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Antibiotic-Resistant *Staphylococcus epidermidis* in Patients Undergoing Cardiac Surgery

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Staphylococcus epidermidis isolates containing subpopulations resistant to 100 μg of methicillin per ml were found on the chests of only 3 of 80 (4%) patients before cardiac surgery, whereas these highly resistant staphylococci were isolated from the chest wounds of 43 of 80 (54%) patients 5 days postoperatively. The percentage of patients colonized with methicillin-resistant *S. epidermidis* increased with time postoperatively. Methicillin-resistant postoperative isolates also contained organisms resistant to other antibiotics frequently used during these patients' hospitalizations. The percentages of patients with organisms resistant to various antibiotics were: nafcillin (100%), penicillin (100%), cephalothin (93%), cefamandole (80%), streptomycin (67%), and gentamicin (20%). Preoperative methicillin-susceptible isolates were generally susceptible to other antibiotics. Two patients with *S. epidermidis* prosthetic valve endocarditis caused by multiple antibiotic-resistant isolates were among the study patients. Antibiotic susceptibility patterns of each isolate from these two patients were identical to those of postoperative chest isolates from the same patient.

Staphylococcus epidermidis is a frequent cause of postoperative infections in patients undergoing cardiac surgery. In addition to being the most common cause of early prosthetic valve endocarditis, this organism has also been responsible for outbreaks of serious postoperative wound infections (4-6). Most of the *S. epidermidis* isolates recovered from these infections exhibit multiple antibiotic resistance, including resistance to methicillin. Antibiotic resistance of *S. epidermidis* is important both for its therapeutic implications and for its potential use as a marker for hospital-acquired strains. The present study investigated prospectively the acquisition of methicillin-resistant *S. epidermidis* in the chest wounds of patients undergoing cardiac surgery and compared the antibiotic susceptibility of these postoperative isolates with isolates obtained from the surface of each patient's chest before surgery.

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MATERIALS AND METHODS

Patients. A total of 80 patients undergoing cardiac surgery was studied. The first 55 patients, all undergoing prosthetic valve insertion, had their chest skin cultured 1 day before and 5 days after surgery. An additional 25 patients, consisting of 14 undergoing valve replacement and 11 having coronary bypass surgery, were cultured 1 day before and 0.5 h, 1 day, 3 days, and 5 days after surgery. No patient in the study had been receiving any antibiotics for 2 weeks before admission for surgery, and only five patients had been hospitalized in the preceding 2 weeks. As preparation for surgery, all patients bathed with an iodine-containing soap the night before operation, and chests were shaved and prepared with Betadine (Purdue Frederick Co., Norwalk, Conn.) in the operating room. Prophylactic antibiotics were given in the operating room and for 2 to 3 days postoperatively. A total of 47 patients received sodium nafcillin, aqueous penicillin G, and streptomycin sulfate, whereas 27 patients received cephalothin sodium or cefamandole nafate during surgery and nafcillin, penicillin G, and streptomycin postoperatively. Six patients allergic to penicillin received either cephalothin or cefamandole during surgery and a combination of cephalothin and streptomycin postoperatively. Cephalothin and gentamicin sulfate were also used frequently in the cardiac surgery intensive care unit to treat postoperative infections. All patients were on cardiopulmonary bypass during surgery, and the same chief surgeon and nurse attended all patients in the study; student and resident assistants varied from month to month. After surgery, all patients were taken to the cardiac surgery intensive care unit where they remained for 1 to 5 days; all patients who left this unit went to one of two surgical floors for the remainder of their periods of hospitalization.

Sampling techniques. Sterile cotton-tipped swabs, moistened in 0.9% NaCl, were used to obtain samples. The sternums of all patients were vigorously rubbed with two swabs on the day of admission to the

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hospital before any skin cleaning was performed in preparation for surgery. The chest wounds of all patients were swabbed again for 4 to 6 days after surgery at the time of permanent removal of occlusive dressings applied in the operating room. In 25 patients, the edge of the dressing was lifted for wound culture 1 and 3 days after surgery and then retaped until permanent removal. Moistened swabs in all patients were rolled across the surface of plain staphylococcal agar 110 (BBL Microbiology Systems, Cockeysville, Md.); swabs of the 25 patients sampled at intervals after surgery were rolled on plain staphylococcal agar 110 and on staphylococcal agar plus 12.5 μg of sodium methicillin per ml. (Bristol Laboratories, Syracuse, N.Y.).

Microbiological studies. Five white colonies were picked from plain staphylococcal 110 agar, and each colony was identified as *S. epidermidis* by its ability to ferment glucose, its inability to ferment mannitol, and its inability to coagulate rabbit plasma. Some isolates were phage-typed by J. Parisi, University of Missouri School of Medicine (8). Five *S. epidermidis* colonies from the same plate were tested for the presence of methicillin-resistant subpopulations, as previously described (1), and combined. With few exceptions, all colonies were either methicillin resistant or methicillin susceptible. For the detection of methicillin-resistant and -susceptible subpopulations, broth-cultured organisms were plated on agar containing sodium methicillin (Bristol Laboratories) at concentrations of 12.5 and 100 μg/ml. With 10^9 cells as inoculum, methicillin-susceptible isolates showed no colonies capable of growing on agar containing 12.5 μg of the antibiotic per ml, whereas methicillin-resistant isolates contained colonies which grew on agar containing either 12.5 or 100 μg of methicillin per ml. Organisms growing on agar containing 100 μg of the antibiotic were considered to have high-level resistance. Methicillin-susceptible and -resistant isolates were also plated on agar containing streptomycin sulfate (Eli Lilly & Co., Indianapolis, Ind.), gentamicin sulfate (Schering Laboratories, Bloomfield, N.J.), sodium nafcillin (Wyeth Laboratories, Philadelphia, Pa.), or cephalothin sodium, cefamandole lithium, or penicillin G potassium (all from Eli Lilly). Resistance was determined by plating a 10^{-1} dilution of an overnight Mueller-Hinton broth culture on antibiotic-containing agar. The inoculum size varied from 5.4×10^6 to 5.1×10^7 colony-forming units (CFU) with a mean of 1.1×10^7 CFU. Resistance was defined as the presence of ≥10 colonies appearing on agar containing the following concentrations of antibiotics after 72 h of incubation at 37°C: gentamicin, 5 μg/ml; streptomycin, 100 μg/ml; penicillin G, 1.0 μg/ml; nafcillin, 100 μg/ml; and cephalothin and cefamandole, 25 μg/ml. The presence of subpopulations of *S. epidermidis* resistant to penicillins and cephalothins has previously been detected by this technique (1). In addition, the minimal inhibitory concentrations (MICs) and the minimal bactericidal concentrations (MBC) of gentamicin-resistant isolates were determined by the microtiter twofold broth dilution method (1). Isolates showing no resistant organisms were plated on agar containing the following concentrations of antibiotic: streptomycin, 10 μg/ml; gentamicin, 0.2 and 1.0 μg/ml; penicillin G, 0.1 μg/ml; or nafcillin, cephalothin, and cefamandole, 12.5 μg/ml.

RESULTS

S. epidermidis was isolated preoperatively from the skin of all of the 80 patients in the study and postoperatively from the wounds of all but two. Isolates from the chest of 16 patients preoperatively and from the wounds 5 days postoperatively were phage typed. Methicillin-susceptible isolates were recovered preoperatively from skin of 12 of the 16 patients. Only 7 of 32 isolates (22%) were phage typable; 4 of the 7 were preoperative isolates and 3 were postoperative isolates; none of the seven was the same phage type.

The methicillin susceptibility of skin isolates is shown in Table 1. Whereas 24% of the 80 patients had skin isolates resistant to 12.5 μg of methicillin per ml preoperatively, 64% of patients had them in their chest wounds 5 days postoperatively ($P < 0.001$, χ^2). Furthermore, highly methicillin-resistant isolates were recovered preoperatively from only three patients (5.5%) whereas they were recovered postoperatively from 53% ($P < 0.001$). Thus, only 3 of 13 (23%) preoperative isolates resistant to methicillin contained subpopulations of the highly resistant phenotype, whereas 29 of 33 (83%) of postoperative methicillin-resistant isolates contained highly resistant colonies ($P < 0.001$).

The time-course of acquisition of methicillin-resistant *S. epidermidis* was studied in 25 additional patients, and the results are summarized in Table 2. As in the earlier study, isolates resistant to 12.5 μg of methicillin per ml were recovered from 5 patients (20%) preoperatively and from 14 patients (56%) 5 days postoperatively ($P < 0.01$). The percentage of patients with methicillin-resistant staphylococci in their chest wounds progressively increased after surgery.

S. epidermidis returned slowly to the chest wounds after surgery. Although *S. epidermidis* was cultured from the chests of all patients preoperatively, staphylococci were cultured from only 8 of 25 (32%) patients 30 min or 1 day postoperatively and from only 14 of 25 (56%) at 3 days. All but two patients were colonized with

TABLE 1. *Methicillin susceptibility of S. epidermidis isolates recovered from the chest of cardiac surgery patients*

Source of isolate	Subpopulations resistant to methicillin concn of:[a]	
	12.5 μg/ml	100 μg/ml
Preoperative chest	13/55 (24)	3/55 (5.5)
Postoperative wound	33/55 (64)	29/55 (53)

[a] Number of patients with resistant isolates/number of patients sampled. Numbers in parentheses are percentages.

TABLE 2. *Appearance of methicillin-resistant S. epidermidis with time in the chests of cardiac surgery patients*

Time of sampling	Subpopulations resistant to methicillin concn of:[a]	
	12.5 μg/ml	100 μg/ml
Preoperative	5/25 (20)	0/25 (0)
Postoperative		
0.5 hr	1/25 (4)	1/25 (4)
day 1	3/25 (12)	3/25 (12)
day 3	7/25 (28)	7/25 (28)
day 5	14/25 (56)	14/25 (56)

[a] Number of patients with resistant isolates/number of patients sampled. Numbers in parentheses are percentages.

staphylococci by day 5 after surgery. The occlusive dressing was removed from the chest wound between 3 and 5 days postoperatively.

These patients colonized with *S. epidermidis* remained colonized on subsequent samplings, but an increasingly greater percentage of patients with staphylococci converted from a methicillin-susceptible to -resistant flora. At 30 min after surgery, 12.5% (1 of 8) of the patients with staphylococci in their wounds carried methicillin-resistant *S. epidermidis*; at day 1, 37.5% (3 of 8) carried it; at day 3, 50% (7 of 14) carried it; and at day 5, 61% (14 of 23) carried methicillin-resistant *S. epidermidis*. All of the methicillin-resistant staphylococci recovered at any time postoperatively contained highly methicillin-resistant subpopulations; none of the five patients with methicillin-resistant organisms preoperatively had any highly resistant colonies (Table 2). In addition, methicillin-resistant *S. epidermidis* was the predominant flora on the chest wounds by day 5 postoperatively in 12 of the 14 patients colonized with methicillin-resistant staphylococci. In these patients, the number of colonies of *S. epidermidis* from chest swabs growing on agar containing methicillin was ≥90% of the number growing on agar without methicillin.

A total of 30 methicillin-susceptible isolates and 30 methicillin-resistant isolates representing preoperative and postoperative pairs, respectively, from 30 patients were tested for resistance to antibiotics which had been given as prophylaxis (penicillin G, nafcillin, streptomycin, cephalothin, and cefamandole) or had been used extensively in the treatment of postoperative infections in the intensive care unit (cephalothin and gentamicin). The results are shown in Table 3. Whereas few of the preoperative methicillin-susceptible isolates contained any detectable organisms resistant at the antibiotic concentrations indicated, two-thirds or more of all postoperative methicillin-resistant isolates contained

TABLE 3. *Antimicrobial resistance of S. epidermidis isolates from cardiac surgery patients to selected antibiotics*

Concn (μg/ml) antibiotic in agar	Source of isolate[a]	
	Preoperative	Postoperative
Methicillin (100)	0/30 (0)[b]	30/300 (100)
Nafcillin (100)	0/30 (0)	30/30 (100)
Cephalothin (25)	0/30 (0)	28/30 (93)
Cefamandole (25)	1/30 (3)	24/30 (80)
Penicillin G (1.6)	4/30 (13)	30/30 (100)
Streptomycin (100)	3/30 (10)	20/30 (67)
Gentamicin (5)	0/30 (0)	6/30 (20)

[a] Isolates are preoperative (methicillin susceptible) and 5 days postoperative (methicillin-resistant) pairs from the chests of 30 patients.

[b] Number of isolates resistant/number of isolates tested. Numbers in parentheses are percentages.

organisms resistant to all of the antibiotics except gentamicin. The MICs and MBCs of gentamicin for the six gentamicin-resistant isolates were either 6.25 μg/ml (two isolates) or 12.5 μg/ml. All methicillin-susceptible isolates which were susceptible at the antibiotic concentrations indicated in Table 3 were also susceptible at the lowest concentrations tested (cefamandole, cephalothin, and nafcillin, <12.5 μg/ml; streptomycin, <10 μg/ml; penicillin G, <0.1 μg/ml; and gentamicin, <0.2 μg/ml).

Two patients involved in this study developed *S. epidermidis* prosthetic valve endocarditis. From both methicillin-resistant organisms were isolated from their chest wounds postoperatively despite susceptible strains having been isolated from the chest skin preoperatively. From one of the two, a gentamicin-resistant (MIC, 12.5 μg/ml) strain was isolated from both the postoperative wound during the study and the blood at the time of diagnosis of prosthetic valve endocarditis. These were the only *S. epidermidis* infections in the 80 study patients.

DISCUSSION

This study documented the acquisition of highly methicillin-resistant *S. epidermidis* isolates in chest wounds of 43 of 80 (54%) patients 5 days after cardiac surgery; in only 3 of 80 (4%) patients were these organisms present at the same anatomical location before surgery. Furthermore, two-thirds or more of the methicillin-resistant postoperative isolates recovered from 30 patients who had methicillin-susceptible isolates on the chest skin preoperatively contained colonies resistant to penicillin, streptomycin, nafcillin, cephalothin, or cefamandole—antibiotics which had been administered prophylactically. Antibiotic prophylaxis may have selected a more highly antibiotic-resistant *S. epidermidis*

population from the hospital environment. Bentley (3) showed that *S. epidermidis* strains containing highly methicillin-resistant subpopulations were present in six cardiac surgery patients receiving methicillin, whereas these organisms were not present in the same patients who were cultured before receiving methicillin. Only 10 of 118 chronic-care patients receiving no or few antibiotics harbored methicillin-resistant *S. epidermidis*.

Since this study only assessed the prevalence of antibiotic-resistant *S. epidermidis* in the wounds of cardiac surgery patients after surgery, no statement can be made about the source or hospital epidemiology of these isolates. However, the absence of resistant isolates on preoperative skin and the progressive increase in the methicillin-resistant phenotype for 5 days postoperatively suggest that the hospital was the source of the isolates. Studies of outbreaks of methicillin-resistant *S. epidermidis* infections in cardiac surgery units have documented the carriage of these isolates by both patients and hospital personnel (4, 6).

There are several implications in this study. First, the antibiotic resistance shown by *S. epidermidis* isolates in this study is similar to that found in isolates from cases of *S. epidermidis* prosthetic valve endocarditis in other studies (3, 6). Infections with these organisms in either humans (2) or experimental animals (9) respond poorly to therapy with semisynthetic penicillins or cephalosporins, the antibiotics usually used or cephalosporins, the antibiotics usually used for antistaphylococcal therapy.

Second, the hospital acquisition of methicillin-resistant *S. epidermidis* may help clarify the pathogenesis of *S. epidermidis* prosthetic valve endocarditis. Previous studies have shown that at least two-thirds of *S. epidermidis* prosthetic valve endocarditis isolates are methicillin resistant (1). Since skin isolates from non-hospitalized patients are methicillin susceptible, this suggests that most *S. epidermidis* prosthetic valve endocarditis is caused by infection with hospital-acquired organisms. Contamination probably occurs during the perioperative period with an incubation period of weeks to months before clinical expression of disease.

Finally, the multiple antibiotic resistance of *S. epidermidis* may serve as an epidemiological marker. If the organisms causing prosthetic valve endocarditis are transmitted to patients in the perioperative period, a knowledge of the hospital reservoir would be essential to interrupt transmission. Phage-typing of *S. epidermidis* for epidemiological purposes is currently of uncertain value (7). Thus, the use of antibiotic resistance patterns or the identification of plasmids which code for this resistance may be more helpful in tracing the hospital spread of these organisms. The role of antibiotic prophylaxis in the selection of antibiotic-resistant *S. epidermidis* also needs to be clarified by the use of careful controls.

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