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Staphylococcus aureus carriage and infections among patients in four haemo- and peritoneal-dialysis centres in Denmark

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Summary: A three-month prospective surveillance study was undertaken in four dialysis centres to establish the prevalence of *Staphylococcus aureus* carriage in a Danish population of patients on haemodialysis (HD) or on continuous ambulatory peritoneal dialysis (CAPD). General data such as sex, age, diagnosis, number of months in dialysis, hospital and ward were registered on a precoded form. Standardized nose and four skin swabs (axillae, groins, perineum) were performed on the first day of the survey. After one and two months, nose swabs were collected. Infections were registered and cultures were sent for phage-typing together with the *S. aureus* strains isolated from the swabs; 59·5% of HD patients and 51·2% of CAPD patients carried *S. aureus*. Permanent carriage was most frequent ($P<0{\cdot}00009$), primarily in the nose (44·0 and 34·9%, respectively in HD and CAPD). Skin carriage alone was rare (2·4 and 4·7%). Approximately one third (36·6 and 40·7%) of infections were caused by *S. aureus*. Although diabetics were not significantly more frequent carriers (60·5%) than non-diabetics (55·0%), the incidence of infection was much higher (26·3% vs. 10·3%, $P=0{\cdot}004$). In CAPD, peritonitis and tunnel/exit-site infections predominated (81·4%), often caused by *S. aureus* (34·8%). More than two thirds

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of the infections in HD patients were related to intravascular catheterization. The most serious infection was septicaemia, in all cases due to *S. aureus*. *S. aureus* infections occurred significantly more frequently among carriers ($P = 0{\cdot}005$), and more than half the patients were infected by the same or possibly the same strain as they carried in the nose or on skin. Different regimens for the elimination of *S. aureus* carriage in dialysis patients are discussed. A policy for risk assessment of patients should be developed, and the elimination of *S. aureus* carriage before dialysis should be encouraged. Controlled trials comparing the cost-effectiveness of recommended regimens to eliminate carriage in HD/CAPD patients are needed. Nose swabs are reliable indicators of carriage in dialysis patients.

Keywords: Haemodialysis, CAPD; carriage; infections; phage-type; elimination; *Staphylococcus aureus*.

Introduction

Device-related infections represent a significant complication of continuous ambulatory peritoneal dialysis (CAPD) as well as of haemodialysis (HD).

In CAPD patients peritonitis, exit-site and tunnel infections may require hospitalization and are refractory to treatment when the catheter is *in situ*.[1,2] *Staphylococcus aureus* has emerged as the major pathogen causing exit-site infections and is the second most frequent cause of CAPD-related peritonitis.

Staphylococcal bacteraemia is a serious consequence of staphylococcal vascular site infection and a leading cause of death in patients on chronic HD, second only to cardiovascular disease. *S. aureus* accounts for 70–92% of vascular access infections.[3–5] Several factors are likely to depress the immune system of these patients, and thus, make them more susceptible to infection, such as old age, concurrent debilitating illnesses, and specific immune defects associated with renal dysfunction. In patients with azotaemia, granulocytes exhibit decreased chemotaxis, lessened ability for phagocytosis, and less effective killing. Immunoglobulin levels are below normal in one third of patients with end-stage renal failure[6] and complement C3 levels are reduced in 90%. Biofilm adherence to the surfaces of indwellling medical devices such as peritoneal catheters[2] or central vein catheters (CVC), and occasional puncturing of the i.v.-access and/or breakage of the tubing provide important sources and routes of infection for *S. aureus*, especially in carriers.

Dialysis patients generally tend to have a higher carrier rate of *S. aureus* (62–76%) than other hospital patients and the personnel working in dialysis units.[6–8] Several reports highlight the importance of *S. aureus* carriage in endogenous infections, in HD, as well as CAPD.[1,7–13] The purpose of this study was to establish the prevalence of *S. aureus* carriers in a Danish population of HD and CAPD patients, to identify high-risk patients and to relate carriage status to the frequency of infections.

Materials and methods

Design

The study took place in four dialysis centres in Denmark and was initiated by The Danish Study Group on Peritonitis in Dialysis (DASPID). All patients in chronic dialysis at the start of the survey (January 1992) were included.

The study was designed as a three-month prospective surveillance of infections and risk factors correlated to bacteriological findings. On the first day nose and skin cultures (both axillae, groins and perineum) were performed. After one and two months, respectively, nose swabs were repeated at outpatient visits, and at the end of the study the four nose and skin cultures were repeated. If one or more swabs were missing, the patient was excluded.

Patients changing from HD to CAPD or vice versa were registered in each dialysis category for the relative number of months. For patients undergoing kidney transplantation in the study period, nose and skin cultures were performed, when possible, before surgery. Patients who died were included, but registered only for the relative number of dialysis months.

The protocol was accepted by the Ethical Committee, and each patient was asked to give informed consent and asked to swab themselves after receiving a protocol and oral instruction/demonstration by nursing staff. If the patient was incapacitated a nurse performed the swabbing.

Surveillance of infections

Infections related to the intravascular access, septicaemia, skin and other infections in HD patients and peritonitis, exit-site/tunnel infections, post-operative wound infections, skin and other infections in CAPD patients were prospectively registered. Data on use of antibiotics, surgical interventions including catheter replacement, cultures and phage-typing were recorded.

Criteria of infection

Septicaemia was defined by clinical criteria and/or a positive blood culture.

Peritonitis. Two of the three following criteria,[1] fever or abdominal pain,[2] clouded dialysis-effluent,[3] positive leucocyte-esterase test ('Cytur'): (2×10^3/mL with >50% neutrophil granulocytes), with or without a positive culture.

Exit-site infection. Redness or pus formation at the exit-site requiring antibiotic treatment and/or surgical intervention, with or without positive culture.

Tunnel infection. Redness and tissue swelling or tenderness was registered as infected if requiring antibiotics or surgical intervention, with or without a positive culture.

Shunts/arterio-venous (AV) fistulas. Redness and induration or tenderness with or without pus formation, over the intravascular access.

Central vein catheters. Redness and induration or tenderness at the insertion site or subcutaneous tissue surrounding the catheter, with or without pus formation.

Nose and skin swabs

A cotton swab was applied by slight pressure lengthwise and crosswise at the inside of each nostril, axillae, groins and perineum three times each with the same swab. After each swabbing the swab was placed in a freshly prepared Stuart's transport medium and closed. If immediate transport to the laboratory was not possible, the culture was stored in a fridge.

Carriage

Three types of carriers were categorized:

Permanent carriers. Two or more *S. aureus* isolates of identical phage-type found with at least one month interval.

Intermittent carriers. One positive culture/two or more *S. aureus* isolates of different phage-type detected.

Non-carriers. *S. aureus* not isolated from nose or skin during the period studied.

Cultures and phage-typing

Specimens were cultured on 5% horse blood agar-plates. Catalase-positive, Gram-positive cocci were identified as *S. aureus* by the coagulase test performed either as a tube test or as a slide test (clumping factor).

Phage-typing was performed at the Staphylococcus Laboratorium, Statens Seruminstitut on all cultures of *S. aureus* from screening swabs or infected sites, with the International Typing Set at routine test dilution (RTD) as well as 1000 × RTD. Strains were according to the phage-type subdivided into phage-type groups I, II and III; all strains of phage-type 95, strains belonging to the 83A complex, the 52,52A,80,81 complex and the 94,96 complex (group V) were recorded separately.[14]

Statistical analysis

Epi-info, version 5·01 (Centers for Disease Control, Atlanta, USA) was used as software for data analysis. Chi-square test and Fisher's exact test and chi-square test for trend were used to determine the impact of risk factors such as carriage and diabetes on *S. aureus* infection and the correlation between time in dialysis and carriage.

Results

Characterization of the study population

A total of 168 HD patients and 129 CAPD patients were studied. The demographic profile is shown in Table I. Relatively more men were

Table I. *Characterization of the patient population in four haemodialysis centres (HD) and four CAPD centres*

Patient data	No. (sex) or mean and percentage (%)	
	HD $N=168$	CAPD $N=129$
Males	94 (55·9)	83 (64·3)
Females	74 (44·0)	46 (35·7)
Age (years)	53·17	55·89
SD	14·73	12·99
Reasons of dialysis		
Glomerulonephritis	42 (25·0)	28 (21·7)
Diabetes mellitus	16 (9·5)	22 (17·1)
Other	110 (65·5)	82 (63·6)
Other illness	65 (38·7)	43 (33·3)
Dialysis months	44·13	22·00
SD	47·64	21·97
Immunosuppressed	12 (7·1)	8 (6·2)
Antibiotics	39 (23·2)	33 (25·6)
Antibiotic episodes per patient month	1 per 9·3	1 per 7·4

undergoing both HD and CAPD (64·5 and 55·9%, respectively). No difference in age was found between HD and CAPD patients (55·9 and 53·7 years). HD patients had on average been twice as long in dialysis as CAPD patients. Approximately one third of both HD and CAPD patients were reported to have concurrent, debilitating illnesses. Glomerulonephritis was the commonest disease leading to chronic dialysis in both groups. Twice as many CAPD patients (17·1%) as HD patients (9·5%) suffered from diabetes mellitus (nonsignificant, $P=5·4\%$, chi-square test).

Types and rate of S. aureus *carriage*

Table II shows frequencies and types of carriage among HD and CAPD patients; 59·5% of HD patients and 51·2% of CAPD patients were carriers of *S. aureus*. Diabetics were not significantly more frequent carriers (60·5%) than non-diabetics (55·0%).

Permanent carriage predominated (45·2% of the HD patients and 31·0% of the CAPD patients) ($P<0·0000001$), only 13·0 and 16·3%, respectively, were temporary carriers. In two HD and five CAPD patients it was impossible to categorize carriage, because one phage-type of the *S. aureus* cultures was missing.

In 44·0 and 34·9% of the HD and CAPD patients *S. aureus* was only found in the nose, while 13·1 and 11·6%, respectively, of patients were both nasal and skin carriers. Only four HD patients (2·4%) and six CAPD patients (4·7%) were exclusively skin carriers.

Table II. *Frequencies of* Staphylococcus aureus *nose and skin carriage among haemodialysis and CAPD patients*

Frequency and localization of carriage	HD $N=168$	CAPD $N=129$
Non-carriers	68 (40·5)	63 (48·8)
Frequency of carriage	100 (59·5)	66 (51·2)
Diabetics	11/16 (68·8)*	12/22 (54·5)
Non-diabetics	89/152 (58·5)	54/107 (50·5)
Permanent	76 (45·2)†	40 (31·0)
Temporary	22 (13·0)	21 (16·3)
Permanent or temporary§	2 (1·2)	5 (3·9)
Localization of carriage		
Nose alone	74 (44·4)‡	45 (34·9)
Nose and skin	22 (13·1)	15 (11·6)
Skin alone	4 (2·4)	6 (4·7)

*$P<0·0000001$, $chi^2=33·5$ (1 degree of freedom).
†$P<0·00009$, $chi^2=15·37$ (confidence limits for OR: 1·94–8·55).
‡$P=5·4\%$, nonsignificant, chi-square test.
§Phage-type missing.

S. aureus carriage was independent of number of months in dialysis in CAPD patients, while HD patients who were carriers had been significantly longer time in dialysis than non-carriers ($P=0·01$).

Incidence and localization of S. aureus *infections in HD and CAPD*

No difference was found between HD and CAPD patients in regard to the total number of infections. During the three months surveillance 41/129 CAPD patients (31·8%) were registered as having 90 episodes of infection, corresponding to one per 4·2 patient months and 47/168 HD patients (28·0%) had 92 episodes of infection, corresponding one per 5·4 patient months (nonsignificant, chi-square test). No difference was found in the administration of antibiotics and immunosuppressive drugs in the two groups (Table I). The incidence of *S. aureus* infection was much higher among diabetics (26·3%) than non-diabetics (10·3%; $P=0·004$, chi-square test).

Approximately one third (36·6 and 40·7%, respectively) of the infections related to HD/CAPD were caused by *S. aureus*. The distribution of the various infection sites is shown in Table III. Skin infections were frequent in both groups and often (34/93) caused by *S. aureus* (36·6%).

HD-related infections

Overall i.v.-related infections (local and systemic) were the most frequent type of infections among HD patients being responsible for more than two thirds (67·6%) of all *S. aureus* infections. The most serious infection was

Table III. *Incidence and distribution of different types of* S. aureus *infections among patients receiving HD or CAPD (three months surveillance)*

Site of infection	Total *S. aureus*/All infect. (%)
HD patients ($N=168$)	
i.v.-Related, local	16/26 (61·5)
Septicaemia	7/7 (100·0)
Others	11/60 (18·3)
Total	34/93 (36·6)
CAPD patients ($N=129$)	
Peritonitis	7/47 (15·2)
Exit-site or tunnel	17/22 (77·3)
Septicaemia	1/1 (100·0)
Others	6/17 (35·3)
Total	31/86 (40·7)

S. aureus septicaemia; all the septicaemias encountered were caused by *S. aureus*.

CAPD-related infections

Peritonitis (15·2%) and local infection related to the peritoneal catheter (tunnel/exit-site) were the most frequent types of infection registered (81·4%) among CAPD patients and were often caused by *S. aureus* (34·8%). One case of peritonitis occurred as a complication to a tunnel and exit-site infection, while five cases occurred solitarily. The only case of *S. aureus* septicaemia occurred as a complication of peritonitis.

S. aureus *infections and carriage*

HD and CAPD-related infections occurred as a whole significantly more often in the 166 patients categorized as *S. aureus* carriers (16·9%) compared with 131 non-carriers (6·1%) ($P=0·005$, chi-square test). CAPD-related exit-site infections occurred significantly more often among carriers (12·1%, $P=1·5$) as compared with non-carriers (1·5%).

Half the patients with septicaemia were carriers, but three cases were caused by strains different from the carrier strain, one was caused by the same strain and one was not phage-typed.

Seven of 14 CAPD patients who were carriers (50%) became infected with the same *S. aureus* strain. Two were infected with different strains, and in five cases *S. aureus* were not sent for phage-typing.

Similarly, eight of 14 (57·1%) HD patients were infected with the carrier strain, two with different strains, and four with possibly the same strain.

Overall, more than half the patients with *S. aureus* infections were infected by the same or possibly the same strain as they carried in the nose or on the skin.

The phage-type pattern of the *S. aureus* strains colonizing the haemodialysis patients did not differ from the normal pattern in Denmark in 1992, whereas the colonizing strains from CAPD patients belonged more often (41%) to phage group II than normal (23%). Among the *S. aureus* strains causing infection in CAPD patients only 11 of the 34 strains were phage-typed and five belonged to group II. In the haemodialysis patients 15 of the 34 infecting strains were typed and only two belonged to group II.

Discussion

Infections represent a serious complication of HD and a frequent cause of catheter loss in CAPD whereby the treatment is disrupted or stopped.[1] High frequencies of *S. aureus* carriage and carriage-related infection have previously been reported in both HD and CAPD patients. A recent investigation[13] confirmed the frequent *S. aureus* carriage among CAPD patients. Patients from seven hospitals in Wales were cultured before peritoneal catheter placement and the establishment of dialysis. *S. aureus* were found in 45% of patients, more in diabetics (77%) than others (36%). The high carriage rate does not seem to be related to presence in a dialysis unit as such, as the staff does not have a high rate.[7] In Denmark the rate of *S. aureus* carriage has not previously been established, either in CAPD or in HD patients. Our data suggest that Danish dialysis patients (Table I) have the same high rate of *S. aureus* carriage as in other countries,[1,8,14] but we could not confirm a significantly higher carriage rate among diabetics. But *S. aureus* infections occurred significantly more often among diabetics than non-diabetics, so that diabetes mellitus might be considered an important predictor for infection rather than for carriage.

A major part of the dialysis-related infections are endogenous. Ralston *et al.*[3] first reported that *S. aureus* infections in a small group of HD patients were caused by strains with the same phage-types as those carried permanently on the skin surrounding the intravascular access. Rebel *et al.*[9] later reported that both nasal and perineal carriage were risk factors for infection with the corresponding phage-type in HD patients. Later investigations have confirmed the relationship between *S. aureus* and the risk of infection in both HD and CAPD patients,[7,11] while the occurrence of other bacteria on skin, e.g. streptococci or Gram-negative bacilli, did not differ from the normal.

S. aureus infection remains a serious problem. One third of all HD-related infections in our survey were caused by *S. aureus*, and approximately 85% of these infections were caused by strains with the same or possibly the same phage-type as the patients carried. Similarly, CAPD-related infections occurred almost exclusively in carriers. Half the infections were caused by the same phage-type, only two phage-types were different. The fact that group II phage-types were dominant in colonization of CAPD

patients, while the colonizing pattern did not differ from the normal, might be explained by the different environment of the two types of patient.

We find it remarkable that all the cases of septicaemia were caused by *S. aureus*, and seven of the eight cases were in HD patients. Our data cannot explain why HD seemed more likely to lead to septicaemia. In the literature, 70–92% of HD-related intravascular infections are claimed to be caused by *S. aureus* with a mortality of 10%.[6] The study period observed was too short to enable a proper clinical risk assessment. In our study, 70% of all intravascular infections were caused by *S. aureus*, usually related to local skin or tissue infection surrounding the i.v. access site.

Our data show that infections related to the peritoneal catheter: peritonitis and tunnel/exit-site infections were the most frequent type of *S. aureus* infections in CAPD patients. Nasal *S. aureus* carriage is reported a risk factor for the development of *S. aureus* exit-site infections.[11–13] Sewel *et al.*[11] found that 57% of 30, mainly male dialysis patients, were intermittent carriers of *S. aureus* and one third (33%) were permanent carriers. Seventy-five percent of the permanent carriers and 50% of the intermittent carriers developed *S. aureus* exit-site infections, compared with only 20% in the non-carrier group. Later investigations have confirmed these findings.[12,13] The fact that exit-site/tunnel infections often precede peritonitis can suggest the route of infection. But as *S. aureus* peritonitis also was occasionally seen without signs of exit-site/tunnel infection, other routes of infection, including colonization of the tunnel, must exist.

Nose and skin carriage is also reported to increase the risk of peritonitis.[1] Sesso *et al.*[15] found that 37% of CAPD patients were permanent carriers, and 28% were intermittent carriers of *S. aureus* in the nose or on skin surrounding the peritoneal catheter. All episodes of *S. aureus* peritonitis occurred in carriers.

Goldblum *et al.*[8] reported twice the incidence of infection among skin carriers compared with non-carriers. *S. aureus* skin carriage is significantly more often related to infection than nasal carriage. While most of the *S. aureus* carriers in our study were categorized as permanent (Table II), only a few were skin carriers.

Finally, attention should be given to susceptible patients who are carriers, especially those who are both nose and skin carriers, with respect to the type of dialysis and to preventive strategies. In 1989 Ludlam *et al.*[16] reported the introduction of a protocol for strict aseptic technique by catheter placement, for per-postoperative wound care and for other CAPD procedures, in combination with the elimination of *S. aureus* from nose and groin carriage before catheter placement. The elimination regime included two daily applications of chlorhexidine and 'neomycin' cream to the anterior nares and local skin wash with 'Hibiscrub' (4% chlorhexidine soap). This regime resulted in a 75% reduction of *S. aureus* wound infection from 49 to 12% over two years without the use of prophylactic antibiotics. No hospital-acquired infections occurred.

We have reported a regime to eliminate skin and nose carriage in patients suffering from recurrent *S. aureus* furunculosis.[17] This regime includes the elimination of nasal and skin carriage by a daily whole-body bath with 'Hibiscrub' (written protocol) and the application of chlorhexidine gel 1% in both nostrils twice daily. Furthermore elimination of the infective strain in the immediate environment is aided by sterilization of mattresses, pillows and other non-washable bedclothes, as well as the implementation of an improved hygienic standard. This regime has shown effective in the prevention of recolonization of these patients.[17]

Mupirocin is available for superficial use and has a high in-vitro activity against staphylococci.[18] It is useful for elimination of nasal carriage of *S. aureus*,[19,20] and has been shown to protect against recolonization for up to one year after a single brief treatment. It also resulted in a decreased hand colonization, which could be detected for up to six months.[21] In haemodialysis patients nasal mupirocin has been used as prophylactic against severe *S. aureus* infections in a long-term study, and the results showed a fourfold reduction in *S. aureus* bacteraemia.[22] It might be interesting to investigate if these results can be extrapolated to CAPD patients. However, the increasing development of high-level mupirocin resistance in both *S. aureus* and coagulase-negative staphylococci, especially associated with chronic use,[23–25] is a matter for concern. The chronic use of mupirocin in closed settings and subsequent development of resistance may limit the use of mupirocin.

Conclusion

Considering that approximately one third of the infections in our study were caused by *S. aureus*, and the serious complications such infections can cause in HD and CAPD, we recommend that a policy for risk assessment of patients (e.g. diabetes and carriage) should be developed, and that the elimination of *S. aureus* carriage before the institution of various types of dialysis should be encouraged whenever possible. Controlled trials for comparison, the cost-effectiveness of recommended effective regimens to eliminate *S. aureus* carriage in both HD and CAPD patients, should be carried out. Because nasal carriage was common and skin carriage alone was extremely rare, we recommend use of nasal swabbing alone as an indicator for *S. aureus* carriage in populations of HD/CAPD patients.

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