MAJOR ARTICLE

Glycopeptide Resistance among Coagulase-Negative Staphylococci that Cause Bacteremia: Epidemiological and Clinical Findings from a Case-Control Study

Evelina Tacconelli,[1] Mario Tumbarello,[1] Katleen de Gaetano Donati,[1] Manola Bettio,[3] Teresa Spanu,[2] Fiammetta Leone,[2] Leonardo A. Sechi,[4] Stefania Zanetti,[4] Giovanni Fadda,[2] and Roberto Cauda[1]

Departments of [1]Infectious Diseases and [2]Microbiology, Catholic University, Rome, [3]Studies' University, Padova, and [4]Department of Biomedical Sciences, Sassari University, Sassari, Italy

A 1-year prospective case-control study (ratio of control patients to case patients, 3:1) was performed to assess the incidence, risk factors, and genotypic patterns of bacteremia caused by glycopeptide-resistant coagulase-negative staphylococci (CoNS) and their correlation with hospital glycopeptide use. Among 535 subjects with CoNS bacteremia, 20 subjects had a glycopeptide-resistant strain (19 strains were resistant to teicoplanin and 1 was resistant to both teicoplanin and vancomycin). The percentage of resistant isolates recovered in 1 year was 8% in intensive care units and 3% and 2% in medical and surgical wards, respectively. Genotypic analysis of resistant strains showed different patterns with a high degree of polymorphism. Use of glycopeptides in individual wards was not statistically associated with the percentage of resistance. Previous exposure to β-lactams and glycopeptides, multiple hospitalization in the previous year, and concomitant pneumonia were significantly associated with the onset of glycopeptide-resistant CoNS bacteremia. Mortality rates were 25% among case patients and 18% among control patients, and they were significantly higher among patients who presented with concomitant pneumonia and a high Acute Physiology and Chronic Health Evaluation III score.

At present, glycopeptides are among the last available antibiotics, with quinupristin-dalfopristin and linezolid [1, 2], for treating multidrug-resistant, gram-positive nosocomial infections, which are mostly caused by methicillin-resistant staphylococci and enterococci [3–6]. The first 2 cases of infection with glycopeptide-resistant *Staphylococcus haemolyticus* were reported in 1986 [7, 8], and, recently, a worldwide increase in the number of observations of glycopeptide-resistant coagulase-negative staphylococci (CoNS) has been described elsewhere [9–13]. Furthermore, Hiramatsu et al. [14] were the first researchers to report a case of infection caused by *S. aureus* with reduced susceptibility to vancomycin in May 1996. Of interest, vancomycin had been in clinical use for almost 30 years before high-level resistant strains emerged. Such strains can naturally occur or they can develop through low-level mutational resistance. In fact, the genes responsible for vancomycin resistance in enterococci can transfer to more-virulent organisms, such as staphylococci [4]. To underline this growing alarm, the Centers for Disease Control and Prevention (CDC) in Atlanta provided recommendations in 1997 for prudent vancomycin use, to prevent the spread of vancomycin-resistant staphylococci [15].

Despite several reports that described microbiological characteristics of glycopeptide-resistant CoNS, to our knowledge, the clinical and epidemiological find-

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Reprints or correspondence: Dr. Evelina Tacconelli, Istituto Malattie Infettive, Università Cattolica, Largo Gemelli 8, 00168 Roma, Italy (etacconelli@rm.unicatt.it).

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ings of these infections have not been extensively described in vivo. Only a single retrospective report from Hong Kong indicated that patients with vancomycin-resistant CoNS bacteremia were preferentially admitted to intensive care units (ICUs) and had previously received vancomycin more often than did control patients [9].

The purposes of this study were to define, through a 1-year surveillance, the incidence and the risk factors of glycopeptide resistance among strains of CoNS that caused bacteremia. We also analyzed the genotypic patterns of glycopeptide-resistant CoNS and the correlation between glycopeptide use in individual wards and the development of glycopeptide resistance.

PATIENTS AND METHODS

Study setting. The Catholic University hospital (Rome) is a 1700-bed tertiary care center with ~60,000 patient admissions each year that come mostly from central and southern Italy and, to a lesser extent, from northern Italy. The hospital has medical, surgical, and neonatal specialties, as well as intensive care and postsurgical units. Kidney, liver, and bone marrow transplantation are performed. There is a 60-bed unit for the admission of HIV-infected patients and a day hospital for their outpatient care.

Study design. From 1 July 1998 through 30 June 1999, all blood cultures processed by the clinical microbiology laboratory and yielded staphylococci were identified through a daily review of the laboratory computer summary report. All subjects aged >18 years with CoNS bacteremia were included in the study. The definition of CoNS bacteremia was based on that of the CDC and required ⩾2 blood isolations of CoNS obtained in presence of fever (body temperature, ⩾38°C) that was not attributable to other causes [16]. In particular, all patients who had CoNS bacteremia caused by glycopeptide-resistant strains were designated "case patients." For each case patient, we randomized (using the table of random numbers) 3 control patients among subjects with CoNS bacteremia caused by glycopeptide-susceptible strains and the same "geography" of infection (nosocomially or community-acquired) of the corresponding case patient. Patients in whom staphylococci were isolated within 48 h after admission were assumed to have a community-acquired infection. The study was observational, because the administration of antimicrobial agents and other therapeutic management was controlled by patients' physicians and not by the investigators.

A standardized questionnaire was administered by the medical investigator, after receiving consent from the patient, during the patient's hospital stay. The following data were obtained: age; sex; presence of underlying diseases; ward; number of hospital admissions in the year prior to the study; number of polymorphonuclears/mm^3; nutritional status (expressed by body weight and albumin level); previous bacterial infections; receipt of corticosteroid therapy; presence and type of central venous catheter or of other catheters; history of surgery, endoscopy, alcoholism, cirrhosis, diabetes, neoplastic disease, and chronic renal failure; previous receipt of antimicrobial therapy or other medications (if the drug was taken for at least 7 of the 30 days before the onset of infection); duration of previous antimicrobial therapy; bacteremia therapy; results of a sensitivity test to antibiotics; vital signs; outcome and/or cause of death, as listed by the attending physicians; and total length of hospitalization. The risk factors were recorded only if they were present during the 30 days before the development of infection. Prognosis immediately prior to the development of bacteremia was assigned by use of the McCabe index [17]. The revised Acute Physiology and Chronic Health Evaluation (APACHE) was assigned by the APACHE III system [18].

To establish the relationship between previous hospital use of glycopeptides and development of glycopeptide-resistant CoNS bacteremia, we calculated the defined daily dose (DDD) for teicoplanin and for vancomycin in individual wards during the study period by analyzing the hospital pharmacy data. Amounts of parenteral glycopeptides were standardized by conversion to DDDs, for which 1 DDD was equivalent to 2 g for vancomycin and 400 mg for teicoplanin. For each ward, mean rates for the study were calculated by dividing the total number of DDDs by the total number of patient-days reported during the study period, and they were expressed as DDDs per 1000 patient-days.

Identification of organisms and susceptibility testing. Species identification was performed using the API test (bioMérieux). Isolates were frozen at 70°C until needed and were tested by means of the broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS), with cation-adjusted Mueller Hinton broth (Difco Laboratories) [19, 20]. The antimicrobial agents tested included ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, penicillin, teicoplanin, trimethoprim-sulfamethoxazole, and vancomycin. In addition, MICs for teicoplanin and vancomycin were determined for each isolate using the E-test (AB Biodisk), in accordance with the manufacturer's instructions. Susceptibility tests were performed by use of a bacterial inoculum whose turbidity was equivalent to that of a 0.5 McFarland turbidity standard. The suspension was used to inoculate Mueller Hinton agar plates by swabbing them with a cotton swab. The plates were incubated for 18 h in air at 35°C. The MICs were interpreted as the point of intersection of the inhibition ellipse with the E-test strip edge. The quality-control strains of *S. aureus* American Type Culture Collection (ATCC) 29213 and *S. aureus* ATCC 43300 were included with each run. The interpretation of results was performed according to recommendations of the NCCLS [20]. In particular, teico-

Table 1. Multiple-antibiotic resistance in 535 strains obtained from subjects with bacteremia caused by coagulase-negative staphylococci (CoNS).

Drug or drug class	No. (%) of CoNS strains resistant to (n = 535)				
	Methicillin	Aminoglycosides	Quinolones	Macrolides	TMP-SMZ
Glycopeptides (n = 20)	19 (95)	19 (95)	17 (85)	17 (85)	18 (90)
Methicillin (n = 372)	372 (100)	307 (83)	228 (61)	298 (80)	241 (65)
Aminoglycosides (n = 339)	298 (88)	339 (100)	227 (67)	291 (86)	231 (68)
Quinolones (n = 249)	228 (92)	230 (92)	249 (100)	212 (85)	181 (73)

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

planin resistance was defined by an MIC of >18 μg/mL, whereas vancomycin resistance was defined by an MIC of ⩾8 μg/mL.

Ribotyping. All glycopeptide-resistant strains were subjected to genotypic analysis. The chromosomal DNA of the isolates was extracted as reported elsewhere [21]. For digestion, DNA was incubated with λ *Hin*dIII restriction enzyme (Promega), according to the recommendations of the manufacturer. Agarose gel electrophoresis was performed using a horizontal gel apparatus (model HE 99; HSI). Samples were loaded into wells in a 0.7% agarose gel (Boerhinger Mannheim) and electrophoresed at 30 V for 14–18 h. Electrophoresis was performed at room temperature in TAE buffer (0.04 M Tris-acetate [Boerhinger Mannheim] and 0.001 M EDTA, pH 8.0). Gels were stained with a solution of ethidium bromide. The 1.8 kb *Apa*I clone [22–24] and λ DNA were used as probes. The DNA of the isolates was transferred to supported nitrocellulose (Nitroplus 200; MSI) by use of a vacuum transfer device (ABN), and Southern blots were performed by a modification of the method of Southern [25]. Hybridization was performed at 68°C, and the blots were washed at 68°C with 0.1 × SSC (0.15 M NaCl and 0.015 M sodium citrate, pH 7.0) and 0.1% sodium dodecyl sulfate. Probes were labeled with enhanced chemiluminescent gene-labeling kit (Amersham International). Autoradiography was performed at room temperature by use of Kodak X-RP films.

Computers analysis of fingerprints. The patterns produced by the ribotyping method were evaluated using the Image master software (Pharmacia Biotechnology). All bands produced were normalized by comparing molecular weight markers (λ *Hin*dIII DNA) between different gels, and the molecular weight of the hybridizing bands was calculated using the Image master software.

Statistical analysis. Quantitative variables were tested for distribution (by use of normal probability plot and Shapiro Wilks test) and compared by use of the Kruskal-Wallis test. Differences in group proportions were assessed with the χ^2 and Fisher's exact tests. Potential risk factors for the development of glycopeptide resistance were analyzed by use of univariate methods, to identify differences in patients who developed and who did not develop glycopeptide-resistant staphylococcal bacteremia. The 95% test-based CIs (95% CIs) were used to determinate the statistical significance of the OR. Stepwise logistic regression models were used for each factor to adjust for the effects of confounding variables. Two-tailed tests of significance at the $P \leqslant 0.05$ level were used to determine statistical significance. Statistical analysis was performed by use of the software program Intercooled Stata, version 6.0, for Windows 98 (Stata Corporation).

RESULTS

During the study period, 46,223 adult patients were hospitalized, and blood samples were obtained from 10,547 for 26,226 blood cultures. Staphylococci were isolated from 1622 blood cultures. A diagnosis of CoNS bacteremia was made for 535 subjects, with 1235 blood cultures that yielded CoNS (5%; 535/10,547). The isolated strains of CoNS were *Staphylococcus epidermidis* (70%), *Staphylococcus hominis* (12%), *S. haemolyticus* (9%), *Staphylococcus capitis* (6%), *Staphylococcus warneri* (2%), and other CoNS species (1%).

Antimicrobial resistance. Table 1 shows details of multiple-antibiotic resistance for 535 strains of CoNS. In particular, 88 (16%) of 535 strains of CoNS were susceptible to all the following antibiotics: methicillin, aminoglycosides, quinolones, macrolides, and trimethoprim-sulfamethoxazole. Among the 163 methicillin-susceptible strains, 44 (27%) were penicillin susceptible.

Glycopeptide resistance. Twenty strains of CoNS were resistant to glycopeptide (19 strains were resistant to teicoplanin only and 1 strain was resistant to both teicoplanin and vancomycin), with an overall incidence of 4%. The incidence of resistance per ward was 8% for the ICU, 3% for the medical wards, and 2% for the surgical wards.

Figure 1 shows the relationship between the incidence of glycopeptide resistance per ward and the ward use of glycopeptides during the study period. If we consider the entire hospital, the median DDD (±SD) for glycopeptide use was 41.67 ± 25.66 for teicoplanin and 34.37 ± 32.71 for vancomycin. The analyzed data did not show any significant corre-

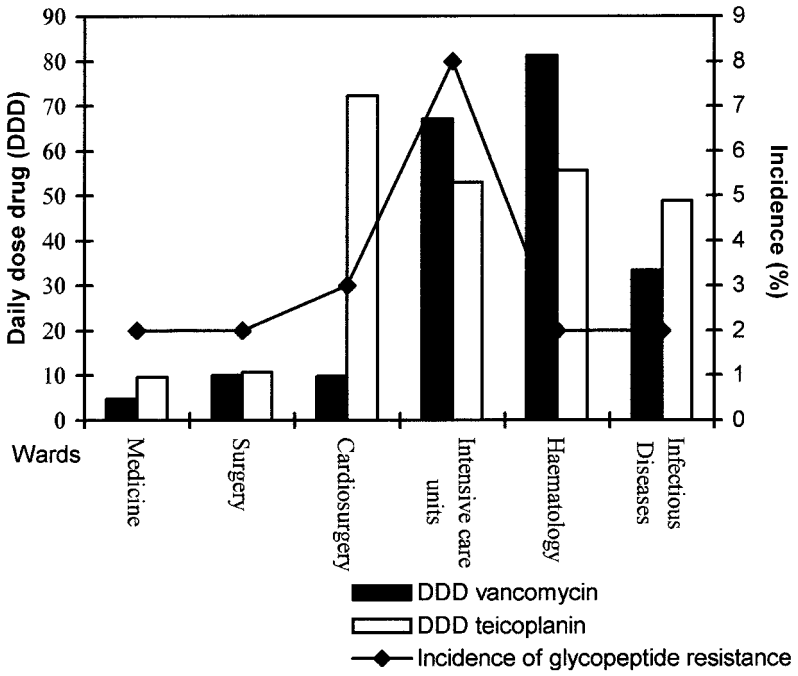

Figure 1. Relationship between the incidence of glycopeptide-resistant coagulase-negative staphylococci bacteremia in individual ward and the glycopeptide ward use.

lation between ward use of glycopeptide (expressed by DDD) and the percentage of glycopeptide-resistant strains of CoNS isolated in the single ward.

Risk factors analysis. Twenty patients with CoNS bacteremia (*S. epidermidis* in 18 cases and *S. haemolyticus* in 2 cases) met the aforementioned case definition, and they were matched with 60 randomized control subjects, for a total of 80 subjects. The majority of cases of bacteremia (69 [86%] of 80) were hospital acquired. Table 2 summarizes the data regarding the study population.

Comparison of the case patients and control patients, by univariate analysis, indicated remarkable differences in the distribution of known and potential risk factors (see table 2). Previous administration of β-lactams and glycopeptides, mechanical ventilation, use of total parenteral nutrition, multiple hospital admissions in the year prior to the study period, concomitant pneumonia, number ($\geq$3) of antibiotic treatments, admission to ICU, and presence of multiple (>3) risk factors for bacteremia were significantly different in the 2 groups of patients. Moreover, isolation of methicillin- (95% vs. 65%; OR, 10.23; 95% CI, 1.27–59.62; $P = 0.008$), aminoglycoside- (95% vs. 57%; OR, 14.52; 95% CI, 1.83–78.04; $P = 0.001$), and quinolone- (85% vs. 50%; OR, 5.66; 95% IC, 1.35–27.31; $P = 0.007$) resistant strains were significantly more common among the case patients than they were among control patients, respectively. Case patients did not differ significantly from controls with regard to the duration of previous antibiotic therapy.

The clinically important conditions and treatments most strongly associated with the development of glycopeptide resistance ($P < 0.2$, by univariate analysis) were further analyzed by use of logistic regression. Previous administration of β-lactams and glycopeptides, multiple hospital admissions, and presence of pneumonia were found to be independent predictors of glycopeptide resistance (see table 3). Stepwise entry of sex and age into the model yielded similar results.

Genotype analysis. Eighteen strains of *S. epidermidis* with an MIC of teicoplanin of >18 μg/ml were clustered into 15 different patterns by ribotyping that used, as a probe, an *rrn* cloned fragment from *Enterococcus hirae*. Unfortunately, 2 strains of *S. haemolyticus* (1 that was resistant to teicoplanin and 1 that was resistant to both glycopeptides) were not available for further evaluation. The patterns were clearly interpretable, with a number of bands ranging from 12 to 20 hybridizing bands. The results showed a high degree of polymorphism among these isolates, which indicates that cases of glycopeptide-resistant bacteremia were not owing to an outbreak of a single or few strains but to several different strains of *S. epidermidis* with a decreased susceptibility to teicoplanin (see table 4 and figure 2). Some of the strains generated the same pattern A (strains 29, 93, and 95) (figure 2, lanes *H, I,* and *L*). These strains were isolated from different wards. Strains 808 and 843, which were isolated from the ICU and medical ward, respectively, produced the same pattern O (table 4).

Outcome. The mean duration of total hospitalization

Table 2. Demographic data for 20 patients with bacteremia caused by glycopeptide-resistant coagulase-negative staphylococci (CoNS; case patients) and 60 randomized patients with bacteremia caused by glycopeptide-susceptible CoNS (control patients).

Characteristic	Case patients (n = 20)	Control patients (n = 60)	P[a]	OR (95% CI)
Sex, no. male/no. female	13/7	42/18	0.67	1.25 (0.44–3.59)
Age, mean years ± SD	56 ± 18	59 ± 18	0.65	—
Hospital ward				
Medicine	7 (35)	36 (60)	0.09	0.35 (0.10–1.15)
Hematology	1 (5)	5 (8)	1.00	0.57 (0.06–5.74)
Infectious diseases	1 (5)	8 (13)	0.53	0.34 (0.04–3.05)
Surgery	2 (10)	11 (18)	0.59	0.49 (0.10–2.75)
Intensive care unit	11 (55)	13 (22)	0.01	4.41 (1.33–14.93)
Mean APACHE III score ± SD	34 ± 15	33 ± 16	0.99	—
McCabe score				
Rapidly fatal	5 (25)	9 (15)	0.49	1.88 (0.46–7.54)
Ultimately fatal	8 (40)	21 (35)	0.89	1.23 (0.38–3.93)
Nonfatal	7 (35)	30 (50)	0.36	0.53 (0.16–1.71)
Nosocomial episodes	17 (85)	52 (87)	0.85	0.87 (0.17–4.70)
Duration of hospitalization, mean days ± SD	83 ± 93	54 ± 64	0.07	—
Concomitant pneumonia	17 (85)	26 (43)	0.001	7.41 (2.07–26.03)
Central catheterization	12 (60)	28 (47)	0.30	1.71 (0.62–4.68)
Total parenteral nutrition	15 (75)	22 (37)	0.003	5.18 (1.70–15.61)
Mechanical ventilation	11 (55)	10 (17)	0.001	6.11 (2.05–18.28)
Previous bacterial infections	4 (20)	7 (12)	0.57	1.89 (0.40–8.60)
Previous antibiotic therapy				
Multiple treatment	13 (65)	21 (35)	0.01	3.44 (1.21–9.72)
Glycopeptides	6 (30)	5 (8)	0.01	4.71 (1.32–16.87)
β-Lactams	17 (85)	21 (35)	0.0001	10.52 (2.91–37.31)
>3 risk factors	6 (30)	5 (8)	0.04	4.71 (1.06–21.55)
Previous hospitalizations, no.				
1	6	12	—	2.62 (0.73–9.34)
2	4	5	—	4.20 (0.86–20.42)
3	2	1	0.007[b]	10.5 (0.73–150.5)

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Significance of finding by comparison of case patients with control patients. P values are 2-tailed and were determined by use of Fisher's exact test and Student's t test, unless otherwise indicated.

[b] χ^2 for trend.

(±SD) was 83 ± 93 days for the 20 case patients and 54 ± 64 days for the 60 control patients ($P = 0.07$). All patients received antibiotic therapy that was initially established according to the most likely etiological agent and later modified, if necessary, when the in vitro susceptibility of the *Staphylococcus* species became known. The overall mortality rate was 45% for case patients and 25% for control patients. The attributable mortality rate was 25% (5 of 20 patients) for the case patients and 18% (11 of 60 patients) for the control patients (P = NS), and the OR for death in patients with glycopeptide-resistant CoNS bacteremia was 1.48 (95% CI, 0.37–5.69). None of the patients had endocarditis or septic shock. Five patients who died had teicoplanin-resistant *S. epidermidis* bacteremia and were treated with vancomycin (3 case patients) or aminoglycosides (2 case patients) for a mean duration (±SD) of 5 ± 3 days before death. The other 4 patients who died were treated with vancomycin, whereas 11 patients who survived were treated with vancomycin (8 patients), imipenem (2 patients), or aminoglycosides (1 patient). The mortality rate among patients who presented with a severe APACHE III score (mean, 51.8 vs. 27.6, for case and control patients, respectively; $P = 0.0007$) and concomitant pneumonia ($P = 0.008$) was significantly higher than that observed in patients without these variables. Treatment of teicoplanin-resistant

Table 3. Logistic regression analysis of predictors for glycopeptide-resistant coagulase-negative staphylococci bacteremia.

Variables	OR	SE	95% CI	*P*
Concomitant pneumonia	5.18	4.31	1.01–26.57	0.05
Previous glycopeptide use	19.86	20.59	2.60–151.60	0.004
Previous β-lactam use	19.64	20.18	2.62–147.21	0.004
No. of hospitalizations during the year prior to the study period	5.00	3.94	1.06–23.44	0.04

NOTE. SE, standard error.

CoNS bacteremia with vancomycin was not associated with a worse prognosis.

DISCUSSION

We determined the antimicrobial resistance of CoNS that cause bacteremia in a large Italian university hospital and, as a novel observation, we prospectively identified the risk factors that can favor the emergence of glycopeptide-resistant infections. Although studies published elsewhere have suggested some in vitro factors that could influence the development of resistance [26, 27], to our knowledge, none of the studies investigated and identified the in vivo risk factors and the clinical significance of "true" (according to CDC definitions) CoNS bacteremia caused by glycopeptide-resistant strains. Previous European studies on CoNS glycopeptide resistance and the European Glycopeptide Susceptibility Survey have indicated an incidence rate (updated to 1995) ranging from 3% to 19% [28–30].

Our prospective study (July 1998–June 1999) shows that 4% of total isolates of CoNS are resistant to glycopeptides, with a peak of incidence of 8% in the ICU. It is of note that all of the strains were resistant to teicoplanin, and only 1 strain was also resistant to vancomycin. This result suggests that the mechanisms of resistance for teicoplanin and vancomycin could be different and that teicoplanin-resistant strains could also be present in other countries where teicoplanin is not used; therefore, resistance against it is not tested. Although, in our study, some staphylococcal strains were isolated in the same ward (ICU), the high number of fingerprinting patterns ($n = 15$) obtained among the 18 teicoplanin-resistant strains of *S. epidermidis* supports the hypothesis that the spreading of a particular strain among the different wards has not occurred.

With regard to the second objective of the study—that is, to assess risk factors—the results of our logistic regression analysis clearly indicate that previous antibiotic therapy with glycopeptides and/or β-lactams, concomitant pneumonia, and multiple hospital admissions during the year prior to the study period were independent predictors for the development of glycopeptide-resistant CoNS bacteremia. It is important to emphasize the relevance of multiple hospital admissions and concomitant pneumonia, because they indirectly suggest the presence of a patient's severe underlying disease, despite a low statistical weight for both of these variables. It is well known, in fact, that such factors as severe clinical status, misuse or abuse of antimicrobial agents, and invasive procedures all may contribute to a decrease in a patient's resistance to exogenous bacteria and to an increase in the risk of antibiotic-resistant infections [31]. Moreover, this observation correlates well with the lack of association between use of glycopeptides in an individual ward and the glycopeptide resistance rate in the same ward, with high DDDs for glycopeptides associated with a high resistance rate in the ICU but not in other wards with identical high DDDs. These data also confirm a recent observation [32] that the susceptibility trend varies in the individual ward, despite similar drug use characteristics, probably because other cofactors, such as the ward "case mix," may play an important role in the development of antimicrobial resistance. Another possible explanation is that, in our opinion, DDD, being the average of the total drug use in an individual ward, might not properly express the patient's individual exposure to a single drug, which is, on the contrary, witnessed by the results of logistic regression analysis. In fact, our multivariate analysis

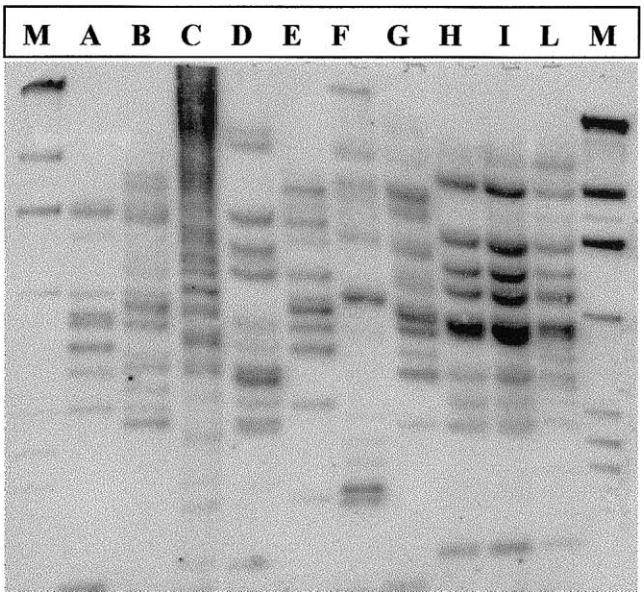

Figure 2. Southern blot of chromosomal DNA showing a representative sample of the different patterns obtained by ribotyping of the analyzed *Staphylococcus epidermidis* isolates. *Lane A,* strain 559 (intensive care unit [ICU]); *lane B,* strain 528 (ICU); *lane C,* strain 520 (ICU); *lane D,* strain 428 (cardiosurgery); *lane E,* strain 427 (medicine); *lane F,* strain 346 (infectious diseases); *lane G,* strain 345 (ICU); *lane H,* strain 95 (medicine); *lane I,* strain 93 (cardiosurgery); *lane L,* strain 29 (ICU); and *lane M,* λ *Hin*dIII marker.

Table 4. Fingerprinting patterns obtained by ribotyping of 18 teicoplanin-resistant strains of *Staphylococcus epidermidis*.

Strain	Ward	Pattern
29	Intensive care unit	A
93	Cardiosurgery	A
95	Medicine	A
345	Intensive care unit	B
346	Infectious diseases	C
427	Medicine	D
428	Cardiosurgery	E
520	Intensive care unit	F
528	Intensive care unit	G
559	Intensive care unit	H
562	Intensive care unit	I
564	Intensive care unit	L
756	Intensive care unit	M
788	Intensive care unit	N
808	Intensive care unit	O
843	Medicine	O
872	Hematology	P
929	Medicine	Q

demonstrates a significant correlation between individual use of a single drug and development of glycopeptide resistance.

The association between prior use of β-lactams and subsequent infection caused by a strain that is resistant to glycopeptides has been reported elsewhere by others [9] who demonstrated that prior use of β-lactams may induce the expression of vancomycin resistance in staphylococci. The mechanisms by which β-lactams enhance the expression of this resistance are presently unknown. Of interest, it has been demonstrated that vancomycin and teicoplanin resistance in *S. aureus* correlates with an increased production of penicillin-binding protein 2 [33].

With regard to outcome, an aspect not previously studied, the difference between mortality rates among case patients and control patients, did not reach statistical significance in our study, probably because of the relatively low number of case patients. In addition, resistance to glycopeptides seems to be a marker of severity of the underlying illness. In fact, patients who died of glycopeptide-resistant bacteremia had concomitant pneumonia and high APACHE III scores. However, it is interesting to speculate that, if we eliminate the impact of glycopeptide resistance, the excess mortality rate attributable to antibiotic resistance might be eventually reduced to a magnitude of 38%.

In summary, we conclude that individual exposure to glycopeptides and β-lactams, in association with a history of multiple hospitalization and concomitant pneumonia, plays a pivotal role as risk factor for the development of glycopeptide resistance. On the basis of our statistical analysis, we are also confident to suggest that it is desirable, although not essential, to implement the antibiotic restriction policy suggested by the CDC [16] for the aforementioned high-risk patients, not only to prevent the spread of CoNS glycopeptide-resistant bacteremia, but also to reduce the mortality rate, duration of hospitalization, and cost of hospital care.

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