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Association of Coagulase-Negative Staphylococcal Slime Production and Adherence with the Development and Outcome of Adult Septicemias

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The relationship of coagulase-negative staphylococcal slime production and adherence with the development and outcome of bloodstream infections in two Finnish hospitals was evaluated. Analysis of 64 strains from 62 adult septicemias disclosed 34 (53%) adherent slime producers. In comparison, only 142 (29%) of 489 single blood culture isolates were adherent slime producers. Although tube adherence test-positive strains were significantly ($P < 0.001$) more common among the septicemia strains than among clinically insignificant isolates, almost half of the septicemia cases were caused by tube test-negative strains. Thus, regarding any single patient isolate, a cautious posture to the clinical impact of positivity in the tube adherence test seems warranted. Moreover, adherence and slime production, as such, apparently played no role in the clinical outcome of these infections. The epidemiologic findings revealed that slime-producing coagulase-negative staphylococci were common in the hospital environment and suggested that epidemic spread of such strains was influenced by antimicrobial therapy. Collectively, these results indicate that, at least in these two hospitals, positivity in the tube test was of minor importance in guiding clinical decisions in treating adult septicemias.

Coagulase-negative staphylococci are among the most important microorganisms in nosocomial bloodstream infections (17, 23, 31). These bacteria can be pathogenic, especially in immunocompromised patients with hematologic and other malignancies and in patients with foreign bodies, such as invasive catheters (2, 4, 20, 26, 33). Coagulase-negative staphylococci are part of the normal skin flora and one of the most common contaminants of bacterial cultures. Thus, a definite diagnosis of septicemia, even in immunocompromised patients with clinical symptoms, is established only upon isolating an identical coagulase-negative staphylococcal strain from multiple blood cultures. In this regard, continuing research efforts have been devoted to developing a simple and reliable laboratory method capable of distinguishing true pathogens from mere contaminants.

Coagulase-negative staphylococci are characterized by their ability to adhere to and grow on solid surfaces and to subsequently produce polysaccharide slime (5, 8, 29). The extracellular slime may protect the bacteria against immunological host defense mechanisms and antimicrobial therapy (14, 15, 19, 28, 32). Thus, slime is considered an important virulence factor (6, 8, 28, 30). Of the various methods described in the literature for demonstrating the slime-producing capacity of an individual bacterial strain (8, 9, 25, 29), only the tube adherence test originally described by Christensen et al. (8) is easily performed and, therefore, suitable for routine diagnostics.

Several comprehensive studies have indicated that coagulase-negative staphylococcal infections are caused mainly by the adherent, slime-producing strains (7, 10, 12, 16, 18, 35). Consequently, it has been suggested that positivity in the tube adherence test could be used as a marker of true pathogenicity in a strain (10). Many studies have also shown that the slime-producing capacity of an infecting strain correlates with the clinical outcome of infection (10, 11). In other studies (1, 22, 24, 27, 34), however, such associations have not been confirmed. The basis for this discrepancy is not apparent at the present time (30).

These conflicting results suggest that even though slime production is undoubtedly an important virulence factor, the positive correlation between slime production and clinically significant infections is, perhaps, not a universal phenomenon. Indeed, there must be virulence factors other than or in addition to slime production that contribute to the pathogenicity of coagulase-negative staphylococci (3, 6, 11, 30). Moreover, it is possible that these factors vary in different environments. This study was performed to evaluate the importance of slime production as a virulence factor of septicemia strains in two Finnish hospitals served by the same microbiological laboratory. Coagulase-negative staphylococcal bloodstream infections diagnosed in adult patients during the years 1983 to 1989 were examined. The role of slime-producing strains in these infections was assessed by comparing the septicemia strains to single blood culture isolates and various other clinical isolates collected during the same study period and, further, by evaluating the clinical outcome of the septicemias. In addition, efforts were made to detect the occurrence of adherent, slime-producing strains in the hospital environment by analyzing the skin flora of hospital patients and personnel.

MATERIALS AND METHODS

This study was carried out at the Department of Medical Microbiology, Turku University (Finland), a laboratory facility serving two hospitals: Turku University Central Hospital and Turku City Hospital. Turku University Central Hospital is a 1,209-bed teaching facility; Turku City Hospital is a 1,206-bed community hospital with geriatric, surgical, infectious diseases, and psychiatric wards. Special attention was focused on the hematologic unit of Turku University Central Hospital and the infectious diseases unit of Turku City Hospital.

Bacterial strains and identification. A total of 1,198 coagu-

lase-negative staphylococcal isolates were studied. These isolates were collected from various clinical samples taken in the two hospitals from early 1983 through late 1989. The collection included 617 isolates recovered from blood cultures, 496 isolates from urine samples, 24 isolates from cerebrospinal fluids, and 61 isolates from intravascular devices. In Turku University Central Hospital, for each blood culture, 10 ml of blood was collected from each patient and cultured as follows. Early in the study (1983 to 1985), double bottles (Supplemented Peptone Broth VACUTAINER [Becton Dickinson, Rutherford, N.J.]) for aerobic and anaerobic cultivation were used. Later (1986 to 1989), the lysis centrifugation method (Isolator [Du Pont de Nemours Inc., Wilmington, Del.]) was used. In Turku City Hospital, the double-bottle method was used throughout the entire study period. Basic identification of staphylococci was determined by Gram staining as well as by catalase and tube coagulase tests. The blood culture isolates were then speciated by the API Staph-Trac procedure (Analytab Products, Plainview, N.Y.).

To investigate the epidemiology of the adherent, slime-producing coagulase-negative staphylococci in hospital environments, the skin flora of health care personnel and patients was studied. Twenty-eight nurses and seven physicians working in the hematologic unit of Turku University Central Hospital were studied simultaneously with 59 patients treated in the same unit. The study was carried out in early 1988, during a sepsis epidemic caused by ciprofloxacin-resistant coagulase-negative staphylococci, described by us earlier (21). Of the patients having their skin flora studied, 28 had severe hematologic diseases with profound granulocytopenia. All of these patients had been hospitalized for more than 1 month preceding the study and received ciprofloxacin either for treatment or prophylaxis of infections. The average hospitalization time of the 31 other patients, none of whom had received ciprofloxacin, was 8.3 days preceding the study. For comparison, the skin flora of 23 nurses working in the infectious diseases unit of Turku City Hospital, 39 medical students from Turku University, and 13 laboratory technicians from the Department of Medical Microbiology, Turku University, were studied.

Each subject placed the fingertips of both hands onto a blood agar plate. After the plates were incubated at 37°C for 48 h, staphylococcal colonies were identified according to colony morphology and studied further, as described above. The species, plasmid profiles, and ciprofloxacin susceptibility of the coagulase-negative staphylococcal cutaneous isolates collected in the hematologic unit of Turku University Central Hospital were determined earlier (21). The septicemia strains from hematologic patients were tested for ciprofloxacin susceptibility, as described earlier (21).

Adherence and slime production. The tube adherence test was used to detect the slime production, associated with adherence, of coagulase-negative staphylococcal isolates to the test tube wall. American Type Culture Collection strains *Staphylococcus epidermidis* ATCC 35983 (tube adherence test positive) and *Staphylococcus hominis* ATCC 35982 (tube adherence test negative) were used as control organisms. The tube test was performed in duplicate on isolates from blood cultures, from cerebrospinal fluids, from intravascular devices, and from the skin flora of the patients and personnel. The test proved reliable, in that results from duplicate assays were always identical. The test was performed once on isolates from urine. The terms adherent slime producers and slime-producing are used interchangeably herein to indicate tube adherence test-positive isolates.

Definition of clinically significant blood culture strains. Hospital records of adult patients with multiple isolates were reviewed. In a patient with a clinical picture consistent with coagulase-negative staphylococcal septicemia, an absolute prerequisite for strain definition as clinically significant was the multiple recovery of an identical strain from two or more blood cultures taken at separate times. The identity of the isolates was determined by antibiotic susceptibility profile, by biotyping using the API Staph-Trac procedure, and by positivity or negativity in the tube test. For the majority (70.9%) of the pathogenic strains, identity was further confirmed by plasmid profile analyses. The plasmid profiles of all clinically significant isolates were determined as described by Etienne et al. (13).

The blood culture isolates collected during the period 1983 to 1989 consisted of 489 single isolates (average, 70 consecutive isolates per year) and 128 multiple isolates from 62 patients. All single blood culture isolates were, for the purposes of this study, defined as insignificant. When multiple isolates from the same patient were determined to be identical by the methods described above, they were considered to be one and the same strain. Duplicate isolates recovered from second and third cultures were, therefore, excluded from the study. Thus, the septicemia strain collection included 64 strains from 62 patients. Two of these patients had a dual infection caused by two different species of coagulase-negative staphylococci. Both strains were considered pathogens. The isolates from various other clinical samples were all single and regarded as insignificant.

Patients. The medical records of the 62 adult septicemia patients were reviewed retrospectively. Also, 25 of these patients were examined by this researcher, as an infectious diseases consultant, during the acute phase of disease. The average age of the patients was 58 years. There were 33 males and 29 females, of which 52 were treated in Turku University Central Hospital and 10 were treated in Turku City Hospital.

Of the 52 patients treated in Turku University Central Hospital, 26 had underlying malignancies, including acute leukemia (18 patients), chronic myelocytic leukemia in blast crisis (4 patients), carcinoma (2 patients), lymphoma (1 patient), and multiple myeloma (1 patient). Nine patients had cardiovascular diseases with extended treatment periods in the intensive care unit, and eight had other severe underlying internal diseases. Eight cases were postoperative, and one patient had severe body burns. Of the 52 University Hospital patients, 33 had invasive catheters and six had peripheral lines. In addition, three patients had prosthetic valves. None had ventriculoperitoneal shunts.

The 10 patients treated in Turku City Hospital were geriatric, all severely debilitated by underlying diseases. Two patient septicemias developed postoperatively. Two others involved malignancies. All 10 patients had central venous catheters. None had ventriculoperitoneal shunts.

Association of slime production with clinical factors and outcome. The clinical factors of the adult patients treated in these two hospitals were evaluated collectively. For evaluation purposes, special attention was focused on the following: (i) relationship between the slime-producing capacity of the septicemia strains and the underlying diseases of the patients, (ii) association between the slime-producing septicemia strains and the presence of invasive catheters as well as the administration of antimicrobial therapy at the onset of septicemia, (iii) connection between the length of the hospital stay and the slime-producing capacity of the infecting strain (patients hospitalized less than 14 days [16 patients]

TABLE 1. Association of slime-producing capacity and species among the coagulase-negative staphylococcal septicemia strains and single blood culture isolates

Species	No. of isolates			
	Septicemia		Single blood culture	
	Total	Slime producing	Total	Slime producing
S. epidermidis	51	33 (65%)[a]	314	126 (40%)[a]
S. hominis	8	1	78	10
S. warneri	2	0	18	3
S. capitis	1	0	21	3
Others	2	0	58	0
Total	64	34 (53%)[b]	489	142 (29%)[b]

[a] Difference is statistically significant ($P = 0.0017$).
[b] Difference is statistically significant ($P < 0.001$).

and those hospitalized more than 14 days [46 patients] preceding the septicemia were analyzed separately), and (iv) relationship between slime production of the septicemia strain and the clinical outcome of the patient. The patients were also investigated for appropriate antimicrobial therapy and removal of invasive catheters. In this context, appropriate antimicrobial therapy was defined as administration of an adequate dose of antibiotics to which the organism was susceptible.

Statistical analysis. Data were analyzed by using the chi-square test.

RESULTS

Characteristics of septicemia strains. The 64 septicemia strains included 51 *Staphylococcus epidermidis* isolates, 8 *Staphylococcus hominis* isolates, 2 *Staphylococcus warneri* isolates, 1 *Staphylococcus capitis* isolate, and 2 strains ungroupable by the API Staph-Trac procedure. Of these strains, 34 (53%) were tube adherence test positive. With the exception of one *S. hominis* strain, tube-adherent bacteria belonged to the species *S. epidermidis* (Table 1). The number of coagulase-negative staphylococcal septicemias diagnosed yearly and the proportion of slime-producing strains among them are shown in Table 2.

Of the 54 septicemia strains recovered at Turku University Central Hospital, 56% were slime producing. Multiple blood cultures from two of these patients simultaneously yielded two different species of coagulase-negative staphylococci. Of the 10 septicemia strains recovered at Turku City Hospital, 40% were slime producing. One of these septicemias was treated in the infectious diseases unit.

TABLE 2. Annual distribution of adherent, slime-producing strains among coagulase-negative staphylococcal septicemia strains and single blood culture isolates

Yr	No. of septicemia strains		No. of single isolates	
	Total	Slime producing (%)	Total	Slime producing (%)
1983	5	3 (60)	77	25 (32)
1984	5	4 (80)	72	16 (22)
1985	9	5 (56)	78	26 (33)
1986	6	3 (50)	118	27 (23)
1987	9	2 (22)	35	8 (23)
1988	18	10 (56)	53	19 (36)
1989	12	7 (58)	56	21 (38)
Total	64	34 (53)[a]	489	142 (29)[a]

[a] Difference is statistically significant ($P < 0.001$).

At Turku University Central Hospital, 24 septicemias were diagnosed in hematologic patients. Ten of them were diagnosed between 1983 and 1987, before ciprofloxacin was used in the hematologic unit. All these septicemia strains were ciprofloxacin susceptible. Of the remaining 14 septicemias diagnosed during 1988 to 1989 after the introduction of the drug, 12 were caused by ciprofloxacin-resistant strains, including 7 *S. epidermidis* (all tube test positive), 2 *S. hominis* (tube test negative), and 2 *S. warneri* (tube test negative), and 1 strain (tube test negative) ungroupable by the API Staph-Trac procedure.

Plasmid profiles were determined for all septicemia strains. Two or more plasmids were detected in 48 strains, one plasmid was found in nine strains, and no plasmids were found in seven strains. Six of the *S. epidermidis* strains (all ciprofloxacin resistant) isolated from hematologic patients in Turku University Central Hospital harbored 2.3- and 1.5-MDa plasmids. Moreover, in four of these strains, a third plasmid of 4 MDa was also seen.

Association of slime production with clinical factors. Endocarditis was diagnosed in five patients, three with prosthetic valves and two with previous valvular diseases. Two prosthetic valve endocarditis cases were caused by tube adherence test-positive strains, while one prosthetic valve endocarditis case and both native valve endocarditis cases were caused by tube test-negative strains.

No significant difference was found in the incidence of slime-producing septicemia strains between patients with various underlying diseases (Table 3). In only 38% of the patients with hospitalization shorter than 14 days preceding the septicemia was the infecting strain slime producing. In contrast, for those patients hospitalized longer than 14 days, as many as 58% of isolates were slime producing. The difference between these groups, however, was not significant. All patients with ciprofloxacin-resistant coagulase-negative staphylococcal septicemias had been hospitalized longer than 14 days. Even when these specific patients were excluded from analysis, the percentage of slime-producing septicemia strains in the long-term patients remained unchanged. Of the other clinical factors analyzed, slime production of the septicemia strains correlated with neither the presence of invasive catheters nor the administration of antimicrobial treatment at the onset of septicemia (Table 3).

Association of slime production with clinical outcome. Of the original 62 patients, 58 were available for analysis of clinical outcome. Of these 58 patients, the five patients with endocarditis were analyzed separately. The two patients with native valve endocarditis (caused by tube test-negative *S. epidermidis* strains) and one with prosthetic valve endocarditis (caused by a tube test-positive *S. epidermidis*) died within 6 weeks. Undoubtedly, these deaths were directly due to infection.

Of the remaining 53 septicemia patients, 17 died within 21 days of the onset of septicemia. In these patients with severe underlying diseases, septicemia may have been either an immediate cause of death or merely a contributing factor. It is noteworthy, that in four of these patients, septicemia was polymicrobial. A total of 10 septicemia patients improved but died of their underlying diseases within 6 months; 26 patients recovered and survived over 6 months. There was no significant difference in the incidence of slime-producing septicemia strains between those patients who succumbed within 21 days and those who survived this period (Table 4).

To determine whether slime production predicted an un-

TABLE 3. Association of adherent, slime-producing coagulase-negative staphylococcal septicemia strains with various clinical characteristics of the 62 septicemia patients

Clinical characteristic	No. of patients	No. of slime-producing strains (%)	No. of non-slime-producing[a] strains
Postoperative cases	10	7 (70)	3
Underlying hematologic malignancy	24[b]	15 (60)[c]	10
Other underlying diseases	28[b]	12 (41)[c]	17
Endocarditis cases	5	2 (40)	3
Hospital stay <14 days[d]	16	6 (38)[e]	10
Hospital stay >14 days[d]	46[f]	28 (58)[e]	20
Presence of invasive catheters[d]	43[b]	25 (57)	19
Receiving antimicrobial treatment[d]	31[b]	18 (56)	14

[a] Non-slime-producing, Tube adherence test negative.
[b] One patient had a dual infection; one slime-producing strain and one non-slime-producing strain were recovered.
[c] Difference is not statistically significant.
[d] At the onset of septicemia.
[e] Difference is not statistically significant.
[f] Two patients had dual infections; one slime-producing strain and one non-slime-producing strain were recovered from each patient.

TABLE 4. Association of clinical outcome with adherent, slime-producing septicemia strains and various clinical characteristics of 53 septicemia patients

Clinical outcome of patients	No. of patients	No. of strains	
		Slime producing	Non-slime producing[a]
Death within 21 days[b]	17	9	8
Receiving proper antimicrobial therapy	13	6	7
Presence of invasive catheters	11	5	6
Removal of invasive catheters[c]	5	4	1
Malignant underlying disease	9	6	3
Survival over 21 days[b]	36[d]	19	19
Receiving proper antimicrobial therapy	27[e]	14	14
Presence of invasive catheters	30[e]	18	13
Removal of invasive catheters[c]	20[e]	14	7
Malignant underlying disease	17[e]	9	9

[a] Non-slime-producing, Tube adherence test negative.
[b] No significant difference was observed in the incidence of slime-producing septicemia strains or in the clinical characteristics between these patient groups.
[c] Within 5 days of the onset of septicemia.
[d] Two patients had dual infections; one slime-producing strain and one non-slime-producing strain were recovered from each patient.
[e] One patient had a dual infection; one slime-producing strain and one non-slime-producing strain were recovered.

favorable prognosis, especially within the *S. epidermidis* species, the *S. epidermidis* septicemias were analyzed separately. No difference in the clinical outcome was observed when patients with tube test-positive and tube test-negative *S. epidermidis* septicemias were compared. Of the 28 patients with tube test-positive *S. epidermidis* septicemias, nine (32%) died within 21 days, and of the 17 patients with tube test-negative *S. epidermidis* septicemias, five (29%) died within 21 days.

The patients were reviewed also for efficacy of treatment. There was no significant difference in the administration of appropriate antimicrobial therapy between those patients who died and those who improved. Although invasive catheters were removed more often in those patients who survived than in those who did not, this difference was not significant. These patients also did not differ in the incidence of malignant underlying diseases (Table 4).

Characteristics of single blood culture isolates. In this study, 489 single isolates were cultured from the blood. Of these, 314 were grouped as *S. epidermidis*, 78 were grouped as *S. hominis*, 21 were grouped as *S. capitis*, 18 were grouped as *S. warneri*, 11 were grouped as *S. haemolyticus*, 5 were grouped as *S. simulans*, 4 were grouped as *S. sciuri*, 3 were grouped as *S. xylosus*, 1 was grouped as *S. cohnii*, 1 was grouped as *S. intermedius*, and 33 were ungroupable by the API Staph procedure. When this species distribution was compared with that of the septicemia strains, the *S. epidermidis* species proved to be significantly ($P = 0.02$) more common among septicemia strains than among single blood isolates (80% vs. 64%).

The annual distribution of the adherent slime producers among single blood culture isolates is depicted in Table 2. Of all single isolates, 29% were tube adherence test positive. The difference between these and the tube test-positive septicemia strains was statistically significant ($P < 0.001$). Among the single isolates, slime production was rare (9%) in species other than *S. epidermidis* (Table 1). Of the single *S. epidermidis* blood isolates, 40% were tube adherence test positive (Table 1). Concomitantly, as many as 65% of the *S. epidermidis* septicemia strains were positive ($P = 0.0017$).

Of the single blood culture isolates, 83 were recovered from samples taken in Turku City Hospital and 406 were recovered from samples taken in Turku University Hospital. The proportion of adherent slime producers was equal in both hospitals (29 versus 29%). A total of 57 single isolates were recovered from patients in the hematologic unit of Turku University Central Hospital. Among them, 14 (25%) isolates were tube test positive. Coagulase-negative staphylococci were rarely recovered from blood cultures in the infectious diseases unit of Turku City Hospital. In that setting, only seven single isolates (one tube test positive) were recovered.

Slime production of other clinical single isolates. A total of 496 isolates were recovered from urine samples, 31% of which proved to be slime producing. Of the 98 urine isolates recovered from patients with urinary catheters, 32% were slime producing. A total of 61 and 24 isolates were recovered from catheter tips and cerebrospinal fluids, of which 26 and 17%, respectively, were adherent slime producers. None of the three cerebrospinal fluid isolates recovered from patients with cerebrospinal fluid shunts was slime producing. Of 1,070 single clinical isolates from blood, urine, catheter tips, and cerebrospinal fluid, 316 (30%) were adherent slime producers. The difference in slime production between these single isolates (defined as insignificant) and the septicemia strains was significant ($P < 0.001$).

Colonization of patients and personnel with slime-producing coagulase-negative staphylococci. From the fingertip flora of 169 hospital patients and personnel, a total of 439 coagulase-negative staphylococcal isolates were collected (average, 2.6 isolates per subject). About half of the subjects harbored 154 (35%) slime-producing isolates. The proportion of subjects with slime-producing isolates was highly variable among patients and various occupational groups (Table 5). In the hematologic unit, the majority of nurses (79%) and of patients with severe hematologic diseases (75%) were colonized with slime-producing strains, while fewer patients with other diseases and requiring shorter hospital stay (35%)

TABLE 5. Adherent, slime-producing coagulase-negative staphylococci on the skin of hospital personnel and patients

Institution and subject	No. of subjects		No. of isolates	
	Total	Slime producing (%)	Total	Slime producing (%)
Turku City Hospital[a] nurses	23	17 (74)	58	28 (48)
Turku University Central Hospital[b]				
Nurses	28	22 (79)[c,d,e]	66	37 (56)
Physicians	7	1 (14)[c]	14	1 (7)
Patients				
Hematologic (ciprofloxacin treated)	28	21 (75)[f]	122	63 (52)
Others	31	11 (35)[f]	59	13 (22)
Turku University				
Medical students	39	8 (21)[d]	83	10 (12)
Laboratory technicians	13	2 (15)[e]	37	2 (5)
Total	169	82 (49)	439	154 (35)

[a] Infectious diseases unit.
[b] Hematologic unit.
[c] Difference is statistically significant ($P < 0.01$).
[d] Difference is statistically significant ($P < 0.00001$).
[e] Difference is statistically significant ($P < 0.0005$).
[f] Difference is statistically significant ($P < 0.01$).

harbored these strains ($P = 0.0054$). Also, the majority (74%) of nurses in the infectious diseases unit of Turku City Hospital were colonized with slime-producing strains. In contrast, the fingertips of the physicians in Turku University Central Hospital as well as laboratory technicians and medical students in Turku University were only rarely colonized with slime-producing coagulase-negative staphylococci. The difference between the nurses and other health care personnel was statistically significant ($P < 0.00000001$).

Most (83%) of the slime-producing isolates recovered from the ciprofloxacin-treated immunocompromised patients in the hematologic unit were ciprofloxacin resistant. In contrast, only 23% of the slime-producing isolates recovered from other patients ($P < 0.001$) and only 21% of those from the nurses in the same hematologic unit were ciprofloxacin resistant ($P < 0.001$). Although 27% of the 15 patients studied within 2 days of admission harbored slime-producing strains, none of those isolates was ciprofloxacin resistant. Of the 118 ciprofloxacin-resistant coagulase-negative staphylococci, regardless of the source, 53% were slime producing.

DISCUSSION

The positive correlation between extracellular slime production and coagulase-negative staphylococcal septicemia strains reported in many earlier studies was also observed here. However, among these septicemia strains, tube adherence test positivity was only slightly more common than was tube test negativity. Thus, based on the positive tube test only, no specific conclusions could be drawn regarding the clinical significance of any particular patient isolate. Moreover, the slime-producing capacity of an individual septicemia strain, in and of itself, apparently played no role in the clinical outcome of infection. Therefore, it can be concluded that, at least in these two hospitals, positivity in the tube adherence test was of little value as a predictor of true septicemia or as a prognostic marker in adult patients.

Consistent with many earlier results (7, 16–18), the *S. epidermidis* species played a pronounced role in disease. In this study, *S. epidermidis* was significantly more common among the septicemia strains than among the single blood culture isolates. *S. epidermidis* was, as well, more likely (40 versus 9%) to be tube test positive than other species of coagulase-negative staphylococci. This phenomenon suggests that the observed positive correlation between slime production and infection could have reflected merely the prevalence of *S. epidermidis* species among the septicemia strains. However, the concomitant finding that adherent slime producers were significantly more common among the *S. epidermidis* septicemia strains than they were among the single *S. epidermidis* blood isolates excluded that possibility.

A cautionary note must be considered. By using the tube adherence test, slime production is demonstrated only in those strains which adhere to the test tube wall (28). In this study, this tendency potentially selected against the detection of nonadherent slime producers. Therefore, the role of putative nonadherent slime producers in these septicemias remains to be investigated.

The basic underlying assumption that the importance of slime production as a virulence factor might vary in different hospitals, depending on epidemiologic factors, was not confirmed in this study. In fact, no epidemiologic differences in the incidence of slime producers among the septicemia strains, single blood isolates, and nurse fingertip flora between the two hospitals studied were documented. Yet, it seems theoretically possible that although not confirmed here, such differences might indeed exist, especially since the distinction between many earlier clinical studies is obvious (1, 7, 18, 24). On the other hand, subtle differences between the methodology used in individual laboratories to detect coagulase-negative staphylococcal slime production could account for some discrepancy, as proposed by Pfaller and Herwaldt (30). Tube test results obtained within the same unit have proved reproducible in many of these studies (10, 11). This however in no way addresses the possibility of variation between different units. Other fundamental differences between these studies are also easily observed: the ages of the patients vary from neonatal to adulthood, and the infections include septicemias, foreign body infections, and continuous peritoneal dialysis peritonitis cases (7, 12, 16, 24, 35).

Admittedly, the impact given to the observed negative correlation between the slime-producing capacity of the septicemia strain and the clinical outcome of infection is difficult to estimate. All patients with nosocomial septicemias were already severely ill at the onset of septicemia. Besides the virulence of any individual septicemia strain, many other factors must have influenced the clinical outcome. Neither the severity of the underlying disease of the patient nor the adequacy of antimicrobial therapy, two obvious candidates to be considered, correlated with clinical outcome. The contributions of many other clinical factors were not investigated; therefore, a cautious posture seems justified.

An interesting epidemiologic finding was the common colonization of the nurses with slime-producing staphylococci compared with other health care personnel. At the present time, the reason for this phenomenon remains unknown. In the infectious diseases unit of Turku City Hospital, colonization of the nurses was associated neither with clinical infections of the patients nor with recovery of single slime-producing isolates from blood cultures. In the hematologic unit of Turku University Central Hospital, the study

of the skin flora was provoked by emergence of ciprofloxacin-resistant coagulase-negative staphylococcal septicemias in leukemia patients (21). The slime-producing cutaneous isolates from the nurses were mostly ciprofloxacin susceptible; ciprofloxacin-resistant slime-producing isolates were detected only occasionally. It seems unlikely, therefore, that colonization of the nurses was influenced by the use of ciprofloxacin in that unit.

On the other hand, it seems evident that colonization of the leukemia patients was greatly affected by ciprofloxacin treatment. Slime-producing isolates from leukemia patients were almost exclusively ciprofloxacin resistant and, as shown by plasmid profile analysis earlier, most likely related epidemiologically (21). Other patients in the unit harbored slime-producing coagulase-negative staphylococci less often, and only rarely were these isolates ciprofloxacin resistant. Further, no slime-producing, ciprofloxacin-resistant isolates were detected in those patients who were studied within 2 days of admission. Collectively, these findings suggest that the patients became colonized with slime-producing staphylococci during extended hospital stays in the hematologic unit. Moreover, epidemic spread of such staphylococci seemed to have been influenced by antimicrobial therapy.

Interestingly, the septicemias of those patients requiring extended hospitalization were more often, although not significantly so, caused by tube adherence test-positive strains compared with patients requiring shorter-term hospitalization. One explanation for this could be colonization of the patients in the hospital environment with slime-producing coagulase-negative staphylococci, which later might involve septicemias. Hospitalization was longest, in fact, for those patients with hematologic malignancies, of whom many were colonized with ciprofloxacin-resistant slime-producing flora. This might lead one to hypothesize that the emergence of the ciprofloxacin-resistant coagulase-negative staphylococcal sepsis epidemic in the hematologic unit might have been the underlying factor for this phenomenon. To investigate this possibility, the ciprofloxacin-resistant septicemias were excluded. Despite such exclusion, the observed association between the slime-producing septicemia strains and extended hospitalizations remained unchanged.

All of the ciprofloxacin-resistant cutaneous isolates collected in the hematologic unit have been previously identified as *S. epidermidis* (21). In addition, the plasmid profile analysis, also reported earlier, shows a common plasmid pair (2.3 and 1.5 MDa) in the majority of those strains. This suggests common origin and spread of epidemiologically related strains within the department (21). Six of the ciprofloxacin-resistant coagulase-negative staphylococcal septicemias in hematologic patients were caused by *S. epidermidis* strains with 2.3- and 1.5-MDa plasmids. In all six cases, the strains were slime producing. Therefore, an unexpected finding in this study was that, indeed, only about half of the ciprofloxacin-resistant *S. epidermidis* cutaneous isolates with similar plasmid profiles were slime producing. The implications of this interesting observation are not presently understood and deserve more attention in the future.

The observations herein neither proved nor disproved the assumption that slime production as a virulence factor varies in different hospitals. This study suggests that in the hospital environment, the spread of slime-producing staphylococci can be influenced by antimicrobial therapy and, in this case, specifically by ciprofloxacin. In conclusion, in any specific hospital setting, the impact of positivity in the tube adherence test should be correlated to the local situation. In the two hospitals studied, staphylococcal positivity in the tube test proved to be of minor practical importance in guiding clinical decisions in treating adult septicemias. Moreover, adherence and slime production of an individual septicemia strain, as such, apparently played no role in the clinical outcome of these infections.

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