

## STAPHYLOCOCCUS AUREUS NASAL CARRIAGE AND INFECTION IN PATIENTS ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

MARY ANNE LUZAR, M.Sc., GERALD A. COLES, M.D., BERNADETTE FALLER, M.D.,  
ALAIN SLINGENEYER, M.D., GEORGE DAH DAH, M.D., CLAUDE BRIAT, M.D., CHRISTIAN WONE, M.D.,  
YEHYA KNEFATI, M.D., MICHELLE KESSLER, M.D.,  
AND FRANCESCO PELUSO, Ph.D.

**Abstract** We studied 140 consecutive patients beginning continuous ambulatory peritoneal dialysis (CAPD) at one of seven hospitals to assess the relation of the nasal carriage of *Staphylococcus aureus* to subsequent catheter-exit-site infection or peritonitis. Shortly before the implantation of the catheters, the patients' anterior nares were cultured for the presence of *S. aureus*. Antibiotics were not prescribed for the *S. aureus* carriers, but all the patients were monitored for signs of catheter infection (median follow-up, 10.4 months).

At the initiation of CAPD, 63 patients (45 percent) carried *S. aureus* in the nares. Nasal carriage was more frequent among the 30 patients with diabetes (77 percent) than among the 110 without the disease (36 percent). The carriers of *S. aureus* had a significantly higher rate of exit-

site infection than the noncarriers (0.40 vs. 0.10 episode per year;  $P = 0.012$ ). Of these episodes, 24 of 34 were caused by *S. aureus*. The rates of peritonitis of all bacterial types did not differ significantly between the groups, but all 11 episodes of peritonitis caused by *S. aureus* occurred among the carriers. In 85 percent of the patients with clinical *S. aureus* infections, the strain from the nares and the strain causing the infection were similar in phage type and antibiotic profile.

We conclude that in patients beginning ambulatory peritoneal dialysis, the nasal carriage of *S. aureus* is associated with an increased risk of catheter-exit-site infection and that the performance of nasal cultures before the implantation of the catheter can identify patients at high risk of subsequent morbidity. (N Engl J Med 1990; 322:505-9.)

THE importance of *Staphylococcus aureus* as an etiologic agent of exit-site infection in continuous ambulatory peritoneal dialysis (CAPD) has been well established.<sup>1-4</sup> Recent studies have shown that pericatheter infections are a major cause of the failure of CAPD catheters. Piraino et al. reported that exit-site infection, independently of peritonitis, was responsible for 57 percent of the cannulas removed during a five-year period.<sup>5</sup> Zimmerman et al. identified *S. aureus* as the chief etiologic agent associated with the removal of catheters due to infection.<sup>1</sup> Davies et al. demonstrated that the late removal of cannulas was due primarily to recurrent peritonitis caused by *S. aureus*.<sup>6</sup> The high rate of recurrence associated with *S. aureus* infection and the serious consequences of disease caused by this pathogen indicate that more information is needed about the

predisposition to *S. aureus* invasion in patients undergoing CAPD.<sup>1,4</sup>

In a five-year prospective, controlled study of patients on hemodialysis, Yu et al. established that *S. aureus* infection occurred significantly more frequently in nasal carriers of the organism than in noncarriers.<sup>7</sup> Previous investigations among patients undergoing CAPD<sup>6,8-10</sup> have suggested a possible link between the nasal carriage of this organism and exit-site infection, peritonitis, or both. However, the numbers of patients studied were relatively small, and most were studied after CAPD was started.

In May 1987 we began monitoring new patients undergoing CAPD at seven European hospitals to investigate any association between the nasal carriage of *S. aureus* before dialysis and infection during CAPD. By identifying the initial strain before the creation of an abdominal-catheter exit site, we were able to follow the evolution of colonization with that organism and its effect on the infection rate.

### METHODS

#### Patient Selection and Study Design

The study population consisted of consecutive patients starting CAPD in seven hospitals. There were no enrollment restrictions based on age, sex, race, end-stage renal disease, or previous dialysis

From Baxter R&D Europe, Nivelles, Belgium (M.A.L., F.P.); the Cardiff Royal Infirmary, Cardiff, United Kingdom (G.A.C.); the Centre Hospitalier Général L. Pasteur, Colmar, France (B.F.); Mas de Rochet, Montpellier, France (A.S.); the Hôpital Régional d'Orléans, Orléans, France (G.D.D.); the Hôpital de la Durance, Avignon, France (C.B.); the Hôpital Saint André, Bordeaux, France (C.W., Y.K.); and the Centre Hospitalier Universitaire de Nancy, Vandœuvre, France (M.K.). Address reprint requests to Ms. Luzar at Baxter R&D Europe, Rue du Progrès 7, B-1400 Nivelles, Belgium.

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therapy. During the 48 hours preceding the implantation of the catheter, the anterior nares of each patient were cultured for the carriage of *S. aureus*. The patients from whom the organism was isolated were designated the carrier group; those who did not harbor *S. aureus* in the anterior nares before the implantation of the catheter were designated noncarriers. After the patients had been discharged on CAPD, nasal and catheter-exit-site cultures were obtained from those in the carrier group at each clinic visit (monthly or bimonthly, depending on the hospital). Cultures were obtained from two thirds of the noncarriers on a similar schedule, and from the remainder every two to three months. All the strains of *S. aureus* isolated at clinic visits were sent to the coordinating laboratory. During each clinic visit, the physician inspected the exit site and reported the patient's status to the coordinating laboratory. All episodes of infection and their causes were documented by one of us at the time of presentation. When a hospital laboratory isolated *S. aureus*, the strain was sent to the coordinating laboratory for comparison with the surveillance strains from the nares of the patient. When strains colonizing the exit site were isolated, they were also compared with the surveillance strains. The strains isolated at different visits and from different sites in the same patient were compared according to phage type, antibiotic profile, and biotype.

The follow-up period was from the implantation of the catheter until January 1989, or until the patient discontinued CAPD, if earlier.

### Culture Methods and Mediums

To obtain the cultures, a dual rayon swab (Culturette, Marion Scientific) was rotated in each anterior naris and streaked onto a medium routinely used by the hospital laboratory for the isolation of *S. aureus*, which was then incubated at 37°C. Gram-positive, coagulase-positive cocci were tested for antibiotic sensitivity according to the routine methods of each hospital. The pure culture was sent on slants of brain-heart infusion agar (Diagnostics Pasteur) to the coordinating laboratory, along with the accompanying antibiotic profile and the appropriate patient form completed by the physician. The pure culture was transferred to mannitol salt agar (BBL Microbiology Systems) and incubated at 37°C for 24 hours, then transferred to trypticase soy agar (Oxoid) and incubated for 24 hours at 37°C. The results of catalase and coagulase tests were confirmed, and the culture was prepared for phage typing and the determination of antibiotic profile and biotype.

*S. aureus* strains isolated from clinically normal exit sites and from cases of exit-site infection, tunnel infection, and peritonitis were obtained and treated in the same manner. The culture collection was maintained in long-term storage in trypticase soy broth and glycerol (15 percent vol/vol) at -70°C.

### Bacteriophage Typing

All the *S. aureus* strains isolated from patients in the study were phage typed with the standard bacteriophages of the International Typing Set.<sup>11,12</sup> All the cultures were typed in a blind manner at the Belgian national reference laboratory for phage typing, the Institut Pasteur Brabant. Cultures that did not react with the phages at the routine test dilution were typed with phages at 100 times that dilution. Eighty-five percent of the cultures could be typed with one of these dilutions.

### Antibiotic Profile and Biotype

Preliminary antibiotic profiles of the cultures were obtained at the hospitals with the use of each laboratory's standard antibiotic selections. At the coordinating laboratory, we standardized antibiotic profiles and obtained biotypes using the autoScan-4 automated scanning system (Baxter Healthcare, Microscan Division) in conjunction with positive combo 21 panels containing biochemicals and dilutions of antimicrobial agents in dehydrated form. Positive identification (probability >85 percent) of the strain was used as the criterion for inclusion in the study.<sup>13</sup> By January 1989, 525 *S. aureus* strains had been collected from patients in all the partici-

pating hospitals. We identified 95 percent of these strains as *S. aureus* using the autoScan-4 (identification probability, 99 percent).

### Definitions

The diagnosis of exit-site infection was based on pericatheter redness or exudate, with or without a positive culture.<sup>3,14</sup> The formation of a crust around the exit site was not considered an indication of infection. The diagnosis of tunnel infection was made if erythema, edema, or tenderness of the subcutaneous tunnel was present, with or without discharge and a positive culture. A cell count was performed in the dialysate when fever, tenderness, abdominal pain, or a turbid dialysate was present. Peritonitis was defined as a dialysate leukocyte count of more than 100 cells per cubic millimeter, with more than 50 percent of these cells being polymorphonuclear leukocytes. Patients were considered to have new episodes of infection by the same organism if they had been free of symptoms at the end of antibiotic therapy and if signs of the infection recurred more than four weeks after the onset of the preceding infection.

### Treatment of Exit-Site Infection, Tunnel Infection, and Peritonitis

Infections were treated according to the routine protocols established by each hospital. Exit-site infection was generally treated with oral antibiotics for 10 days. Peritonitis was treated with intraperitoneal antibiotics for 4 to 10 days. *S. aureus* infections were generally treated with vancomycin or floxacillin for 10 days; however, the choice of antibiotic and the duration of treatment were modified according to the culture reports, clinical response to treatment, and condition of the patient. The nasal carriage of *S. aureus* was not treated. No antibiotic therapy was administered when *S. aureus* was present at the exit site but there were no clinical signs of infection.

### Statistical Analysis

For the purposes of statistical analysis and in order to ascertain whether a nasal culture before CAPD was predictive of subsequent *S. aureus* exit-site infection or peritonitis, the patients were considered either pre-CAPD carriers or noncarriers for the entire follow-up period. The negative binomial model<sup>15</sup> was used to compare exit-site infections and peritonitis and to calculate the probability of remaining free of exit-site infection. The occurrence of tunnel infection in patients with diabetes and those without diabetes was analyzed with Fisher's exact test. All P values are two-tailed.

## RESULTS

### Patient Characteristics and Nasal Carriage of *S. aureus*

One hundred forty patients were enrolled in the study between May 1987 and September 1988. The cumulative follow-up time as of January 1989 was 122 patient-years. The median duration of follow-up was 10.4 months. CAPD was the initial mode of dialysis therapy in 82 percent of the patients. Fourteen percent of both the carrier and noncarrier groups had previously undergone hemodialysis, and approximately 4 percent of the patients in each group received transplants before entering the study. On the basis of pre-CAPD cultures by nasal swab, 63 patients (45 percent) entered the study as carriers of *S. aureus*, and 77 patients (55 percent) entered as noncarriers. The characteristics of the two groups are shown in Table 1. Of the 30 patients with diabetes enrolled in the trial, 23 (77 percent) were nasal carriers; of the 110 patients who did not have diabetes, only 40 (36 percent)



Table 1. Patients' Characteristics and Causes of End-Stage Renal Disease in Carriers and Noncarriers of *S. aureus*.\*

GROUP	AGE (Yr)†			SEX		CAUSE OF END-STAGE RENAL DISEASE		
	≤44	45-64	≥65	MALE	FEMALE	DIABETES	GLOMERULO- NEPHRITIS	OTHER
	percent							
Carrier (n = 63)	28	43	29	64	36	37	6	57
Noncarrier (n = 77)	23	37	40	70	30	9	12	79

\*Forty-five percent of the patients enrolled in the study were positive for the nasal carriage of *S. aureus* before the implantation of the CAPD catheter.

†The mean age in the carrier group was 53.3 years, and in the noncarrier group 59 years.

were carriers of *S. aureus*. Diabetes was the most common cause of end-stage renal disease among the carriers. There were more than 12 causes of end-stage renal disease reported in both groups, and no single form of the disease dominated among the noncarriers. The mean age of the carriers was 53.3 years, 5 years less than that of the noncarriers (P not significant).

There was no important difference between the two groups in the type of catheter implanted. Tenckhoff double-cuffed catheters were implanted (primarily by midline insertion) in 79 percent of the carriers and 81 percent of the noncarriers. Eight patients received the Missouri Swan Neck catheter, and 20 patients had Toronto Western Hospital Type II catheters implanted surgically through the rectus muscle. Long-term care of the exit site was also similar in the two groups. Seventy-four percent of the noncarrier group and 80 percent of the carrier group used nonocclusive, sterile gauze dressings and povidone-iodine. Thirty-six percent of the patients employed either single-use or reusable disconnecting systems for dialysis. No significant difference in the choice of system existed between the two groups.

There were 11 deaths in the carrier group and 9 in the noncarrier group. Patients in the carrier group left the study because of transplantation (7 patients), transfer to hemodialysis (1), and other medical reasons (1). Noncarriers left the study because of transplantation (11 patients), the recovery of renal function (3), and transfer to hemodialysis (2).

#### Causes and Rates of Exit-Site Infection and Peritonitis

The analysis of infection rates is shown in Table 2. There was a significant difference in the rate of exit-site infection between the *S. aureus* carriers and the noncarriers. Whereas the probability of remaining free of exit-site infection after 18 months on CAPD was 92 percent among the patients whose nares were not colonized by *S. aureus* before dialysis, it was only 54 percent among those whose nares were colonized (P = 0.012). Catheters were replaced because of infection in three patients in the carrier group; none of the noncarriers had catheter replacements.

The etiologic agents of exit-site infection and peritonitis are shown in Table 3. In the carrier group, *S. aureus* was responsible for 85 percent of the exit-site infections and 35 percent of the episodes of peritonitis. Three episodes of *S. aureus* peritonitis occurred in carriers at the same time as an exit-site infection caused by the organism. Six noncarriers acquired *S. aureus* in the nares during the follow-up period. Among the noncarriers there were eight episodes of exit-site infection,

only two of which were caused by *S. aureus*. There was no peritonitis due to *S. aureus* in the noncarrier group.

Six of the 23 patients with diabetes who were *S. aureus* carriers (26 percent) had *S. aureus* infections at the catheter exit site, and 5 (22 percent) had *S. aureus* peritonitis. Of the 40 *S. aureus* carriers without diabetes, 14 (35 percent) had *S. aureus* exit-site infections and 1 had *S. aureus* peritonitis. In contrast, the seven noncarriers with diabetes had no exit-site infection and no peritonitis due to *S. aureus*. Two of the 70 noncarriers who did not have diabetes (3 percent) had *S. aureus* exit-site infections, but none had peritonitis caused by *S. aureus*.

#### Tunnel Infections

Although infrequent, all seven episodes of infection of the subcutaneous-catheter tunnel were caused by *S. aureus*. Five of the seven occurred in the carrier group. All five patients had diabetes. The incidence of tunnel infection was higher in the carriers than the noncarriers (0.09 vs. 0.02 episode per year). There was a significant association between diabetes and tunnel infection. Six of the 30 patients with diabetes had an episode of tunnel infection, as compared with only 1 patient without diabetes (P = 0.0003 by Fisher's exact test).

#### Specificity of the Organism

Unless they had received antibiotics to treat *S. aureus* infection, the carriers of *S. aureus* before CAPD tended to have persistent carriage of the same organism, as demonstrated by the phage type. After treatment, the nares culture remained negative for one to four months in half the patients. In most patients, the

Table 2. Rates of Exit-Site Infection and Peritonitis among Carriers and Noncarriers of *S. aureus*.

GROUP	EXIT-SITE INFECTION	PERITONITIS
	episodes/patient-year	
Carrier (n = 63)	0.40	0.50
Noncarrier (n = 77)	0.10	0.52
P value	0.012	>0.50



Table 3. Etiologic Agents and Number of Episodes of Exit-Site Infection and Peritonitis in Carriers and Noncarriers of *S. aureus*.

GROUP	ETIOLOGIC AGENT							
	<i>S. AUREUS</i>	<i>S. EPIDER- MIDIS</i>	<i>PSEUDOMONAS AERUGINOSA</i>	COLIFORMS	NO GROWTH*	FUNGI	STREPTOCOCCUS SPECIES	OTHER
	number of episodes							
Carrier (n = 63)								
Exit-site infection (20 patients)	22	0	1	0	2	1	0	0
Peritonitis (20 patients)	11	8	3	2	3	0	2	2
Noncarrier (n = 77)								
Exit-site infection (6 patients)	2	1	1	0	1	0	0	3
Peritonitis (22 patients)	0	16	2	6	2	1	1	8

\*Clinical infection in which no organism was isolated.

same organism returned. The results to date of phage typing suggest that a wide variety of phage types are responsible for infection. In 85 percent of the patients with clinical infection, the strain from the nares and the strain causing the infection had a similar phage type and antibiotic profile.

### DISCUSSION

This study presents a detailed investigation of the relation between the nasal carriage of *S. aureus* in patients beginning CAPD and their subsequent risk of infection. The permanent catheters used in CAPD are associated with complications, such as exit-site infections, that may lead to peritonitis and catheter removal.<sup>1,5,6,16,17</sup> Recent research suggests that the nasal carrier of *S. aureus* may be at higher risk of exit-site infection during CAPD.<sup>6,8-10</sup> Sewell et al. isolated *S. aureus* from the nares of 17 patients at least once during their study, and one third of the 30 patients they monitored were chronic and intermittent carriers.<sup>8</sup> The nasal carriage of *S. aureus* has been well documented in patients on hemodialysis.<sup>7,18-21</sup> Kirmani et al. reported a carriage rate of 62 percent in patients undergoing hemodialysis, which is higher than the rate of 10 percent to 30 percent reported in the general population.<sup>19,22</sup>

The objective of our study was to establish whether there is a definitive epidemiologic link in CAPD between the nasal carriage of *S. aureus* before the insertion of the cannula and a subsequent infection. For practical reasons, the patients' nares were cultured only once during the 48 hours preceding the implantation of the catheter. With this technique, we observed that the carriage rate before CAPD was 45 percent, higher than in the general population.<sup>6,19,22</sup> Furthermore, this carrier group had a significantly higher rate of exit-site infection than noncarriers. It remains possible that previous treatment with antibiotics may have transiently abolished the nasal carriage of *S. aureus* in a few patients at the time of the first sampling. This possibility may explain the two episodes of exit-

site infection caused by the organism in patients who were originally classified as noncarriers. In one noncarrier, *S. aureus* was cultured from the nares two months before the discovery of an exit-site infection by the same organism, as judged by the phage type.

One of our centers obtained pre-CAPD cultures simultaneously from the anterior nares, groin, and abdomen of participating patients. The nasal cultures proved to be the most sensitive (it was possible to culture *S. aureus* before CAPD from the groin or abdomen of only 10 percent of the carrier patients). In

every case in which *S. aureus* was isolated from another location in the patient before CAPD, the nasal swabs were also positive.

The results of this study indicate that patients undergoing CAPD become infected by endogenously carried strains of *S. aureus*. It is important to note that 77 percent of the patients with diabetes were carriers and that those with diabetes had significantly more tunnel infections than those without diabetes. This observation deserves further evaluation in view of the increasing number of diabetic patients with end-stage renal disease who now undergo CAPD. It is reported that repeated needle puncture of the skin is a risk factor for the nasal carriage of *S. aureus*. Patients undergoing hemodialysis,<sup>7</sup> intravenous drug abusers,<sup>23</sup> otherwise healthy patients who are receiving allergy injections,<sup>24</sup> and patients with insulin-dependent diabetes<sup>25,26</sup> carry *S. aureus* in the anterior nares at rates up to three times those among control populations. Most of the diabetic patients in our study had insulin-dependent diabetes, which may help explain their high rate of carriage. It should be acknowledged that increased numbers of exit-site infections did not correlate with an increase in episodes of peritonitis; more important, a decrease in the number of exit-site infections (in noncarriers) was not associated with decreased episodes of peritonitis. Although *S. aureus* did not cause peritonitis in the noncarrier group, peritonitis remains the most serious complication of CAPD.

Persistent nasal carriage did not always lead to exit-site infection during CAPD. One explanation for this may be the erratic shedding of *S. aureus* from the nose to other parts of the body. Another reason may be that factors in the host, such as nutritional status, predispose some patients to infection, whereas others are only colonized. Finally, some strains of *S. aureus* may cause infection in patients undergoing CAPD, and other strains may be merely colonizing bacteria. However, we have found no evidence to date that any particular phage type is more likely to be associated with exit-site infection. Whatever the ex-



planation, the majority of clinical events occurred in patients who, in spite of frequent checks, had had no detectable exit-site colonization. *S. aureus*-positive but clinically normal exit sites were reported in 25 patients, but clinical infection occurred thereafter in only 3. Further monitoring should clarify the importance of exit-site colonization in relation to nasal carriage and infection.

Previous studies have reported an overall incidence of *S. aureus* peritonitis of approximately 20 percent.<sup>6,27,28</sup> In our experience, all *S. aureus* peritonitis was confined to the carrier group. In sharp contrast, noncarriers had peritonitis that was predominantly due to *S. epidermidis*; to date, no *S. aureus* peritonitis has occurred in this group.

Thus, this study shows that the isolation of *S. aureus* from the nares before the insertion of the catheter identifies patients at high risk of morbidity. Further research should evaluate the merits of suppressing the nasal carriage of *S. aureus* in patients about to undergo CAPD and should determine how to improve the care of the exit site in those at risk for exit-site infection.

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