

Sequential Analysis of Staphylococcal Colonization of Body Surfaces of Patients Undergoing Vascular Surgery

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Slime-producing coagulase-negative staphylococci are pathogens in vascular surgery by virtue of their ability to adhere to and persist on prosthetic graft material. Inguinal and abdominal skin sites were cultured in 41 patients upon hospitalization, and slime production and antimicrobial susceptibility were assessed in all recovered staphylococcal isolates. Twenty-one patients eventually underwent lower-extremity revascularization. In the operative population, cultures were also obtained on the day of surgery and fifth postoperative day. All 21 patients received perioperative cefazolin. Of 327 coagulase-negative staphylococci recovered, *Staphylococcus epidermidis* (47%), *S. haemolyticus* (21%), and *S. hominis* (10%) were the predominant isolates. Slime-producing coagulase-negative staphylococci were recovered from 17 of 21 patients at admission but only from 8 of 21 patients on day 5 postoperation ($P < 0.05$). *S. epidermidis* isolates demonstrated increasing multiple resistance from admission to 5 days postoperation to methicillin, gentamicin, clindamycin, erythromycin, and trimethoprim-sulfamethoxazole ($P < 0.05$). All coagulase-negative staphylococcal isolates were susceptible to ciprofloxacin and vancomycin. Slime-producing capability was not associated with increased methicillin resistance for the recovered isolates. The data demonstrate that patients enter the hospital colonized with slime-producing strains of coagulase-negative staphylococci and that during hospitalization the staphylococcal skin burden shifts from a predominately susceptible to a resistant microbial population, which may enhance the importance of slime production as a risk factor in lower-extremity revascularization.

Infection associated with the use of implanted biomaterials continues to be a significant source of morbidity and mortality (24). The coagulase-negative staphylococci are recognized as the major pathogens infecting prosthetic materials (19). *Staphylococcus epidermidis* is the most common coagulase-negative staphylococcal species recovered from infection of orthopedic devices (11), intravenous catheters (26), prosthetic heart valves (33), central nervous system shunts (4), peritoneal dialysis catheters (29), and vascular grafts, (13, 17). Because of the ecological distribution of the staphylococci in humans, the cut skin surface, hair follicles, sweat glands, lymph nodes, and lymph channels are all potential sources of microbial contamination (5, 23). Furthermore, within the hospital environment, patients have been shown to acquire staphylococcal skin populations that exhibit multiple antimicrobial resistance (2). A change in the microbial ecology of the skin, which includes the acquisition of organisms expressing multiple resistance or enhanced virulence, amplifies the risk of infection to patients receiving a prosthetic implant.

The incidence of vascular graft infection varies between 1 and 4%. However, the indolent nature of these infections often results in a failure to detect microbial colonization of the graft months to years after implantation. Advances in surgical technique, improvements in prosthetic design and fabrication, and routine antibiotic prophylaxis have all contributed to a change in the epidemiology of vascular graft infections (3, 12, 18). Historically, graft infections most often present as acute episodes involving pyogenic microorganisms such as *Escherichia coli* or *Staphylococcus aureus* (12). It has only been within this decade that vascular surgeons have recognized the pathogenic potential of *S. epidermidis*.

The primary reason for the late appreciation of the coagulase-negative staphylococci as pathogens in vascular surgery has been due to difficulties in recovering these organisms from the infected grafts. This has necessitated the development of specialized culture techniques, which include mechanical disruption of surface colonization and culture in broth media (31, 36). By using these techniques we have been able to determine that the coagulase-negative staphylococci are truly vascular pathogens and not simply skin contaminants.

Slime produced by *S. epidermidis* is viewed as a virulence factor promoting bioprosthetic infections (30). The importance of slime production was first suggested by Bayston and Penny in 1972 in their description of a cerebrospinal fluid shunt infection caused by *S. epidermidis* (4). Kaebnick et al. demonstrated slime production in 87% of *S. epidermidis* strains recovered from patients undergoing reoperative surgery for anastomotic dehiscence (17). This characteristic of pathogenic *S. epidermidis* strains has subsequently been confirmed in numerous clinical and experimental settings (15, 28, 35, 37). Slime production has been suggested as participating in initial bacterial adherence and persistence to the biomaterial surface (9, 27, 31). In addition, bacterial colonies encased in extracellular slime are protected from antibiotics, polymorphonuclear leukocyte chemotaxis, phagocytosis, and degranulation (14, 16).

In the present study we used sequential body surface cultures to prospectively study changes in staphylococcal skin flora in patients undergoing vascular surgery before and after prosthetic implantation. Susceptibility studies were performed on all isolates to demonstrate whether resistance occurred with time. The capacity of the recovered isolates to demonstrate slime production was assessed by polysaccharide staining and scanning electron microscopy.

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MATERIALS AND METHODS

Patients. Body surface cultures were obtained from the abdomens and inguinal regions of 41 consecutive patients admitted for aortic or infrainguinal revascularization. Patients were excluded if they were receiving antibiotics at the time of admission, were admitted with soft-tissue infections requiring antibiotic therapy, or had been hospitalized during a 30-day period before admission. Twenty-one patients underwent lower-extremity revascularization during this hospitalization. Before surgery, patients showered with povidone-iodine soap. In the operating room, the surgical site was shaved, scrubbed, and painted with povidone-iodine. Cefazolin sodium (1 g) was administered intravenously 1 to 2 h before surgery as prophylaxis against wound infection and at 8-h intervals for 2 to 3 days postoperatively. Patients were cared for in a surgical intensive care unit for 1 to 4 days after the operation and then transferred to a surgical ward for the remainder of their hospitalization. Surgical wounds were inspected daily and covered with sterile gauze.

Body surface cultures. Cultures were obtained by rubbing the skin of the midline abdomen and both groins with sterile cotton-tipped swabs moistened in 0.9% NaCl. The skin was cultured in the area of the incisions typically used in lower-extremity revascularization. Cultures were performed on the day of admission from the 41 prospective surgical candidates. The 21 patients undergoing revascularization were cultured immediately preoperatively, before shaving or cleansing of the skin, and on the fifth postoperative day. The mean time from first culture to last culture (5 days after surgery) was 9 days.

Microbiologic studies. The surface of plain staphylococcus 110 agar (Difco Laboratories, Detroit, Mich.) was inoculated with culture swabs, streaked for isolation, and incubated at 35°C. After overnight growth the plates were examined with a dissecting microscope, and colonies demonstrating distinct morphologies were transferred to blood agar plates and incubated overnight at 35°C. Colonies were then characterized by using a miniaturized identification procedure (Staph-Trac; Analytab Products, Plainview, N.Y.) and frozen in skim milk at -70°C.

Slime production was assessed by scanning electron microscopy and polysaccharide staining with alcian blue. Briefly, bacteria were removed from frozen stock and plated on blood agar for overnight growth, transferred to test tubes containing a glass cover slip and 10 ml of Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.) with 0.25% dextrose (TSBD) and incubated for 18 h at 35°C. The glass cover slips were removed from the test solutions, washed with 50 ml of phosphate-buffered saline, and placed in a test tube containing 10 ml of alcian blue. After 10 min, the cover slips were removed and washed three times in phosphate-buffered saline. Slime production was considered present if a visible blue stained film layered the cover slip. Known positive (RP62) and negative (SP2) slime-producing strains of coagulase-negative staphylococci were tested as strain controls (7). Inoculated glass cover slips for scanning electron microscopy were prefixed for 24 h in 2% glutaraldehyde buffered with 0.15 M sodium cacodylate (pH 7.4). The specimens were washed twice in buffer, followed by

TABLE 1. *Staphylococcus* species obtained upon hospitalization from 41 patients admitted for evaluation of peripheral artery atherosclerosis

Organism	No. of isolates	% of total isolates
<i>S. epidermidis</i>	117	34
<i>S. hominis</i>	93	27
<i>S. haemolyticus</i>	49	15
<i>S. capitis</i>	20	6
<i>S. warneri</i>	20	6
<i>S. simulans</i>	12	4
<i>S. hyicus</i>	8	3
<i>S. saprophyticus</i>	6	2
<i>S. cohnii</i>	3	1
<i>S. xylosus</i>	2	1
<i>S. scuri</i>	1	0.3
<i>S. aureus</i>	7	2

postfixation in 2% osmium tetroxide. After three buffered rinses the specimens were serially dehydrated in ethanol, critical point dried from liquid carbon dioxide, mounted, and coated with gold-palladium. Specimens were examined by scanning electron microscopy at 25 kV and a spot size of 8 nm. Previous scanning electron microscopy studies with RP26 and SP2 have demonstrated that slime positive cultures appear as large clumps of cocci embedded in gelatinous strands of polysaccharide material and that non-slime producers appear as single isolated cocci free of exopolysaccharide.

Antibiogram. All isolates were tested by agar dilution with a Steers replica inoculating device and Mueller-Hinton agar. Antimicrobial susceptibility was determined for cefazolin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamicin, methicillin, rifampin, trimethoprim-sulfamethoxazole, and vancomycin. Methicillin was tested in agar supplemented with 4% NaCl (1). The agar dilution test was prepared by suspending five colonies from a sheep blood agar plate in Trypticase soy broth. This inoculum was incubated at 35°C until visibly turbid, and the density of the culture was adjusted to a 0.5 McFarland standard by the addition of sterile broth. The final inoculum concentration was approximately 4.5 log₁₀ CFU per inoculated spot. *S. aureus* (ATCC 29213) was used as a control organism to verify drug potency and procedure adequacy. The plates were incubated at 35°C and read at 24 and 48 h. Breakpoints recommended by the National Committee for Clinical Laboratory Standards in micrograms per milliliter were used to determine susceptibility and resistance (25).

RESULTS

A total of 338 staphylococcal species (mean, 8.2 isolates per patient) were recovered from three skin sites (abdominal and inguinal regions) from 41 patients on admission to the hospital (Table 1). *S. epidermidis* (117 isolates), *Staphylococcal hominis* (93 isolates), and *S. haemolyticus* (49 isolates) were the predominant organisms recovered, with eight other coagulase-negative staphylococcal species comprising the other isolates. Only seven *S. aureus* isolates were recovered. Cultures from the subgroup of 21 patients who were revascularized yielded similar results at the time of admission (Table 2). A total of 330 staphylococcal species were recovered from these patients upon admission (mean, 7.2 isolates per patient), at the time of operation (mean, 4.1 isolates per patient), and 5 days after surgery (mean, 4.4

TABLE 2. *Staphylococcus* species recovered from 21 patients undergoing lower-extremity revascularization

Organism	No. of isolates recovered		
	Day of admission	Day of surgery	Day 5 postsurgery
<i>S. epidermidis</i>	68	49	46
<i>S. haemolyticus</i>	27	14	33
<i>S. hominis</i>	22	6	4
<i>S. warneri</i>	14	8	1
<i>S. capitis</i>	8	7	3
<i>S. aureus</i>	2	0	1
Other staphylococcal species ^a	10	3	4

^a *S. saprophyticus*, *S. hyicus*, *S. scuri*, *S. xylosus*, *S. cohnii*, and *S. simulans*.

isolates per patient). *S. epidermidis* and *S. haemolyticus* were the predominant species, which persisted throughout the period of hospitalization. *S. aureus* was recovered from only one patient at 5 days postoperation.

On admission, 80% of the patients had at least one slime-producing coagulase-negative staphylococcal strain as part of their skin flora. Figure 1A demonstrates the typical presentation of a slime-producing clinical isolate on a glass cover slip after 24 h of incubation in TSDB medium, and Fig. 1B shows a non-slime-producing strain. In the revascularized group, slime-producing coagulase-negative staphylococci were recovered from 17 of 21 patients on the day of admission (Fig. 2). At the time of surgery, 10 of 21 patients yielded slime-producing strains, and by the fifth postopera-

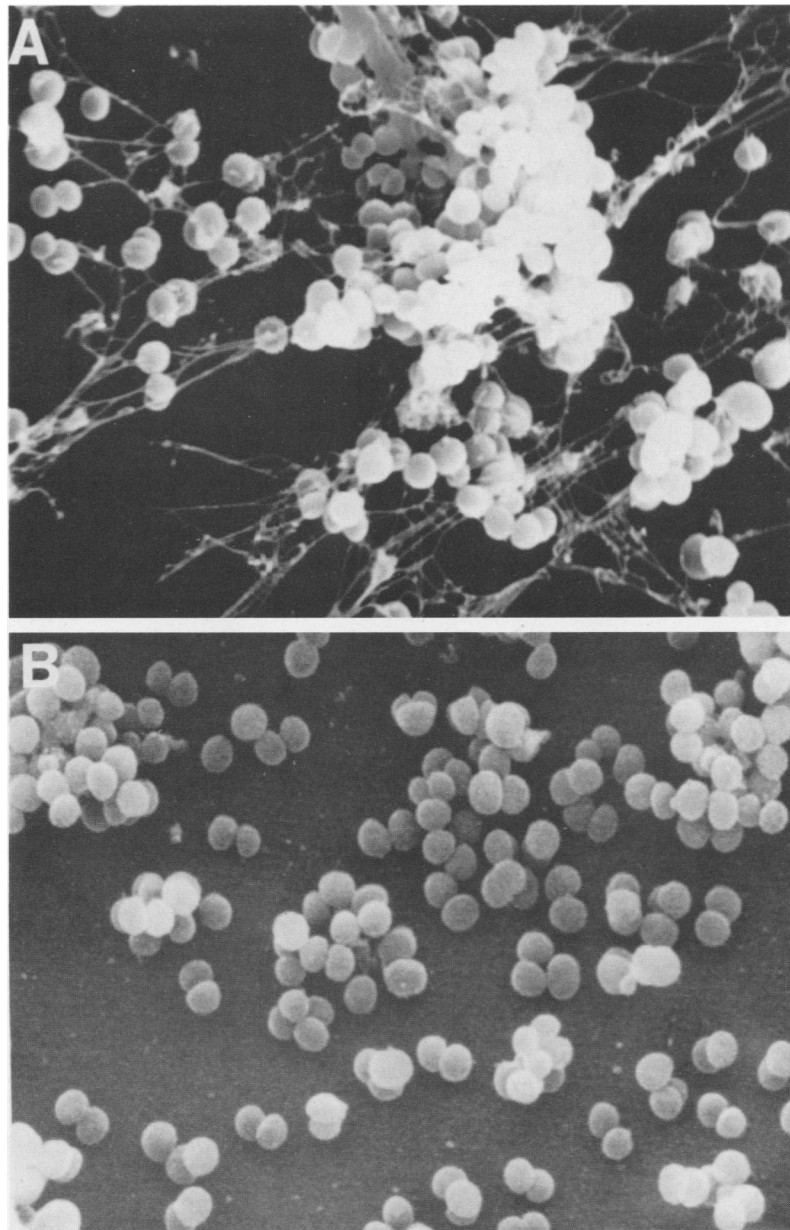


FIG. 1. (A) Typical presentation of clinical isolate of slime-producing *S. epidermidis* after 24 h of incubation on glass cover slips in TSDB medium (magnification, $\times 5,000$). (B) Non-slime-producing isolate of *S. epidermidis* demonstrating no extracellular exopolysaccharide matrix (magnification, $\times 5,000$).

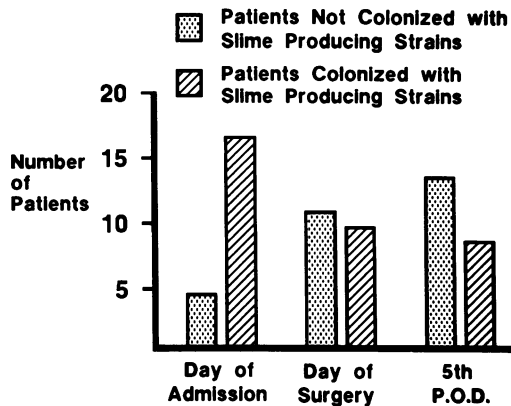


FIG. 2. Number of revascularized patients from which at least one slime-producing strain was recovered by body surface culture. P.O.D., Postoperative day.

tive day only eight patients had body surface cultures that were positive for slime-producing isolates ($P < 0.05$ [chi-square test] compared with preoperative cultures). It is significant to note that slime production was not limited to *S. epidermidis* but was also observed in some *S. hominis* and *S. haemolyticus* strains (Fig. 3).

Table 3 presents the antibiogram data for the 327 coagulase-negative staphylococcal isolates from the group of 21 revascularized patients cultured upon admission, preoperatively, and at 5 days postoperation. No significant change in the antimicrobial susceptibility of *S. epidermidis* isolates to cefazolin, chloramphenicol, ciprofloxacin, rifampin, and vancomycin was observed. A significant increase ($P < 0.05$, chi-square test) in antimicrobial resistance was observed for *S. epidermidis* at preoperative and day 5 postoperative cultures with clindamycin, gentamicin, erythromycin, trimethoprim-sulfamethoxazole, and methicillin. Furthermore, this increased resistance was observed in both slime-positive and slime-negative strains preoperatively and at 5 days postsurgery. No significant change in antibiotic resistance was seen in either the slime-positive or slime-negative *S. hominis* isolates. However, a shift from a sensitive to a resistant antibiogram was observed for the *S. haemolyticus* isolates. At 5 days postoperation, both slime-positive and slime-negative *S. haemolyticus* strains exhibited significant multiple resistance. Multiple resistance was also observed for several miscellaneous coagulase-negative isolates at 5 days postsurgery. Little or no resistance was seen with chloramphenicol, ciprofloxacin, rifampin, or vancomycin in the 327 strains tested.

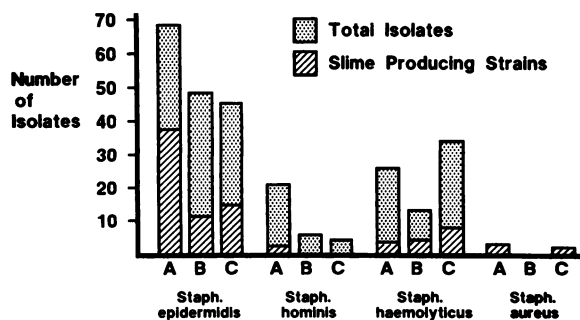


FIG. 3. Slime production by staphylococcal isolates recovered during hospital course: A, day of admission; B, day of surgery; C, fifth postoperative day.

DISCUSSION

The coagulase-negative staphylococci are a ubiquitous group of microorganisms that colonize the epidermis of the skin, adjacent glands, and hair follicles. The axilla, inguinal, and perineal regions, areas of excessive surface humidity, carry high staphylococcal burdens that preferentially include *S. epidermidis*, *S. hominis*, and *S. haemolyticus* (21, 22). We identified staphylococcal strains that comprise normal skin flora at common vascular surgical sites. Postoperative recovery of coagulase-negative staphylococcal species did not differ greatly from the preoperative culture. We found *S. epidermidis* and *S. haemolyticus* to be the most prevalent isolates on the fifth postoperative day. *S. aureus* was not recovered from cultures in the operating room and was only rarely isolated from the preoperative and postoperative cultures.

This study demonstrated that there is an increase in the recovery of antibiotic-resistant coagulase-negative staphylococci from the wound sites of patients undergoing lower-extremity revascularization (Table 3). There was a significant difference in antimicrobial susceptibility to clindamycin, erythromycin, gentamicin, methicillin, and trimethoprim-sulfamethoxazole between *S. epidermidis* isolates recovered at the time of hospital admission to those recovered on the fifth postoperative day ($P < 0.05$, chi-square analysis). All *S. epidermidis* isolates recovered in this study were susceptible to both ciprofloxacin and vancomycin. *S. haemolyticus* emerged as a significant postoperative isolate and demonstrated multiple drug resistance. In vitro activity suggested that both *S. epidermidis* and *S. haemolyticus* exhibited low resistance to cefazolin. This may be misleading, since cephalosporin therapy often fails in patients infected with methicillin-resistant staphylococci. Our results are similar to those reported by Archer and Tenenbaum in a study of wound colonization by antibiotic-resistant *S. epidermidis* after cardiac surgery (2). They also noted the emergence of methicillin-resistant strains in the postoperative period. Furthermore, the increase in resistance to a variety of antibiotics used for prophylaxis suggests that antimicrobial prophylaxis results in a preferential selection for the more highly resistant hospital strains. The present study does not identify the epidemiologic relationship between the initial and later cultured staphylococcal isolates. However, Kernodle et al. recently demonstrated by using antibiograms and plasmid profiles that endogenous staphylococcal skin flora may acquire antimicrobial resistance after surgical antibiotic prophylaxis (20). The frequency in which antimicrobial resistance emerges among intrinsic staphylococcal skin flora compared with nosocomial acquisition of resistance is unknown for our patient population.

A major finding of this study is the documentation of a high incidence of skin colonization by slime-producing coagulase-negative staphylococcal strains at the time of admission to the hospital. Although the recovery of slime-producing coagulase-negative staphylococci decreased during the course of hospitalization, the slime-producing strains recovered from the skin surface exhibited an increase in antimicrobial resistance. To date, slime-producing strains of *S. epidermidis* have been recovered from numerous clinical settings (4, 17, 37). At present, we have recovered few *S. haemolyticus* from clinical vascular graft infections. Preliminary evidence suggests that *S. haemolyticus* is a potent slime producer that also acquires multiple drug resistance and therefore may be a potentially important clinical isolate.

The epidemiology of slime-producing coagulase-negative

TABLE 3. Antimicrobial susceptibility of 327 coagulase-negative staphylococcal isolates from patients undergoing revascularization

Organism and mucin ^a	No. of isolates ^b																			
	CEF		CHL		CIP		CLN		ERY		GEN		MET		RIF		TMP-SMX		VANC	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
<i>S. epidermidis</i>																				
A+	37	0	36	1	37	0	28	9	22	15	35	2	30	7	34	3	31	6	37	0
A-	31	0	31	0	31	0	30	1	26	5	29	2	28	3	31	0	30	1	31	0
B+	11	0	11	0	11	0	5	6	4	7	8	3	7	4	11	0	10	1	11	0
B-	38	0	35	3	38	0	29	9	26	12	35	3	29	9	37	1	31	7	37	0
C+	16	0	16	0	16	0	1	15	1	15	12	4	6	10	16	0	6	10	16	0
C-	30	0	29	1	30	0	9	21	7	23	21	9	12	18	30	0	19	11	30	0
<i>S. hominis</i>																				
A+	1	0	0	1	1	0	1	0	1	0	1	0	1	0	1	0	0	1	1	0
A-	21	0	19	2	21	0	21	0	16	5	21	0	20	1	18	3	17	4	21	0
B+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B-	6	0	6	0	6	0	6	0	5	1	6	0	6	0	6	0	6	0	6	0
C+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C-	4	0	2	2	4	0	2	2	2	2	4	0	4	0	3	1	1	3	4	0
<i>S. haemolyticus</i>																				
A+	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0
A-	24	0	24	0	24	0	22	2	14	10	23	1	23	1	24	0	22	2	24	0
B+	4	0	4	0	4	0	3	1	4	0	4	0	4	0	4	0	4	0	4	0
B-	10	0	10	0	10	0	7	3	4	6	10	0	7	3	10	0	10	0	10	0
C+	5	4	9	0	9	0	1	8	1	8	5	4	1	8	9	0	3	6	9	0
C-	20	4	20	4	24	0	4	20	3	1	14	10	5	19	21	3	14	10	24	0
Other isolates ^c																				
A	32	0	32	0	32	0	28	4	25	7	31	1	28	4	32	0	30	2	32	0
B	17	1	18	0	18	0	17	1	16	2	17	1	16	2	18	0	18	0	18	0
C	7	1	2	6	8	0	1	7	1	7	3	3	1	7	8	0	6	2	8	0

^a Slime production determined by alcian blue staining: +, slime positive; -, mucin negative; A, isolates recovered on the day of admission; B, isolates recovered on the day of surgery; C, isolates recovered on the fifth postoperative day.

^b Antimicrobial susceptibility (S) and resistance (R) determined by National Committee for Clinical Laboratory Standards breakpoints as follows: CEF (cefazolin: S, ≤ 8 $\mu\text{g/ml}$; R, ≥ 32 $\mu\text{g/ml}$); CHL (chloramphenicol: S, ≤ 8 $\mu\text{g/ml}$; R, ≥ 32 $\mu\text{g/ml}$); CIP (ciprofloxacin: S, ≤ 1 $\mu\text{g/ml}$; R, ≥ 4 $\mu\text{g/ml}$); CLN (clindamycin: S, ≤ 0.5 $\mu\text{g/ml}$; R, ≥ 4 $\mu\text{g/ml}$); ERY (erythromycin: S, ≤ 0.5 $\mu\text{g/ml}$; R, ≥ 8 $\mu\text{g/ml}$); GEN (gentamicin: S, ≤ 4 $\mu\text{g/ml}$; R, ≥ 16 $\mu\text{g/ml}$); MET (methicillin: S, ≤ 8 $\mu\text{g/ml}$; R, ≥ 16 $\mu\text{g/ml}$); RIF (rifampin: S, ≤ 1 $\mu\text{g/ml}$; R, ≥ 4 $\mu\text{g/ml}$); TMP-SMX (trimethoprim-sulfamethoxazole: S, $\leq 2/38$ $\mu\text{g/ml}$; R, $\geq 4/76$ $\mu\text{g/ml}$); and VANC (vancomycin: S, ≤ 4 $\mu\text{g/ml}$; R, ≥ 32 $\mu\text{g/ml}$).

^c Other coagulase-negative staphylococci included *S. saprophyticus*, *S. hyicus*, *S. sciuri*, *S. xylosus*, *S. cohnii*, *S. simulans*, and *S. capitis*.

staphylococci is poorly understood. While the acquisition of multiple resistance by coagulase-negative staphylococci in the hospital environment has been documented by several investigators, the present findings suggest that slime production among the coagulase-negative staphylococci is not a hospital-acquired trait but rather a characteristic expressed by some components of normal skin flora.

The ability of coagulase-negative staphylococcal isolates to produce an extracellular slime has been identified as a virulence factor marking the isolate as a true pathogen (6, 7, 30, 37). Ishak et al. demonstrated slime production in 13 of 14 *S. epidermidis* isolates recovered from the bloodstream in clinically septic patients (15). Eighty-seven percent of *S. epidermidis* strains recovered from vascular grafts removed due to clinical infection produced slime in Trypticase soy broth supplemented with glucose (17). However, slime production may be altered by environmental conditions that exist in and around the implanted bioprosthesis. Christensen and Baddour have suggested that phenotypic differences in slime production may occur depending upon the conditions under which the organisms are cultured (G. D. Christensen and L. M. Baddour, Abstr. Annu. Meet. Am. Soc. Microbiol. 1987, B208, p. 59).

Previous studies have used body surface cultures to identify colonization by pathogenic strains as a predictive factor

of future clinical infection (8, 32). Evans and colleagues found that body surface cultures recovered potential pathogens with a sensitivity and specificity of 56 and 82%, respectively (10). However, their cultures resulted in a positive predictive value for future invasive infection of only 7.5%. The recovery and identification of slime-producing staphylococci may suggest a greater clinical role in patients who eventually have a vascular prosthesis implanted into their arterial system. Although reoperation in the early perioperative period after arterial bypass is not a frequent necessity, recognizing changes in the patient's body surface flora with the emergence of pathogenic organisms would alter the choice and duration of antibiotic therapy required for prophylaxis in reoperative surgery.

The results of the present study suggests the following scenario. Patients enter the hospital with a low incidence of resistant staphylococcal strains. However, a significant number of these strains demonstrate the capacity to produce an exopolysaccharide slime. In the course of the patients' hospitalization, antibiotic prophylaxis reduces the staphylococcal strain burden of both slime-positive and slime-negative strains. Strains recovered from the skin surface demonstrate a significant increase in antibiotic resistance in both slime-positive and slime-negative isolates.

The clinical significance of slime production by *S. epider-*

midis and its adherence to bioprosthetics is incompletely understood. The presence of slime-producing strains of staphylococci on the skin before hospitalization and antimicrobial prophylaxis constitute two independent risk factors for vascular graft infection. In the hospital, antimicrobial pressure may amplify the potential risk of infection by the selection of slime-positive strains that exhibit multiple resistance.

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