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Effect of hospitalization and antimicrobial therapy on antimicrobial resistance of colonizing *Staphylococcus epidermidis*

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Summary. Endogenous infections with multi-resistant *S. epidermidis* are among the leading causes of nosocomial infections. The effect of hospitalization and antimicrobial therapy on antimicrobial resistance of colonizing staphylococci was determined from swabs of the nose, hand, axilla and groin from 157 patients on one day. Hospitalization for > 72 hours, compared with < 72 hours, was associated with a higher percentage of isolates resistant to oxacillin (56% versus 19%), gentamicin (40% versus 15%), trimethoprim (36% versus 17%), clindamycin (56% versus 17%), and fusidic acid (20% versus 4%; $p < 0.01$ for all), but not to rifampicin (6% versus 1%) or fosfomycin (43% versus 34%, $p > 0.05$ for both). Concurrent antimicrobial therapy resulted in increased resistance to oxacillin (61% versus 28%), gentamicin (43% versus 20%), and clindamycin (60% versus 26%; $p < 0.01$ for all), but not to trimethoprim (39% versus 23%), fusidic acid (19% versus 9%), rifampicin (6% versus 3%), or fosfomycin (46% versus 38%, $p > 0.05$ for all). The increase in resistant isolates was not independent, since hospitalization and antimicrobial therapy were correlated ($p < 0.001$). After adjustment for potential risk factors such as diabetes mellitus, central venous catheters, and hemodialysis, the odds ratio for oxacillin resistance was 2.8–3.6. None of the risk factors showed statistically significant results, except for the presence of neoplastic disease, which had a significant interaction ($P = 0.035$). The within-subgroup odds ratios for patients with and without neoplasm were 4.2 (95% CI, 2.3–5.7) and 2.1 (95% CI, 0.78–3.12), respectively. These results show that hospitalization for more than three days, with or without antimicrobial therapy, and the presence of neoplastic disease are associated with increased antimicrobial resistance in colonizing *S. epidermidis*.

Key words: Hospitalization, antimicrobial resistance, colonizing staphylococci.

Introduction

Nosocomial infections are responsible for about 98,000 deaths per year and affect about two million people per year in the USA [1, 2]. Coagulase-negative staphylococci (CNS) are among the leading causes of nosocomial infections of the bloodstream [3]. Surveillance of nosocomial infections in intensive care showed that CNS dominated in primary blood-stream infections associated with central venous catheters [4]. Colonized patients are a pivotal source of infecting strains, and carriage of staphylococci in the nose appears to play a key part in the pathogenesis of infection [5–9]. A recent study showed that a substantial proportion of cases of bacteremia appears to be endogenous, originating from staphylococci in the nares [7].

Antimicrobial resistance is a growing concern as the number of multi-resistant isolates increases and they become more widespread [10–19]. For more than 40 years the transmissibility of staphylococci, principally drug-resistant staphylococci, has been known to be considerably increased among patients receiving therapy with doxycycline [20]. In many hospitals more than 50% of staphylococci are methicillin-resistant [21]. In another study it was shown that anti-infective therapy, which is excreted in the sweat through eccrine and apocrine glands, may influence the skin flora, mainly *S. epidermidis* [22]. For example, sensitive strains in the axilla were rapidly replaced by strains showing intermediate resistance to ciprofloxacin, with MICs just above the concentrations measured in the sweat, and by highly resistant strains. These findings suggest that excretion of antibiotics in the sweat is responsible for the development of highly resistant *S. epidermidis* strains on the human skin [22].

This descriptive study investigated the effect of hospitalization and antimicrobial therapy on antimicrobial resistance of colonizing *S. epidermidis*.

Methods

On Friday, January 21st 2000, swabs of the nose, hand, axilla and groin were taken from 157 (75 female/82 male) inpatients in the Department of Medicine, University Hospital of Graz. Written informed consent was obtained from all enrolled patients and the study was approved by the local ethics committee. All admitted patients (n = 243) were screened. Patients with a history of previous, not concurrent, antimicrobial therapy in the month prior to the study (n = 56) and those not giving informed consent (n = 30) were excluded.

Clinical data such as age, sex, duration of hospitalization, underlying diseases (pulmonary disease, cirrhosis of the liver, renal failure, hemodialysis, heart disease, neutropenia, neoplas-

Table 1. Clinical characteristics of patients (n = 157)

Characteristic	Hospitalization		Antimicrobial therapy		Total
	< 72 hours (n = 69)	> 72 hours (n = 88)	without (n = 80)	with (n = 67)	(n = 157)
Age (mean ± SD*)	62 ± 17	62 ± 17	60 ± 17	65 ± 17	62 ± 17
Sex (F/M)	35/34	40/48	41/49	33/34	75/82
Hours of hospitalization median (range)	27 (1–69)	214 (76–2884)	67 (1–771)	206 (10–2884)	102 (1–2884)
Pulmonary disease (n)	3	17	5	15	20
Smoking (> 5 pack years) (n)	15	26	25	16	41
Alcohol (> 50 g/d) (n)	18	22	28	12	40
Liver cirrhosis ≥ Child-Pugh B (n)	4	1	3	2	5
Renal failure (n)	8	8	6	10	16
Hemodialysis (n)	2	11	6	7	13
Heart disease (n)	19	24	27	16	43
Neutropenia** (n)	1	13	1	13	14
Neoplasm (n)	13	31	24	20	44
Diabetes mellitus (n)	11	17	15	13	28
Infection (n)	19	50	2	67	69
Central venous catheter (n)	5	19	10	14	24
No risk factor	23	11	27	7	34
One risk factor	31	25	38	18	56
Two risk factors	13	37	29	31	50
≥ 3 risk factors	2	15	6	11	17
Leukocyte count (G/L) median (range)	7 (0.1–19)	7.4 (0.01–72)	7.2 (3–72)	7.2 (0.01–29)	7.2 (0.1–72)
CRP-level (g/L) median (range)	7 (0–243)	22.5 (0–465)	7 (0–130)	52 (0–465)	15 (0–465)

* Standard deviation, ** Leukocyte count < 1 G/L.

tic disease, diabetes mellitus), central venous catheter, antimicrobial therapy, risk factors and hospital ward were collected. The isolates were assigned into two groups based on the length of patients' hospitalization: isolates from patients staying for less than 72 hours before 8 a. m. Jan. 21st were defined as "community acquired" and isolates from those staying longer than or exactly 72 hours before 8 a. m. Jan. 21st were defined as "nosocomial" [23–26].

The swabs were plated on chocolate agar (bioMerieux sa, Marcy l'Etoile, France), MacConkey agar (bioMerieux), Schädler agar (BD, Cockeyville, USA) and sheep blood agar (BD) and cultured at 37 °C in air for 48 hours. Organisms were identified to species level using catalase, coagulase and Api Staph tests (bioMerieux, Vienna, Austria) according to the manufacturer's instructions. Only *S. epidermidis* isolates were further analysed. Antimicrobial-disk susceptibility tests were used for sensitivity testing, according to NCCLS M2–A7 [27, 28], against the following substances: penicillin, amoxicillin/clavulanic acid, oxacillin, cefazolin, cefotaxim, cefepime, clindamycin, erythromycin, vancomycin, fosfomycin, fusidic acid, gentamicin and rifampicin. The NCCLS breakpoints were used for the interpretation of the tests [28]. A total of 250 *S. epidermidis* isolates were cultured. In all patients with more than one cultured isolate (n = 98), antimicrobial susceptibility was identical in all isolates. Hence, duplicates were omitted.

Chi-square tests or Fisher's exact tests were used for statistical analyses. Univariate stratified analyses for the characteristics in Table 1 were performed using the Cochran-Mantel-Haenszel test to determine the effect of potential confounding variables, such as underlying diseases or risk factors, on the sensitivity of *S. epidermidis* with respect to hospitalization and antimicrobial treatment. The Breslow-Day test was used for interactions of the stratified odds ratios for each baseline characteristic analysed. Differences where $p < 0.05$ were considered statistically significant.

Results

Clinical characteristics

The clinical characteristics of the patient groups are shown in Table 1. Pulmonary disease, hemodialysis, neutropenia, neoplasm, infection, and central venous catheters were more common in patients hospitalized for more than 72 hours than in those hospitalized for a shorter time ($p < 0.05$ for all comparisons). Pulmonary disease, neutropenia and infections were more common in patients receiving current antimicrobial therapy than in those who were not ($p < 0.05$ for all). After adjustment for each baseline characteristic shown in Table 1, the odds ratio was

Table 2. Antimicrobial therapy (n = 67)

Antimicrobial therapy	Number	Duration (h) prior to sampling median (range)	Last application (h) prior to sampling median (range)
Betalactams	19	144 (13–504)	4 (1–24)
Macrolides	7	98 (16–356)	8 (3–12)
Vancomycin	4	145 (19–336)	8 (2–48)
Quinolones	6	65 (11–140)	6 (1–24)
Others	2	312,413	24,3
Combinations	29	168 (15–672)	2 (1–24)

2.8–3.6. None of the tests for interactions showed significant results, except for the presence of neoplastic disease ($P = 0.035$). The within-subgroup odds ratios for patients with and without neoplasm were 4.2 (95% CI, 2.3–5.7) and 2.1 (95% CI, 0.78–3.12), respectively.

Other risk factors were equally distributed between the groups. 69/157 patients were admitted for an infectious disease (influenza n = 6, soft tissue infection n = 4, meningitis n = 2, peritonitis n = 1, blood stream infection n = 7, acute exacerbation of chronic bronchitis n = 15, pneumonia n = 13, urinary tract infection n = 5, neutropenic fever n = 14, enteritis n = 2) and 67 of them were treated with antimicrobial therapy. Table 2 shows the duration of antimicrobial therapy with different compounds and combinations and the time of the last dose prior to sampling.

Microbiological results

Table 3 shows the percentage of resistant isolates in patients admitted for < 72 hours, > 72 hours and in patients with and without antimicrobial therapy. Antimicrobial therapy was correlated with the duration of hospitalization ($p < 0.001$). Hospitalization for > 72 hours, compared with < 72 hours, was associated with a higher percentage of isolates that were resistant to oxacillin (56% versus 19%), gentamicin (40% versus 15%), trimethoprim (36% versus 17%), clindamycin (56% versus 17%), and fusidic acid (20% versus 4%; $p < 0.01$ for all), but not to rifampicin (6% versus 1%) or fosfomycin (43% versus 34%, $p > 0.05$ for both). Concurrent antimicrobial therapy resulted in increased antimicrobial resistance to oxacillin (61% versus 28%), gentamicin (43% versus 20%), and clindamycin (60% versus 26%; $p < 0.01$ for all), but not to trimethoprim (39% versus 23%), fusidic acid (19% versus 9%), rifampicin (6% versus 3%), or fosfomycin (46% versus 38%, $p > 0.05$ for all). Presence or absence of oxacillin resistance was used to analyse confounding variables such as risk factors. The odds ratios for various risk factors are shown in Fig. 1. ICU-admission, heart disease, pulmonary disease, diabetes mellitus, central venous catheter, renal disease or hemodialysis were not per se associated with an increased risk of *S. epidermidis* resistance (Fig. 1.) The odds ratio for hospitalization for more than 72 hours was 3.4 (95% CI 1.47–7.95), for antimicrobial therapy 3.0 (95% CI 1.34–6.72), and for neoplastic disease 2.26 (95% CI 0.98–5.19) ($p < 0.05$ for all). After adjustment for each baseline characteristic (Table 1), the odds ratio was 2.8–3.6. None of the tests for interactions had significant re-

Table 3. Effect of hospitalization for > 72 and < 72 hours and antimicrobial therapy on the number (percentage) of resistant isolates in colonizing *S. epidermidis*

Antimicrobials	Hospitalization		Antimicrobial therapy		p-values
	< 72 hours (n = 69)	> 72 hours (n = 88)	without (n = 80)	current (n = 67)	hospitalization/ antimicrobial therapy
Penicillin	28 (41)	67 (76)	38 (48)	57 (85)	0.004/0.001
Amoxi/Clav	13 (19)	50 (57)	22 (28)	41 (61)	0.001/0.001
Oxacillin	13 (19)	49 (56)	21 (27)	41 (61)	0.001/0.001
Cefazolin	13 (19)	49 (56)	21 (27)	41 (61)	0.001/0.001
Cefotaxim	13 (19)	51 (58)	23 (28)	41 (61)	0.001/0.001
Cefepim	13 (19)	49 (56)	22 (28)	41 (61)	0.001/0.001
Imipenem	13 (19)	49 (56)	22 (28)	41 (61)	0.001/0.001
Vancomycin	0 (0)	0 (0)	0 (0)	0 (0)	0.999/0.999
Erythromycin	22 (32)	57 (65)	28 (35)	51 (76)	0.001/0.001
Gentamicin	10 (15)	35 (40)	16 (20)	29 (43)	0.001/0.001
Rifampicin	1 (1)	5 (6)	2 (3)	4 (6)	0.210/0.207
Trimethoprim	12 (17)	32 (36)	18 (23)	26 (39)	0.002/0.051
Fosfomycin	23 (33)	38 (43)	30 (38)	31 (46)	0.470/0.444
Clindamycin	12 (17)	49 (56)	21 (26)	40 (60)	0.001/0.001
Fusidic acid	3 (4)	18 (29	8 (9)	13 (19)	0.010/0.081

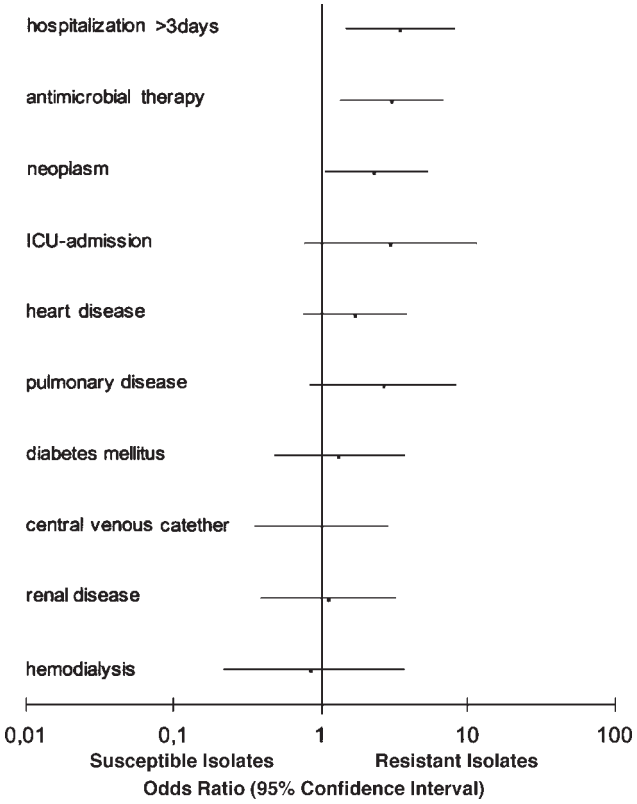

Fig. 1. Odds ration for Oxacillin-resistant *S. epidermidis* for underlying diseases and risk factors

sults, except for the presence of neoplastic disease, which had a significant interaction ($P = 0.035$). The within-subgroup odds ratios for patients with and without neoplasm were 3.6 (95% CI, 1.4–6.7) and 1.9 (95% CI, 0.68–3.12), respectively.

Discussion

These results show that hospitalization for more than three days, with or without antimicrobial therapy, and the presence of neoplastic disease are associated with increased antimicrobial resistance in colonizing *S. epidermidis*.

The cross-sectional study design could have led to a selection bias through over-representation of patients with a long duration of hospitalization. A longitudinal study, which unfortunately was not possible because of limited resources, would have been more appropriate for the analysis of causalities. However, such a study would not be able to prove that colonising staphylococci acquire resistance after 72 hours or as a result of antimicrobial therapy, since selection of resistant strains that are already present in low numbers or transmission from health care workers could occur.

CNS live naturally on the skin and mucous membranes of humans and are therefore often found in clinical specimens. Distinguishing clinically significant, pathogenic strains from contaminant strains is one of the major challenges facing daily practice. In recent years CNS have emerged as the most frequent organisms isolated from blood cultures [29, 30]. In the study year, 233 of 530 (44%) positive blood cultures from patients of our department grew CNS and 181 of 233 (78%) CNS isolates were resistant to oxacillin. In this cross-sectional study, only *S. epidermidis* isolates were analysed, and other species such as *S. capitis*, *S. hominis*, *S. hemolyticus* etc. could show a different percentage of resistance. This could be an explanation for the observed lower resistance rate, in particular in patients hospitalized for < 72 hours or patients not receiving antimicrobial therapy (19% and 27%, respectively). In some areas of Europe high proportions (60–70%) of CNS are oxacillin resistant, although there are marked geographic variations [31]. In a German study of bacteremia associated with central venous catheters, CNS dominated (30.9%), followed by *S. aureus* (15.4%) and *Enterococcus* spp. (11.6%) [4]. In a recent Italian study, CNS accounted for 41% of all isolates from blood cultures in ICU patients; of these, 64% were methicillin resistant and showed high rates of resistance to many other antibiotics [32].

CNS cause bloodstream infections in both immunocompetent and immunosuppressed patients and are particularly responsible for bacteremia relating to catheters and medical devices [33]. In these patients, the host defense mechanisms often seem unable to handle the infection and, in particular, to eliminate the staphylococci from the infected device because of a biofilm on the surface of the foreign body [5]. CNS are also a main cause of contamination of blood cultures, and contamination rates up to 8% have been reported [34]. The introduction of blood-culture teams, consisting of dedicated phlebotomists, and defined culture procedures can lower the contamination level to 1%. [34]. Some CNS that cause bacteremia are skin colonizers and may gain access to the blood through a transcutaneous vascular device. A recent article reports that "more frequent use of current hygiene practices may not necessarily be better, and the same recommendations cannot be applied to all users or situations" [35]. However, the necessity for hand hygiene among health care workers has been emphasised [36–42]. Two studies argue that more than half the strains at the insertion sites of central venous catheters are different from CNS strains causing bacteremia. This supports previous publications where mucous membranes were shown to be the primary sources of CNS strains causing bacteremia, especially in immunocompromised patients [33, 43].

A number of studies show a relationship between antibiotic use and resistance [44–48]. Increasing antimicrobial resistance reduces the effectiveness of antimicrobial treatment, leading to increased morbidity, mortality and health-care expenditure [49, 50]. However, there is disagreement about the major mechanisms by which antibiotics select resistant strains, in particular nosocomial strains. Lipsitch and Samore argue that the relationship between antibiotic usage and development of resistance for many types of pathogens is largely mediated by indirect effects or population-level selection [51]: "For infections like tuberculosis, in which resistance can emerge in treated hosts through mutation, prevention of antimicrobial resistance in individual hosts is a primary method of preventing the spread of resistant organisms in the community. By contrast, for many other important resistant pathogens, such as penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*,

and vancomycin-resistant *Enterococcus faecium* resistance is mediated by the acquisition of genes or gene fragments by horizontal transfer; resistance in the treated host is a relatively rare event. For these organisms, indirect, population-level mechanisms of selection account for the increase in the prevalence of resistance. These mechanisms can operate even when treatment has a modest, or even negative, effect on an individual host's colonization with resistant organisms". In addition, the authors [51] discuss that "simply by eradicating susceptible organisms, and thereby reducing the opportunities for transmission of susceptible strains, antibiotics received by treated hosts can increase the probability that other hosts will acquire resistant variants. For many pathogens, acquisition of one strain reduces a person's chances of acquiring other strains, either via immune responses, via direct interference, or both" [52–56]. The use of antibiotic management programs to maintain consistency among providers has been encouraged [57–59]. It has been argued that, after culture and sensitivity results are obtained, curtailment of broad-spectrum therapy and use of the least broad agent possible is important [60–62]. The need to stem the growing problem of antimicrobial resistance has prompted multiple, sometimes conflicting, calls for changes in the use of antimicrobial agents.

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