Staphylococcus aureus poststernotomy mediastinitis: Description of two distinct acquisition pathways with different potential preventive approaches

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Objective: Determining the acquisition routes of infection is crucial to designing specific preventive approaches against *Staphylococcus aureus* poststernotomy mediastinitis.

Methods: From 2002 to 2004, a nasal sample was obtained from patients before cardiac surgery. We collected clinical and microbiologic data of all episodes of *S aureus* poststernotomy mediastinitis. A case–control study (3:1) was performed to confirm the role of previous preoperative nasal colonization by *S aureus* as a risk factor for *S aureus* poststernotomy mediastinitis. Pulsed field gel electrophoresis molecular analysis of nasal and surgical site *S aureus* isolates was performed to analyze their relatedness in each patient with poststernotomy mediastinitis and with other patients of the study cohort.

Results: *S aureus* nasal cultures were positive in 228 (15.9%) of 1432 patients: methicillin-susceptible *S aureus* in 222 (15.5%) and meticillin-resistant *S aureus* in 6 (0.4%). *S aureus* poststernotomy mediastinitis was diagnosed in 17 (1.2%) of 1432 patients: 9 (3.95%) of 228 in colonized patients versus 8 (0.66%) of 1204 in noncolonized patients ($P < .0001$). Seven of 9 patients (1.2%) with methicillin-susceptible *S aureus* had an identical isolate by pulsed field gel electrophoresis in preoperative nasal and surgical-site cultures, but no clonal relatedness was shown among the isolates from these 9 patients. None of the 8 patients with methicillin-resistant *S aureus* poststernotomy mediastinitis had an identical isolate by pulsed field gel electrophoresis in preoperative nasal and surgical-site cultures, and the same clone of methicillin-resistant *S aureus* was responsible for all these cases.

Conclusions: Nasal colonization often precedes methicillin-resistant *S aureus* poststernotomy mediastinitis, which suggests that decontamination is adequate for preventing methicillin-resistant *S aureus* poststernotomy mediastinitis, whereas hospital infection control measures seem to be the major factor for preventing methicillin-resistant *S aureus* poststernotomy mediastinitis.

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Postsurgical mediastinitis (PSM) is a serious complication that occurs in 1% to 2% of cardiothoracic surgery procedures and carries high morbidity and mortality.[1] *Staphylococcus aureus* is a major cause of this complication and carries a worse prognosis than that of other etiologies.[2] The assumption of the endogenous pathway for some cases resulting from methicillin-sensitive *S aureus* (MSSA),[3] supported by the demonstration that MSSA nasal colonization is an independent risk factor for PSM,[4] has made prevention of some cases possible by preoperative nasal *S aureus* eradication with mupirocin.[5,6] Methicillin-resistant *S. aureus* (MRSA) has become a prevalent cause of PSM in recent years,[7,8] but there is scarce information regarding the pathogenesis of such cases and the role of preoperative nasal mupirocin or other measures in their prevention.

Abbreviations and Acronyms
MRSA = methicillin-resistant *Staphylococcus aureus*
MSSA = methicillin-susceptible *Staphylococcus aureus*
PFGE = pulsed field gel electrophoresis
PSM = postsurgical mediastinitis

The aim of the present study was to analyze the hypothesis that the endogenous pathway is responsible for the acquisition of *S aureus* in a large series of patients with PSM (including patients with MRSA mediastinitis) and to describe other potential acquisition routes of infection susceptible to being prevented by directed measures.

Patients and Methods

Study Population

The study population comprised all consecutive adult patients who underwent sternotomy for a cardiovascular operation during the period between January 2002 and December 2004 at the Department of Cardiothoracic Surgery, University Hospital "12 de Octubre," Madrid, Spain. Preparation of the patient's skin included a preoperative shower with chlorhexidine soap and cleaning with ethyl alcohol in the operating theater. Antibiotic prophylaxis was done with vancomycin (1 g every 12 hours) and cefotaxime (1 g every 8 hours) for 24 hours since January 2001 owing to the emergence of MRSA as a major cause of PSM at our institution. The first antibiotic dose was administered during anesthetic induction, and prophylaxis was maintained for 48 hours after incision. Mupirocin nasal decontamination was used only occasionally. To control the spread of hospital-acquired MRSA colonization, our institution routinely applies isolation measures for colonized patients (including the use of single-bed rooms and barrier precautions, such as use of aprons or gowns, gloves, and, in some cases, masks by health care workers as the only physical barrier to transmission). An educational program to promote hand hygiene among health care workers has also been implemented at our hospital.

Cases and Control Study

From January 2002 to December 2004, all *S aureus* PSM identified cases were prospectively evaluated and assessed in a case–control study. For the definite diagnosis of PSM, we included patients with all of the following criteria: (1) partial or complete sternal dehiscence and/or purulent discharge from the mediastinal area, directly observed by the surgeon, and/or fever, as defined by the National Nosocomial Infection Surveillance System of the Centers for Diseases Control[9]; (2) requirement of surgical debridement with or without plastic reconstruction; and (3) isolation of *S aureus* from mediastinal samples obtained by needle aspiration or during debridement surgery. Three controls for each patient were selected: the patient who directly preceded and the 2 patients who followed the index case with at least 1 month of follow-up and who had not developed PSM. Cases and controls were matched only temporally in order not to lose these other potential risk factors apart from preoperative *S aureus* nasal colonization that are needed for adjustment in the risk factor analysis.

Analyzed Variables

Data were obtained by a retrospective review of the patients' charts. We collected patient-related factors, operation-related factors, and postoperative factors as depicted in Table 1.

Microbiologic Procedures

Nasal carriage of *S aureus* was routinely investigated at admission in all patients undergoing cardiac surgery (usually 24–48 hours before surgery) in the study period. Nasal cultures were obtained by rubbing a premoistened Dacron swab in the anterior vestibule of each naris. Samples were inoculated onto phenol-red mannitol salt agar plates that were incubated at 37°C for 48 hours. Cultures were obtained from surgical sites when signs and symptoms of infection were observed. Isolation and identification of *S aureus* were based on standard microbiologic procedures. All patients provided written informed consent to participate in the protocol of nasal sampling approved by University Hospital "12 de Octubre" Review Board.

In vitro susceptibility of the isolates to oxacillin was determined by disk-diffusion testing, performed according to methods specified by the National Committee for Clinical Laboratory Standards.

Molecular characterization of *S aureus* isolates was performed using pulsed field gel electrophoresis (PFGE) after DNA extraction and digestion with SmaI according to previously described methods.[10] Restriction fragments were separated at 14°C in a counter-clamped homogeneous electric field system (CHEF-DR III; Bio-Rad, Richmond, Calif) using 1% agarose with a field strength of 6 V/cm and two blocks of pulses: a first block of 11.5 hours with pulses from 5 to 15 seconds and a second block of another 11.5 hours with pulses from 15 to 40 seconds. Migration of DNA fragments was normalized between different gels with a molecular weight standard (lambda ladder; New England Biolabs, Beverly, Mass) that was run in two lanes on each gel. Computer-assisted analysis of PFGE was performed with GelCompar software (Applied Maths, Kortrijk, Belgium). A 1.8% tolerance was used for comparisons of DNA patterns. Cluster analysis was performed with the unweighted pair group method, and DNA relatedness was calculated on the basis of the Dice coefficient. Isolates were considered to be genetically related if their macrorestriction DNA patterns differed by 6 or fewer bands[11] and the Dice coefficient of correlation was 80% or more.

Statistical Analysis

Continuous variables were expressed as the mean and standard deviation and 95% confidence interval for those with a normal distribution, or as the median and interquartile range for those with a skewed distribution. Discrete variables were expressed as percentages. The Student unpaired *t* test was used to compare continuous variables, the Mann–Whitney *U* test to compare continuous variables with non-normal distribution, and the χ^2 or Fisher exact test to compare proportions. All statistical tests were 2-tailed.

Odds ratios were calculated for variables with statistically significant differences between cases and controls. Binary logistic regression was applied individually to each variable to obtain the odds ratio in the univariate analysis. Quantitative variables were

TABLE 1. Comparative characteristics of patients with *S aureus* PSM and controls

	Cases (n = 17)	Controls (n = 51)	*P* value
Patient-related factors			
Age: mean (SD)	69 (11)	65 (12)	NS
Male sex (%)	35.3%	41.2%	NS
BMI >30 (%)	17.6%	19.6%	NS
Diabetes (%)	23.5%	17.5%	NS
Smoker (%)	26.5%	39.6%	NS
Arterial hypertension (%)	53%	44%	NS
Peripheral vasculopathy (%)	35.3%	8.3%	.02
COPD (%)	41.2%	8.3%	.005
Serum creatinine levels (mg/dL): mean (SD)	1.16 (0.4)	1.14 (0.6)	NS
Serum albumin levels (mg/dL): mean (SD)	3.6 (0.6)	3.9 (0.5)	.04
Admitted in other wards apart from cardiac surgery or cardiology (%)	17.6%	2%	.004
Preoperative length of stay >1 wk (%)	23.5%	23.5%	NS
Catheterization in the same stay (%)	47.1%	38%	NS
Left ventricular dysfunction (%)	35.3%	19.6%	NS
Pulmonary hypertension (%)	17.6%	5.9%	NS
New Year Heart Association class ≥ III (%)	53%	58%	NS
Preoperative mechanical ventilation (%)	7.7%	0%	NS
Preoperative *S aureus* nasal colonization (%)	52.9%	19.6%	.02
Operation-related factors			
Revascularization surgery (%)	36.4%	37.3%	NS
Use of internal thoracic artery (%)	43%	65%	NS
Urgent surgery (%)	29.4%	9.8%	NS
Duration of surgery (min): mean (SD)	239 (123)	182 (62)	NS
Duration of cardiopulmonary bypass (min): mean (SD)	132 (67)	98 (43)	.04
Duration of aortic crossclamping (min): mean (SD)	103 (47)	85 (36)	NS
Experienced surgeon (>5 y) (%)	61.5%	58.8%	NS
Use of aprotinin (%)	29.4%	39.6%	NS
Postoperative factors			
Time on mechanical ventilator (h): mean (SD)	13 (9.6)	22 (66)	NS
Duration of intensive care stay (h): mean (SD)	62 (42)	67 (74)	NS
Duration of inotropic treatment (h): mean (SD)	25.3 (33)	30.2 (66)	NS
Postoperative blood loss (mL): Mean (SD)	543 (563)	454 (324)	NS
Transfusion (%)	40%	38%	NS
Blood transfusion (mL): mean (SD)	520 (829)	554 (953)	NS
IABP (%)	25%	3.9%	.03
Perioperative myocardial infarction (%)	17.6%	3.9%	NS
Postoperative reoperation (%)	11.8%	9.8%	NS
Acute renal failure (%)	35.3%	8.2%	.02
Perioperative stroke (%)	5.9%	3.9%	NS

PSM, Postsurgical mediastinitis; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *IABP*, intra-aortic balloon pump; *NS*, not significant.

previously converted into qualitative variables for that task. To analyze *S aureus* nasal colonization as an independent risk factor for postoperative *S. aureus* mediastinitis, we performed a multivariate logistic regression model including the latter and all other clinically relevant variables with a *P* value of < .05 and possible confounding factors with a *P* value of < .1.

We used SSPS for Windows statistical package, version 12.0 (SPSS Inc, Chicago, Ill).

Results

During the study period, 1432 sternotomies were performed at our institution. *S aureus* preoperative nasal cultures were positive in 228 (15.9%) patients: MSSA grew in 222 (colonization rate of 15.5%) and MRSA in 6 (0.4%). Preoperative nasal decontamination was performed in only 3 patients during December 2004, and all of them were colonized by MSSA.

Preoperative *S aureus* Nasal Colonization As a Risk Factor for *S aureus* PSM

We identified 17 cases of *S aureus* PSM (8 cases by MRSA and 9 cases by MSSA) that met our case definition criteria, which represented an overall incidence of 1.2%. *S aureus*

TABLE 2. Comparative clinical characteristics between patients with MRSA or MSSA PSM

	MRSA (n = 8)	MSSA (n = 9)	*P* value
Age: mean (SD)	71 (7.5)	67 (8.8)	NS
Male sex: n (%)	5 (62%)	6 (67%)	NS
BMI >30: n (%)	13%	22%	NS
Diabetes: n (%)	25%	22%	NS
Smoker: n (%)	2 (25%)	2 (22%)	NS
Peripheral vasculopathy: n (%)	4 (50%)	2 (22%)	NS
COPD: n (%)	5 (63%)	2 (22%)	NS
New Year Heart Association class ≥ III: n (%)	5 (63%)	4 (45%)	NS
Serum creatinine levels (mg/L): mean (SD)	1.2 (0.3)	1.13 (0.5)	NS
Serum albumin levels (mg/dL): mean (SD)	3.7 (0.5)	3.5 (0.5)	NS
Preoperative *S. aureus* nasal colonization: n (%)	2* (25%)	7 (78%)	.08
Preoperative length of stay: mean (SD)	5.3 (5)	6.7 (8)	NS
Catheterization in the same stay: n (%)	3 (38%)	5 (56%)	NS
Revascularization surgery: n (%)	2 (40%)	2 (33%)	NS
Urgent surgery: n (%)	3 (38%)	2 (22%)	NS
Duration of surgery (min): mean (SD)	257 (141)	228 (120)	NS
Duration of cardiopulmonary bypass (min): mean (SD)	149 (78)	120 (59)	NS
Duration of intensive care stay (h): mean (SD)	47 (23)	75 (51)	NS
Duration of inotropic treatment (h): mean (SD)	15 (7)	33 (43)	NS
IABP: n (%)	1 (13)%	2 (22)%	NS
Postoperative reoperation: n (%)	1 (13%)	1 (11%)	NS
Acute renal failure: n (%)	4 (50%)	2 (22%)	NS
Previous *S aureus* infection in the postoperative period: n (%)†	2 (25%)	0	NS

M*RSA*, Methicillin-resistant *S. aureus*; *MSSA*, methicillin-susceptible *S. aureus*; *PSM*, postsurgical mediastinitis; *SD*, standard deviation. *NS*, $P > .1$; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *IABP*, intra-aortic balloon pump. *Both patients with previous colonization with MSSA. †Both cases of catheter-related MRSA bacteremia.

mediastinitis developed in 9 (3.95%) of 228 colonized patients in comparison with 8 (0.66%) of 1204 noncolonized patients ($P < .00001$).

We performed a univariate analysis comparing the latter and other clinical variables potentially related to the development of PSM between these 17 cases and 51 controls (Table 1). *S aureus* colonization was related to an increased risk of developing *S aureus* PSM (odds ratio: 4.6; 95% confidence interval: 1.4-15).

We tried to adjust *S. aureus* nasal colonization as a risk factor for *S. aureus* PSM with other potential risk factors detected in the univariate analysis. Owing to the paucity of events, we could not perform a unique multivariate logistic regression model including all the major potential risk factors for *S aureus* PSM. We performed instead an exploratory analysis of major significant variables obtained in the univariate analysis, adjusting each of theses variables with the variable "*S aureus* preoperative colonization" by performing different logistic regression models that included a maximum of 2 variables. *S aureus* nasal colonization was constantly retained in all the models, which suggests that it is independently related with a higher risk of *S aureus* PSM although interactions between variables are difficult to exclude.

Comparison Between MSSA and MRSA Episodes of PSM

In Table 2, clinical characteristics of patients with MRSA or MSSA mediastinitis are compared, although owing to the limited number of cases we could not demonstrate statistically significant differences.

Preoperative nasal colonization with *S aureus* was found in 7 of 9 patients having MSSA mediastinitis but in only 2 of 8 patients with MRSA mediastinitis ($P = .08$). In both cases of MRSA mediastinitis, previous nasal colonizations were due to MSSA.

Clinical baseline characteristics were similar between patients with MRSA and MSSA PSM except for chronic obstructive pulmonary disease, which was more frequent in patients with MRSA mediastinitis. On the other hand, there was an antecedent of previous *S aureus* catheter-related bacteremia in the postoperative period in 2 of 8 patients with MRSA PSM but in none of 9 patients with MSSA PSM. PSM in-hospital mortality was 22.2% for MMSA and 37.5% for MRSA ($P = .1$).

Seven of the 9 patients with MSSA PSM had an identical isolate by PFGE in preoperative nasal and surgical-site cultures (Figure 1). We could demonstrate clonal relatedness in only 2 of the 9 strains from patients with MSSA

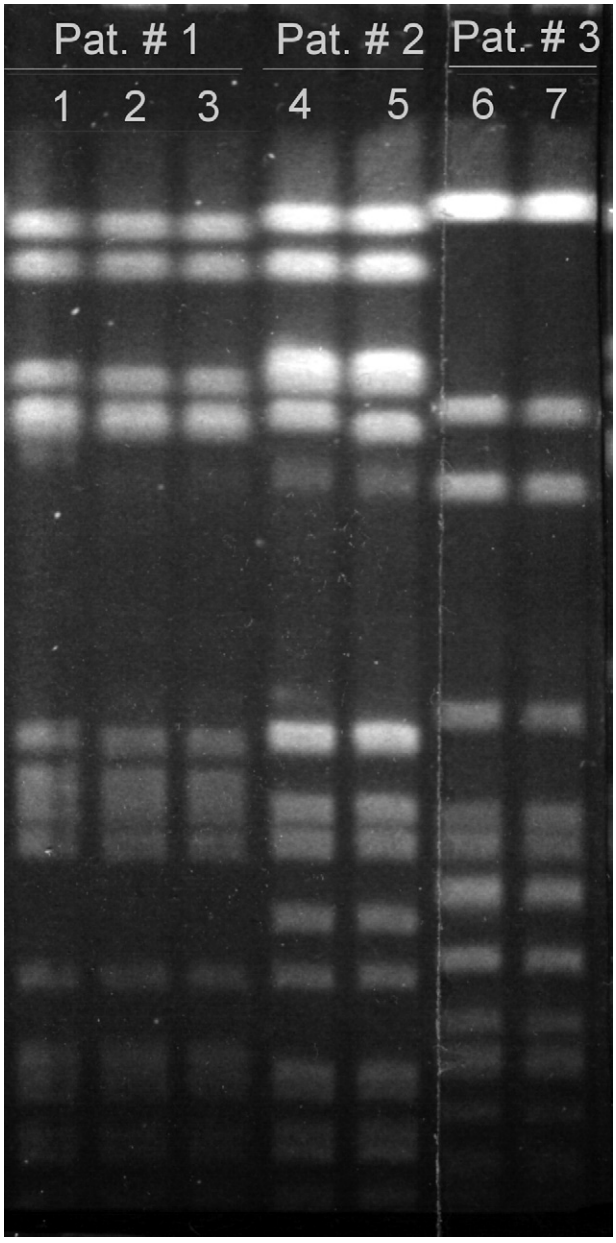

Figure 1. PFGE DNA patterns of MSSA isolates from nasal and mediastinal/blood samples in selected clinical cases. Patient 1: *1,* Nasal sample (01-23-2002); *2,* blood sample (02-03-2002); *3,* mediastinal sample (02-04-2002). Patient 2: *4,* Nasal sample (07-16-2004); *5,* mediastinal sample (08-07-2004). Patient 3: *6,* Nasal sample (01-03-2002); *7,* blood sample (01-10-2002). *PFGE,* Pulsed field gel electrophoresis; *MSSA,* methicillin-susceptible *Staphylococcus aureas.*

PSM (Figure 2). On the other hand, it was not possible to find an identical isolate by PFGE in preoperative nasal and surgical-site in any of the 8 patients with MRSA PSM, and the same clone of MRSA was responsible for all these cases (Figure 2).

Discussion

Determining the acquisition routes of PSM is crucial to designing specific preventive approaches. Unfortunately, little is known regarding the precise pathogenesis of PSM. Endogenous pathogenesis has been demonstrated in other infectious syndromes owing to *S aureus,* as in bacteremia,[12] and a single study that referred to *S aureus* PSM[3] reported an identical *S. aureus* isolate either in nasal preoperative cultures or in mediastinal samples in 4 of 5 patients in whom mediastinitis developed (all of them owing to MSSA). In fact, this and other previous studies[4,13] have demonstrated that previous nasal colonization is an independent risk factor for the development of PSM, and the efficacy of nasal preoperative decontamination with mupirocin in the prevention of *S aureus* PSM has been recently reported.[5,6]

In the present study, which includes a large sample of patients in whom PSM developed, we have confirmed that the same PGFE type of *S aureus* that had been previously found in nasal cultures was responsible of the majority of MSSA mediastinitis episodes (7/9 cases) and that previous *S. aureus* nasal colonization is an independent risk factor for the development of *S. aureus* PSM. Such findings support the endogenous pathogenesis theory in most cases of MSSA mediastinitis.

However, that is not the case with MRSA mediastinitis, inasmuch as none of the 8 patients in our study having this complication had a preoperative nasal culture with growth of the same microorganism found in the infection site. That can be partially explained by the low rate of MRSA colonization in our cohort of patients in the preoperative period ($<0.5\%$), a figure similar to that recently reported from a population-based study in the United States.[14] In view of our results, we cannot exclude that some patients in whom MRSA mediastinitis developed were previously colonized not at admission but during the postoperative period, because we did not perform surveillance of MRSA colonization in this group of patients. Although such strategy has been proven as effective in detecting MRSA colonized patients in special settings such as intensive care units, where directed mupirocin nasal application has been related to reductions in MRSA infection rates,[15-17] it is doubtful that they could be implemented in all the patients undergoing cardiac surgery.

Other crucial difference between MSSA and MRSA mediastinitis is the type of transmission. In the case of MSSA, the spread of infection is polyclonal in nature, involving numerous genetically distinct strains of the organism, which makes improbable the transmission between patients. Similar findings have been recently reported by our group in a study that analyzed the clonal nature of nosocomial *S aureus* bacteremia.[18] In contrast, MRSA transmission appears to be predominantly monoclonal, inasmuch as most cases are associated with a single, well-defined genotype that is globally the most frequent genotype in MRSA isolates at

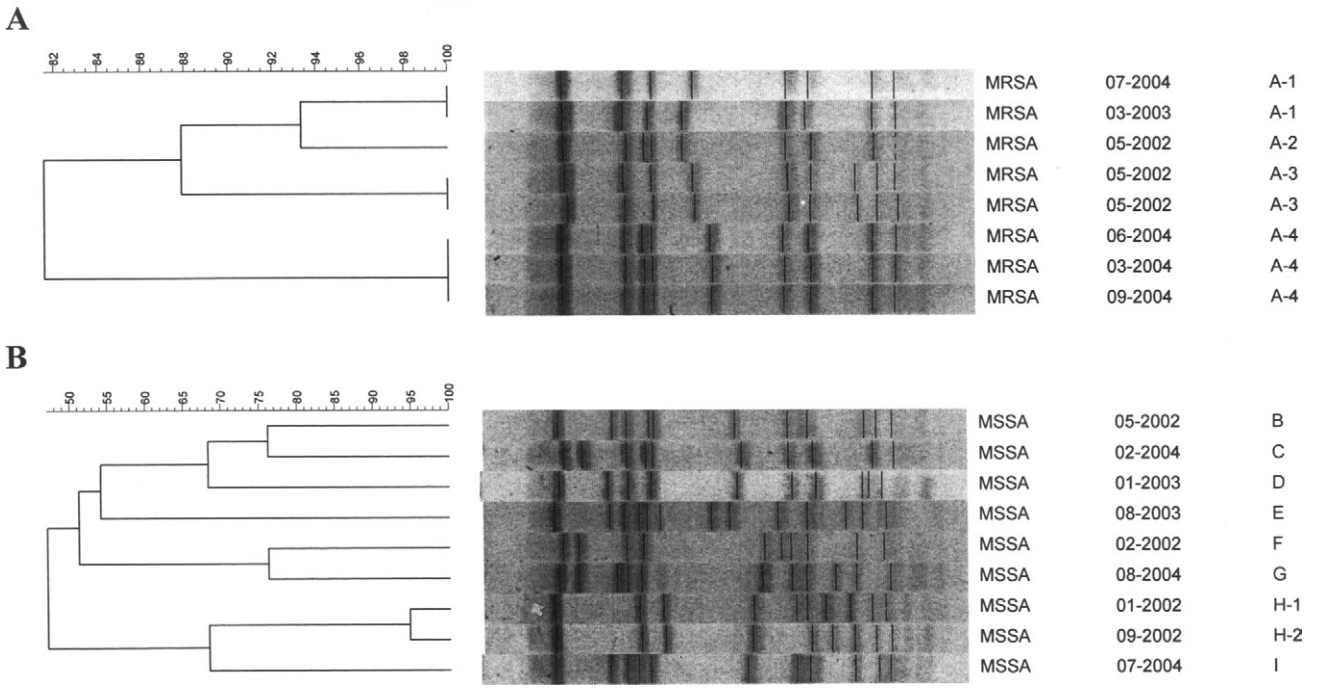

Figure 2. Dendrograms containing PFGE patterns of MRSA (A) and MSSA (B) from PSM patients illustrating the clonal diversity of *S aureus* population. One major genotype is distinguished among 8 MRSA isolates (A) and 8 among 9 MSSA isolates. (B). *Scales* at the top of the dendrograms represent similarity. The *columns* represent the date of isolation (mo/y) and the PFGE types. *PFGE*, Pulsed field gel electrophoresis; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin susceptible *Staphylococcus aureus*; *PSM*, postsurgical mediastinitus.

our institution.[18] That fact, added to the finding that 2 of the 8 patients with MRSA mediastinitis in our study had an antecedent of catheter-related MRSA bacteremia, points out that nosocomial transmission is highly probable in most cases of MRSA PSM. Accordingly, global infection control measures in the postoperative period could be crucial in the prevention of at least some cases of PSM.

In view of the results of our study, preoperative nasal decontamination is an adequate preventive measure against MSSA PSM, whereas postoperative hospital infection control measures seem to be the major factor in preventing MRSA PSM.

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