Adverse Clinical and Economic Outcomes Attributable to Methicillin Resistance among Patients with Staphylococcus aureus Surgical Site Infection

Author(s): John J. Engemann, Yehuda Carmeli, Sara E. Cosgrove, Vance G. Fowler, Melissa Z. Bronstein, Sharon L. Trivette, Jane P. Briggs, Daniel J. Sexton and Keith S. Kaye

Source: *Clinical Infectious Diseases,* Vol. 36, No. 5 (Mar. 1, 2003), pp. 592-598
Published by: Oxford University Press
Stable URL: http://www.jstor.org/stable/4462364
Accessed: 22-06-2018 14:49 UTC

MAJOR ARTICLE

Adverse Clinical and Economic Outcomes Attributable to Methicillin Resistance among Patients with *Staphylococcus aureus* Surgical Site Infection

John J. Engemann,[1] Yehuda Carmeli,[4] Sara E. Cosgrove,[5] Vance G. Fowler,[1] Melissa Z. Bronstein,[2] Sharon L. Trivette,[3] Jane P. Briggs,[3] Daniel J. Sexton,[1,2,3] and Keith S. Kaye[1,2,3]

[1]Division of Infectious Diseases, Department of Medicine, and [2]Department of Infection Control, Duke University Medical Center, and [3]Department of Infection Control, Durham Regional Hospital, Durham, North Carolina; [4]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, Massachusetts; and [5]Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland

Data for 479 patients were analyzed to assess the impact of methicillin resistance on the outcomes of patients with *Staphylococcus aureus* surgical site infections (SSIs). Patients infected with methicillin-resistant *S. aureus* (MRSA) had a greater 90-day mortality rate than did patients infected with methicillin-susceptible *S. aureus* (MSSA; adjusted odds ratio, 3.4; 95% confidence interval, 1.5–7.2). Patients infected with MRSA had a greater duration of hospitalization after infection (median additional days, 5; $P < .001$), although this was not significant on multivariate analysis ($P = .11$). Median hospital charges were $29,455 for control subjects, $52,791 for patients with MSSA SSI, and $92,363 for patients with MRSA SSI ($P < .001$ for all group comparisons). Patients with MRSA SSI had a 1.19-fold increase in hospital charges ($P = .03$) and had mean attributable excess charges of $13,901 per SSI compared with patients who had MSSA SSIs. Methicillin resistance is independently associated with increased mortality and hospital charges among patients with *S. aureus* SSI.

Although methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasingly common pathogen, the independent contribution of methicillin resistance to the outcomes for patients with *S. aureus* infection is unclear because patients who develop MRSA infections are typically older and sicker than are patients who develop methicillin-susceptible *S. aureus* (MSSA) infection. Surgical site infection (SSI) complicates 2%–5% of all surgeries in the United States, resulting in a total of 300,000–500,000 infections each year [1, 2]. SSIs are associated with increased morbidity rates, mortality rates, and costs, and they are responsible for additional annual hospital charges of ~$1.6 billion in the United States alone [1]. *S. aureus* is a virulent pathogen and the most common cause of SSI [3, 4]. Methicillin resistance further complicates therapy for *S. aureus* SSI. The prevalence of MRSA has increased dramatically since it was first described in the 1960s [5].

The authors of the majority of published studies that have analyzed the impact of MRSA infection on clinical outcome have studied patients with bacteremia [6–26]. Results from studies comparing mortality rates and lengths of hospital stay in patients with MRSA and MSSA bacteremia are inconsistent and, in some instances, conflicting [10–26]. Costs have been higher for patients with MRSA bacteremia than have been costs for patients with MSSA bacteremia [24, 25]. Two studies

Received 29 July 2002; accepted 26 November 2002; electronically published 7 February 2003.

Presented in part: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 2001, Chicago, Illinois (abstract 2056).

Financial support: Unrestricted educational grant from Aventis Pharmaceuticals, fellowship from the Agency for Healthcare Research and Quality (to J.J.E.), and National Institutes of Health (grant AI-01647; to V.G.F.).

Reprints or correspondence: Dr. John J. Engemann, Div. of Infectious Diseases, Duke University Medical Center, Durham, NC 27710 (john.engemann@duke.edu).

Clinical Infectious Diseases 2003; 36:592–8

1058-4838/2003/3605-0008$15.00

found higher costs in patients with a variety of MRSA infections compared with uninfected control subjects [27, 28].

The authors of one study reported an increase in length of hospital stay but no increase in the mortality rate among surgical patients infected with MRSA compared with patients infected with MSSA [8]. Mekontso-Dessap et al. [12] demonstrated an increased risk for mortality and longer duration of hospitalization for patients with SSI due to MRSA compared with patients with SSI due to MSSA. To our knowledge, no studies have addressed the attributable impact of methicillin resistance on hospital costs among patients with SSI. The objective of this study was to evaluate the attributable impact of methicillin resistance on clinical outcomes and hospital charges in patients with *S. aureus* SSI.

METHODS

Hospital setting and study design. This study included patients undergoing surgery at Duke University Medical Center (Durham, NC), a 900-bed tertiary care academic medical center, and Durham Regional Hospital (Durham, NC), a 350-bed community hospital. Both hospitals had active infection-control surveillance programs for SSI during the study period, and both hospitals used National Nosocomial Infection Surveillance (NNIS) criteria for the diagnosis of SSI [29]. This study was approved by the Duke University Medical Center Institutional Review Board.

This was a cohort study. All patients who underwent surgical procedures for which SSI surveillance was conducted during the period of 1 January 1994 through 30 November 2000 were prospectively identified, as was the subset of patients with SSI and positive cultures for *S. aureus*. Patients were included in the cohort if they were identified as having a SSI at admission for their original surgical procedure or if they were readmitted with a SSI after their primary surgical admission. The intent was to include only the first episode of SSI for each patient; however, no patient experienced >1 episode.

Three patient groups were studied: (1) patients with SSI due to MRSA, (2) patients with SSI due to MSSA, and (3) uninfected control patients. Control patients were randomly selected from the group of uninfected patients who underwent the same type of surgical procedure and who had the same calendar years of surgery as the case patients. The number of uninfected control subjects selected for each procedure equaled the number of patients with SSI due to either MSSA or MRSA, whichever number was larger. As a result, the total number of patients selected for the control group was greater than the total number of patients in either the MRSA or MSSA SSI groups.

Data collection and microbiological characteristics. Data that were collected prospectively included patient demographic characteristics, date and type of surgical procedure, and NNIS risk index variables (i.e., the American Society of Anesthesiologists (ASA) score [30], duration of surgery, and wound class) [31]. For patients who developed an SSI due to *S. aureus*, microbiological data, including date on which samples were obtained for culture, site of culture specimen, and type of pathogen recovered, were recorded. The date of onset of SSI was defined as the collection date for incision or organ-space samples for which the initial culture was positive for *S. aureus*. Limb amputations and saphenous vein graft harvest site infections were excluded. All infections were deep or organ-space infections; superficial infections were excluded [29].

Additional data were retrospectively obtained from the hospital billing and admission-discharge-transfer databases. Data obtained from hospital billing records included comorbid conditions (identified by the codes of the *International Classification of Diseases, Ninth Revision* [ICD-9]), dates of hospitalization and intensive care unit (ICU) admission, and whether a patient had been transferred from another hospital. In addition to the use of ICD-9 codes, we used billing data to identify patients with diabetes mellitus and noted the presence of intravenous insulin drips and glucometer use.

Data collected pertaining to the 90-day postoperative outcomes included mortality (in-hospital and outpatient; data were obtained from patient charts and the United States Social Security Death Index [http://www.ancestry.com]), total hospital days (including readmissions), and hospital charges, including charges for readmissions. Charges were used as a surrogate for cost because direct cost data were not available; hereafter, "hospital cost" will refer to hospital charges. All data were collated into a single database (Access 97; Microsoft).

Microbiological and antimicrobial susceptibility results were obtained from the clinical microbiology database. *S. aureus* isolates were identified by growth of coagulase- and catalase-positive gram-positive cocci. Methicillin resistance was determined by lack of inhibition of growth by an oxacillin disc on mannitol salt agar, according to the criteria of the National Committee for Clinical Laboratory Standards [32].

Statistical analysis. Statistical analyses were performed with use of SAS software, version 8.1 (SAS Institute). Continuous variables were compared by 2-sided Wilcoxon rank sum test and Student's *t* test. The χ^2 test and Fisher's exact test were used to analyze dichotomous and ordinal variables. Spearman correlation coefficients were calculated to detect trends among continuous variables.

Multivariate analyses were performed to assess the impact of methicillin resistance on 90-day mortality rate, total hospital days, and hospital costs (the latter were discounted at a 3% annual rate, with the year 2000 serving as the reference year). Risk models for mortality were derived by logistic regression. Risk models for hospital costs and total hospital days were derived by linear regression after these outcomes were log transformed. Variables

from bivariate analysis with a P value of $< .20$ were included as candidate variables for the risk models. Risk factor models were derived by a stepwise selection procedure. All predictors were checked for confounding and collinearity. If the addition of a confounding variable affected the β coefficient for the effect measure of a selected candidate variable by >10%, it was left in the model. All tests were 2 tailed, with $P \leq .05$ considered to be statistically significant.

Adjusted mean attributable outcomes per SSI for methicillin resistance were calculated as follows for total hospital days and charges. The β coefficient was obtained from the corresponding linear regression model. Mean attributable charges are used as an example: mean attributable charges per SSI = [(mean charges for patients with MSSA SSI) × (inverse log of the β coefficient for adjusted MRSA variable)] − (mean charges for patients with MSSA SSI).

RESULTS

During the period of 1 January 1994 through 30 November 2000, 173 patients with SSI due to MSSA and 127 patients with SSI due to MRSA were identified, and 193 uninfected control patients were selected. A total of 14 patients with SSI (8 patients with MSSA SSI and 6 with MRSA SSI) were excluded from analysis because of incomplete or unavailable hospital billing data. A total of 165 patients with SSI due to MSSA and 121 patients with SSI due to MRSA had complete data available and were included in the analysis. No patients who were excluded died during the 90-day postoperative period. No patient had >1 SSI due to *S. aureus*.

The majority of procedures for the 3 study groups were cardiothoracic (205 [42.8%]) and orthopedic (154 [32.2%]). Other types of procedures performed included neurosurgical (55 [11.5%]), general surgical (31 [6.4%]), vascular (16 [3.3%]), and gynecological (18 [3.8%]). Overall, the distribution of type of surgical procedure was similar among the 3 study groups, although compared with the patients with MSSA SSI, there were fewer patients who acquired MRSA infection after undergoing orthopedic procedures (table 1). All SSIs that occurred after cardiothoracic procedures were classified as mediastinitis by NNIS criteria [29].

Patient demographic characteristics are shown in table 1. The mean age of uninfected control patients was 57.3 years, and 42.7% were men. Control patients had a lower frequency of comorbid conditions and had a shorter duration of surgery than did patients with SSI.

Compared with patients who had MSSA SSI, patients who had SSI due to MRSA were older (mean age, 63.9 years for the MRSA SSI group vs. 55.1 years for the MSSA SSI group; $P < .001$) and were more likely to have diabetes mellitus (48.8% vs. 34.6%; $P = .02$) and renal disease (15.7% vs. 7.9%; $P = .06$). There were no differences in the prevalence of obesity or ASA scores between the patients with MRSA SSI and those with MSSA SSI. Patients with MRSA SSI had a longer median duration of hospital stay before the diagnosis of infection than did patients with MSSA SSI (8 days vs. 5 days; $P < .001$). Median duration of surgery was 38 min longer in the MRSA group than it was in the MSSA group ($P = .01$). The median NNIS risk index group for both the MRSA and MSSA groups was 1, although more patients with SSI due to MRSA were in risk index category 3 than were patients with SSI due to MSSA ($P = .06$).

Mortality. A total of 40 patients died during the 90-day postoperative period (table 2). Four (2.1%) of 193 uninfected control patients died. The presence of *S. aureus* SSI significantly increased the risk for mortality compared with the risk for control subjects (OR for control subjects compared with patients who had MRSA SSI, 12.3 [$P < .001$]; OR for control subjects compared with patients who had MSSA SSI, 3.4 [$P = .04$]).

Among patients with SSI, 25 (20.7%) of the 121 patients with MRSA SSI died during the 90-day postoperative period, compared with 11 (6.7%) of the 165 patients with MSSA SSI (OR, 3.6; 95% CI, 1.7–7.4; $P < .001$). Seventeen (68.0%) of the 25 patients with MRSA SSI who died and 7 (63.6%) of the 11 patients with MSSA SSI who died had mediastinitis. In addition to MRSA SSI, other predictors of mortality among the *S. aureus* SSI group included increasing age, ASA score, duration of surgery, NNIS risk index, and length of hospital stay before infection (table 3). On multivariate analysis, after adjusting for age, an ASA score of 4 (there were no patients with an ASA score of 5), and surgical duration greater than the median time for the entire cohort, the independent impact of methicillin resistance on mortality remained unchanged (OR, 3.4; 95% CI, 1.5–7.2; $P = .003$).

Hospital days. Uninfected patients had significantly fewer total hospital days after surgery (median, 5 days) than did patients with SSI due to MSSA (median, 14 days; $P < .001$) and patients with MRSA SSI (median, 23 days; $P < .001$; table 2). The median number of days of hospitalization after infection (i.e., the culture date) was 5 days greater for patients with SSI due to MRSA (median, 15 days; mean, 22.0 days) than for patients with SSI due to MSSA (median, 10 days; mean, 13.2 days; $P < .001$), as was the number of days spent in the ICU (median number of days in the ICU after infection for patients with MRSA SSI, 0 [mean, 5.1; interquartile range, 0–3]; median number of days in the ICU for patients with MSSA SSI, 0 [mean, 1.9; interquartile range, 0–1]; $P = .02$). Increasing age, ASA score, duration of surgery, NNIS risk index, length of stay before culture, length of ICU stay before culture, receipt of treatment at Duke University Medical Center, and the presence of diabetes, hypertension, pulmonary disease, and renal disease

Table 1. Descriptive characteristics of patients in a study of methicillin-resistant surgical site infection (SSI).

Variable	Uninfected control subjects (n = 193)	Patients with MSSA SSI (n = 165)	Patients with MRSA SSI (n = 121)	P[a]
Demographic characteristics				
Age, mean years ± SD	57.3 ± 18.3	55.1 ± 17.4	63.9 ± 15.4	<.001
Male sex, no. (%) of patients	92 (42.7)	90 (54.5)	55 (45.5)	.15
Comorbid condition, no. (%) of patients				
Diabetes mellitus	66 (34.2)	57 (34.5)	59 (48.8)	.02
Hematologic disorder	1 (0.5)	2 (1.2)	1 (0.8)	1.00
HIV infection	1 (0.5)	0 (0)	0 (0)	1.00
Hypertension	75 (38.9)	80 (48.5)	64 (52.9)	.48
Liver disease	1 (0.5)	2 (1.2)	4 (3.3)	.25
Pulmonary disease	23 (11.9)	32 (19.4)	21 (17.4)	.76
Renal disease	9 (4.7)	13 (7.9)	19 (15.7)	.06
Malignancy	14 (7.3)	13 (7.9)	15 (12.4)	.23
Obesity	12 (6.2)	18 (10.9)	10 (8.3)	.55
Peripheral vascular disease	3 (1.6)	9 (5.5)	12 (9.9)	.17
Receipt of solid-organ transplant	0 (0)	0 (0)	1 (0.8)	.42
Alcohol abuse	2 (1.0)	6 (3.6)	4 (3.3)	1.00
Tobacco use	20 (10.4)	24 (14.6)	16 (13.2)	.86
Hospital event				
Surgical procedure, no. (%) of patients				
Cardiothoracic	81 (42.0)	68 (41.2)	56 (46.3)	.39
Orthopedic	63 (32.6)	62 (37.6)	29 (24.0)	.02
Neurosurgical	22 (11.4)	19 (11.5)	14 (11.6)	.99
Other[c]	27 (14.0)	16 (9.7)	22 (18.2)	.04
Surgery performed at academic tertiary care facility, no. (%) of patients	125 (64.8)	109 (66.1)	94 (77.7)	.03
LOS, median days (IQR)				
Surgical admission	6 (4–10)	6 (3–11)	9 (5–16)	<.001
Before surgery	0 (0–3)	0 (0–2)	1 (0–4)	.01
Before culture	NA	5 (3–10)	8 (5–14)	<.001
ICU stay before surgery	0	0	0	.704
ICU stay before culture	NA	1 (0–1)	1 (0–3)	.004
Perioperative variables				
ASA score, median (IQR)	3 (2–4)	3 (2–4)	3 (3–4)	.15
ASA score of 4[c]	63 (32.6)	65 (39.4)	52 (43.0)	.55
Duration of surgery, median min (IQR)	194 (113–276)	202 (116–285)	240 (166–305)	.01
Wound class, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	.56
NNIS risk index, median (IQR)	1 (1–1)	1 (1–2)	1 (1–2)	.06

NOTE. ASA, American Society of Anesthesiologists; IQR, interquartile range; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus;* NNIS, National Nosocomial Infection Surveillance.

[a] For patients with MSSA SSI vs. patients with MRSA SSI.
[b] No patients had an ASA score of 5.
[c] General, vascular, or gynecological.

Table 2. Unadjusted clinical outcomes and hospital charges for patients in the 3 study groups.

Outcome	Uninfected control subjects (n = 193)	Patients with MSSA SSI (n = 165)	Patients with MRSA SSI (n = 121)	P		
				MSSA group vs. control group	MRSA group vs. control group	MRSA group vs. MSSA group
Death, no. (%) of patients	4 (2.1)	11 (6.7)	25 (20.7)	.04[a]	<.001[b]	<.001[c]
Total duration of hospitalization, median days (IQR)						
After surgery	5 (3–8)	14 (7–25)	23 (12–38)	<.001	<.001	<.001
After infection	NA	10 (4–17)	15 (7–30)	NA	NA	.001
Stay in ICU, days after infection	NA	0 (0–1)	0 (0–3)	NA	NA	.02
Hospital charges, median $ (IQR)	29,455 (15,637–41,764)	52,791 (29,074–91,805)	92,363 (40,198–136,479)	<.001	<.001	<.001

NOTE. ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus;* NA, not applicable; SSI, surgical site infection.

[a] OR, 3.4 (95% CI, 1.1–10.8)

[b] OR, 12.3 (95% CI, 4.2–36.4).

[c] OR, 3.6 (95% CI, 1.7–7.4).

were also associated with an increased number of hospital days after infection. After controlling for ASA score, hospital, surgical duration, diabetes, renal disease, and length of stay before infection, the association between methicillin resistance and an increase in total hospital days (1.20-fold increase; 2.6 additional hospital days after infection per case of *S. aureus* SSI) among patients with *S. aureus* SSI was not found to be significant ($P = .11$).

Hospital costs. The median hospital cost for uninfected control subjects was $29,455 (mean, $34,395) (table 2). Hospital costs were significantly lower for control subjects than for patients with SSI due to either MSSA or MRSA ($P < .001$). The median hospital cost was ~$40,000 greater for patients with SSI due to MRSA (median, $92,363; mean, $118,415) than for patients with SSI due to MSSA (median, $52,791; mean, $73,165; $P < .001$; table 2). Other predictors of increased hospital cost included increasing age, ASA score, duration of surgery, NNIS risk index, length of hospital stay before samples were obtained for culture, length of ICU stay before culture, receipt of care at Duke University Medical Center, and the presence of diabetes, hypertension, peripheral vascular disease, pulmonary disease, or renal disease. After adjusting for duration of surgery, hospital, length of hospitalization before infection, length of ICU stay before infection, renal disease, and diabetes mellitus, methicillin resistance was found to be associated with a 1.19-fold increase in the median hospital cost ($P = .03$). The mean cost per case attributable to methicillin resistance was $13,901 per case of *S. aureus* SSI. Costs were not confounded by year of surgery. For all outcomes, analyses restricted to the orthopedic and cardiothoracic subgroups yielded similar results (data not shown).

DISCUSSION

In this study, patients with MRSA SSI were found to be at greater risk for mortality and increased hospital costs than patients were with MSSA SSI. Compared with uninfected control subjects, patients with MRSA SSI also had longer durations of hospitalization. Studying a large cohort of patients undergoing a variety of surgical procedures allowed us to evaluate the independent contribution of methicillin resistance on adverse outcomes among patients with SSI due to *S. aureus.* Only 1 published article has addressed the attributable impact of the presence of MRSA on the clinical outcomes of patients with SSI [12]. The authors reported similar findings regarding the independent contribution of methicillin resistance to increased mortality and prolonged hospitalization among patients with mediastinitis due to *S. aureus.*

We found that the presence of MRSA in a surgical wound was associated with a >12-fold increase in the 90-day postoperative mortality rate compared with the rate for patients without SSI; compared with patients who had SSI due to MSSA, the adjusted risk of death was increased >3 fold. We observed that patients with SSI due to MRSA had greater hospital costs than did patients with SSI due to MSSA (adjusted mean attributable hospital cost per SSI, $13,901). Although patients with SSI due to MRSA had longer durations of hospitalization after surgery than did patients with SSI due to MSSA, this did not reach statistical significance. This was surprising, because increased hospital costs usually correlate with an increased length of hospital stay. One explanation for this result may be the fact that patients with MRSA infections had longer lengths of ICU stay after infection than did patients with MSSA infection. Stays in the ICU are costly, and the increased number

Table 3. Predictors of 90-day mortality, increased hospitalization cost, and total length of hospital stay (LOS) among patients with *Staphylococcus aureus* surgical site infection (SSI; unadjusted results).

	P		
Variable	Mortality	LOS	Hospitalization cost
Demographic characteristic			
Age	<.001	<.001	<.001
Male sex	.86	.35	.54
Comorbid condition			
Diabetes mellitus	.28	<.001	<.001
Hematologic disorder	1.00	.19	.53
Hypertension	1.00	<.001	<.001
Liver disease	.56	.11	.14
Malignancy	.76	.74	.32
Obesity	.55	.94	.23
Peripheral vascular disease	.32	.07	.01
Pulmonary disease	.36	.02	.004
Renal disease	.15	<.001	<.001
Tobacco use	.19	.79	.52
Receipt of a solid-organ transplant	1.00	.09	.10
Hospital event			
ASA score	<.001	<.001	<.001
Duration of surgery	.03	<.001	<.001
Wound class	.93	.99	.12
NNIS risk index	.007	<.001	<.001
LOS before culture	<.001	<.001	<.001
ICU LOS before culture	<.001	<.001	<.001
Surgery at academic tertiary care facility	.24	<.001	<.001

NOTE. For each outcome of interest (mortality, LOS, and hospitalization cost), variables with a *P* value of ≤.2 were included in the multivariate model. ASA, American Society of Anesthesiologists; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus;* NNIS, National Nosocomial Infection Surveillance.

of ICU days among patients with MRSA SSI probably accounted for the increased hospital costs, at least in part.

Patients who received care at Duke University Medical Center had higher hospital costs and longer durations of hospital stay than did patients who received care at Durham Regional Hospital. This probably relates to a greater severity of underlying illness among the surgical population at Duke University Medical Center; ASA scores were higher among patients at the Duke University Medical Center than among those who received care at Durham Regional Hospital.

Although data regarding the contribution of methicillin resistance to increased mortality are conflicting, our results are consistent with those of other investigators, including a recent meta-analysis of patients with *S. aureus* bacteremia in which methicillin resistance was associated with a 2-fold increase in the mortality rate [33]. The majority of deaths in our cohort occurred among patients with mediastinitis. Vancomycin is less bactericidal against MSSA than are β-lactam agents, vancomycin therapy has been associated with clinical failure in the treatment of MSSA infection, and vancomycin has been shown to have suboptimal sternal bone penetration [15, 34–36]. Thus, therapy for patients with MRSA infection, which usually requires vancomycin, would logically be expected to be less effective than β-lactam therapy for patients with MSSA infection.

There are some limitations to this study. Our results may underestimate the impact of methicillin resistance on outcomes, because some patients (especially those with MSSA infections) may have been treated as outpatients with oral antibiotics. Another limitation is that, if patients were readmitted to another hospital for diagnosis and treatment of SSI, they would not have been included in the study cohort. Daily hospital costs were not available, so attributable costs that occurred after infection could not be directly analyzed. As an alternative, overall hospital costs were modeled, and we controlled for length of stay before *S. aureus* infection in the model. We did not study the different types of antimicrobial therapy used or the time from infection to debridement, because these were not objectives of this study.

To our knowledge, this is the largest cohort used to analyze attributable mortality and length of stay related to methicillin resistance among patients with *S. aureus* SSI, and this is also the first study to investigate attributable hospital costs among this population. Because a high percentage of SSIs are diagnosed at readmission, all hospital readmissions occurring in the 90-day postoperative period were included in the analysis. Other strengths of the study include the fact that attempts were made to control for the severity of comorbid illnesses and hospital events before the diagnosis of infection.

MRSA SSIs are responsible for adverse patient outcomes and the use of large amounts of additional hospital resources. During the cohort period, among patients with *S. aureus* SSI, methicillin resistance was responsible for a total excess cost of $240,289 per year at the 2 study institutions. Interventions geared toward the prevention of MRSA SSI should be pursued.

The adverse clinical and economic outcomes associated with MRSA SSI relate to the complicated nature of MRSA infections, the availability of only suboptimal antimicrobial agents to treat this pathogen, and the clinical complexities of patients who become infected with MRSA. Preoperative antimicrobial prophylaxis typically does not include an agent active against MRSA. Vancomycin prophylaxis has been modeled for use in coronary-artery bypass graft surgery, and the results were encouraging [37]. For hospitals with appreciable rates of MRSA SSI, risk factors for MRSA SSI should be evaluated, and preoperative antimicrobial prophylaxis with an agent active against MRSA should be

considered for high-risk patients. Efforts should also be made to aggressively treat MRSA SSI with debridement and to rapidly introduce effective antimicrobial therapy.

References

1. Martone WJ, Nichols RL. Recognition, prevention, surveillance, and management of surgical site infections: introduction to the problem and symposium overview. Clin Infect Dis **2001**; 33(Suppl 2):S67–8.
2. Weinstein RA. Nosocomial infection update. Emerg Infect Dis **1998**; 4:416–20.
3. National Nosocomial Infections Surveillance (NNIS) report, data summary from October 1986–April 1996, issued May 1996: a report from the National Nosocomial Infections Surveillance (NNIS) System. Am J Infect Control **1996**; 24:380–8.
4. Petti CA, Sanders LL, Trivette SL, Briggs J, Sexton DJ. Postoperative bacteremia secondary to surgical site infection. Clin Infect Dis **2002**; 34:305–8.
5. National Nosocomial Infections Surveillance (NNIS) System Report. Data summary from January 1992–June 2001, issued August 2001. Am J Infect Control **2001**; 29:404–21.
6. Menon KV, Whiteley MS, Burden P, Galland RB. Surgical patients with methicillin resistant *Staphylococcus aureus* infection: an analysis of outcome using P-POSSUM. J R Coll Surg Edinb **1999**; 44:161–3.
7. Hershow RC, Khayr WF, Smith NL. A comparison of clinical virulence of nosocomially acquired methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* infections in a university hospital. Infect Control Hosp Epidemiol **1992**; 13:587–93.
8. Gleason TG, Crabtree TD, Pelletier SJ, et al. Prediction of poorer prognosis by infection with antibiotic-resistant gram-positive cocci than by infection with antibiotic-sensitive strains. Arch Surg **1999**; 134: 1033–40.
9. Rello J, Torres A, Ricart M, et al. Ventilator-associated pneumonia by *Staphylococcus aureus:* comparison of methicillin-resistant and methicillin-sensitive episodes. Am J Respir Crit Care Med **1994**; 150:1545–9.
10. French GL, Cheng AF, Ling JM, Mo P, Donnan S. Hong Kong strains of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* have similar virulence. J Hosp Infect **1990**; 15:117–25.
11. Mylotte JM, Aeschlimann JR, Rotella DL. *Staphylococcus aureus* bacteremia: factors predicting hospital mortality. Infect Control Hosp Epidemiol **1996**; 17:165–8.
12. Mekontso-Dessap A, Kirsch M, Brun-Buisson C, Loisance D. Poststernotomy mediastinitis due to *Staphylococcus aureus:* comparison of methicillin-resistant and methicillin-susceptible cases. Clin Infect Dis **2001**; 32:877–83.
13. McClelland RS, Fowler VG Jr, Sanders LL, et al. *Staphylococcus aureus* bacteremia among elderly vs. younger adult patients: comparison of clinical features and mortality. Arch Intern Med **1999**; 159:1244–7.
14. Wisplinghoff H, Seifert H, Coimbra M, Wenzel RP, Edmond MB. Systemic inflammatory response syndrome in adult patients with nosocomial bloodstream infection due to *Staphylococcus aureus.* Clin Infect Dis **2001**; 33:733–6.
15. Gonzalez C, Rubio M, Romero-Vivas J, Gonzalez M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus:* a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis **1999**; 29:1171–7.
16. Selvey LA, Whitby M, Johnson B. Nosocomial methicillin-resistant *Staphylococcus aureus* bacteremia: is it any worse than nosocomial methicillin-sensitive *Staphylococcus aureus* bacteremia? Infect Control Hosp Epidemiol **2000**; 21:645–8.
17. Soriano A, Martinez JA, Mensa J, et al. Pathogenic significance of methicillin resistance for patients with *Staphylococcus aureus* bacteremia. Clin Infect Dis **2000**; 30:368–73.
18. Lewis E, Saravolatz LD. Comparison of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* bacteremia. Am J Infect Control **1985**; 13:109–14.
19. Roghmann MC. Predicting methicillin resistance and the effect of inadequate empiric therapy on survival in patients with *Staphylococcus aureus* bacteremia. Arch Intern Med **2000**; 160:1001–4.
20. Harbarth S, Rutschmann O, Sudre P, Pittet D. Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus.* Arch Intern Med **1998**; 158:182–9.
21. Conterno LO, Wey SB, Castelo A. Risk factors for mortality in *Staphylococcus aureus* bacteremia. Infect Control Hosp Epidemiol **1998**; 19: 32–7.
22. Craven DE, Kollisch NR, Hsieh CR, Connolly MG Jr, McCabe WR. Vancomycin treatment of bacteremia caused by oxacillin-resistant *Staphylococcus aureus:* comparison with beta-lactam antibiotic treatment of bacteremia caused by oxacillin-sensitive *Staphylococcus aureus.* J Infect Dis **1983**; 147:137–43.
23. Romero-Vivas J, Rubio M, Fernandez C, Picazo JJ. Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus.* Clin Infect Dis **1995**; 21:1417–23.
24. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charge [abstract K-1221]. In: Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology, **2001**:415.
25. Abramson MA, Sexton DJ. Nosocomial methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* primary bacteremia: at what costs? Infect Control Hosp Epidemiol **1999**; 20:408–11.
26. Marty L, Flahault A, Suarez B, Caillon J, Hill C, Andremont A. Resistance to methicillin and virulence of *Staphylococcus aureus* strains in bacteremic cancer patients. Intensive Care Med **1993**; 19:285–9.
27. Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus:* a cost-benefit analysis in an intensive care unit. JAMA **1999**; 282:1745–51.
28. Kim T, Oh PI, Simor AE. The economic impact of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals. Infect Control Hosp Epidemiol **2001**; 22:99–104.
29. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control **1988**; 16: 128–40.
30. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. Anesthesiology **1978**; 49:239–43.
31. Culver DH, Horan TC, Gaynes RP, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. Am J Med **1991**; 91:152S–7S.
32. National Committee for Clinical Laboratory Standards (NCCLS). Performance standards for antimicrobial susceptibility testing: 12th international supplement. NCCLS document M100–S12:22:1. Wayne, PA: NCCLS, **2002**.
33. Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis. Med J Aust **2001**; 175:264–7.
34. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. Ann Intern Med **1991**; 115:674–80.
35. Hartstein AI, Mulligan ME, Morthland VH, Kwok RY. Recurrent *Staphylococcus aureus* bacteremia. J Clin Microbiol **1992**; 30:670–4.
36. Wilson WR, Karchmer AW, Dajani AS, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. American Heart Association. JAMA **1995**; 274:1706–13.
37. Zanetti G, Goldie SJ, Platt R. Clinical consequences and cost of limiting use of vancomycin for perioperative prophylaxis: example of coronary artery bypass surgery. Emerg Infect Dis **2001**; 7:820–7.