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Nasal carriage of *Staphylococcus aureus* and cross-contamination in a surgical intensive care unit: efficacy of mupirocin ointment

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Summary: A six month prospective study was carried out in a surgical intensive care unit (SICU) of a university hospital to assess the incidence and routes of exogenous colonization by *Staphylococcus aureus*. A total of 157 patients were included in the study. One thousand one hundred and eleven specimens (nasal, surgical wound swabs, tracheal secretions obtained on admission and once a week thereafter, and all clinical specimens) were collected over a four month period from patients without nasal decontamination (A). They were compared with 729 specimens collected over a two month period from patients treated with nasal mupirocin ointment (B). All *S. aureus* strains were typed by restriction fragment length polymorphism (RFLP) pulsed-field gel electrophoresis after *Sma*I macrorestriction. The nasal colonization rates on admission were 25·5 and 32·7% in groups A and B, respectively. Thirty-one untreated patients (31·3%) and three patients (5·1%) treated with nasal ointment, acquired the nasal *S. aureus* in the SICU ($P=0·00027$). Nasal carriers were more frequently colonized in the bronchopulmonary tract (Bp) and surgical wound (Sw) (62%) than patients who were not nasal carriers (14%) ($P<0·00001$). The patterns were identical for nasal, Bp and Sw strains from the same patient. RFLP analysis characterized seven epidemic strains of methicillin-resistant *S. aureus* (MRSA) which colonized 60% of group A and 9% of group B patients ($P<0·00001$). The bronchopulmonary tract infection rate was reduced in group B ($P=0·032$). In conclusion, in an SICU, nasal carriage of *S. aureus* appeared to be the source of endogenous and cross-colonization. The use of nasal mupirocin ointment reduced the incidence of Bp and Sw colonization, as well as the MRSA infection rate.

Keywords: *S. aureus*; surgical ICU; nasal carriage; mupirocin.

Introduction

It is now clear that methicillin-resistant strains of *Staphylococcus aureus* are as pathogenic as methicillin-sensitive strains.[1] Severe staphylococcal

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infections are an increasing problem, particularly in intensive care and burns units[2] where methicillin-resistant *S. aureus* (MRSA) are responsible for 30–60% of such infections.[3–5] In our university hospital, MRSA colonization is endemic, with grouped cases and sudden onset, suggesting cross-colonization.[3,4,6–8] MRSA-induced morbidity and mortality,[9] first observed in Europe, are now widespread in many countries (Australia, America and Africa).[10–12] Nasal carriage is the principal endogenous reservoir for infection of patients in surgical wards, as demonstrated by phage typing,[7] and patients with chronic renal failure on maintenance haemodialysis.[13] Nasal mupirocin in these patients leads to total eradication of *S. aureus* nasal carriage, a 4·26-fold reduction in the incidence of bacteraemia and a substantial cost saving.[15] Detection and treatment of nasal carriers with intranasal mupirocin, associated with other measures contributed to the control of large epidemic of MRSA.[16,17] Hospitalization in a surgical intensive care unit (SICU) is associated with numerous risk factors for infection with *S. aureus*, i.e. the number of care procedures, proximity of colonized/infected patients, presence of foreign materials and surgical wounds, and lengthy antibiotic therapy.[18,19] Tracheal tubes and surgical wounds, as well as staff and patients' nares, are frequently colonized and are thus potential reservoirs for cross-infection.[14,20–23] With the advent of molecular biology, several, highly discriminatory techniques, based on DNA polymorphism, have been developed for strain comparisons in epidemiological studies.[24–26] As a result, the incidence of cross-colonization can now be evaluated accurately by genotyping methods. This six month prospective study was performed to assess the incidence and routes of exogenous colonization and hospital-acquired infections caused by *S. aureus*, and to evaluate the efficacy of nasal mupirocin ointment in reducing cross-colonization in a SICU.

Materials and methods

Study design

In a two-step prospective study, a total of 1740 specimens, collected from 157 patients admitted to the SICU (15 beds) of the University Hospital of Besançon, France, were screened for the presence of *S. aureus*. Nasal and surgical wound swabs and tracheal secretions were collected on admission and once a week during hospitalization in the SICU, together with all clinical specimens. Over a four month period 1011 specimens were collected from patients without nasal decontamination (A). During the second period, 729 specimens were collected over a two month period from patients treated with nasal mupirocin ointment (B). All *S. aureus* strains were typed. Nasal ointment was applied twice a day in each nostril for the first week, beginning on the day of admission and continuing whatever the screening results.

Bacteriological techniques
Specimens were cultured using standard blood agar (blood agar base + 7% horse blood) and Chapman agar (both freshly prepared). Plates were incubated in air at 37°C for 48 h. *S. aureus* was identified by colony morphology and by the slide and tube coagulase tests. Methicillin sensitivity was checked at 30°C by the conventional Kirby-Bauer disc-diffusion method.

Epidemiologic genotyping
Unsheared DNA was prepared by the method of Prévost *et al.*,[27] digested with the restriction endonuclease *Sma*I according to the manufacturer's instructions and subjected to pulsed-field gel electrophoresis (PFGE) using the CHEF-DRII system (BioRad Ltd) (pulse times of 20 s for 12 h and then 5–15 s for 17 h at 150 V and 14°C). Gels were stained with ethidium bromide (0·1%) for 30 min.

Analysis of DNA relatedness
The electrophoretic restriction patterns (number and size of fragments) were analysed by scanning photographic negatives with a LKB 2222-020 Ultrascan laser densitometer (LKB Pharmacia, Uppsala, Sweden) as described by Prévost *et al.*[27] The restriction pattern of each strain was compared to the profile of all other strains. The DNA fingerprint of each isolate was scored for the presence or absence of individual bands (negative character: absence of a band; positive character: presence of a band). A similarity index was determined for each pair of strains by the Jaccard-Sneath formula: $S_{(i,j)} = N_a/(N_a + N_b)$,[28] where N_a is the number of characters shared by i and j, and N_b the number of different characters. We compared intergel restriction fragment length polymorphisms (RFLPs) by including an internal reference strain in each gel. Major restriction genotypes were defined according to Struelens *et al*[29] (common restriction patterns differed by three or fewer fragments and showed a similarity coefficient >85%). Major genotypes were labelled by numerals, and each of their variant subtypes was indicated by a letter suffix.

Definition of cases
Case definitions were based on Centers for Disease Control (CDC) criteria.[30] A case of colonization was defined as any patient with a culture positive for *S. aureus* without evidence of tissue invasion.

Statisical analysis
The two-sided χ^2 test and the Fisher's exact two-sided test were used for contingence univariate analysis on a computer Epi-Info 5·01.

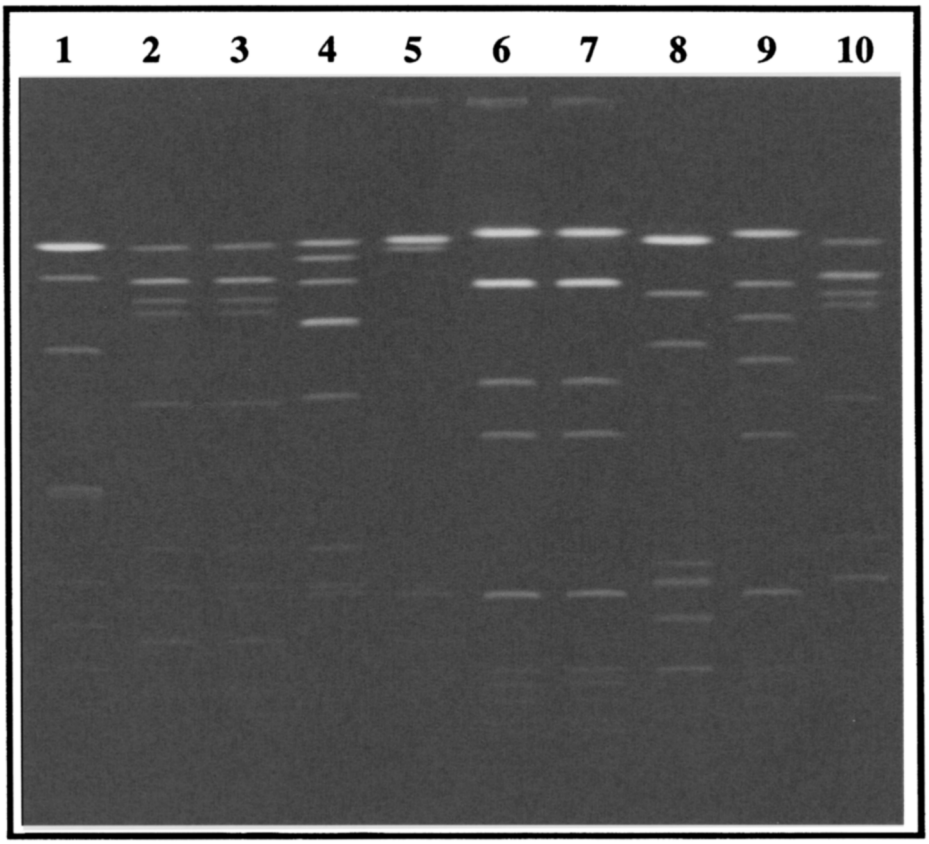

Figure 1. Pulsed-field gel electrophoresis of *Dra*I digested DNA from *Staphylococcus aureus* isolates. Lane 1: pattern 50; lanes 2 and 3: pattern 4a; lane 4: pattern 51; lane 5: pattern 52; lanes 6 and 7: pattern 47; lane 8: pattern 35; lane 9: pattern 53; lane 10: pattern 4b.

Results

One hundred and fifty non-repetitive MRSA and methicillin-sensitive *S. aureus* (MSSA) strains showed 65 distinct major DNA patterns (Figure 1). Eleven variant subtypes (types 4a–k) clustered in a clonal group of patterns accounting for 59 isolates. Three other major patterns could be subdivided into types (types 9a–c, 11a–b and 55a–b). Sixty-one other major patterns clustered at less than 85% similarity.

The nasal colonization rates on admission were respectively 25·5% (22 patients) and 32·7% (19 patients) in periods A and B ($P>0·05$). 31·3% of patients ($n=31$) vs only 5·1% ($n=3$) acquired the nasal *S. aureus* in the SICU [$P<0·00027$; RR = 6·05 (1·94–18·93)]. The prevalence of MRSA/MSSA among nasal isolates was 35/18 and 6/16 in the first and second periods [$P=0·0048$; RR = 2·42 (1·19–4·92)].

Table I. *Nasal colonization by epidemic strains*

	Methicillin-sensitive			Methicillin-resistant	
	No. of colonized patients			No. of colonized patients	
No. RFLP	On admission	SICU-acquired	No. RFLP	On admission	SICU-acquired
11	2	0	1	1	3
28	1	1	2	0*	3
37	1	1	4a	4	13
48	3	0	4b	4	0
			7	2	0
			22	1	1
			32	1	1
Total number of patients	7	2		13	21

* Pattern present in one patient at the beginning of the study.
RFLP, restriction fragment length polymorphism.
SICU, surgical intensive care unit.

Over the six months of this study, 13 patients were colonized with an MRSA on admission to the SICU and 28 paients had an MSSA; 28 patients acquired an MRSA in the SICU and six patients acquired an MSSA [$P<0{\cdot}0001$; RR = 2·60 (1·61–4·18)]. Genomic analysis characterized 30 different patterns isolated from single patients and 11 patterns isolated from several patients. As shown in Table I, most, epidemic strains were MRSA before SICU admission as in the SICU and MSSA were sporadic strains. Seven MRSA strains colonized 60% of nasal carriers in group A and 9% in group B [$P=0{\cdot}0001$; RR = 6·64 (1·74–25·35)].

During the two study periods, *S. aureus* colonized various other sites in 54 patients. Among the 75 nasal carriers, 42 were also colonized at another site, as were 12 patients among the 82 who were not nasal carriers [$P<0{\cdot}0001$; RR = 3·83 (2·19–6·70)]. Table II shows the distribution of colonized sites. Two, the bronchopulmonary tract and surgical wounds, were colonized by the nasal strain of the same patient ($P<0{\cdot}0001$ and $P=0{\cdot}009$, respectively).

The three major SICU-acquired patterns (1, 2 and 4a) occurred consecutively during the first period. Among 17 patients with nasal colonization by a pattern 4a strain, four were carriers on admission: one in February (index case), one in March, one in May (period A) and one in June (period B). Thirteen patients acquired nasal colonization with this pattern in the SICU and three patients acquired it at another site without nasal colonization. The epidemic curve (Figure 2) shows that cross-colonization in the SICU was very frequent during period A (12 patients) and was rapidly reduced during period B (only one case, at the beginning of period B). In period B, bronchopulmonary tract colonization persisted in three patients,

Table II. *Distribution of* Staphylococcus aureus-*positive sites*

Specimen	No. (%) of patients with positive cultures ($n=160$)	Nasal colonization		P (RR)
		Positive with the same strain	Negative or positive with another strain	
Tracheal secretion	43 (26·8)	28	15	<0·0001 (2·38)
Surgical wound swab	12 (7·5)	9		3·009 (2·18)
Blood	9 (5·6)	4	5	NS
Vascular line	5 (3·1)	2	3	NS
Urine	5 (3·1)	2	3	NS
Rectal swab	1 (0·6)	1	0	NS

NS, non-significant.

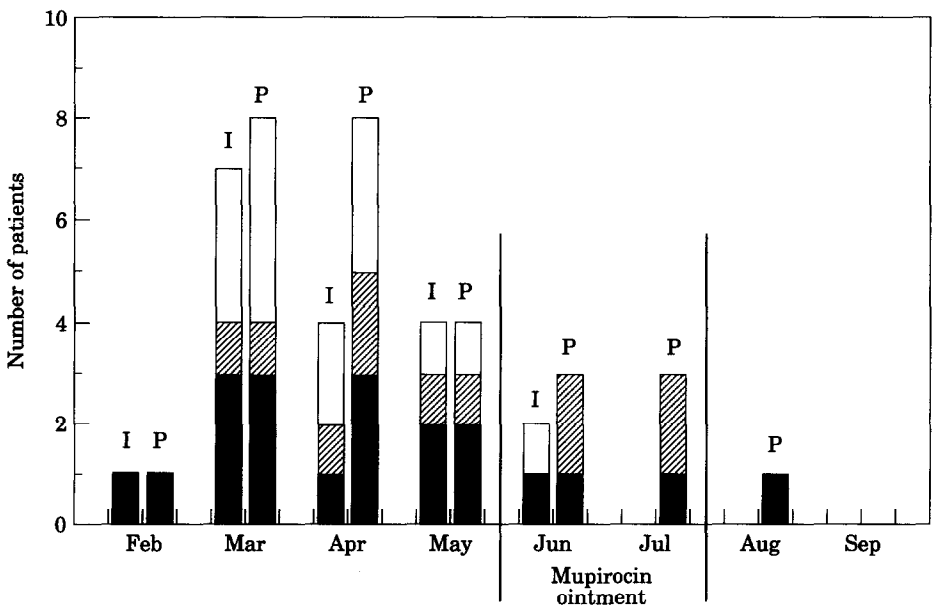

Figure 2. Epidemic curve of 4a pattern. (□), Nasal carriage; (▨), other sites of colonization; (■), nasal carriage and other sites of colonization. I, Incidence; P, prevalence.

one with simultaneous nasal colonization. All the strains isolated during both period A and period B were susceptible to mupirocin (CMI<0·25 mg l^{-1}).

During the study period, we observed no acquired methicillin resistance. Seven patients initially colonized with an MSSA pattern acquired an MRSA with a different pattern in the SICU. Nineteen patients developed an infection with an *S. aureus* strain during period A and four during period

Table III. *Infections*

Infections	Period A	Period B	*P*
Pulmonary tract	13	1	0·032
Bacteraemia/septicaemia	6	1	NS
Surgical wound	2	0	NS
Urinary tract	2	1	NS
Surface	1	1	NS
Vascular line	1	0	NS

NS, non-significant.

B [$P=0·036$; RR=2·78 (1·00–7·78)]. The incidence of infections was 28 per 100 patients admitted ($n=25$) before decontamination and 6·8 during the treatment period ($n=4$) [$P=0·0001$; RR=4·0 (1·83–8·73)]. The two major infections (Table III) were pneumonia and bacteraemia/septicaemia, and both were reduced during period B, the first significantly ($P=0·032$).

Discussion

The epidemiology and routes of MRSA transmission must be identified, in order to control the spread by means of specific measures.[31] Accurate epidemiologic typing is of primary importance. Markers include the lysotype, serotype and capsular type. Molecular subtyping methods include protein electrophoretyping,[32] plasmid content and plasmid DNA restriction pattern,[33,34] restriction analysis of total genomic DNA[35] and RFLP generated by Southern hybridization with DNA probes.[34,35] Recently, DNA fingerprinting by PFGE has provided a higher level of strain discrimination.[26,36] This method is more effective than ribotyping[37] and polymerase chain reaction genome fingerprinting[25] in distinguishing between MRSA isolates.

The use of a highly discriminant typing method confirmed that the major vector of MRSA infections in the SICU is cross-colonization and not the selection of resistant mutants of susceptible strains, despite the frequent use of β-lactam antibiotics.[7,38] This method also showed that, during period A, the situation was 'pseudo-endemic', as the stable high rate of colonization was due to the successive spread of different epidemic patterns. The staff can be the reservoir for epidemic spread of MRSA[14,29,40] but this was not the case in our study, as three different strains followed one another during A, and only patient decontamination alone was successful during B. Transient hand carriage during the numerous patient care procedures, especially during bronchopulmonary tract and surgical wound care, was probably the source of cross-colonization by a strain with the same DNA pattern.

RFLP PFGE was used for the first time to compare isolates from the nose and other sites. This comparison, with a very effective typing method,

allowed us to carry out an accurate study of MRSA epidemiology. Colonization of the bronchopulmonary tract before nasal colonization was also found by Walsh *et al.*[21] but we demonstrated that the DNA pattern of the bronchopulmonary strains were identical to that of the nasal strains.

Mupirocin ointment applied to the anterior nostrils was very effective in eradicating *S. aureus* nasal carriage ($P=0{\cdot}00027$) as previously suggested.[17,41–44] Nasal decontamination, which has been used with varying degrees of success in several outbreaks,[16,45–47] significantly reduced the rate of infections and the incidence of pneumonia due to MRSA and MSSA. The three ventilated patients who acquired nasal colonization during period B carried the same strain in the bronchopulmonary tract, and all three strains were mupirocin-susceptible. The presence of the ventilator tube probably explains the recolonization of the nares without selection of mupirocin-resistant strains.[48,49]

Detailed guidelines for the control of epidemic MRSA have been published by the British Society of Antimicrobial Chemotherapy and the Hospital Infection Society. These guidelines emphasize the importance of isolating positive patients, staff hand disinfection, and eliminating skin and nasal carriage. Routine nasal decontamination on admission was effective in reducing colonization and infection rates without screening, isolation measures and skin disinfection. Such a strategy can be used in a single small unit like ours (15 beds) but is more problematic for an entire hospital. The use of mupirocin alone to treat nasal colonized patients delays decontamination and requires strict isolation of patients until clearance swabs have proved negative.

Conclusions

Nasal carriage appears to be the major source of endogenous and cross-colonization in the SICU. The use of mupirocin nasal ointment reduces the incidence of both colonization and infection. Routine identification and decontamination of nasal carriers on admission, especially after transfer from other units, can probably avoid the spread of *S. aureus* epidemics.

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