Emergence of teicoplanin-resistant coagulase-negative staphylococci.

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Over a period of 5 years we have recovered 32 clinical isolates of coagulase-negative staphylococci (CoNS) exhibiting either decreased levels of susceptibility to teicoplanin (MICs, 16 to 128 μg/ml); these isolates make up 0.55% of the total CoNS isolated by us. Twenty-nine of the strains were methicillin resistant, and all were susceptible to vancomycin. Fourteen of the strains were Staphylococcus epidermidis, fourteen were Staphylococcus haemolyticus, and four were Staphylococcus hominis. In one case, a strain of S. haemolyticus was isolated with a vancomycin-resistant, teicoplanin-resistant Enterococcus faecalis strain. All strains were nosocomially acquired and were isolated from 17 different wards. Teicoplanin resistance occurred as a sporadic phenomenon, and none of the isolates were epidemiologically related. The isolates were from 30 patients, 13 of whom presented with true infections (43%). Five (38%) of the 13 patients with true infections had been previously treated with vancomycin. None of the infected patients were previously treated with teicoplanin. The in vivo development of resistance to teicoplanin among CoNS strains limits the therapy of infections caused by these microorganisms. There is a need for surveillance of nosocomial isolates of CoNS to determine resistance to glycopeptides.

Coagulase-negative staphylococci (CoNS) are among the most frequently isolated microorganisms in clinical microbiology laboratories. Because of their prevalence on human skin and mucous membranes and their relatively low virulence, they have in the past been dismissed as culture contaminants; however, in recent years, CoNS have been assuming greater importance as true pathogens (3, 23). Infections caused by these organisms derive mainly from indwelling foreign bodies, and their roles as significant pathogens following cardiothoracic, ophthalmologic, and neurologic surgery, as etiologic agents of osteomyelitis, and in immunocompromised patients have been well established (3, 23). In addition, a large proportion of nosocomial isolates of CoNS are resistant to multiple antibiotics, including penicillinase-resistant penicillins (4). Given the extremely high frequency of these isolates, vancomycin has been recommended empirically for the treatment of infections produced by these microorganisms (3, 4, 15, 23). Until recently, CoNS have displayed uniform susceptibilities to glycopeptides; however, the emergence of strains with decreased levels of susceptibility to vancomycin and teicoplanin has been noticed in several studies (1, 5–9, 11, 12, 14, 19, 24, 26–28). Nevertheless, these studies have selected either specific groups of patients or specific clinical isolates of CoNS for investigation, and none of them has evaluated globally the incidence and clinical significance of these isolates (1, 4–7, 9, 11, 14, 19, 27).

In recent years we have detected in our hospital an emergence of CoNS with decreased levels of susceptibility to teicoplanin. The purposes of this study were to characterize all teicoplanin-resistant CoNS isolated in our hospital over a 5-year period, to perform an epidemiological study of the isolates, and to evaluate their clinical significance. This work was presented in part at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., October 1993.

MATERIALS AND METHODS

The study was performed at the Hospital General Universitario Gregorio Marañón, a 2,300-bed general, teaching, and referral hospital serving a population of approximately 800,000 in Madrid. From January 1991 to December 1995, all isolates of CoNS with decreased levels of susceptibility to teicoplanin (MICs, ≤16 μg/ml) were subjected to uniform microbiological and clinical studies.

Microbiological study. All isolates were identified by conventional methods (16). Species identification was performed with Pos Combo type 41 MicroScan panels (Baxter Diagnostics, Inc., West Sacramento, Calif.) and confirmed by the API 20 Staph system (Biomerieux, Marcy l’Etoile, France). Antimicrobial susceptibility testing was performed with Pos Combo type 41 MicroScan panels, which include susceptibility testing for 22 antimicrobial agents. MICs of teicoplanin and vancomycin for the isolates with decreased levels of susceptibility to teicoplanin were confirmed by the standard agar dilution technique in Mueller-Hinton agar (National Committee for Clinical Laboratory Standards (20). Streptococcus faecalis ATCC 29212 and Staphylococcus aureus ATCC 29213 were used as control strains. By following the National Committee for Clinical Laboratory Standards guidelines (21), we considered a CoNS to have a decreased level of susceptibility to teicoplanin when the MIC of teicoplanin for the isolate was 16 μg/ml, and the isolate was considered resistant when the MIC was ≥32 μg/ml. In order to clarify the terminology used in Results and in Discussion, we grouped all isolates with decreased levels of susceptibility and all resistant isolates as nonsusceptible.

Clinical study. We reviewed the records of all patients from whom CoNS with decreased susceptibility levels or with resistance to teicoplanin were isolated. The following data were obtained routinely: age, sex, hospital ward, underlying disease(s), duration of hospitalization, prior antimicrobial treatment, and clinical outcome. The sources of the isolates were recorded. Infections were classified as either community acquired or nosocomial. The latter category included all infections that were detected only after at least 72 h of hospitalization. True infection was defined as the isolation of CoNS nonsusceptible to teicoplanin from clinically significant material (e.g., blood [two or more positive blood cultures] or normally sterile fluids) in the presence of clinical manifestations not attributable to other causes or isolation of nonsusceptible CoNS from other samples in the presence of clinical evidence of infection not attributable to other microorganisms. Catheter-related infection was defined as a significant colony count in the culture of the catheter tip by the method described by Maki et al. (18) in the presence of fever not attributable to other causes. Colonization was defined as the isolation of nonsusceptible CoNS from clinically insignificant samples in the absence of clinical manifestations or in the presence of such manifestations that were attributable to other causes.
RESULTS

During the study period, in our hospital, a total of 4,458 *Staphylococcus epidermidis* strains and 1,355 other CoNS were isolated (total CoNS isolates, 5,813). Among them, 32 either presented decreased levels of susceptibility (23 strains) or were fully resistant to teicoplanin (9 strains), corresponding to a percentage of 0.55% nonsusceptible strains. The nonsusceptible strains were made up of 14 *S. epidermidis*, 14 *Staphylococcus haemolyticus*, and 4 *Staphylococcus hominis* strains. During the same period, a total of 7,739 *S. aureus* strains were isolated, and all were susceptible to both teicoplanin and vancomycin (Table 1).

Teicoplanin was introduced in our hospital in 1993; however, its use has been minimal in many areas of the hospital and nonexistent in other areas. Before the introduction of teicoplanin, we isolated 15 strains of CoNS nonsusceptible to teicoplanin, and since 1993 we have isolated 17 strains. Among these 17 strains, 11 were isolated from areas in which teicoplanin had never been used. Of the 32 nonsusceptible CoNS isolates, 4 occurred in 1991, 11 occurred in 1992, 9 occurred in 1993, 5 occurred in 1994, and 3 occurred in 1995. Among the 32 isolates, teicoplanin MICs were 128 μg/ml (1 *S. haemolyticas* isolate and 1 *S. hominis* isolate), 64 μg/ml (3 *S. haemolyticas* isolates and 1 *S. hominis* isolate), 32 μg/ml (2 *S. haemolyticas* isolates and 1 *S. hominis* isolate), and 16 μg/ml (14 *S. epidermidis* isolates, 8 *S. haemolyticas* isolates, and 1 *S. hominis* isolate). Twenty-nine of the isolates (90.6%) were also methicillin resistant, 26 (81.2%) were gentamicin resistant, 27 (84.3%) were ciprofloxacin resistant, 7 (21.8%) were resistant to trimethoprim-sulfamethoxazole, and all were susceptible to vancomycin; 81% of the CoNS were resistant to more than 10 antimicrobial agents (data not shown).

The origins of the isolates were 11 intravenous devices (central catheters), seven wounds, four blood samples, three urine samples, two sterile fluid samples, and five others. The strains were recovered from 30 patients, 13 of them (43%) presenting with true. The remaining 17 patients were colonized. The isolates were recovered from 17 different wards, occurred as sporadic phenomena, and were not epidemiologically related. Although some strains were isolated from the same ward (i.e., the neonatology unit), differences in the biotypes, susceptibility patterns (22 antimicrobial agents, data not shown) and dates of isolation (at least 2 months apart) indicate that the isolates were not epidemiologically related. Eight of the 30 patients had been previously treated with vancomycin, and none was previously treated with teicoplanin.

Table 2 summarizes the clinical characteristics of the 13 patients infected with CoNS nonsusceptible to teicoplanin. Five were males and eight were females. Their ages ranged from 7 days to 79 years, and five (38%) of the infected patients had been previously treated with vancomycin. None of the patients had been previously treated with teicoplanin. All isolates were nosocomially acquired. Most of the infections were catheter related, and all patients but one recovered after catheter withdrawal; the remaining patient required in addition antimicrobial therapy (vancomycin). We found one case of bacteremia and two cases of urinary tract infection in immunocompromised patients and two cases of wound infection; from one of these wound infections a vancomycin- and teicoplanin-resistant strain of *Enterococcus faecalis* was also isolated, and in the other case the infection was monomicrobial. In all cases the clinical outcome of the patients was good after adequate treatment and all recovered from the infections.

**DISCUSSION**

CoNS have become increasingly recognized as important agents of nosocomial infection (3, 23). One of the characteristics of CoNS is their resistance to multiple antimicrobial agents, including methicillin and other drugs commonly used for the treatment of staphylococcal infections (4, 29). In these cases, treatment of severe infections is usually undertaken with either teicoplanin or vancomycin; however, in recent years, resistance to glycopeptides among CoNS has been reported from several hospitals (1, 5–9, 11, 12, 14, 19, 24, 26–28). Our

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### Table 1. Distribution of teicoplanin resistance among staphylococci isolated in our hospital from January 1991 to December 1995

<table>
<thead>
<tr>
<th>Strain</th>
<th>Total no. of strains</th>
<th>No. of teicoplanin-resistant strains from:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Infected patients</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>7,739</td>
<td>0</td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>4,458</td>
<td>3</td>
</tr>
<tr>
<td>Other CoNS</td>
<td>1,355</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13,552</strong></td>
<td><strong>14</strong></td>
</tr>
</tbody>
</table>

### Table 2. Clinical characteristics of the patients infected with CoNS with decreased levels of susceptibility to teicoplanin

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Medical problem or procedure</th>
<th>Origin</th>
<th>Previous antimicrobial agent(s)</th>
<th>Microorganism</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>F</td>
<td>Renal failure</td>
<td>IVD</td>
<td>Vancomycin plus cefotaxime</td>
<td><em>S. hominis</em></td>
</tr>
<tr>
<td>53</td>
<td>M</td>
<td>Cardiac transplant</td>
<td>IVD</td>
<td>Ceftriaxone</td>
<td><em>S. epidermidis</em></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Low birth weight</td>
<td>IVD</td>
<td>None</td>
<td><em>S. haemolyticus</em></td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>Renal transplant</td>
<td>Wound</td>
<td>Vancomycin plus cefazolin</td>
<td><em>S. haemolyticus</em></td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>Necrotizing enterocolitis</td>
<td>Peritoneal fluid</td>
<td>Vancomycin plus cefotaxime</td>
<td><em>S. haemolyticus</em></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Intraventricular distress</td>
<td>IVD</td>
<td>Gentamicin plus ampicillin</td>
<td><em>S. haemolyticus</em></td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>Colorectal cancer</td>
<td>Blood</td>
<td>Vancomycin</td>
<td><em>S. hominis</em></td>
</tr>
<tr>
<td>79</td>
<td>F</td>
<td>Cholecystectomy</td>
<td>Wound</td>
<td>Cefazolin</td>
<td><em>S. haemolyticus</em></td>
</tr>
<tr>
<td>66</td>
<td>F</td>
<td>Cardiac transplant</td>
<td>Urine</td>
<td>None</td>
<td><em>S. hominis</em></td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>Renal lithiasis plus diabetes mellitus</td>
<td>Urine</td>
<td>Ciprofloxacin</td>
<td><em>S. epidermidis</em></td>
</tr>
<tr>
<td>72</td>
<td>F</td>
<td>Ischemic heart disease</td>
<td>IVD</td>
<td>Cefazolin</td>
<td><em>S. epidermidis</em></td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>Cardiac valve replacement (mitral and aortic)</td>
<td>IVD</td>
<td>Vancomycin plus rifampin</td>
<td><em>S. epidermidis</em></td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>Cirrhosis</td>
<td>IVD</td>
<td>Norfloxacin</td>
<td><em>S. haemolyticus</em></td>
</tr>
</tbody>
</table>

*a* F, female; *M*, male.

*a* All patients were cured.

*a* IVD, intravenous device.
study summarizes the incidence and evolution of teicoplanin resistance among CoNS in a general hospital over a period of 5 years. The percentage of nonsusceptible CoNS was 0.55%, and we did not observe any increase over the study period. To our knowledge, resistance to teicoplanin among CoNS has been described only as a result of in vitro studies, as sporadic cases, or in studies selecting specific groups of patients (1, 2, 6, 7, 9, 11, 14, 15, 19, 26–28); however, the global incidence of the resistance and its clinical significance have not been reported. Moreover, although the emergence of CoNS with decreased levels of susceptibility to teicoplanin has been reported in several studies, the existence of isolates with high levels of resistance has been anecdotal (1, 6, 22, 28). In our study, the MIC of teicoplanin for four of the isolates was 64 μg/ml and the MIC was 128 μg/ml for two of the isolates. None of the previous studies indicate MICs of teicoplanin as high as 128 μg/ml. The most frequently isolated CoNS species nonsusceptible to teicoplanin were S. epidermidis, S. haemolyticus, and then S. hominis.

Although some of the strains were isolated from the same ward, they were not epidemiologically related. Recently, Mainardi et al. described a series of cases of cross-infection due to non-glycopeptide-susceptible S. aureus in which seven of the isolates were epidemiologically related (17). We have not found any series of cases in the literature describing epidemiological and clinical characteristics of patients with teicoplanin-resistant CoNS.

All the isolates were nosocomially acquired. Since teicoplanin was introduced in our hospital in 1993 and since the use of this antimicrobial agent has been very limited, the emergence of teicoplanin resistance among CoNS could be the result of selective pressure from other glycopeptides (19); in our hospital, a very important increase in the use of vancomycin has occurred during the last 5 years because of the presence of endemically spread methicillin-resistant S. aureus. Moreover, we recovered 15 CoNS strains nonsusceptible to teicoplanin before the introduction of this antimicrobial agent. In our study, 38% of the patients infected with nonsusceptible CoNS had been previously treated with vancomycin and none had been treated with teicoplanin.

Thirteen of the 30 patients (43%) with nonsusceptible CoNS presented with true infections. Infections due to these isolates occurred in immunocompromised patients or in patients with severe underlying diseases, and 23% of the infections occurred in patients with solid organ transplantation. In our series, all the isolates but three were resistant to methicillin; moreover, 80% of the isolates were resistant to more than 10 antimicrobial agents. In the case of infections from CoNS nonsusceptible to teicoplanin, all isolates but one were methicillin resistant and 11 of 13 were also resistant to gentamicin and ciprofloxacin. This is a cause of clinical concern, since CoNS may be a reservoir for antibiotic resistance genes in the hospital environment and may spread these resistance factors among other hospital pathogens (4, 23). In fact, the conjugative transfer of resistance to gentamicin and other antimicrobial agents from CoNS to S. aureus has been demonstrated (10, 13, 25).

In conclusion, CoNS must be included in the category of nosocomially acquired pathogens of immunosuppressed patients, and special attention should be paid to transplant recipients to detect these pathogens. These microorganisms can no longer be considered pathogens with uniform and predictable susceptibilities to glycopeptides because of the in vivo development of resistance to teicoplanin. Although vancomycin is still the reasonable choice for the treatment of severe infections due to multiresistant CoNS, there is a need for surveillance of nosocomial isolates of CoNS for resistance to glycopeptides. We suggest that routine testing of susceptibility to glycopeptides be performed for all CoNS producing infections.

REFERENCES


