank Correlation test (StatXact). A *P* value of less than or equal to 0.05 was considered to be statistically significant. Correlations were considered to be strong when r>0.7, moderate when r was between 0.4 and 0.7, and weak when r<0.4. We calculated two indicators of antibiotic use: the number of prescriptions for 100 patients and the number of treatment days per 1,000 patient-days (the days of antibiotic therapy were calculated by subtracting the therapy start date from the end date). We tested two indicators for decreased susceptibility to teicoplanin: the number of cases of bacteraemia caused by CNS-DST per 100 admitted patients and per 1,000 patient-days.

Results

Incidence of Blood Infections Caused by Coagulase-Negative Staphylococci

During the study period, 31,482 patients were admitted to our institution for a total of 145,622 days: 18,636 patients were hospitalised for 132,776 days and 12,846 were admitted as outpatients (day care). Sixty-one cases of CNS blood infection occurred in 58 of these patients. Forty-eight of these infections occurred in hospitalised

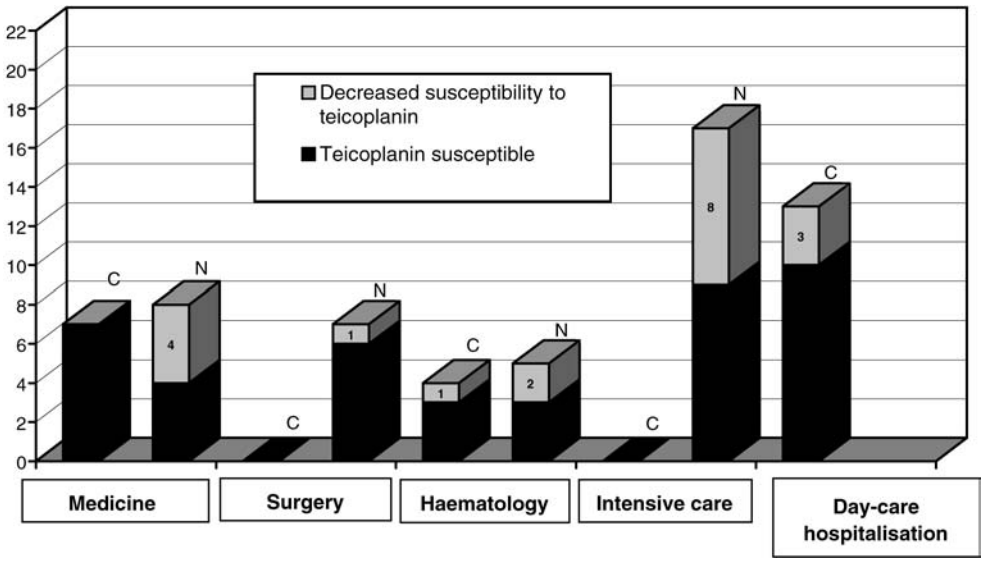

Fig. 1 Number of cases of bacteraemia caused by coagulase-negative staphylococci according to hospital ward, showing the breakdown between nosocomial and community-acquired cases. N, nosocomial; C, community-acquired

Table 1 Incidence of bacteraemia caused by coagulase-negative staphylococci according to the type of acquisition and hospital ward

Type of acquisition/ hospital ward	Incidence per 100 patients	Incidence per 1,000 patient-days
Community-acquired		
Total	0.06	0.082
Medicine	0.09	0.1
Surgery	0	0
Intensive care	0	0
Haematology	0.58	0.6
Hospital-acquired		
Total	0.2	0.27
Medicine	0.1	0.11
Surgery	0.071	0.11
Intensive care	3	3.15
Haematology	0.73	0.76
Outpatients	0.11	

patients (37 hospital-acquired cases and 11 community-acquired cases) and 13 in outpatients. We determined the incidence of CNS blood infection according to the type of acquisition and the hospital ward (Table 1). CNS were responsible for 28.6% of all cases of bacteraemia in our hospital during this period. They were the second most common cause of bacteraemia after *Escherichia coli* (29.1%) and before *Staphylococcus aureus* (19.7%).

Phenotyping

The phenotypic results (species and antibiotype) showed that 90 different CNS isolates were recovered from the 61 cases of bacteraemia. The following strains of CNS were isolated: *Staphylococcus epidermidis* (*n*=66, 73.3%), *Staphylococcus haemolyticus* (*n*=10, 11.1%), *Staphylococcus hominis* (*n*=10, 11.1%), *Staphylococcus capitis* (*n*=2, 2.2%), *Staphylococcus warneri* (*n*=1, 1.1%), and *Staphylococcus lugdunensis* (*n*=1, 1.1%). Twenty of the isolates showed decreased susceptibility to teicoplanin (corresponding to 19 cases of bacteraemia). None of the isolates showed decreased susceptibility to vancomycin. We also determined the frequency of decreased susceptibility to teicoplanin according to the type of acquisition and the type of hospital ward (Fig. 1).

The mean MICs of isolates with decreased susceptibility to teicoplanin were 17.7 mg/l (ranging from 8 to 96 mg/l) for teicoplanin and 2.35 mg/l (2 or 3 mg/l) for vancomycin. The resistance patterns were highly heterogeneous and there was no dominant antibiotype. The strains exhibiting decreased susceptibility to teicoplanin were significantly more likely to be resistant to ofloxacin (RR=5.73 [1.42–23.18]) but not to methicillin (RR=1.96 [0.89–4.33]).

Genotyping

Genotyping of the 90 CNS revealed 63 major PFGE patterns, including 50 unique patterns from unique patients and 13 multiple patterns (7 patterns were isolated from 2 patients, 3 patterns were isolated from 3 patients, 1 pattern was isolated from 4 patients, and 2 patterns were isolated from 5 patients). Given the dates of hospitalisation, the wards involved, and patient transfer, it is unlikely that cross-transmission can account for these multiple patterns (data not shown). Forty-one cases of bacteraemia had a unique PFGE pattern, 14 had two PFGE patterns, 3 had three PFGE patterns, and 3 had four PFGE patterns. Isolates with multiple patterns were not more likely to have decreased susceptibility to teicoplanin or to be nosocomially acquired than isolates with unique patterns (Table 2).

Table 2 Relationship between DNA pattern, antibiotic susceptibility phenotype, and type of acquisition of the 87 isolates of coagulase-negative staphylococci

DNA pattern	Antibiotic susceptibility phenotype[a]			Type of acquisition (%)[a]		
	Percent without DST (*n*=69)	Percent with DST (*n*=18)	*P* value	Nosocomial (*n*=75)	Community-acquired (*n*=12)	*P* value
Unique PFGE pattern	56.5 (*n*=39)	61.1 (*n*=11)	0.72	60 (*n*=45)	41.6 (*n*=5)	0.23
Multiple PFGE pattern	43.4 (*n*=30)	38.8 (*n*=7)		40 (*n*=30)	58.3 (*n*=7)	

[a] Three isolates with the same pulsotype yielded different antibiotypes
DST, decreased susceptibility to teicoplanin

Table 3 Characteristics of patients, treatment administered, and bacteraemia

Characteristic	Total no. (%) of cases caused by CNS	No. of cases caused by CNS-DST (*n*=19)	No. of cases caused by teicoplanin-susceptible CNS (*n*=42)	Relative risk	*P* value
Patients					
Male	41 (67.21)	12	29	0.84 [0.39–1.79]	0.64
Age >60 years	28 (45.9)	9	19	0.87 [0.50–2.24]	0.87
Hospitalisation >6 days	48 (78.68)	16	32	1.44 [0.50–4.21]	0.36
Hospitalisation >6 days before onset of bacteraemia	31 (50.81)	11	20	1.33 [0.62–2.85]	0.45
Hospitalisation in ICU	17 (27.86)	6	11	1.19 [0.54–2.63]	0.66
Nosocomial infection	50 (82)	17	33	1.87 [0.50–6.94]	0.25
Antibiotic treatment					
Antibiotics given before onset of bacteraemia	29 (47.54)	9	20	0.99 [0.47–2.10]	0.98
Glycopeptides given before onset of bacteraemia	15 (24.59)	5	10	1.10 [0.47–2.53]	0.53
Glycopeptide treatment >5 days	10 (16.39)	3	7	0.75 [0.18–3.14]	0.56
Bacteraemia					
No. of culture sets >1	50 (81.96)	15	35	1.17 [0.41–3.34]	0.53
No. of CNS isolates >1	20 (32.78)	7	13	1.20 [0.56–2.57]	0.64
Previous CNS bacteraemia	10 (16.39)	2	8	0.55 [0.13–2.36]	0.40

CNS, coagulase-negative staphylococci; CNS-DST, coagulase-negative staphylococci with decreased susceptibility to teicoplanin

Trends in Glycopeptide Use

The amount of glycopeptides consumed in our hospital has remained stable between 1994 and 2000: approximately 700 g of teicoplanin per year and approximately 12,000 g of vancomycin per year. During the 4-month study period, 311 g (5.3 DDD per 1,000 days of hospitalisation) of teicoplanin and 4,600 g (15.8 DDD per 1,000 days of hospitalisation) of vancomycin were prescribed and given.

Statistical Analysis

We looked at whether various characteristics of the patients, bacteraemia, and treatment were associated with an increased risk of CNS blood infection (Table 3). None of the characteristics studied were found to be significantly associated with bacteraemia caused by CNS-DST, particularly a treatment with glycopeptides during the hospital stay.

A correlation was observed between the use of vancomycin and decreased susceptibility to teicoplanin using different combinations of indicators at the unit level. However, no correlations were observed between the use of teicoplanin and decreased susceptibility to teicoplanin for any of the combinations of indicators (Table 4).

Discussion

This prospective study, conducted in our teaching hospital, shows that CNS is responsible for a high proportion of all cases of bacteraemia (28.6%). This result is consistent with those obtained by other groups [21, 22]. However, the frequency of decreased susceptibility to teicoplanin was higher in our hospital (22.2%) than in other studies, which showed that the frequency was between 0.5 and 19.8% [23, 24, 25]. It is difficult to compare these data because susceptibility tests, particularly those used to determine susceptibility to teicoplanin, are affected by a number of technical factors, including the basal medium, supplements, the size of the inoculum, the incubation time, and the cutoff value for resistance. Non-automated quantitative methods (broth and agar dilution

Table 4 Correlation coefficients using different combinations of indicators relative to antibiotic use and to decreased susceptibility to teicoplanin

Antibiotic	Combination of indicators	Correlation coefficient	*P* value
Teicoplanin	no. of cases of bacteraemia caused by CNS-DST per 100 patients admitted/no. of courses of teicoplanin per 100 patients admitted	–0.16	0.38
Teicoplanin	no. of cases of bacteraemia caused by CNS-DST per 1,000 patient-days/no. of days of treatment with teicoplanin per 1,000 patient-days	–0.25	0.17
Vancomycin	no. of cases of bacteraemia caused by CNS-DST per 100 patients admitted/no. of courses of vancomycin per 100 patients admitted	0.37	0.0076
Vancomycin	no. of cases of bacteraemia caused by CNS-DST per 1,000 patient-days/no. of days of treatment with vancomycin per 1,000 patient-days	0.47	0.0006

CNS-DST, coagulase-negative staphylococci with decreased susceptibility to teicoplanin

tests) appear to be the best means of detecting staphylococci with reduced susceptibility to glycopeptides in the laboratory [26]. The E test method appears to be an accurate method for determining the MICs of antibiotics for CNS, although this test tends to give slightly lower values than the standard agar dilution method [27]. In our study, these two methods gave exactly the same results.

Only two of the species isolated exhibited decreased susceptibility to teicoplanin: *Staphylococcus haemolyticus* (*n*=7) and S*taphylococcus epidermidis* (*n*=13). This specificity of expression in two species has been reported in numerous papers [10, 11, 12, 24, 28]. We also observed that all of the CNS-DST isolates were susceptible to vancomycin. This has been widely reported [23], but the reasons for this difference remain unknown. Many reports have shown that decreased susceptibility to teicoplanin occurs mainly in methicillin-resistant CNS isolates [29, 30, 31]. We made the same observation, but the association between these two types of resistance was not statistically significant; our isolates were significantly more likely to be resistant to fluoroquinolones.

In our study, cross-transmission did not play an important role in the spread of decreased susceptibility to teicoplanin among CNS. Indeed, the percentage of CNS-DST belonging to a multiple PFGE pattern was not higher than the percentage of susceptible CNS belonging to a multiple PFGE pattern (Table 2). The dates of hospitalisation, the wards involved, and the transfer of patients infected by a strain of CNS-DST with a PFGE pattern that included two or more isolates were not consistent with the occurrence of cross-transmission. This finding is consistent with published data showing that the frequency of decreased susceptibility to teicoplanin among CNS is more likely to be due to the selection of resistance by susceptible isolates than to the hospital dissemination of epidemic resistant isolates [21, 23, 26, 32, 33, 34]. Murphy et al. [8] found that the percentage of teicoplanin-intermediate or -resistant CNS was significantly higher in departments in which relatively large amounts of teicoplanin were prescribed and in which teicoplanin was the first choice of glycopeptide. Two other studies have provided evidence that the switch from vancomycin to teicoplanin as the first choice was responsible for the emergence of CNS with decreased susceptibility to teicoplanin [13, 25].

In our hospital, where the proportion of CNS-DST is high, a significant correlation was observed between the incidence of CNS-DST and the use of vancomycin, whereas no such correlation was found with teicoplanin use. The fact that teicoplanin is used to a lesser extent than vancomycin may mask the role of teicoplanin in the selection of CNS-DST strains. This correlation was established taking the ward as a statistical unit, but not when the patient was used as a statistical unit. There are two possible reasons for this, the first being that we only counted the glycopeptides prescribed during the current period of hospitalisation. However, many patients (in particular those hospitalised in intensive care or haemodialysis or haematology units) are likely to receive glycopeptides during a previous period of hospitalisation. This means that the carriage of resistant staphylococci may be prolonged (>3 years) [35]. A second possible reason is that antibiotic selection pressure (i.e. the pressure exerted by antibiotics in the hospital environment) may have greater "ecological" effects on cutaneous species, which frequently come into contact with the environment.

CNS cause a major proportion of cases of nosocomial bacteraemia, especially those related to the insertion and maintenance of intravascular catheters. The most effective method for preventing catheter-related bloodstream infection is the use of a catheter coated with antimicrobial agents [36]. The implementation of this type of catheter in our hospital, in conjunction with appropriate infection control measures, may contribute to a decrease in bacteraemia cases caused by CNS. Moreover, the implementation of programmes to reduce the unnecessary use of glycopeptides should have a significant impact on the rate of CNS with reduced susceptibility because (i) strains probably become resistant as a result of antibiotic pressure and (ii) vancomycin is misused in about 33% of cases in our hospital [37].

In conclusion, it is essential to continue monitoring the spread of CNS-DST in our hospital, even though the clinical significance of such strains has not been well established. Further investigations are needed to clarify their real clinical impact. However, glycopeptides should be used carefully to minimise the spread of resistance.

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