MAJOR ARTICLE

Risk Factors for Postoperative Mediastinitis Due to Methicillin-Resistant *Staphylococcus aureus*

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(See the editorial commentary by Baum and Dooley on pages 1561–3)

Risk factors for developing postoperative mediastinitis (POM) due to methicillin-resistant *Staphylococcus aureus* (MRSA) were analyzed in a case-case control study of patients who underwent median sternotomy during the period from 1994 through 2000. Three patient groups were studied. The first consisted of 64 patients with POM due to MRSA; the second consisted of 79 patients with POM due to methicillin-susceptible *S. aureus* (MSSA); and the third consisted of 80 uninfected control patients. In multivariable analysis, patients who were diabetic (adjusted OR, 2.86; 95% CI, 1.22–6.70), female (OR, 2.70; 95% CI, 1.25–5.88), and >70 years old (OR, 3.43; 95% CI, 1.53–7.71) were more likely to develop POM due to MRSA. In contrast, the only independent risk factor associated with POM due to MSSA was obesity (OR, 2.49; 95% CI, 1.25–4.96). Antimicrobial prophylaxis consisted primarily of cephalosporin antibiotics (administered to 97% of the patients). Changes in perioperative antimicrobial prophylaxis, in addition to other interventions, should be considered for prevention of POM due to MRSA in targeted, high-risk populations.

Mediastinal infection after median sternotomy is a devastating postsurgical complication, affecting 1%–4% of patients who undergo cardiothoracic surgery. Current therapy for postoperative mediastinitis (POM) includes extensive surgical revision and is associated with prolonged hospitalization, increased morbidity, and higher hospital costs [1–4].

Staphylococcus aureus is one of the most common pathogens associated with POM [5–6]. The proportion of *S. aureus* isolates that are methicillin resistant has progressively increased with time in most US medical centers, with the nationwide prevalence of methicillin-resistant *S. aureus* (MRSA) exceeding 50% of nosocomial *S. aureus* isolates at many hospitals [7]. Surgical site infection (SSI) due to MRSA is a growing problem in both tertiary care and community hospitals [2–8] and complicates the management of SSI. Recently, we demonstrated that MRSA-related SSI (including POM) is independently associated with increases in mortality, duration of hospitalization, and hospital charges when patients with such infections are compared with uninfected surgical patients and also with patients with methicillin-susceptible *S. aureus* (MSSA) SSI [2].

Few investigators have studied risk factors for development of POM due to MRSA infections, but these studies have been limited by small sample size [9] and lack of an uninfected control group [4]. We attempted to identify specific variables associated with POM due to MRSA by conducting a case-case-control study [10–12]. We defined 2 case groups, the first consisting of patients with POM due to MRSA and the second consisting of patients with POM due to MSSA. These 2 groups were compared with a control group of uninfected cardiothoracic surgery patients. The resulting risk models for POM due to MRSA and POM due to MSSA were compared and contrasted, and risk factors uniquely associated with POM due to MRSA were iden-

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tified. Such a study is important because, if the risk factors for the development of POM due to MRSA are distinct from those for POM due to MSSA, unique interventions might be necessary to prevent POM due to MRSA and POM due to MSSA.

PATIENTS, MATERIALS, AND METHODS

Study design. A case-case-control study was performed [10–12] on a subset of patients from a larger cohort study that was designed to assess the clinical and financial outcomes of patients with *S. aureus* SSI. This original cohort of 493 patients from 2 hospitals in Durham, North Carolina, included all prospectively identified patients with SSI due to *S. aureus,* as well as randomly selected uninfected control subjects who underwent the same types of surgical procedures during the same calendar year as patients with SSI. This cohort is discussed in detail elsewhere [2]. The current study was restricted to a single institution, Duke University Medical Center (DUMC).

Case and control patients. For the current study, 2 case groups were studied: the first case group included patients who developed POM due to MRSA, and the second case group consisted of patients who developed POM due to MSSA. A third group (the control group) consisted of randomly selected patients who also underwent median sternotomy during the same calendar year as case patients but who did not develop sternal infection. All POM cases were identified prospectively by infection control practitioners using standard criteria from the Centers for Disease Control and Prevention (Atlanta, GA) [13]. To summarize, patients with POM must have had ≥ 1 of the following: (1) positive cultures of mediastinal tissue or fluid; (2) evidence of mediastinitis during surgical exploration; or (3) either fever, chest pain, or sternal instability and ≥ 1 of the following: purulent drainage from the mediastinal area, positive blood culture results, positive results of cultures from drainage fluid samples, or mediastinal widening on chest radiography. The infection control practitioners used the operative database, microbiology data, and hospital admission data to identify cardiothoracic surgery patients who had undergone operative procedures in the prior 30 days who had possible SSIs and/or were readmitted to the hospital. When patients with suspected SSIs were identified, diagnosis of mediastinitis was confirmed through chart review and discussion with the primary surgeon. Patients with superficial infections as well as those with POM due to other pathogens were excluded from the study. Only adult patients (age, >17 years) were included. The institutional review board at DUMC approved this study.

Identification of pathogens. Identification of pathogens and antibiotic susceptibility testing were performed by the DUMC clinical microbiology laboratory. *S. aureus* isolates were identified as gram-positive cocci that had positive coagulase and catalase test results. Methicillin resistance was confirmed by a lack of growth inhibition by an oxacillin disk on mannitol salt agar [14].

Study site. DUMC is a 730-bed tertiary care hospital located in Durham, North Carolina. Approximately 3000 cardiothoracic surgeries are performed annually. During the study period, 11,185 patients underwent median sternotomy at DUMC.

Data collection. Data were collected from infection control, pharmacy, laboratory, and billing databases and medical records. All data were stored and maintained in a computerized database (Excel; Microsoft). The following 20 variables were collected for each patient: age, sex, weight, height, body mass index, comorbid illnesses (including diabetes mellitus, chronic renal insufficiency and end-stage renal disease, liver disease, and history of infection or colonization due to MRSA), transfer from an outside hospital, number of days hospitalized before surgery, number of hospitalizations within the previous year; blood glucose level within 48 h before surgery, blood glucose level within 24 h after surgery, emergent nature of surgery, wound class, duration of surgery, perioperative American Society of Anesthesiology (ASA) score, and prior history of median sternotomy. The antimicrobial agents given for perioperative prophylaxis, as well as the time of administration in relation to surgical incision, were also recorded. Appropriate timing of prophylaxis was defined as an agent given within 2 h before surgical incision. Patients >70 years old were classified as "elderly," and obesity was designated as a BMI of >27.0 for women and >27.7 for men [15].

Statistical analysis. Statistical analyses were performed with SAS software, version 8.1 (SAS Institute). Analysis 1 compared patients with POM due to MRSA with control subects without sternal infection. Analysis 2 compared patients with POM due to MSSA with the same control subjects. Bivariable analyses were performed for each variable independently. *P* values were calculated with Fisher's exact test for binomial variables, the χ^2 test for ordinal variables, and Student's *t* test or the Wilcoxon rank sum test for continuous variables. ORs and 95% CIs were calculated for binomial variables.

Logistic regression was used to determine independent predictors of POM. Variables with a *P* value $\leq .2$ in bivariable analysis were included as candidate variables for multivariable model inclusion. A stepwise selection process was used. Risk factors were checked for confounding. Confounders were included in multivariable models if covariable inclusion changed the coefficient of any statistically significant variable in the regression model by $\geq 10\%$. All tests were 2-tailed, and a *P* value of $\leq .05$ was considered significant in the multivariable model.

RESULTS

Sixty-four patients with POM due to MRSA and 79 patients with POM due to MSSA were identified during the study period. compared with patients with POM due to MSSA, patients in the MRSA group were more likely to be female ($P < .05$), diabetic ($P < .05$), and older ($P < .05$). The control group consisted of 80 randomly selected patients who underwent median sternotomy during the study period and who did not develop POM. Most subjects were male (63%), and the average age was 63.2 years at the time of surgery. The majority of patients underwent coronary artery bypass grafting (92%), with the remainder undergoing valve replacement only (table 1). The most common antimicrobial perioperative prophylaxis regimen consisted of a cephalosporin antibiotic (administered to 97% of the patients). For patients included in the case-case-control study, 195 (87%) of 223 received antimicrobial prophylaxis within the appropriate preoperative window; data were missing for 6 patients (4 control subjects and 1 each in the MRSA and MSSA groups). For the remaining 22 patients, antimicrobial prophylaxis was considered inappropriate because it was administered after surgical incision (for 4 patients); or prophylaxis was ordered, but not documented as having been given (for 5 patients); or prophylaxis was not ordered (for 13 patients).

POM due to MRSA group compared with uninfected control group. Bivariable results for POM due to MRSA are listed in table 1. In addition to being older (mean age, 67.3 years, compared with 63.5 years in the control group; $P = .03$), the group of patients with POM due to MRSA included more female subjects (55% vs. 30%; $P = .004$), obese patients (63% vs. 45%; $P = .04$), and more diabetics (58% vs. 34%; $P = .007$). In addition, a greater proportion of patients in the MRSA mediastinitis group had preoperative blood glucose levels of >200 mg/dL (20% vs. 7%; $P = .03$).

In multivariable analysis (table 2), female sex (OR, 2.70; 95% CI, 1.25–5.88; $P = .01$), diabetes mellitus (OR, 2.86; 95% CI, 1.22–6.70; $P = .02$), and age >70 years (OR, 3.43; 95% CI, 1.53–7.71; $P = .003$) were significantly associated with POM due to MRSA. The confounding effects of the presence of an ASA score of >3, a history of prior MRSA infection, and obesity were included in this multivariable analysis.

POM due to MSSA group compared with uninfected control group. Compared with the uninfected control group, the

Table 1. Demographic and clinical characteristics of patients with postoperative mediastinitis (POM) due to methicillin-resistant *Staphylococcus aureus* (MRSA group), patients with POM due to methicillin-susceptible *S. aureus* (MSSA group), and uninfected control subjects (control group).

Variable	MRSA group ($n = 64$)	Control group ($n = 80$)	MRSA group vs. control group		MSSA group ($n = 79$)	MSSA group vs. control group	
			P	OR (95% CI)		*P*	OR (95% CI)
Demographic characteristic							
Female sex	35 (54.7)	24 (30.0)	.004	0.36 (0.18–0.71)	24 (30.4)	1.0	0.98 (0.49–1.93)
Age, mean years	67.3	63.5	.03		61.8	.44	
Comorbid condition							
Diabetes mellitus	37 (57.8)	27/79 (34.2)	.007	2.64 (1.33–5.21)	22 (27.9)	.49	0.74 (0.38–1.46)
Hospitalization within 1 year before surgical admission	44 (68.8)	48 (60.0)	.30	1.47 (0.73–2.93)	43 (54.4)	.52	0.79 (0.42–1.49)
Hemodialysis	2 (3.1)	1/79 (1.3)	.59	2.52 (0.22–28.4)	0 (0)	1.00	0.33 (0.01–8.31)
Peritoneal dialysis	0 (0)	1 (1.3)	1.00	0.41 (0.02–10.13)	0 (0)	1.00	0.33 (0.01–8.31)
History of MRSA colonization or infection	2 (3.1)	0 (0)	.19	6.44 (0.30–136.57)	0 (0)	NT	NT
Obesity	40 (62.5)	36 (45.0)	.04	2.04 (1.04–3.98)	49/77 (63.6)	.02	2.14 (1.13–4.06)
Liver disease	0 (0)	0 (0)	NT	NT	1 (1.3)	.50	3.07 (0.12–76.70)
Surgical factor							
Valve surgery only	2 (3.1)	7 (8.8)	.30	0.34 (0.07–1.70)	7 (8.9)	1.0	1.03 (0.34–3.04)
Emergency surgery	5 (7.8)	3/79 (3.8)	.47	2.15 (0.49–9.35)	4 (5.1)	1.0	1.35 (0.29–6.24)
History of previous sternotomy	5 (7.8)	3/79 (3.8)	.47	2.15 (0.49–9.35)	5 (6.3)	.72	1.71 (0.39–7.42)
Transfer from outside hospital	27 (42.2)	37/79 (46.8)	.58	0.83 (0.40–1.70)	26/64 (40.6)	.46	0.78 (0.38–1.60)
Antimicrobial prophylaxis administered appropriately	56/63 (88.9)	71/76 (93.4)	.38	0.56 (0.17–1.87)	68/78 (87.2)	.28	0.48 (0.16–1.47)
48 h preoperative glucose level >200 mg/dL	12/59 (20.3)	5/74 (6.8)	.03	3.52 (1.16–10.66)	5/61 (8.2)	.75	1.23 (0.34–4.47)
24 h postoperative glucose level >200 mg/dL	26/61 (42.6)	34/75 (45.3)	.86	0.90 (0.45–1.77)	24/63 (38.1)	.49	0.74 (0.38–1.47)
Duration of operation of >300 min	16/58 (27.6)	17/76 (22.4)	.55	1.32 (0.60–2.91)	27/71 (38.0)	.05	2.13 (1.04–4.38)
ASA score >3	59 (92.2)	65 (81.3)	.09	2.72 (0.93–7.95)	74 (93.7)	.03	3.40 (1.18–9.91)

NOTE. Data are no. (%) or *n/N* (%) of patients, unless otherwise indicated. ASA, American Society of Anesthesiology.

Table 2. Multivariable analysis of risk factors for postoperative mediastinitis (POM) due to methicillin-resistant *Staphylococcus aureus* (MRSA) and POM due to methicillin-susceptible *S. aureus* (MSSA).

Risk factor for POM	OR (95% CI)	*P*
Due to MRSA[a]		
Female sex	2.70 (1.25–5.88)	.01
Age >70 years	3.43 (1.53–7.71)	.003
Diabetes mellitus	2.86 (1.22–6.70)	.02
Due to MSSA[b]		
Obesity	2.49 (1.25–4.96)	.01

[a] Controlled for American Society of Anesthesiology score >3, history of infection or colonization due to MRSA, and obesity.

[b] Controlled for American Society of Anesthesiology score >3 and duration of operation.

MSSA group had a higher proportion of obese patients (64% vs. 45%; $P = .02$) (table 1) and a higher proportion of patients with an operative duration of >300 min (38% vs. 22%; $P = .05$). No other statistically significant differences were found in comparing patients with POM due to MSSA and uninfected control subjects.

In multivariable analysis (table 2), obesity was an independent predictor of POM due to MSSA (OR, 2.49; 95% CI, 1.25–4.96; $P = .01$). The confounding effects of the presence of an ASA score of >3 and an operative duration of >300 min were included in this multivariable analysis.

Comparison of the 2 models. The independent predictors of POM due to MRSA were different from the independent predictors of POM due to MSSA. Female sex, age of >70 years, and diabetes mellitus were risk factors for POM due to MRSA, but they were not predictive of POM due to MSSA. Obesity was an independent predictor of POM due to MSSA, but it was not an independent predictor for POM due to MRSA.

DISCUSSION

In addition to its staggering effect on morbidity, quality of life, and mortality, POM has a profound economic impact [16]. POM due to MRSA is particularly costly and deadly, and it is associated with an 11-fold increase in attributable mortality and approximately $41,000 in attributable excess charges per SSI [17]. Identifying risk factors for POM due to MRSA could help facilitate the design and implementation of effective preventive strategies, which would require careful evaluation to document their effectiveness. Our study may be a useful first step in this process.

This study, to our knowledge, is the first comprehensive analysis of risk factors for POM due to MRSA. Although several studies have focused on risk for postoperative sternal infection in general, the results of such studies are limited because superficial and deep infections were grouped together [18–21]. In addition, prior studies often included both infections due to virulent organisms and those due to less pathogenic organisms [18–21]. In contrast, the current study included only cases of organ space infection due to a single type of virulent organism.

We identified 3 unique risk factors for POM due to MRSA: age, female sex, and diabetes mellitus. Advanced age is a well-known risk factor for the development of both infection due to MRSA [22–23] and POM [24, 25], so it is not surprising that elderly patients represent a population at increased risk for POM due to MRSA. The increased risk of MRSA infection in elderly patients merits further investigation, particularly because elderly patients with *S. aureus* SSIs are at increased risk for death, compared with younger infected patients [26]. Moreover elderly patients are a clearly defined and readily identified risk group in which to focus future preventive interventions.

For reasons we cannot explain, diabetes mellitus was an independent predictor of POM due to MRSA but not of POM due to MSSA. Diabetes has also been previously noted to be a risk factor for infection and colonization with drug-resistant *S. aurues* [27–29] as well as an independent risk factor for POM [21, 30–31]. Thus, persons with diabetes are also at increased risk for POM due to MRSA. Hyperglycemia increases the risk of POM [32, 33] and is associated with increased resource utilization [34]. These findings, coupled with the knowledge that insulin infusions reduce the risk of POM [35] and infections in surgical patients [36], suggest that aggressive glycemic control might be particularly effective at reducing the rate of POM due to MRSA.

Female sex was an independent predictor of POM due to MRSA. In some studies, female sex has been associated with an overall increased risk for poor outcome after coronary artery bypass graft surgery [37, 38]. Potential causes for this elevated risk in women include anatomical differences of the sternum, increased incidence of vascular disease, more frequent comorbid conditions, increased age, large breast size, and decreased functional status at the time of surgery [37–39]. However, as with diabetes, we cannot explain why female subjects had more infections due to MRSA but were not at increased risk for POM due to MSSA. The issue of sex and specific risk of POM requires further study.

Obesity was a risk factor for POM due to MSSA but not for POM due to MRSA. The association between obesity and risk for POM has been demonstrated previously [18, 30, 40] and might relate to insufficient patient preparation before performing an operation, underdosed antimicrobial prophylactic agents, and associated comorbid conditions. Interventions to improve the appropriateness of skin preparation and antimi-

crobial prophylactic dosing might decrease the risk for POM in obese patients.

It is notable that in this study, risk factors for POM due to MRSA and POM due to MSSA were completely different, suggesting that POM due to MRSA and POM due to MSSA are fundamentally different diseases and affect different patient populations. In addition, the pathogenesis of POM might be different for infections caused by MRSA than for those caused by MSSA.

Perioperative antimicrobial prophylaxis is the cornerstone of SSI prevention. During the time period of this study, cephalosporins were the most frequently prescribed preoperative antimicrobial agents (in 97% of patients). Because no cephalosporin has in vitro activity against MRSA, <3% of our patients received an agent with reliable activity against MRSA before undergoing surgery.

There were limitations to this study. The retrospective nature of the study limited our ability to collect surveillance data relating to preoperative colonization with MRSA and earlier antibiotic use. The study was also performed at a single institution and was limited by a relatively small sample size because of the fact that POM due to MRSA occurs relatively infrequently.

In a previous study, we noted that patients with SSI due to MRSA were at increased risk for poor outcome. The adjusted OR for death for patients with POM due to MRSA infection compared with patients with POM due to MSSA infection was 3.4 ($P = .003$), and hospital costs attributable to methicillin resistance were $13,901 per case of MRSA-related SSI ($P = .03$) [2]. Compared with uninfected control subjects, patients with POM due to MRSA had an adjusted 11-fold increase in risk of death ($P < .001$) and attributable hospital charges of ~$40,000 per case ($P < .001$) [17]. Interventions geared specifically towards preventing POM due to MRSA should be further explored. These may include strategies focused specifically towards female patients and elderly patients and aggressive perioperative control of glucose levels for diabetic patients. In addition, at institutions where POM due to MRSA is prevalent, the utility of perioperative prophylaxis with agents active against MRSA and/or of preoperative treatment with mupirocin for high-risk patients undergoing cardiothoracic surgery should be studied. At our institution, on the basis of the results from this study, antimicrobial perioperative prophylaxis with an agent active against MRSA is considered for elderly or diabetic patients undergoing cardiothoracic surgery. This type of intervention might help prevent POM due to MRSA and limit the excess use of broad-spectrum antibiotics. Finally, if additional studies validate our findings, more research is needed to understand why factors such as sex and age predispose an individual to POM, and further research is needed to understand what factors within such groups are responsible for the findings we observed.

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