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Staphylococcus aureus Carriage Patterns and the Risk of Infections Associated with Continuous Peritoneal Dialysis

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The epidemiology and risks of *Staphylococcus aureus* carriage in continuous peritoneal dialysis (CPD) patients was studied in a single tertiary-care institution. On outpatient visits samples for culture were routinely taken prospectively from the CPD catheter exit site and the vestibulum nasi. Seventy-five patients with at least one culture positive for *S. aureus* in this period were included: 43 had genotypically identical *S. aureus* strains in over 80% of the cultures and were classified as persistent carriers; 32 were intermittent carriers. Persistent carriage was associated with a threefold higher risk for CPD-related infections and sixfold higher rates of vancomycin consumption compared to those for the intermittent carriers. No methicillin or vancomycin resistance was detected.

Continuous peritoneal dialysis (CPD) is commonly used in patients with end-stage renal failure. CPD-catheter related infections are, however, major and frequent complications and the cause of significant morbidity and mortality (4). Earlier cross-sectional studies have found *Staphylococcus aureus* nasal carrier rates to be about 50% in CPD patients and demonstrated that *S. aureus* nasal carriage is a major risk factor for the development of *S. aureus* infections (7, 10, 17). Typing of the causative strains has revealed that the strain isolated from the infection site and the strain that colonizes the nares are frequently identical (7, 13).

In order to effectively intervene with the infectious process, additional insight into the long-term epidemiology of staphylococcal carriage in the specific CPD patient group is required. Since *S. aureus* carriage has already been established as a major risk factor for the development of CPD-related infections compared to the risk factors for noncarriers (12, 17), we studied the long-term epidemiology of *S. aureus* carriage within carriers only. Thus, we aimed to identify subgroups of *S. aureus* carriers in CPD patients and their associated risks for CPD-related (*S. aureus*) infections. Furthermore, we wanted to investigate if glycopeptide resistance developed in the *S. aureus* strains from CPD patients in a single tertiary-care institution where glycopeptides were not used as the first-line antibiotics for CPD-related (staphylococcal) infections.

The Jeroen Bosch Hospital is a 600-bed tertiary-care teaching hospital with about 50 adult patients on CPD. CPD patients were monitored every 6 to 8 weeks. Between January 1995 and December 1998, samples of the nares (vestibulum nasi) and CPD catheter exit site were routinely cultured during follow-up visits. Samples from other sites (CPD dialysis fluid, wounds, blood, etc.) were cultured only on the basis of clinical indication. Based on these culture results, the patients were subsequently divided into four categories of carriers (noncarriers, intermittent carriers, cyclic carriers, and persistent carriers), according to the definitions stated in Table 1. The intermittent, cyclic, and persistent carriers were further analyzed; and data on CPD-related infections, antibiotic use, and clinical course were collected retrospectively by chart review. CPD-related infections were defined according to international standards (6). The empirical antimicrobial therapy for CPD-related peritonitis consisted of cephalothin plus tobramycin administered intraperitoneally. Antimicrobial therapy was adjusted according to the culture results and was given for at least 2 weeks. Exit and tunnel infections were treated according to (routine) culture results. This study was approved by the institutional medical ethics review committee of the Jeroen Bosch Hospital (METC 165.585/1997/164).

Culture of skin, catheter exit site, nares (vestibulum nasi), blood, and CPD dialysis fluid samples was performed by standard procedures (5). Vitek 2 equipment (bioMérieux Vitek, Hazelwood, Mo.) was used for the identification of microorganisms. Staphylococcal isolates were identified by the catalase test, followed by a latex agglutination test (Staphaurex Plus; GenProbe). All staphylococcal isolates were stored at −70°C in glycerol-containing liquid medium. The methicillin susceptibilities of staphylococci were tested by the disk diffusion method according to the CLSI guidelines with cefoxitin. All staphylococcal isolates in this study were subsequently tested for glycopeptide (vancomycin) susceptibility by the method described by Hiramatsu et al. (2). Pulsed-field gel electrophoresis (PFGE) was subsequently performed based on protocols as described previously (8, 9, 11).

Percentages were compared by the chi-square test. Poisson regression analysis was used to compare the number of CPD-related infections and the number of antibiotic courses used during follow-up between the different *S. aureus* carrier states. All statistical tests were two-tailed and performed at the 0.05 significance level.

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TABLE 1. Definitions of the different *S. aureus* carrier states

Carrier state	Definition
Noncarriers	No cultures positive for *S. aureus*
Intermittent carriers	At least one but less than 80% of cultures positive for *S. aureus*
Cyclic carriers	More than 80% of cultures positive for *S. aureus* but with genotypically different serial *S. aureus* isolates
Persistent carriers	More than 80% of cultures positive for *S. aureus* with genotypically identical *S. aureus* isolates

A total of 98 patients (60 males and 38 females) were treated with CPD at the Bosch Medicenter over the 5-year period of the study. For 23 (23%) patients none of the cultures was positive for *S. aureus*. These patients were classified as noncarriers and were not monitored any further. Seventy-five (76%) patients had at least one culture positive for *S. aureus* and were included in this study. The total duration of follow-up in these 75 patients was 2,402 months, with a median of 27.2 months (mean, 32.0 months; range, 6.7 to 60 months). Table 2 summarizes the main characteristics of this study population.

TABLE 2. Characteristics of CPD study population[a]

Characteristic	Value
Gender (no. of patients)	
Male	46
Female	29
Median age (range)[b]	
Male	49 (18–75)
Female	53 (36–74)
Cause of end-stage renal disease (no. of patients)	
Vascular disease	22
Diabetes mellitus	18
Glomerulonephritis	16
Urinary tract infections	15
TTP/HUS[c]	2
Other	2
Median duration of end-stage renal disease prior to start of study (range)[d]	3 (0–120)
Median duration of CPD prior to start of study (range)[d]	1 (0–119)
No. of CPD catheters	
First	60
Second	14
Fourth	1
Diabetes mellitus (no. of patients)	
No	49
Insulin dependent	20
Non-insulin dependent	6
Prior kidney transplantation (no. of patients)	
None	70
1	4
4	1

[a] Intermittent, cyclic, and persistent carriers only.
[b] Values are numbers of years.
[c] TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic-uremic syndrome.
[d] Values are numbers of months.

TABLE 3. *S. aureus* carriage patterns of CPD patients

Gender	No. (%) of patients				
	Noncarrier	Intermittent carrier	Cyclic carrier	Persistent carrier	Total
Male	14 (23)	13 (22)	5 (8)	28 (47)	60 (100)
Female	9 (24)	9 (24)	5 (13)	15 (39)	38 (100)
Total	23 (23)	22 (22)	10 (10)	43 (44)	98 (100)

Twenty-two patients (22%) carried *S. aureus* in their nares and/or the catheter exit site only now and then and had culture-positive and culture-negative periods (Table 3). These patients were classified as intermittent carriers. Fifty-three (54%) patients had three or more cultures positive for *S. aureus* on two or more outpatient visits. All cultures of 43 of these patients had genotypically identical strains during their follow-up, while 10 of them sometimes had a second *S. aureus* strain that could be isolated in one or more cultures. These 43 (44%) patients were classified as persistent carriers. The remaining 10 patients were chronically colonized with *S. aureus*, but all *S. aureus* strains were genotypically different when their serial culture isolates were compared. Therefore, the latter 10 (10%) patients were classified as cyclic carriers.

All *S. aureus* isolates were unique to each of the patients, as defined by the PFGE analysis, suggesting that cross-colonization and cross-infection were not problems in this CPD population during the monitoring period.

Persistent *S. aureus* carriage was associated with significantly higher incidences of all CPD-related infections (Table 4). Cyclic and intermittent carriers had similar risks for all CPD-related infections analyzed. The relative risk for CPD-related infections of all causes for persistent carriers compared to that for the combined intermittent or cyclic carrier group was 2.91 (95% confidence interval [CI], 2.17 to 3.90), and the relative risk for *S. aureus* CPD-related infections was 3.42 (95% CI, 2.40 to 4.88).

The overall amount of vancomycin used during this study was 196 g. The amount of vancomycin used in the persistent carrier group (145 mg/month) than was sixfold higher than the amounts used in the cyclic carrier group (23 mg/month) and the intermittent carrier group (24 mg/month) ($P < 0.0001$). In total, 446 *S. aureus* strains were isolated, and all strains were methicillin sensitive. Neither high-level nor intermediate glycopeptide resistance was detected.

Thus, 44% of all CPD patients were persistently colonized with a single unique *S. aureus* strain, indicating that long-term persistent *S. aureus* carriage is common in this group of patients. Furthermore, persistent carriage was associated with a threefold increased risk for all CPD-related infections. Whether the cyclic carrier group should also be defined as persistent carriers is a matter of definition and debate (16). Although these patients apparently carry *S. aureus* for prolonged periods of time, their risk of invasive *S. aureus* infections was similar to that of the intermittent carrier group. As such, in our opinion, cyclic carriers should be viewed as "high-level" intermittent carriers and should be separated from persistent carriers. Why our so-called cyclic carriers are at a lower

TABLE 4. Infection incidence rates by *S. aureus* nasal carriage patterns

Characteristic	Value for group[c]			Total[c]	*P* value[a]	RR[b,c]
	Intermittent carriers	Cyclic carriers	Persistent carriers			
Follow-up (mo at risk)						
Mean	37.6 (29.9–45.2)	43.0 (31.2–54.8)	26.6 (21.5–31.7)	32.0 (27.9–36.1)		
Total	827	430	1,145	2,401		
No. of patients in follow-up	22	10	43	75		
No. of patients with CPD-related infections						
All	48	21	193	262		
Exit site infections	30	12	117	159		
Peritonitis	18	9	76	103		
Incidence of CPD-related infections (no. of infections/person/mo at risk)						
All	0.06 (0.04–0.09)	0.05 (0.03–0.09)	0.17 (0.15–0.19)	0.11 (0.10–0.12)	<0.0001	2.91 (2.17–3.90)
Exit site infections	0.04 (0.02–0.07)	0.03 (0.01–0.06)	0.10 (0.09–0.12)	0.07 (0.06–0.08)	<0.0001	2.82 (1.94–4.11)
Peritonitis	0.02 (0.01–0.05)	0.02 (0.01–0.05)	0.07 (0.05–0.08)	0.04 (0.03–0.05)	0.0011	3.04 (1.92–4.85)
No. of *S. aureus* CPD-related infections						
All	32	13	149	194		
Exit site infections	26	10	100	136		
Peritonitis	6	3	49	58		
Incidence of *S. aureus* CPD-related infections (no. of infections/person/mo at risk)						
All	0.04 (0.02–0.07)	0.03 (0.01–0.06)	0.13 (0.11–0.15)	0.08 (0.07–0.09)	<0.0001	3.42 (2.40–4.88)
Exit site infections	0.03 (0.02–0.06)	0.02 (0.01–0.05)	0.09 (0.07–0.11)	0.06 (0.05–0.07)	<0.0001	2.84 (1.89–4.27)
Peritonitis	0.01 (0.00–0.02)	0.01 (0.00–0.03)	0.04 (0.03–0.06)	0.02 (0.02–0.03)	0.0023	5.76 (2.74–12.10)

[a] *P* value for the univariate comparison of incidence rates in intermittent, cyclic and persistent carriers using Poisson regression.
[b] RR, relative risk (or, more precisely, incidence rate ratio). The relative risk compares the incidence rates in persistent carriers and those in intermittent or cyclic carriers in a Poisson regression model, adjusting for age and sex.
[c] Values in parentheses are 95% CIs.

risk for CPD-related infections is unclear. However, bacterial factors could well play a role in this, since it was suggested earlier that factors promoting the ecological fitness of *S. aureus*, i.e., the capacity to colonize people, also increase its virulence and that *S. aureus* is not solely an opportunistic pathogen (1). Further research is needed to confirm this hypothesis.

We did not present comparative data from the noncarrier group in this CPD population. However, as we demonstrated before, among CPD patients intermittent carriers behave like noncarriers, as they are not at an increased risk for CPD-related infections (12). Now we also demonstrate that it is only the genuinely persistent *S. aureus* carriers who are at an increased risk of CPD-related infections. Thus, accurate determination of the true *S. aureus* carrier state would enable us to improve the prevention of *S. aureus* infections in CPD patients and thus limit antibiotic (including vancomycin) usage.

No methicillin resistance and, thus, no glycopeptide resistance were demonstrated in *S. aureus* in a center where glycopeptides are not routinely used for the empirical treatment of CPD-related infections. This suggests that the epidemiology of glycopeptide resistance in *S. aureus* is different from that in enterococci. Whereas in enterococci glycopeptide usage in the environment (hospitals and the veterinary industry) is related to glycopeptide resistance development (14), in staphylococci resistant strains seem to emerge only after frequent and long-term exposure of the individual patient to glycopeptides (2, 3, 12, 15).

In conclusion, 44% of CPD patients were persistent carriers of *S. aureus* and were at a threefold higher risk than intermittent and cyclic carriers for CPD-related infections. Precise determination of the *S. aureus* carrier state, including bacterial genotyping, is possible, makes sense, and is needed to adequately target prevention strategies. No vancomycin resistance in *S. aureus* was encountered in this setting of low-level glycopeptide use. However, continued screening for the emergence of glycopeptide-resistant isolates of *S. aureus* remains a prudent strategy.

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