

## **The use of nasal mupirocin ointment to prevent *Staphylococcus aureus* bacteraemias in haemodialysis patients: an analysis of cost-effectiveness**

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**Summary:** Nasal carriage of *Staphylococcus aureus* is a risk factor for the development of infections caused by *S. aureus* in haemodialysis patients. This study compared the incidence of bacteraemia caused by *S. aureus* during 6 months of use of nasal 2% calcium mupirocin ('Nasal Bactroban') 3-times a week for nasal carriers with the incidence observed previously in the same dialysis unit without the use of mupirocin. Nasal mupirocin led to the total eradication of nasal carriage of *S. aureus*, a 4.26-fold reduction in the incidence of *S. aureus* bacteraemia, and a substantial cost saving. After a cumulative experience of nasal mupirocin in haemodialysis patients of more than 43 patient-years, the development of mupirocin resistance was not observed.

**Keywords:** Mupirocin; *Staphylococcus aureus*; haemodialysis; bacteraemia.

### **Introduction**

Infection is known to be the principal cause of morbidity and the second commonest cause of mortality in patients with chronic renal failure, treated by maintenance haemodialysis.<sup>1,2</sup> *Staphylococcus aureus* is the microorganism most commonly implicated in these infections.<sup>2,3</sup> Nasal carriage is considered to play an important role in the pathogenesis of infections caused by *S. aureus* in patients on haemodialysis<sup>4</sup> or on continuous ambulatory peritoneal dialysis.<sup>5</sup> Elimination of staphylococcal nasal carriage, either by oral rifampicin combined with nasal bacitracin<sup>1</sup> or by nasal calcium mupirocin,<sup>3</sup> has been reported to reduce the rate of staphylococcal infection in haemodialysis patients.

The present study compares the incidence of bacteraemia caused by *S. aureus* in a haemodialysis unit before and after the use of nasal mupirocin for the elimination of nasal carriage. Particular emphasis is given to the analysis of cost effectiveness.

### Patients and methods

Between September 1989 and the end of March 1990, all patients on maintenance haemodialysis in a haemodialysis unit were screened for nasal carriage of *S. aureus*. They were considered carriers if two nasal swabs taken one week apart were positive for *S. aureus*. All carriers, after giving their consent, were prescribed 2% calcium mupirocin ('Nasal Bactroban'). The ointment was applied to the anterior nares three times daily for the first five days and subsequently at the end of each haemodialysis session, i.e. three times weekly. The methods for sampling the nares and for the isolation, identification, minimum inhibitory concentration (MIC) determination, and phage typing of *S. aureus* were as previously reported.<sup>6</sup> Repeat swabs were obtained from both anterior nares at the end of the third and the sixth month of the trial.

The patients were followed prospectively for the development of bacteraemia caused by *S. aureus*. When a patient presented with fever  $>38^{\circ}\text{C}$ , with or without signs of infection, three pairs of blood cultures were collected using a standard aseptic technique. Blood culture isolates of *S. aureus* were considered as relevant if grown from more than two of the six culture bottles. The incidence of *S. aureus* bacteraemia in the total haemodialysis population, during the six months in which nasal carriers were treated with mupirocin, was compared with the incidence of *S. aureus* bacteraemia during a 2-year period when mupirocin prophylaxis had not been used (which had been previously prospectively assessed<sup>3</sup>). In order to allow comparison between the two study periods, the episodes of *S. aureus* bacteraemia that occurred within the first month of haemodialysis, excluded from the previous 2-year incidence study,<sup>6</sup> were included in the present comparison. Of the 106 patients in the present trial, 71 (67%) treated with mupirocin had also been assessed for bacteraemia caused by *S. aureus* in the previous pre-mupirocin trial.

The combined costs of prophylaxis and treatment of *S. aureus* bacteraemia were compared for the two study periods, with and without mupirocin prophylaxis. In the absence of mupirocin prophylaxis, the costs assessed were those of the treatment of *S. aureus* bacteraemia, namely the cost of hospitalization, diagnostic investigation and drug treatment. For the 6 months of mupirocin prophylaxis, the costs included, in addition, the cost of nasal cultures plus the cost of 2% calcium mupirocin ointment (which is commercially available in the UK). The costs, in US dollars, were expressed per patient-year at risk.

### *Statistical analysis*

The characteristics of the patients in the two study periods were compared by contingency table analysis. The incidence of bacteraemia caused by *S. aureus* was compared by the Fisher's exact test.

## Results

During the 6 months of the study, 106 patients in our unit were on maintenance haemodialysis, with a total follow-up of 44.1 patient-years. Their characteristics are shown in Table I. There was no significant difference between the two patient groups concerning the age distribution and the fraction of patients with diabetes mellitus, with iron overload (defined by a serum ferritin  $>1\text{mg l}^{-1}$ ) or with dialysis through a central venous catheter. Of the 106 patients, 43 (41%) were nasal carriers of *S. aureus* which was always sensitive to mupirocin. These 43 nasal carriers received mupirocin nasal ointment prophylactically for a total follow-up of 16.75 patient-years: 29 patients were followed for 6 months, 8 for 2–4 months and 6 for less than 2 months. A total of 60 nasal cultures was taken from 31 patients 3 and 6 months after the start of the 6 months study of mupirocin prophylaxis; none of the swabs yielded *S. aureus*.

There was only one episode of *S. aureus* bacteraemia recorded during the 44.1 patient-years of follow-up, an incidence of 0.0227 per patient-year at risk. The source of *S. aureus* for the single bacteraemic episode could not be identified, and a nasal culture taken at the time of bacteraemia, prior to antibiotic therapy, failed to yield *S. aureus*. The *S. aureus* isolated from the blood was sensitive to mupirocin and was of the same phage type as the strain isolated from the patient's nose prior to mupirocin use. The 2% calcium mupirocin ointment was well tolerated in all patients.

Table I. Patient characteristics and incidence of *S. aureus* bacteraemia with, and without, mupirocin

Patient characteristics	Without mupirocin* (N=158)	With mupirocin to carriers (N=106)
Percentage of patients aged		
$\leq 65$ years	62%	60.4%
$> 65$ years	38%	39.6%
No. (%) with nasal carriage of <i>S. aureus</i>	NT	43 (40.5%)
No. of patient-years of follow up	185.8	44.1
Percentage of patient-years with:		
diabetes mellitus	10.9%	13.8%
serum ferritin $\leq 1\text{ mg l}^{-1}$	81.0%	87.5%
$> 1\text{ mg l}^{-1}$	19.0%	12.5%
central venous dialysis catheter	3.2%	5.5%
No. of bacteraemias caused by <i>S. aureus</i>	18	1
Incidence of <i>S. aureus</i> bacteraemia per patient-year	0.0969	0.0227†

\* Results previously reported by Boelaert *et al.*

NT: Not tested.

†  $P=0.08$  (Fisher's exact test).

In the absence of mupirocin prophylaxis there were 18 bacteraemias caused by *S. aureus* during 185.8 patient-years, an incidence of 0.0969 per patient-year at risk. The incidence of *S. aureus* bacteraemia during mupirocin prophylaxis was reduced 4.26-fold, when compared to the previous 2 years when mupirocin was not used ( $P=0.08$ ).

The cost of treating and/or preventing *S. aureus* bacteraemia was compared for the two study periods: without and with mupirocin prophylaxis. In our previous study when nasal mupirocin was not used, the cost for the treatment of an episode of *S. aureus* bacteraemia ranged from \$763 to \$87 229 (mean=\$9249; median=\$3429). The mean cost per patient-year at risk for the treatment of *S. aureus* bacteraemia was \$896. During mupirocin prophylaxis, the calculated mean cost for the treatment of *S. aureus* bacteraemia per patient-year at risk was \$210. The cost of monitoring nasal cultures every 3 months was \$32 per patient-year and the eradication of nasal staphylococcal carriage by mupirocin in c.40% of the haemodialysis population was  $\$60 \times 0.4$ , or \$24 per patient-year. Thus, when using mupirocin prophylaxis, the average total cost was \$266. This cost is only 30% of the cost of treating *S. aureus* bacteraemia in the period prior to using mupirocin prophylaxis.

### Discussion

We previously reported the results of a double-blind, placebo-controlled trial which showed that 2% calcium mupirocin nasal ointment was effective in eradicating nasal carriage of *S. aureus* and in decreasing the rate of *S. aureus* infections in patients on maintenance haemodialysis.<sup>6</sup> A subsequent study in the same patient population showed that some weeks or months after a single 5-day course of nasal mupirocin, *S. aureus* tended to recolonize the nares, while staphylococcal nasal recolonization did not occur when nasal mupirocin application was continued thrice weekly, i.e. after each haemodialysis.<sup>7</sup> Therefore, nasal mupirocin was applied 3 times per week throughout the present study, after an initial 5-day-course. Eradication of nasal *S. aureus* and the absence of recolonization during mupirocin prophylaxis in 43 carriers in the present study confirms our previous results.

*Staphylococcus aureus* infections in haemodialysis patients frequently lead to bloodstream invasion with potential complications, such as *S. aureus* endocarditis, osteomyelitis or pulmonary infarction. The incidence of *S. aureus* bacteraemia during the period of mupirocin use was compared with that previously observed without mupirocin in a comparable dialysis population. Risk factors for infection, such as diabetes mellitus,<sup>2</sup> transfusional iron overload<sup>3</sup> and dialysis through a central venous catheter<sup>8</sup> were not significantly different between the two patient populations. The present study shows that mupirocin prophylaxis in nasal carriers decreases the incidence of *S. aureus* bacteraemia 4.26-fold, as compared with the

incidence observed in haemodialysis patients in the pre-mupirocin era. The difference was not statistically significant in the Fisher's exact test ( $P=0.08$ ), but this may reflect the much shorter period of observation in the mupirocin trial and a more prolonged study is required. However, even if not statistically significant, a 4.26-fold decrease in the incidence of *S. aureus* bacteraemia is clinically relevant.

The median cost for the treatment of one episode of *S. aureus* bacteraemia in the pre-mupirocin era was \$3429. However, one of these episodes of infection was complicated by endocarditis, requiring the insertion of a prosthetic valve and prolonged hospitalization, which accounts for the mean cost of \$9249.<sup>6</sup> Expressed per patient-year at risk, the cost for the treatment of *S. aureus* bacteraemia was \$986. This contrasts to the calculated cost of \$266 when mupirocin prophylaxis is applied. The use of mupirocin prophylaxis in haemodialysis patients with staphylococcal nasal carriage is therefore cost effective, as it leads both to a >4-fold reduction in the incidence of *S. aureus* bacteraemia, and to substantial saving.<sup>9</sup>

Several reports have mentioned a small number of cases where mupirocin resistance existed naturally or was induced, either experimentally or during long-term mupirocin therapy. This problem has recently been reviewed.<sup>10</sup> During a cumulative experience of more than 43 patient-years of nasal application of mupirocin 3-times per week in haemodialysis patients, we have not observed emergence of mupirocin resistance in our unit. However, caution is warranted. A lower frequency of mupirocin application might be as effective as our thrice weekly regimen and might reduce the risk of the development of resistance. We are presently studying such a once-weekly regimen.

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### References

1. Yu VL, Goetz A, Wagener M *et al.* *Staphylococcus aureus* nasal carriage and infection in patients on hemodialysis. Efficacy of antibiotic prophylaxis. *N Engl J Med* 1986; **315**: 91-96.
2. Keane WF, Maddy MF. Host defenses and infectious complications in maintenance haemodialysis. In: Maher JF, Ed. *Replacement of Renal Function by Dialysis* 1988; 865-880.
3. Boelaert JR, Daneels RF, Schurgers ML *et al.* Iron overload in haemodialysis patients increases the risk of bacteraemia: a prospective study. *Nephrol Dial Transplant* 1990; **55**: 130-134.
4. Chow JW, Yu VL. *Staphylococcus aureus* nasal carriage in hemodialysis patients. Its role in infection and approaches to prophylaxis. *Arch Intern Med* 1989; **149**: 1258-1262.
5. Luzar MA, Coles GA, Faller B *et al.* *Staphylococcus aureus* nasal carriage and infection in patients on continuous ambulatory peritoneal dialysis. *N Engl J Med* 1990; **322**: 505-509.
6. Boelaert JR, De Smedt R, De Baere YA *et al.* The influence of calcium mupirocin nasal ointment on the incidence of *Staphylococcus aureus* infections in haemodialysis patients. *Nephrol Dial Transplant* 1989; **4**: 278-281.
7. Boelaert JR, De Baere Y, Godard C, Van Landuyt HW. Eradication of *Staphylococcus*

*aureus* in dialysis by nasal mupirocin. Abstract 1262. *29th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Houston 1989.

8. Cheesbrough JS, Finch RG, Burden RP. A prospective study of the mechanisms of infection associated with hemodialysis catheters. *J Infect Dis* 1986; **154**: 579–589.
9. Doubilet P, Weinstein MC, McNeil BJ. Use and misuse of the term 'cost effective' in medicine. *N Engl J Med* 1986; **314**: 253–256.
10. Cookson BD. Mupirocin resistance in staphylococci. *J Antimicrob Chemother* 1990; **25**: 497–503.