Nasal Mupirocin Prevents *Staphylococcus aureus* Exit-Site Infection During Peritoneal Dialysis[1,2]

The Mupirocin Study Group[3]

ABSTRACT

A total of 1144 patients receiving continuous ambulatory peritoneal dialysis in nine European centers was screened for nasal carriage of *Staphylococcus aureus*. Two hundred sixty-seven subjects were defined as carriers of *S. aureus* by having had at least two positive swab results from samples taken on separate occasions, and were randomly allocated to treatment or control groups. Members of each group used a nasal ointment twice daily for 5 consecutive days every 4 wk. The treatment group used calcium mupirocin 2% (Bactroban nasal; SmithKline Beecham, Welwyn Garden City, United Kingdom) and the control group used placebo ointment. Patients were followed-up for a maximum period of 18 months. There were 134 individuals in the mupirocin group, and 133 individuals acted as control subjects. There were no differences in demographic data, cause of renal failure, type of catheter, system used, or method of exit-site care between the groups. Similarly, there were no differences in patient outcome or incidence of adverse events between both groups. Nasal carriage fell to 10% in those subjects who received active treatment and 48% in those who used the placebo ointment. There were 55 exit-site infections in 1236 patient-months in the control group and 33 in 1390 patient-months in the treatment group (not significant). *S. aureus* caused 14 episodes of exit-site infection in the mupirocin group and 44 in the control group ($P = 0.006$, mixed effects Poisson regression model). There were no differences in the rate of tunnel infection or peritonitis. There was no evidence of a progressive increase in resistance to mupirocin with time. Regular use of nasal mupirocin in continuous ambulatory peritoneal dialysis patients who are nasal carriers of *S. aureus* significantly reduces the rate of exit-site infections that occurs because of this organism.

Key Words: *CAPD, exit-site infection, S. aureus, prevention, mupirocin*

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[3] Correspondence to Dr. G.A. Coles, Institute of Nephrology, Cardiff Royal Infirmary, Newport Road, Cardiff, CF2 1SZ Wales, UK.

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It is estimated that nearly 100,000 patients worldwide with end-stage renal failure are being treated by peritoneal dialysis, primarily by use of continuous ambulatory peritoneal dialysis (CAPD).

Infection still remains one of the most common complications of this form of therapy. The introduction of Y-tubing sets designed to flush before being filled have significantly reduced the incidence of peritonitis (1,2). Catheter exit-site infections, however, are still an important problem (3). The organism that most commonly causes this complication is *Staphylococcus aureus* (*S. aureus*) (4), and nasal carriage of this species of bacteria appears to be associated with an increased risk of exit-site infection (5–7). Peritonitis that results from infection with *S. aureus* may be clinically severe and is often associated with exit-site infection with the same organism (4). Hemodialysis patients who are nasal carriers of this organism are also reported to have an increased risk of access infections and bacteremia (8).

Mupirocin is a unique antibiotic that acts by interfering with the action of isoleucyl-transfer RNA synthetase. It is available as a nasal ointment and is extensively used for the eradication of methicillin-resistant *S. aureus* (9). Boelaert *et al.* (10) found that the use of nasal mupirocin significantly reduced the incidence of *S. aureus* infections in hemodialysis patients. Treatment of exit-site infections in CAPD patients is often unsatisfactory, with a high chance of relapse. Therefore, there is increasing interest in the possibility of prophylaxis.

The aim of the study presented here was to determine whether regular nasal application of mupirocin by CAPD patients who were proven carriers of *S. aureus* would decrease the incidence of infection resulting from this organism. To test this hypothesis, we carried out a double-blind, placebo-controlled, randomly allocated, prospective trial.

MATERIAL AND METHODS

Patients undergoing CAPD in nine European renal centers were screened for *S. aureus* nasal carriage. A moistened, sterile rayon swab was rotated in both anterior nares and streaked onto a culture medium routinely used by the hospital laboratory for the isolation of *S. aureus* using standard microbiological techniques. Patients were defined as carriers if at least two out of three swabs grew this organism. The minimum elapsed time between nasal samples was 2 days and the maximum was 10 wk. Only *S. aureus* carriers were entered into the trial proper and were randomly allocated to treatment or control groups. Patients who had received antibiotics for a peritoneal dialysis–related infection within the preceding month were excluded from the study, as was any individual with active exit-site infection. No subject had received mupirocin in the previous 6 months. Each patient

was prescribed a nasal ointment to be applied to the inside of both anterior nares twice daily for 5 consecutive days every 4 wk. In the control group, the ointment consisted solely of a white soft paraffin and glycerin base. In the treatment group, the ointment also contained 2% calcium mupirocin. The ointment was supplied in identical 3-g tubes; therefore, the trial was double-blind. One tube was supplied for each 5-day course. Patients were reviewed every 8 wk or if an infection occurred. At each clinic visit, patients were given a diary in which the dates for the next two courses of treatment or placebo had already been entered. Every time the patients applied the ointment, they were required to record it in their diaries. At each visit, the previously dispensed tubes and diaries were collected for the assessment of compliance, and inquiry was made regarding any adverse events and/or use of antibiotics. If it was evident from the diary that less than 60% of the doses had been applied, the patient was deemed noncompliant.

Nasal swabs were taken every 8 wk just before commencing the next course of nasal ointment, or if a peritoneal dialysis–related infection occurred. Patients were continued in the trial for up to 18 months. All participants gave written informed consent and the protocol was approved by the local ethics committees.

For the purposes of this study, the following definitions were used:

Exit-site infection: pericatheter erythema of greater than 2 mm and/or exudate with or without a positive culture.

Tunnel infection: erythema, edema, or tenderness of the subcutaneous catheter tunnel.

Peritonitis: a dialysate leukocyte count of greater than 100 cells per mm^3 with more than 50% being neutrophils.

New episode of infection: infection by the same or different organism occurring more than 2 wk after stopping the previous antibiotic(s) and provided the patient was symptom-free after the preceding course of treatment.

Each center continued its usual policy for catheter selection, exit-site care, and antibiotic treatment.

All Gram-positive, coagulase-positive cocci obtained in the study were forwarded to the microbiological laboratories of SmithKline Beecham for confirmation of identity and for sensitivity testing. Mupirocin susceptibility was determined as minimum inhibitory concentrations in a dilution method using Mueller-Hinton agar medium containing twofold dilutions of mupirocin at final concentrations in the range of 0.0625 to 512 mg/L. Confirmation of identity and susceptibility to other agents was conducted using the Baxter Microscan system (Baxter Healthcare, West Sacramento, CA).

Statistical Analysis

To determine the required patient-months per group for the study, it was assumed that the control group would have an exit-site infection rate of 1 episode per 30 patient months and that a 50% reduction in this rate was required for success. Assuming a 5% chance of showing a difference between test and placebo groups (when in fact there was no difference) was acceptable and 80% power for the study, a comparison of two Poisson rates using a standard Z-test revealed that 1413 patient-months would be required in each group. Comparison of infection rates was made using the mixed effects (negative binomial) Poisson regression model (11) on an intention to treat basis. Goodness of fit of the model was assessed using the Kolmogorov-Smirnov test. Comparison of the patient groups in terms of demography, underlying disease, peritoneal dialysis system, *etc.*, was done using the chi-squared test.

An efficacy evaluable analysis was also performed, taking into account only those individuals who received more than 60% of the medication, attended the clinic regularly, and fulfilled all the entrance criteria. This did not alter the findings from this study. The primary measure of efficacy was a 50% or greater reduction in the incidence of exit-site infections. Secondary measures were a reduction in the incidence of tunnel infections and/or peritonitis.

RESULTS

A total of 1144 individuals receiving CAPD in the nine centers were screened for *S. aureus* nasal carriage. Of these individuals, 267 (23.3%) were defined as carriers, met the selection criteria, and entered the study proper. The demographic data and the causes of the underlying renal disease in the treatment and control groups are shown in Table 1. There were no significant differences in the composition of the groups, including the prevalence of diabetes, and there were no differences in mean or median height or weight (data not shown). There was no difference in the ratio of new to follow-up patients between the groups. Information regarding type of catheter, peritoneal dialysis system, and method of exit-site care is shown in Table 2. Once again, the groups were comparable. Randomization within the centers was equal for exit-site care and implantation. Patient outcome is shown in Table 3. A total of 1390 patient months were observed in the treatment group and 1236.3 patient months in the control group. None of the differences in outcome was statistically significant. The number of adverse events considered to be related or probably related to use of the nasal ointment was very small (six episodes in six patients in the mupirocin group *versus* eight events in seven patients in the placebo group). These adverse events were usually mild and consisting primarily of nasal irritation and/or discharge. One mupirocin patient and one placebo patient withdrew because of adverse events that were probably related to study medication—rhinitis for the former and rhinorrhea and sneezing for the latter.

TABLE 1. Demographic data

Variable	Mupirocin	Placebo
N	134	133
Male (%)	60.4	60.2
Caucasian (%)	94	93.2
Mean Age (yr)	60.3	60.3
Glomerulonephritis (%)	26.1	19.5
Diabetes (%)	17.2	22.6
ADPKD[a] (%)	10.4	5.3
Pyelonephritis (%)	5.2	7.5
Hypertension/Vascular Complications (%)	16.4	8.3
Other (%)	24.6	36.8

[a] ADPKD, autosomal dominant polycystic kidney disease.

TABLE 2. Technical Data (%)

Catheter Variables	Mupirocin	Placebo
Cannula		
Tenckhoff double-cuff	76.1	78.2
Swan neck	20.1	20.3
Toronto Western II	1.5	1.5
Other	0.7	0
System		
Single-use disconnect	50.0	45.1
Reusable disconnect	3.7	6.0
Standard luer/spike	18.7	23.3
UV	20.9	21.8
CXD	1.5	0
Other	3.7	3.0
Exit-Site Care		
Disinfectant	64.1	66.2
Soap and water	6.7	3.8
Other	3.7	4.5
Combination	25.4	24.8
None	0	0.8

TABLE 3. Patient Outcome[a]

Outcome	Mupirocin	Placebo
Completed	32.8	27.8
Death	16.4	18.8
Transplant	14.9	15.0
Hemodialysis	1.5	1.5
Adverse Event	3.0	2.3
Protocol Violation	2.2	7.5
Lack of Compliance	1.5	3.8
Still in Study	17.9	13.5
Other	9.8	9.8
Total Patient-Months	1390	1236.3

[a] The values represent percentages except where stated.

Nasal Carriage

By definition, all patients had 100% nasal carriage of *S. aureus* at the start of the investigation. Subsequent swabs taken from the control groups at the 8-wk clinic visits grew this organism at a rate of 48 to 61% of individuals, the value remaining stable throughout the 18 months of the study. In contrast, nasal carriage in the mupirocin group fell to 10% after 8 wk from the start of the study and remained between 10 and 18% for the rest of the trial. The differences were statistically significant at all time points ($P < 0.001$ [chi square]).

Infections

As reported previously by Luzar *et al.* (12), the negative binomial Poisson regression model fitted the data very well ($P = 0.96$). There were 33 exit-site infections caused by any organism in the mupirocin group and 55 in the control group, giving rates of 1 in 42.1 and 1 in 22.5 patient-months, respectively. This difference was not significant ($P = 0.17$). *S. aureus* caused 14 episodes of exit-site infection in nine individuals receiving active treatment, compared with 44 episodes in 20 subjects using placebo ointment. This gives rates of 1 in 99.3 and 1 in 28.1 patient-months, respectively ($P = 0.006$; mixed effects Poisson regression model). The organisms that caused exit-site infections are listed in Table 4. Besides *S. aureus*, none of the differences was statistically significant.

Tunnel-infection rates were 1 in 154.4 patient-months in the mupirocin group and 1 in 123.6 in the control group. The total peritonitis rate was 1 in 18.1 patient-months in those receiving active treatment and 1 in 19.3 in those using placebo. The *S. aureus* peritonitis rate was 1 in 81.8 and 1 in 53.8 patient-months, respectively. None of these differences was statistically significant. The organisms that caused peritonitis are shown in Table 5. Again, none of the differences was significant. Fungal peritonitis occurred twice in the mupirocin group (one being a mixed infection) and four times in the placebo group (two being mixed infections).

The peritoneal catheter was removed because of infection on eight occasions in the mupirocin group and nine in the control group. *S. aureus* was the cause of infection in three episodes in patients receiving active treatment and five times in those using placebo. In one patient in the mupirocin group and three individuals in the control group, there was active exit-site infection at the time of catheter removal when this was precipitated by peritonitis resulting from *S. aureus* infection. Two patients in each group lost their catheters because of fungal peritonitis.

Resistance

Resistance to mupirocin was defined as a minimum inhibitory concentration in the range of 8 to 256 mg/L (low-level resistance) or >256 mg/L (high-level resistance). Individual resistant isolates of *S. aureus* in both ranges occurred during the trial in patients in both the mupirocin and placebo-treated groups. In both groups, the clearance of the resistant isolates occurred with similar frequency. There was thus no evidence that treatment with mupirocin resulted in colonization with resistant *S. aureus*.

TABLE 4. Organisms Causing Exit-Site Infection

Organism	Mupirocin	Placebo
Staphylococcus aureus	14	44
Other Gram-Positive	2	1
Pseudomonas aeruginosa	4	0
Other Gram-Negative	3	1
Mixed	4	2
No Growth	3	3
Missing	3	3

TABLE 5. Organisms Causing Peritonitis

Organism	Mupirocin	Placebo
Staphylococcus aureus	18	24
Staphylococcus epidermidis	12	11
Other Gram-Positive	12	7
Gram-Negative	13	5
No Growth	9	8
Mixed	7	2
Other	1	3
Missing	5	4

DISCUSSION

This study clearly shows that the regular use of nasal mupirocin by CAPD patients who are nasal carriers of *S. aureus* significantly reduces the chances of their developing an exit-site infection with this organism. In this study, the actual rate of infection fell by more than two thirds.

Exit-site and tunnel infections are an important cause of morbidity and are the most frequent reason for removal of the cannula during CAPD treatment (13). *S. aureus* is the most common cause of pericatheter infection (4). Zimmerman *et al.* (4) reported that patients with *S. aureus* exit-site infection were significantly more likely to have catheter replacement and to have an episode of peritonitis than those who did not have this complication. It is important to note that the incidence of *S. aureus* infections during CAPD has not been reduced by the introduction of disconnect systems (3).

Several studies have shown that nasal carriage of this organism is associated with an increased chance of exit-site infection (5–7). This was confirmed by Luzar and colleagues (12). They reported that 45% of patients had *S. aureus* in the nares before insertion of the cannula, as judged by a single nasal swab. Exit-site infection occurred at a rate of 0.4 episodes per yr in carriers but was significantly less frequent in non-carriers (only 0.1 episode per yr). It was for this reason that we confined our study of prophylaxis to proven carriers. The prevalence of nasal carriage (23%) in the current study was lower than that reported by Luzar *et al.* (12), but we required two isolates to classify a patient as positive. The difference is probably the result, at least in part, of this more stringent definition, which reduced the chances of including transient carriers. Furthermore, because most of our patients were established on CAPD, it is more likely that they would have received prior antibiotics for indications other than peritoneal dialysis–related infections, which could have (on occasion) temporarily eliminated nasal carriage and given a false low rate. Luzar's subjects were swabbed before starting treatment and thus were less likely to include false negatives.

The current treatment of exit-site infections is unsatisfactory. There is a recognized risk of relapse (14), and catheter removal may be necessary to control the problem (13). It is for this reason that there is considerable interest in the possibility of prophylaxis. Early infection may be reduced by a dose of a parenteral antibiotic before catheter implantation (15). A more extensive decolonization regime has also been claimed to be of value (16). The type of exit-site care used may be of benefit. A controlled trial of regular cleansing with povidone iodine was associated with a significantly lower rate of exit-site infection, compared with soap and water (17). It should be pointed out, however, that this report did not compare the results in nasal carriers of *S. aureus* with non-carriers. Immunization with a staphylococcal vaccine is of no value (18).

Zimmerman *et al.* (19) randomly assigned patients to oral rifampicin, 300 mg twice daily for 5 days every 3 months, or no treatment. During follow-up periods of an average of 10 to 12 months, the time to the first catheter-related infection and the rate of infection was significantly reduced in the rifampicin group, primarily because of a reduction in *S. aureus*–related episodes. This investigation did not specifically treat only *S. aureus* carriers. It is important to note that *S. aureus* resistance to rifampicin was seen in a few surveillance cultures after 6 months of therapy. In contrast, Sesso *et al.* (20) were unable to show any benefit with topical sodium fusidate or oral ofloxacin in the prevention of *S. aureus* infection.

The use of a single 5-day course of intranasal mupirocin identical to the one we utilized in the study presented here has been shown to reduce nasal carriage of *S. aureus* in previously positive healthy volunteers to 29% 12 wk later (21). This had risen to 48% at 6 months but was still significantly less than that of placebo treatment (22). Our study clearly shows that regular use of mupirocin reduces nasal carriage in CAPD patients to between 10 and 18%. In contrast, using just placebo caused a reduction to a minimum of 48%. These data suggest that an ointment alone may interfere with nasal colonization by *S. aureus* but, clearly, including the antibiotic is much more effective. An alternative explanation is that intercurrent use of antibiotics may have reduced nasal colonization. Hemodialysis subjects with *S. aureus* nasal carriage who received mupirocin three times daily for 5 days had a mean time to recurrence of 3.8 wk after cessation of therapy (23). Boelaert *et al.* (24) reported that regular use of intranasal mupirocin by nasal carriers of *S. aureus* who are undergoing hemodialysis significantly reduces the incidence of bacteremia resulting from this organism.

Pérez-Fontán *et al.* (25) recently presented their findings from a sequential study of nasal mupirocin. A total of 94 CAPD patients were screened at monthly intervals for *S. aureus* nasal carriage. Individuals with a positive culture at any time point were given nasal mupirocin three times a day for 7 days. The infection rate in the 94 patients as a whole was compared with retrospective data from a further 74 patients. During

the treatment phase, the rate of *S. aureus* peritonitis and exit-site infections decreased markedly. However, there was no significant change in the overall rates, apparently because of an increase in the number of Gram-negative infections. Our results confirm a marked reduction in *S. aureus*–induced exit-site infections. We did see an overall reduction in exit-site infections from 55 in 1236 patient-months to 33 in 1390 patient-months but this was not statistically significant. There were more Gram-negative isolates from our treatment group but the differences were not significant. We have calculated that we would have needed to enter 400 patients into a trial to show a difference in the rate of *S. aureus* peritonitis. Similarly, a much longer follow-up period or considerably more patients would have been necessary to show whether either the fall in total exit-site infections or the rise in the Gram-negative episodes were statistically meaningful. It should be noted, however, that the actual number of Gram-negative infections was small, even in the treatment group. Fungal peritonitis has been thought to be associated with the prior use of antibiotics. There was no evidence that this was true with the use of regular nasal mupirocin because the treatment group had half the number of episodes of the control group.

Piraino *et al.* (26) compared the rifampicin regime used by Zimmerman *et al.* (19) to daily mupirocin applied to the exit site in a randomly allocated prospective trial. There was no difference in the rate of catheter-related infections or peritonitis, but both treatments were associated with significantly lower rates of catheter infections, compared with historical control subjects. One report suggested that if mupirocin is applied directly to one particular type of catheter, structural damage may occur (27). Prolonged treatment for infected skin lesions has been associated with resistance to mupirocin (9). In contrast, there was no evidence of increasing resistance with time, either in the study of Boelaert *et al.* (24) or in our own.

Side effects related or probably related to the study medication in our investigation were infrequent and mild, being equally common in treatment and placebo groups, and only a few patients were unable to tolerate the ointment. Thus, in conclusion, the regular monthly use of nasal mupirocin significantly reduces the incidence of *S. aureus* exit-site infections in CAPD patients with nasal carriage of this organism, without producing resistance or serious side effects. We would therefore recommend that this regime become part of the routine management of such individuals.

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