

# New Strategies to Prevent *Staphylococcus Aureus* Infections in Peritoneal Dialysis Patients

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**Abstract.** The importance of *Staphylococcus aureus* as etiological agent for catheter-related infections and peritonitis in peritoneal dialysis patients is well established. To evaluate groups at risk of developing *Staphylococcus aureus* infections, nasal and exit-site cultures were performed in 76 peritoneal dialysis patients monthly over a period of 3 yr. The risk of *Staphylococcus aureus* catheter infection was significantly higher in diabetic (group 1) and immunosuppressed (group 2) patients compared with nondiabetic and nonimmunosuppressed (group 3) patients. In diabetic patients, *Staphylococcus aureus*-positive nasal cultures were more frequent than positive cultures taken from the bland exit-site (73.3% versus 60.0%). On the other hand, both positive and negative exit-site cultures had a better prognostic value for *Staphylococcus aureus* catheter infection compared with nasal cultures. In immunosuppressed patients, both nasal and exit-site carriage were associated with

a very high risk of *Staphylococcus aureus* catheter infection, but nasal swabs were far more often positive than swabs from the bland exit-site (72.7% versus 25.0%). However, the risk of infection was also high for non-nasal and non-exit-site carriers in this group. In nondiabetic and nonimmunosuppressed patients, the risk of *Staphylococcus aureus* catheter infection was increased only if two or more positive nasal cultures were detected. It is concluded that in diabetic patients, antibiotic prophylaxis should be performed in all *Staphylococcus aureus* exit-site carriers. All immunosuppressed patients should be treated prophylactically. In contrast, in nondiabetic and non-immunosuppressed patients, prophylactic treatment should be considered only in nasal carriers with two or more positive cultures. The overall low peritonitis rate does not influence this prevention strategy. (J Am Soc Nephrol 9: 669-676, 1998)

Continuous ambulatory peritoneal dialysis (CAPD) has become a standard mode of therapy for end-stage renal disease. Recent studies have shown that catheter-related infections are the major cause of CAPD catheter failure (1-6). The importance of *Staphylococcus aureus* as etiological agent of catheter-related infections and peritonitis in short- and long-term peritoneal dialysis patients is well established (1-15). Several studies have demonstrated that *Staphylococcus aureus* is the most common organism causing catheter-related infections, and that these infections are difficult to cure and catheter removal is required in up to 67% of cases (3,11,16-18). As early as 50 yr ago, attention was drawn toward *Staphylococcus aureus* carrier status (19). Many studies have been performed in drug abusers, surgical patients, and hemodialysis and peritoneal dialysis patients, demonstrating that *Staphylococcus aureus* nasal carriage is associated with increased susceptibility for *Staphylococcus aureus* infections in these populations (7,9,16,20-29). Therefore, several attempts have been made to treat *Staphylococcus aureus* carriers prophylactically to dimin-

ish the risk of *Staphylococcus aureus* infections (17,30-47). In a few studies, patients, independent of their carrier status, were treated prophylactically (27,48-50). Although several studies showed that it was possible to eradicate *Staphylococcus aureus* temporarily and to reduce the *Staphylococcus aureus* infection rate at the same time by different prophylactic regimens (17,22,24,34,35,38,46,49-53), several clinical problems, such as resistance against antimicrobial therapy, recolonization of the nose, and adverse effects of systemic antibiotic treatment, occurred (17,22,31,34,37,41,42,45,46,49,54-58). Because of these observed problems, several authors (34,38,59) have suggested identifying patients at risk of developing *Staphylococcus aureus* infections who may benefit from prophylactic intervention. However, until now, no general guidelines existed regarding how to handle the *Staphylococcus aureus* carrier problem in dialysis patients. The aim of this study was to evaluate groups at risk of developing *Staphylococcus aureus* catheter infections in peritoneal dialysis patients, in whom prophylactic treatment should be considered.

## Materials and Methods

### Patients

Between August 1993 and August 1996, 76 patients (37 women, 39 men; mean age, 47.5 ± 1.63; range, 19 to 76 yr) were treated with peritoneal dialysis in our center. During the entire study period, we used curled Tenckhoff and swan neck catheters with a single cuff. The mean duration of dialysis was 20.4 ± 1.0 mo. The minimal observa-

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on period was 6 mo, and the maximal observation time was 32 mo. During this observation period, cultures of the nares were obtained monthly and analyzed by standard techniques in the microbiology laboratory. In contrast to nasal cultures, exit-site cultures were obtained from each patient beginning in October 1994. Examination of the exit-site was performed during each clinic visit.

To evaluate possible risk factors for developing *Staphylococcus aureus* catheter-related infections, we divided the patients into three groups. Group 1 consisted of 15 patients with diabetes mellitus (10 women, five men), group 2 included 22 patients with chronic graft failure after renal transplantation who continued immunosuppressive therapy because of residual graft function (15 women, seven men), and group 3 was composed of 39 patients without immunosuppressive therapy or diabetes mellitus (12 women, 27 men).

Patients were defined as *Staphylococcus aureus* nasal carriers from the time of first positive nasal culture until the end of the observation period. Patients were defined as noncarriers as long as no positive nasal culture was obtained. *Staphylococcus aureus* exit-site carrier status was diagnosed when *Staphylococcus aureus* was cultured from an exit-site without clinical signs of acute or chronic exit-site infection. Like nasal carriers, *Staphylococcus aureus* exit-site carriers were defined from the time of the first positive *Staphylococcus aureus* culture taken from the bland exit-site. *Staphylococcus aureus* exit-site infection was diagnosed clinically, if erythema and/or exudate was present. A culture from the exit-site was obtained in these cases to confirm the causative organism. *Staphylococcus aureus* peritonitis was diagnosed if clinical signs of peritoneal inflammation (cloudy dialysate, leukocytes  $>200/\mu\text{l}$ , abdominal pain) were present and *Staphylococcus aureus* was cultured from the dialysate.

*Staphylococcus aureus* catheter infection rates and peritonitis rates were calculated as all infections in each group within the observation period divided by the composite observation time. The data are expressed as episodes per year. To determine the time-dependent risk of *Staphylococcus aureus* catheter infection and *Staphylococcus aureus* peritonitis of each patient group, we analyzed the time from initiation of peritoneal dialysis treatment until occurrence of the first episode of *Staphylococcus aureus* catheter infection or *Staphylococcus aureus* peritonitis, using Kaplan-Meier survival estimates. Another Kaplan-Meier survival estimate was calculated from the time when the first *Staphylococcus aureus*-positive nasal culture was obtained until the first catheter infection occurred. The same calculation was done for positive exit-site cultures. In the latter calculation, we included only patients who began treatment after October 1994, when regular exit-site cultures were performed ( $n = 52$ ; group 1,  $n = 10$ ; group 2,  $n = 16$ ; group 3,  $n = 26$ ).

The risk of developing *Staphylococcus aureus* catheter infection

for patients with negative nasal cultures was also assessed with Kaplan-Meier survival estimates for each patient group. To examine differences between nasal/exit-site carriers and noncarriers within each group, the patients were divided into two separate categories: patients without positive culture and those with at least one positive culture. To determine whether nasal carriage tends to precede exit-site carriage, we again analyzed the time from start of peritoneal dialysis therapy until the first occurrence of *Staphylococcus aureus*-positive nasal and exit-site cultures. Informed consent according to the Declaration of Helsinki was obtained from all patients.

### Statistical Analyses

Raw data were divided into several subsets to perform time-splitting investigations. Depending on a specific question, time from a defined starting point to an event point was analyzed using Kaplan-Meier estimates. If a patient did not undergo the event of interest, this observation was censored. To detect differences of the survival functions across strata (patient groups, carrier status), the log-rank test was performed. To compare the time to positive nasal culture and positive exit-site culture, only patients with at least one positive location could be analyzed. These times were compared using the sign test separately for each patient group. Continuous variables are presented as mean values  $\pm$  SEM. Differences between continuous variables were calculated using ANOVA and Tukey's test (for multiple comparisons). For all tests performed, a  $P$  value  $<0.05$  was considered significant. All data analyses were done within the Statistical Analysis System<sup>®</sup> Software Package (SAS Institute, Cary, NC).

### Results

Patient characteristics are shown in Table 1. There was no significant difference between the groups considering duration of dialysis, body mass index, mean Kt/V per week, and mean creatinine clearance per week.

*Staphylococcus aureus* was cultured from the nose at least once in 65.8% of all patients, in 73.3% of the diabetic patients (group 1), in 72.7% of the patients under immunosuppressive treatment (group 2), and in 59.0% of the patients without immunosuppressive therapy and without diabetes mellitus (group 3). *Staphylococcus aureus* was cultured from the bland exit-site on at least one occasion in 32.7% of all patients, in 60.0% of group 1, in 25.0% of group 2, and in 26.9% of group 3.

Figure 1 shows that the probability of remaining free from *Staphylococcus aureus* catheter-related infection was lowest in

Table 1. Patient characteristics<sup>a</sup>

Characteristic	Group 1 (Diabetic Patients)	Group 2 (Immunosuppressed Patients)	Group 3 (Others)
<i>n</i>	15	22	39
Age (years)	52.5 $\pm$ 3.3	40.4 $\pm$ 2.1 <sup>b,c</sup>	50.4 $\pm$ 2.6
Duration of dialysis (months)	21.3 $\pm$ 2.1	20.9 $\pm$ 1.7	19.9 $\pm$ 1.4
Body mass index	23.8 $\pm$ 1.2	22.2 $\pm$ 0.7	22.7 $\pm$ 0.4
Mean Kt/V (per week)	2.1 $\pm$ 0.08	2.2 $\pm$ 0.08	2.2 $\pm$ 0.07
Mean creatinine clearance (L/wk)	62.8 $\pm$ 3.4	63.2 $\pm$ 3.8	72.0 $\pm$ 3.9

<sup>a</sup> Mean values  $\pm$  SEM.

<sup>b</sup>  $P < 0.05$ , group 1 versus group 2.

<sup>c</sup>  $P < 0.05$ , group 2 versus group 3.

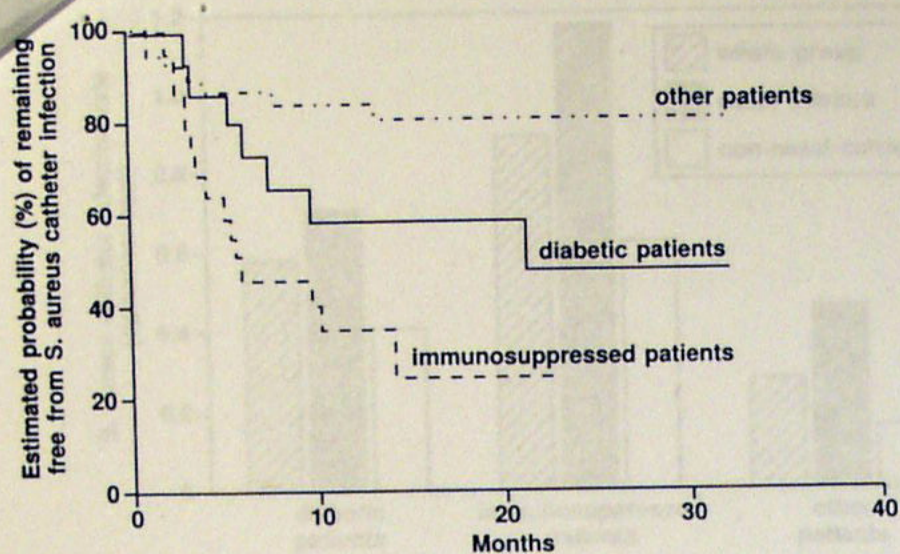


Figure 1. Estimated probability (%) of remaining free from *Staphylococcus aureus* catheter infection in diabetic patients (—), immunosuppressed patients (---), and nondiabetic, nonimmunosuppressed patients (- · - · -).

the immunosuppressed patients (group 2) (group 2 versus group 3,  $P < 0.0001$ ; group 2 versus group 1,  $P = 0.052$ , log-rank test). Moreover, there also was a significantly higher probability of *Staphylococcus aureus* catheter infection in diabetic patients (group 1) compared with the nondiabetic, nonimmunosuppressed patients (group 3) (group 1 versus group 3,  $P = 0.046$ , log-rank test).

Figure 2 demonstrates a very low probability of developing *Staphylococcus aureus* peritonitis in nondiabetic and nonimmunosuppressed patients (group 3). A significantly higher probability of *Staphylococcus aureus* peritonitis was found in both diabetic (group 1) and immunosuppressed (group 2) patients compared with nondiabetic and nonimmunosuppressed patients (group 3) (group 1 versus group 3,  $P = 0.039$ ; group 2 versus group 3,  $P = 0.044$ , log-rank test). However, the overall *Staphylococcus aureus* peritonitis incidence was low in all three groups. This is also confirmed by calculating the *Staphylococcus aureus* peritonitis rate for the different patient groups (Table 2: 0.19 episodes per year for group 1, 0.16

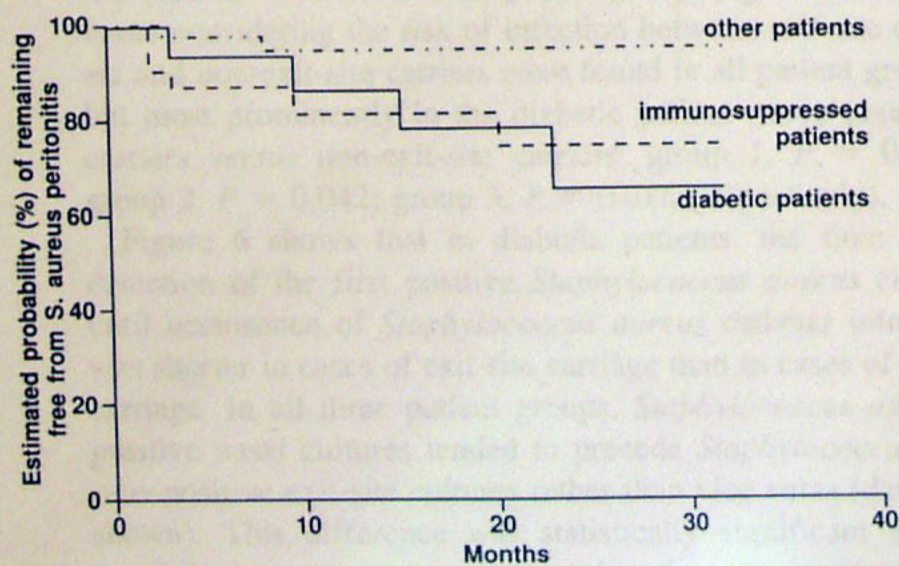


Figure 2. Estimated probability (%) of remaining free from *Staphylococcus aureus* peritonitis in diabetic patients (—), immunosuppressed patients (---), and nondiabetic, nonimmunosuppressed patients (- · - · -).

Table 2. *Staphylococcus aureus* peritonitis rates (episodes/year)

Group	All Patients	Group 1 (Diabetic Patients)	Group 2 (Immunosuppressed Patients)	Group 3 (Others)
Whole group	0.10	0.19	0.16	0.03
Nasal carriers	0.12	0.19	0.16	0.04
Non-nasal carriers	0.09	0.18	0.15	0.03

episodes per year for group 2, 0.03 episodes per year for group 3). The peritonitis rate of nasal carriers was comparable to that of non-nasal carriers in all patient groups (Table 2).

Figure 3 shows the probability of remaining free from *Staphylococcus aureus* catheter infection for nasal carriers and non-nasal carriers of each patient group. Both nasal carriers and non-nasal carriers of the immunosuppressed patient group (group 2) demonstrated a comparable high risk of *Staphylococcus aureus* catheter infection (NS). Immunosuppressed non-nasal carriers had an even higher risk of *Staphylococcus aureus* catheter infection compared with nasal carriers of the other two groups. There was a low probability of *Staphylococcus aureus* catheter infection in nondiabetic and nonimmunosuppressed patients (group 3) compared with the other two groups (nasal carriers: group 3 versus group 1, NS; group 3 versus group 2,  $P = 0.001$ ; non-nasal carriers: group 3 versus group 1, NS; group 3 versus group 2,  $P = 0.001$ , log-rank test). The risk of infection was higher for nasal carriers than for non-nasal carriers in this group (NS). In diabetic patients (group 1), there was a slightly, but not significantly, increased risk of *Staphylococcus aureus* catheter infection for nasal carriers compared with non-nasal carriers.

Figure 4 depicts the number of infections per year for each

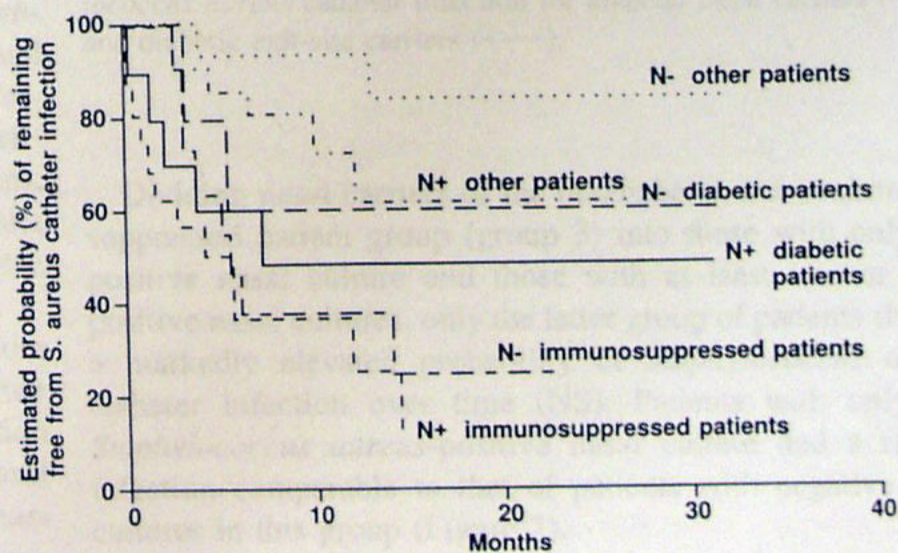


Figure 3. Estimated probability (%) of remaining free from *Staphylococcus aureus* catheter infection for nasal carriers (N+) and non-nasal carriers (N-) of each patient group. —, diabetic nasal carriers; — —, diabetic non-nasal carriers; ---, immunosuppressed nasal carriers; — - —, immunosuppressed non-nasal carriers; - · - · -, nondiabetic, nonimmunosuppressed nasal carriers; · · · ·, nondiabetic, nonimmunosuppressed non-nasal carriers.

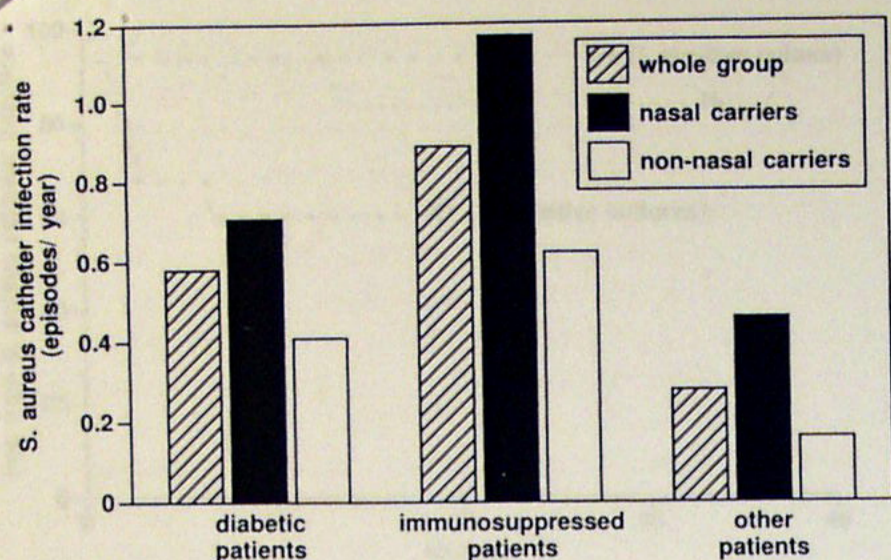


Figure 4. *Staphylococcus aureus* catheter infection rate (episodes/year) for the whole population (▨), nasal carriers (■), and non-nasal carriers (□) of each patient group.

group and for *Staphylococcus aureus* nasal carriers and non-nasal carriers. There was a higher *Staphylococcus aureus* catheter infection rate in the diabetic (group 1) and the immunosuppressed (group 2) patient group compared with nondiabetic, nonimmunosuppressed patients (group 3) (group 1 versus group 3: 0.58/yr versus 0.28/yr, NS; group 2 versus group 3: 0.89/yr versus 0.28/yr,  $P < 0.05$ , respectively). In the entire population and in all patient groups, the number of *Staphylococcus aureus* catheter infections per year was higher for *Staphylococcus aureus* nasal carriers than for non-nasal carriers (whole population: nasal carriers 0.75/yr, non-nasal carriers 0.33/yr; group 1: nasal carriers 0.71/yr, non-nasal carriers 0.41/yr; group 2: nasal carriers 1.17/yr, non-nasal carriers 0.62/yr; group 3: nasal carriers 0.46/yr, non-nasal carriers 0.16/yr). It is remarkable that the *Staphylococcus aureus* catheter infection rate of immunosuppressed non-nasal carriers was even higher than the infection rate of *Staphylococcus aureus* nasal carriers of group 3 (nondiabetic, nonimmunosuppressed patients).

Figure 5 shows the probability of remaining free from *Staphylococcus aureus* catheter infection for exit-site carriers and non-exit-site carriers of each patient group. Significant differences considering the risk of infection between exit-site carriers and non-exit-site carriers were found in all patient groups, but most prominently in the diabetic patient group (exit-site carriers versus non-exit-site carriers: group 1,  $P = 0.019$ ; group 2,  $P = 0.042$ ; group 3,  $P = 0.016$ , respectively).

Figure 6 shows that in diabetic patients, the time from detection of the first positive *Staphylococcus aureus* culture until occurrence of *Staphylococcus aureus* catheter infection was shorter in cases of exit-site carriage than in cases of nasal carriage. In all three patient groups, *Staphylococcus aureus*-positive nasal cultures tended to precede *Staphylococcus aureus*-positive exit-site cultures rather than vice versa (data not shown). This difference was statistically significant in the nondiabetic, nonimmunosuppressed patient group (group 3) (sign test:  $P = 0.002$ ). *Staphylococcus aureus*-positive exit-site cultures without simultaneous nasal carriage were detected in only one patient of each group.

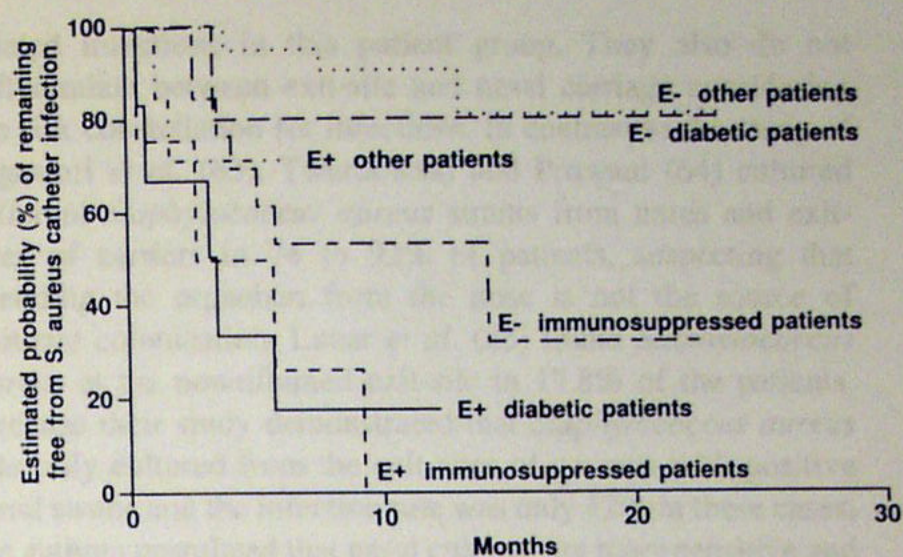


Figure 5. Estimated probability (%) of remaining free from *Staphylococcus aureus* catheter infection for exit-site carriers (E+) and non-exit-site carriers (E-) of each patient group. —, diabetic exit-site carriers; — —, diabetic non-exit-site carriers; - - - -, immunosuppressed exit-site carriers; - - - -, immunosuppressed non-exit-site carriers; - · · · -, nondiabetic, nonimmunosuppressed exit-site carriers; · · · ·, nondiabetic, nonimmunosuppressed non-exit-site carriers.

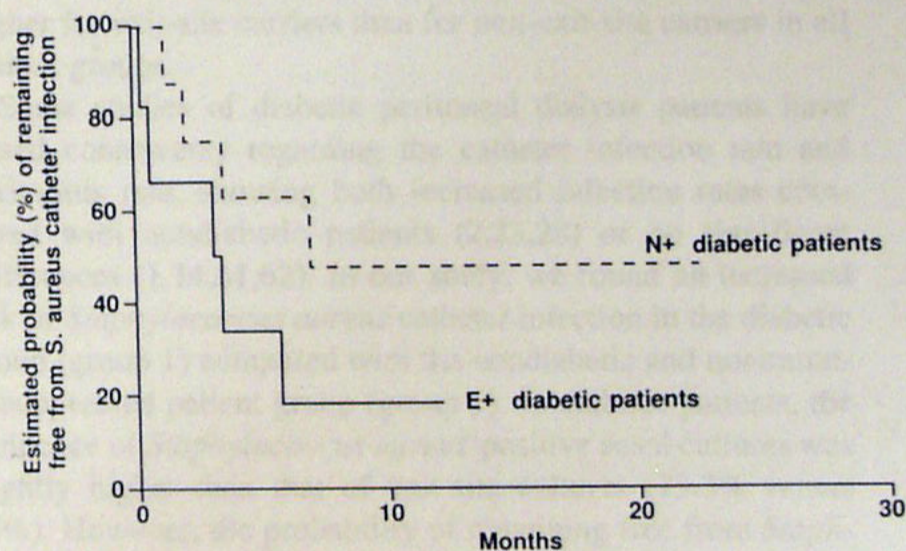


Figure 6. Estimated probability (%) of remaining free from *Staphylococcus aureus* catheter infection for diabetic nasal carriers (- - -) and diabetic exit-site carriers (—).

Dividing nasal carriers of the nondiabetic and nonimmunosuppressed patient group (group 3) into those with only one positive nasal culture and those with at least two or more positive nasal cultures, only the latter group of patients showed a markedly elevated probability of *Staphylococcus aureus* catheter infection over time (NS). Patients with only one *Staphylococcus aureus*-positive nasal culture had a risk of infection comparable to that of patients with negative nasal cultures in this group (Figure 7).

## Discussion

In the present study, we divided the patients into three groups (group 1, diabetic patients; group 2, patients with immunosuppression; and group 3, patients without diabetes mellitus and without immunosuppression) and looked at the prog-

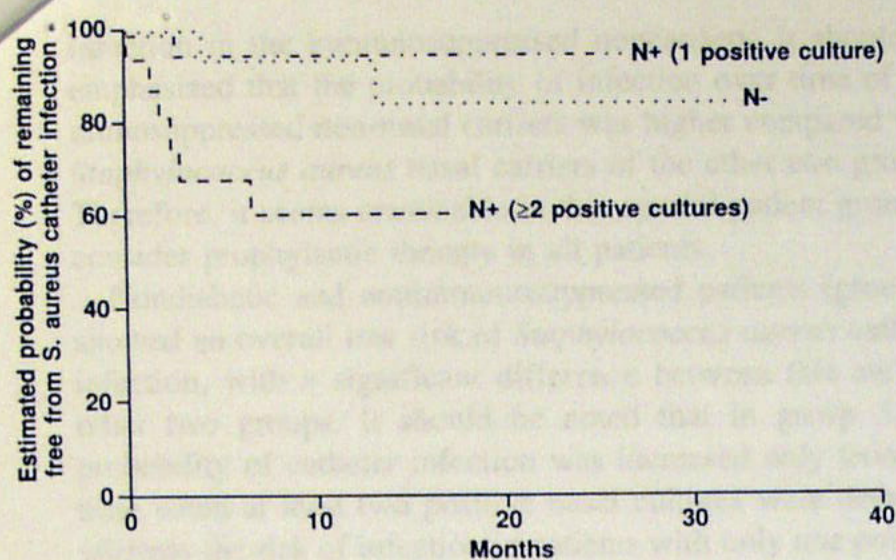


Figure 7. Estimated probability (%) of remaining free from *Staphylococcus aureus* catheter infection for nondiabetic, nonimmunosuppressed patients with only one positive nasal culture (· · · · ·), patients with two or more positive nasal cultures (---), and for patients with negative nasal culture (· · · · ·).

nostic value of cultures taken from the nose and from the bland exit-site to devise strategies for prophylactic treatment.

Our results with a nasal carrier rate of 65.8% are in agreement with the published data (17,23,40,60). Different results are reported in the literature considering the nasal carrier rate in diabetic patients. Luzar *et al.* (23) found that 77% of diabetic peritoneal dialysis patients were carriers, compared with 36% of nondiabetic patients. The study of Wanten *et al.* (60) showed similar results, with a nasal carrier rate of 78% in diabetic patients. Other studies (9,28,61,62) could not find any difference in carrier status between diabetic and other peritoneal dialysis patients. Examining the different groups, we noticed a slightly higher incidence of *Staphylococcus aureus* nasal carriers among diabetic and immunosuppressed patients (group 1, 73.3%; group 2, 72.7%; group 3, 59.0%). According to the literature (7,9,16,23,24,26–29), we found an elevated *Staphylococcus aureus* catheter infection rate in nasal carriers compared with noncarriers in the entire population (0.75/yr versus 0.33/yr), but also in all subgroups (group 1: 0.71/yr versus 0.41/yr; group 2: 1.17/yr versus 0.62/yr; group 3: 0.46/yr versus 0.16/yr). Several studies showed an increased risk of *Staphylococcus aureus* peritonitis for *Staphylococcus aureus* nasal carriers (7,9,27–29,60). In our center, a very low overall incidence of *Staphylococcus aureus* peritonitis was found, with comparable infection rates for nasal carriers and non-nasal carriers.

Only few data exist concerning the relevance of detection of *Staphylococcus aureus* at the bland exit-site. Sesso *et al.* (9) cultured *Staphylococcus aureus* from routinely performed exit-site swabs in 69.7% of patients. In 93.3% of these patients, *Staphylococcus aureus* was also cultured from the nose. In 95% of patients with both nasal and pericatheter colonization, the same subtypes of *Staphylococcus aureus* were present, according to the study of Pignatari *et al.* (63). In these two studies, the authors only discuss the fact that *Staphylococcus aureus* exit-site carrier status is associated with an increased risk of peritonitis; they do not comment on the risk of catheter-

related infections in this patient group. They also do not differentiate between exit-site and nasal carriage considering the risk constellation for infections. In contrast to the study of Pignatari *et al.* (63), Twardowski and Prowant (64) cultured different *Staphylococcus aureus* strains from nares and exit-sites of carriers in 74 to 92% of patients, suspecting that shedding the organism from the nose is not the source of exit-site colonization. Luzar *et al.* (23) found *Staphylococcus aureus* at the noninflamed exit-site in 17.8% of the patients. Because their study demonstrated that *Staphylococcus aureus* was only cultured from the exit-sites of patients with positive nasal swabs and the infection rate was only 12% in these cases, the authors postulated that nasal cultures are more sensitive and therefore sufficient for the determination of at-risk patients. In our population, *Staphylococcus aureus* could be cultured from the noninflamed exit-site in 32.7% of patients. There was no difference in the exit-site carrier status between immunosuppressed patients (group 2) and nondiabetic, nonimmunosuppressed patients (group 3), but a higher incidence of *Staphylococcus aureus* exit-site colonization in the diabetic group (group 1) (group 1, 60.0%; group 2, 25.0%; group 3, 26.9%). The risk of *Staphylococcus aureus* catheter infection was higher for exit-site carriers than for non-exit-site carriers in all patient groups.

Some studies of diabetic peritoneal dialysis patients have raised controversy regarding the catheter infection rate and peritonitis rate, showing both increased infection rates compared with nondiabetic patients (2,23,28) or no significant differences (1,14,61,62). In our study, we found an increased risk of *Staphylococcus aureus* catheter infection in the diabetic group (group 1) compared with the nondiabetic and nonimmunosuppressed patient group (group 3). In diabetic patients, the incidence of *Staphylococcus aureus*-positive nasal cultures was slightly higher than that of exit-site cultures (73.3% versus 60%). However, the probability of remaining free from *Staphylococcus aureus* catheter infection was high in cases of negative exit-site culture but very low in *Staphylococcus aureus* exit-site carriers of this group. Furthermore, the time from detection of *Staphylococcus aureus* to catheter infection was shorter for diabetic exit-site carriers compared with diabetic nasal carriers (Figure 6). Therefore, according to our results, it seems of greater value to take routine swabs from the exit-site rather than from the nose as a screening method in diabetic patients. For this group, we would recommend performing antibiotic prophylaxis in all *Staphylococcus aureus* exit-site carriers. Prospective studies with larger patient numbers should be carried out to confirm this hypothesis.

The immunosuppressed patients (group 2) displayed the lowest probability of remaining free from *Staphylococcus aureus* catheter infection of all of the groups, with a significant difference between this group and the nondiabetic and nonimmunosuppressed patients (group 3). In this patient group, both nasal and exit-site carriage were connected to a very high risk of *Staphylococcus aureus* catheter-related infection. However, the probability of remaining free from *Staphylococcus aureus* infection in patients with negative cultures from nares or exit-sites was low, being tantamount to a relatively high risk of

infection in the immunosuppressed noncarriers. It should be emphasized that the probability of infection over time of immunosuppressed non-nasal carriers was higher compared with *Staphylococcus aureus* nasal carriers of the other two groups. Therefore, it seems reasonable in this special patient group to consider prophylactic therapy in all patients.

Nondiabetic and nonimmunosuppressed patients (group 3) showed an overall low risk of *Staphylococcus aureus* catheter infection, with a significant difference between this and the other two groups. It should be noted that in group 3, the probability of catheter infection was increased only from the time when at least two positive nasal cultures were detected, whereas the risk of infection in patients with only one positive nasal culture was comparable to that of non-nasal carriers. Similar results were observed by Piraino *et al.* (29), who found increased catheter infection rates only in patients with two or more positive nasal cultures. Therefore, for nondiabetic and nonimmunosuppressed patients, we would recommend that nasal cultures be performed as routine screening and that prophylactic therapy be considered only for patients with two or more positive nasal cultures. The studies of Piraino *et al.* (29) and Wanten *et al.* (60) showed an increased risk of *Staphylococcus aureus* peritonitis even after one positive nasal culture. However, the low incidence of *Staphylococcus aureus* peritonitis in these studies and in our population does not influence our strategy of prevention. In agreement with Luzar *et al.* (23), we could not find any beneficial effect of performing cultures from the bland exit-site in comparison to nasal swabs in the nondiabetic and nonimmunosuppressed patient group (group 3).

In conclusion, our data indicate that in diabetic patients routine swabs should be taken from the bland exit-site and prophylactic treatment should be performed in all *Staphylococcus aureus* exit-site carriers. Because of the high infection rate of both (nasal and exit-site) carriers and noncarriers of the immunosuppressed patients, it is advisable to treat all patients of this group prophylactically. In nondiabetic and nonimmunosuppressed patients, nasal cultures as routine screening should be performed and prophylactic treatment should be considered only in patients with two or more positive nasal cultures. A prospective multicenter study is necessary to confirm our guidelines.

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