ORIGINAL ARTICLE

Excess Costs and Utilization Associated with Methicillin Resistance for Patients with *Staphylococcus aureus* Infection

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OBJECTIVE. To determine differences in healthcare costs between cases of methicillin-susceptible *Staphylococcus aureus* (MSSA) infection and methicillin-resistant *S. aureus* (MRSA) infection in adults.

DESIGN. Retrospective study of all cases of *S. aureus* infection.

SETTING. Department of Veterans Affairs hospital and associated clinics.

PATIENTS. There were 390 patients with MSSA infections and 335 patients with MRSA infections.

METHODS. We used medical records, accounting systems, and interviews to identify services rendered and costs for Minneapolis Veterans Affairs Medical Center patients with *S. aureus* infection with onset during the period from January 1, 2004, through June 30, 2006. We used regression analysis to adjust for patient characteristics.

RESULTS. Median 6-month unadjusted costs for patients infected with MRSA were $34,657, compared with $15,923 for patients infected with MSSA. Patients with MRSA infection had more comorbidities than patients with MSSA infection (mean Charlson index 4.3 vs 3.2; $P < .001$). For patients with Charlson indices of 3 or less, mean adjusted 6-month costs derived from multivariate analysis were $51,252 (95% CI, $46,041–$56,464) for MRSA infection and $30,158 (95% CI, $27,092–$33,225) for MSSA infection. For patients with Charlson indices of 4 or more, mean adjusted costs were $84,436 (95% CI, $79,843–$89,029) for MRSA infection and $59,245 (95% CI, $56,016–$62,473) for MSSA infection. Patients with MRSA infection were also more likely to die than were patients with MSSA infection (23.6% vs 11.5%; $P < .001$). MRSA infection was more likely to involve the lungs, bloodstream, and urinary tract, while MSSA infection was more likely to involve bones or joints; eyes, ears, nose, or throat; surgical sites; and skin or soft tissue ($P < .001$).

CONCLUSIONS. Resistance to methicillin in *S. aureus* was independently associated with increased costs. Effective antimicrobial stewardship and infection prevention programs are needed to prevent these costly infections.

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Methicillin and other semisynthetic penicillins represented important advances in the treatment of *Staphylococcus aureus* infections, but within 2 years of their introduction the first clinical isolates of methicillin-resistant *S. aureus* (MRSA) appeared.[1] Since then, the incidence of MRSA infection has increased relentlessly. Until the late 1990s, MRSA infection occurred mostly in healthcare settings.[2] During the past decade, healthy people within community settings have developed infections with new MRSA strains (community-associated MRSA), representing a new burden of disease.[3-6] National data indicate that hospitalizations for MRSA infection have increased 119% from 1999 through 2005.[5]

S. aureus infections are costly, and studies have suggested that MRSA infections are more costly than MSSA infections, but these studies have limitations. Some studies have investigated only one type of *S. aureus* infection, others have quantified costs for only short periods after onset, and still others have used hospital charges, which may not reflect utilization and costs accurately.[7-15] To contribute toward a more comprehensive assessment of costs to society, we quantified resources used for patients with MRSA infections and for patients with MSSA infections and the costs of these resources at a tertiary care Department of Veterans Affairs (VA) hospital using the VA decision support system (DSS) to determine utilization and costs. DSS is an activity-based costing system that measures costs of VA departments, intermediate healthcare products, hospital stays, and outpatient encounters.[16,17] Others[17] have found that DSS is accurate, complete, and consistent, and because of the VA's fixed annual budgets, VA unit costs are less likely to be distorted by the use of reimburse-

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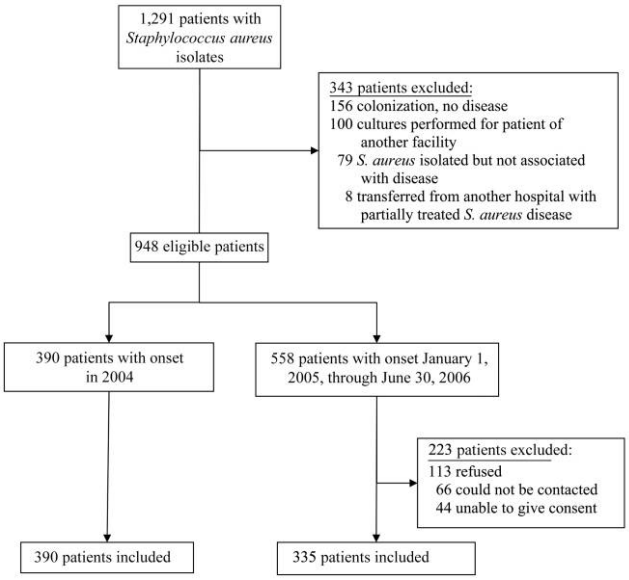

FIGURE 1. Flowchart depicting patient participation and exclusion from the study.

ment-maximizing strategies than are private systems paid on a per unit basis.

METHODS

S. aureus Illness

We extracted information from the Minneapolis VA Medical Center microbiology laboratory database on all *S. aureus* isolations during the study period, January 1, 2004, through June 30, 2006. We reviewed medical records for all patients with *S. aureus* isolates to find cases of *S. aureus* disease. Diseases were categorized according to National Nosocomial Infections Surveillance system definitions.[18] Patients with more than one manifestation during the first episode of disease (eg, cystitis and pyelonephritis) were categorized according to the most severe disease on the basis of criteria that included (1) whether infection was deep or superficial, (2) the severity of signs and symptoms, and (3) the sequence of onset and resolution of separate manifestations. Patients with multiple episodes of *S. aureus* disease were enrolled only for the first one. We characterized these illnesses, other medical problems, and complications of illness or therapy during the 6 months after onset of signs or symptoms of the index *S. aureus* infection. Methicillin resistance was determined by use of standard methods.[19] Two patients who had both MSSA isolates and MRSA isolates were included as MRSA patients.

Data Sources and Costs

Clinical data were collected from the VA electronic clinical patient record system,[20] and utilization and cost data were collected from the DSS.[16,17] The DSS details all direct and indirect costs of care, including services provided by contracted non-VA providers (on a fee basis); bundles costs according to user specifications; and stores data on every service received by each patient. Services included clinic visits, hospital bed–days adjusted for type of unit and acuity, procedures, contracted services, medications, and supplies. We quantified services and costs for each day during the 6 months after onset of *S. aureus* illness. VA care is provided to veterans of United States uniformed services. Veterans are charged only copayments for medications and certain services, and lower income veterans pay a means-adjusted rate.

Clinical data, including demographic information and clinical details on infections, tests, treatments, complications, underlying comorbidities, and outcomes, were extracted with standardized case report forms. The cases of 40 (5.5%) patients randomly selected among the 725 participants were reviewed independently by study personnel to ensure accuracy, consistency, and completeness. The cases of an additional 108 (15%) patients were discussed by 2 or more reviewers because the classification decisions were complex or difficult. Final classifications were decided by means of consensus.

Beginning in January 2005, we conducted interviews to estimate costs incurred by patients or third-party payers for care received from sources outside the Minneapolis VA Medical Center. To minimize recall problems, we interviewed patients with recent cases (onset after December 31, 2004). Patients or authorized family members or friends were asked about health care received in non-VA settings and out-of-pocket costs for health care and associated expenses (eg, transportation) on 2 occasions, 4–16 weeks and 28–40 weeks after onset. For those who received care in non-VA settings, we sought permission to validate with other providers the numbers and types of clinic visits and/or length of stay in community hospitals or nursing homes.

Statistical Analysis

The primary and secondary outcomes were differences in healthcare costs and utilization, respectively, between the MRSA group and the MSSA group. Costs were adjusted to 2007 US dollar amounts with the Consumer Price Index as recommended by the VA.[21] We used the Student t and χ^2 tests to determine the significance of differences in baseline characteristics. Because healthcare cost distributions were skewed, we tested differences between groups in univariate cost analyses with the nonparametric Mann-Whitney U test.

We used a semilogarithmic ordinary least-squares model for multivariate cost analyses, with the natural log of total healthcare costs as the dependent variable.[22] We did not use a generalized linear model, because substantial kurtosis of the log healthcare costs indicated that precision would have been inadequate.[22] The regression equation for log-costs included variables for infection site, age, Charlson index,[23] urban residency, death, and methicillin resistance. The Charlson index is used to quantify the effect of comorbidity on health and

TABLE 1. Baseline Characteristics of Patients Infected with *Staphylococcus aureus*

Characteristic	All participants (N = 725)	Patients infected with MRSA (n = 335)	Patients infected with MSSA (n = 390)	Odds ratio, MRSA : MSSA	P
Age					.07[a]
Mean ± SD, years	65.4 ± 14.0	66.4 ± 14.1	64.5 ± 13.9		
18–34 years	15 (2)	7 (2)	8 (2)		
35–49 years	73 (10)	31 (9)	42 (11)		
50–64 years	270 (37)	116 (35)	154 (39)		
65–79 years	226 (31)	107 (32)	119 (31)		
⩾80 years	141 (19)	74 (22)	67 (17)		
Male sex	704 (97)	324 (97)	380 (97)		.56[b]
Rural residence	226 (31)	101 (30)	125 (32)		.58[b]
Charlson index, mean ± SD	3.7 ± 2.8	4.3 ± 2.9	3.2 ± 2.5		<.001[a]
Infection site or disease					
Bone and/or joint[c]	74 (10)	27 (8)	47 (12)	0.64	
Bronchitis	22 (3)	10 (3)	12 (3)	0.97	
Bacteremia	85 (12)	44 (13)	41 (11)	1.29	
Cardiovascular system[d]	7 (1)	2 (1)	5 (1)	0.46	
Eyes, ear, nose, throat	40 (6)	7 (2)	33 (8)	0.23	
Gastrointestinal	1 (0.1)	0 (0.0)	1 (0.3)	…	
Pneumonia	76 (10)	59 (18)	17 (4)	4.69	
Surgical site	90 (12)	31 (9)	59 (15)	0.57	
Skin, soft tissue	221 (30)	87 (26)	134 (34)	0.67	
Urinary tract	109 (15)	68 (20)	41 (11)	2.17	
Died within 6 months	124 (17)	79 (24)	45 (12)	…	.002[b]

NOTE. Data are no. (%) unless otherwise indicated. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a] Calculated with use of the Student t test.

[b] Calculated with use of the χ^2 test.

[c] Includes infections involving prosthetic devices in bone or joint.

[d] Includes endocarditis.

is based on the presence of diseases and in some cases on severity in the categories of human immunodeficiency virus/AIDS, circulatory, atherosclerotic cardiovascular, chronic pulmonary, connective tissue, peptic ulcer, malignant, liver, or kidney diseases; diabetes mellitus; dementia; or hemiplegia. We tested for possible interactions between methicillin resistance, death, and Charlson index. To simplify analysis, we collapsed infection sites into 4 broad categories: (1) respiratory included pneumonia and bronchitis; (2) skeletal included bone and joint infections, including infected bone or joint prostheses; (3) blood and cardiovascular included bloodstream and cardiovascular system infections; and (4) skin, mucosal, and soft tissue included eye, ear, nose, throat, skin and soft tissue, urinary tract, and gastrointestinal infections and was designated the reference group. An analysis performed with initial infection sites before we collapsed them into categories produced similar results.

To estimate actual dollar amounts, we transformed the results from natural logarithm scale costs back to dollar amounts. There was no evidence of heteroscedasticity with the Breusch-Pagan test, which allowed for a single smearing estimate for transformation.[24-26] To isolate the effect of MRSA status on healthcare costs while controlling for all covariates, we used the "method of recycled prediction."[26] We predicted total healthcare costs as if all study participants had MRSA infection or as if all study participants had MSSA infection. All estimates were 2 tailed, and P values of less than .05 were considered to show a statistically significant difference. Statistical analyses were performed using Stata, version 9.1 (StataCorp). The institutional review boards of the Minneapolis VA Medical Center, the University of Minnesota, and the Minnesota Department of Health approved the study.

RESULTS

S. aureus was isolated 2,614 times from 1,291 patients during the study period. Of these 1,291 patients, 948 (73%) had *S. aureus* illnesses that met inclusion criteria (Figure 1). All 390 patients with onset in 2004 were enrolled, comprising 184 patients with MRSA infection and 206 patients with MSSA infection. For patients with onset after December 31, 2004, we asked for consent to conduct interviews. Of the 558 patients or authorized family members or friends whom we attempted to contact, 113 (20%) refused to participate, 44 (8%) were not capable of giving informed consent, and 66 (12%) could not be reached. This left 335 patients with onset

TABLE 2. Complications Associated with *Staphylococcus aureus* Infection

Complication type	Patients infected with MRSA (n = 335)	Patients infected with MSSA (n = 390)	Odds ratio, MRSA : MSSA
Any type, at least 1 complication[a]	88 (26.3)	46 (11.8)	2.66
Adverse drug effect	17 (5.1)	12 (3.1)	1.68
Cardiovascular	4 (1.2)	4 (1.0)	1.17
Central nervous system	15 (4.5)	7 (1.8)	2.56
Genitourinary	14 (4.2)	11 (2.8)	1.50
Hematological	5 (1.5)	5 (1.3)	1.17
Limb loss	11 (3.3)	10 (2.6)	1.29
Local progression of infection	5 (1.5)	1 (0.3)	5.89
Respiratory	37 (11.0)	12 (3.1)	3.91
Shock	14 (4.2)	13 (3.3)	1.26
Other	5 (1.5)	8 (2.1)	0.72

NOTE. Data are no. (%) of patients. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a] Some patients experienced more than 1 type of complication. Occurrence of 1 or more complications was significantly more common among patients with MRSA infection ($P < .001$, χ^2 test).

after January 1, 2005, 151 with MRSA infection and 184 with MSSA infection. Overall, there were 335 patients with MRSA infection and 390 patients with MSSA infection (Table 1), which represented 73% (335 of 456) and 79% (390 of 492) of the total number of patients with illnesses in these categories, respectively. Median age, median Charlson index, proportions with MRSA infection or MSSA infection, and mortality rates were similar for patients with onset before or after January 1, 2005.

We completed 2 interviews with 266 patients with onset in 2005 or 2006. Median reported out-of-pocket costs were $5 for cases of MRSA infection and $7 for cases of MSSA infection, and the distributions were skewed. Fifty-three of the 266 interviewed patients reported receiving non-VA healthcare services, but recall was difficult and inconsistent. We were able to estimate costs from utilization records from non-VA providers for only 29 of these patients, and these costs totaled $86,497. Because reported out-of-pocket and non-VA expenses were less accurate and marginal, compared with total DSS and fee-basis costs ($37,053,893), out-of-pocket and non-VA costs were excluded from further analyses.

Age and sex distributions were similar for patients with MRSA infection and patients with MSSA infection (Table 1). Seven hundred four (97%) of 725 patients were male, and 226 (31%) patients lived in rural areas. Patients infected with MRSA had higher mean Charlson indices than did patients infected with MSSA (4.3 vs 3.2; $P < .001$). Death within 6 months of onset occurred more often among patients infected with MRSA (79 patients [23.6%]) than among patients infected with MSSA (45 patients [11.5%]; $P < .001$). Sites of *S. aureus* disease differed significantly between the 2 groups ($P < .001$). Patients infected with MRSA were more likely to have pneumonia, urinary tract infections, or bacteremia. Patients infected with MSSA were more likely to have bone or joint infections; infections of eyes, ears, nose, or throat; surgical site infections; or infections of skin or soft tissue. One hundred thirty-four (18%) of 725 patients had complications of *S. aureus* infection or its treatment (Table 2). Complications were significantly more common among patients with MRSA.

Costs

Unadjusted median costs were more than twice as large for patients with MRSA infection as for patients with MSSA infection ($P < .001$; Table 3). The excess was attributable to greater inpatient hospital costs. The unadjusted median outpatient costs of antimicrobial agents, laboratory tests, and imaging tests were significantly greater for patients infected with MSSA than for patients infected with MRSA, but overall median outpatient costs were not significantly different.

We isolated the influence of methicillin resistance on total costs with the use of multivariate regression analysis (Table 4). In the main model, we found a single significant interaction, between MRSA and Charlson index ($P = .02$). The analysis was run again separately for patients with lower Charlson indices (0–3) and for patients with higher Charlson indices (4 or more). Methicillin resistance was a significant predictor of increased healthcare costs within each stratum after adjustment for age, Charlson index, death, initial infection site, and urban residency. In the stratum with lower Charlson indices, costs were 70% greater for patients infected with MRSA than for patients infected with MSSA. In the stratum with higher Charlson indices, costs were 43% greater for patients infected with MRSA. Among patients in the lower stratum, Charlson index accounted for 27% of excess costs, independent of other variables. Among patients in both strata, infections of the blood and cardiovascular, skeletal, or respiratory systems were associated with significantly greater costs than were infections of the skin, mucosa, or soft tissues.

TABLE 3. Unadjusted Median Healthcare Costs of *Staphylococcus aureus* Infections

Cost category	Patients infected with MRSA (n = 335)	Patients infected with MSSA (n = 390)	P [a]
Total cost	$34,657 ($11,517–$98,287)	$15,923 ($5,270–$45,684)	<.001
Inpatient treatment[b]			
Overall inpatient costs	$26,274 ($4,531–$86,974)	$6,748 ($0–$35,089)	<.001
Basic inpatient costs	$16,416 ($2,661–$54,180)	$3,820 ($0–$21,913)	<.001
Antimicrobial agents	$142 ($6–$508)	$21 ($0–$337)	<.001
Other drugs	$1,530 ($242–$5,502)	$406 ($0–$2,394)	<.001
Laboratory tests	$1,002 ($179–$2,749)	$362 ($0–$1,249)	<.001
Imaging	$1,048 ($0–$5,453)	$227 ($0–$1,597)	<.001
Surgical procedures	$0 ($0–$3,432)	$0 ($0–$378)	.02
PMR	$0 ($0–$731)	$0 ($0–$98)	<.001
Mental, social, and spiritual	$459 ($33–$1,280)	$80 ($0–$750)	<.001
Hemodialysis	$0 ($0–$0)	$0 ($0–$0)	.42
Other[d]	$1,307 ($9–$5,818)	$100 ($0–$1,980)	<.001
Outpatient treatment			
Overall outpatient costs	$4,322 ($1,395–$9,438)	$4,495 ($2,076–$8,979)	.30
Basic clinic costs	$1,169 ($345–$2,494)	$1,344 ($626–$2,571)	.05
Antimicrobial agents	$2 ($0–$28)	$7 ($0–$32)	.01
Other drugs	$766 ($41–$1,979)	$793 ($173–$1,678)	.72
Laboratory tests	$171 ($0–$450)	$232 ($95–$484)	.005
Imaging	$95 ($0–$446)	$146 ($0–$506)	.04
Surgical procedures	$0 ($0–$374)	$44 ($0–$451)	.13
PMR	$0 ($0–$0)	$0 ($0–$0)	.75
Mental, social, and spiritual	$0 ($0–$108)	$0 ($0–$83)	.09
Hemodialysis	$0 ($0–$0)	$0 ($0–$0)	.63
Other[e]	$661 ($51–$2,106)	$652 ($158–$1,976)	.37

NOTE. Data are median (range). MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; PMR, physical medicine and rehabilitation.

[a] Calculated with the Wilcoxon-Mann-Whitney test.

[b] Includes room and board, patient acuity costs, nutrition, and some identified in-hospital medical care costs.

[d] Includes home care costs while the patient was hospitalized, inpatient fee-basis costs, and other noncategorized costs.

[e] Includes costs for outpatient observation (room and board, acuity, nutrition, and some costs incurred while patient was under observation status), outpatient fee-basis costs, and other noncategorized costs.

Neither urban residency nor death was a significant predictor of excess costs.

For the stratum with lower Charlson indices, the adjusted mean cost of medical services received by patients infected with MRSA was $51,252 (95% CI, $46,041–$56,464), compared with $30,158 (95% CI, $27,092–$33,225) for those infected with MSSA. For the stratum with higher Charlson indices, the adjusted mean cost of medical services received by patients infected with MRSA was $84,436 (95% CI, $79,843–$89,029), compared with $59,245 (95% CI, $56,016–$62,473) for patients infected with MSSA.

Utilization

Patients infected with MRSA spent more days hospitalized on wards and in intensive care units, and while hospitalized, they received more laboratory tests, imaging tests, and physical medicine and rehabilitation services than did patients infected with MSSA (Table 5). Outpatient utilization was similar for the 2 groups, except that patients infected with MSSA received more laboratory tests.

DISCUSSION

Costs associated with MRSA infection were significantly greater than those associated with MSSA infection. The relative disparity was greater for patients with lower Charlson indices, but the absolute disparity was greater for patients with higher Charlson indices. For 6 months after onset, mean adjusted costs associated with methicillin resistance averaged $21,094 more for patients with Charlson indices of 3 or lower and $25,191 more for patients with higher Charlson indices.

This study included all clinically important *S. aureus* infections rather than infections of a single organ or a single type of infection. Because VA patients have nearly complete coverage for medical expenses and strong loyalty to the VA healthcare system, nearly all costs for the 6 months after onset were captured for each patient. Information gleaned from

TABLE 4. Multivariate Analysis of Log Total Cost

Variable	Estimate (95% CI)	Standard error	*P*	Effect on cost, %[a]
Charlson index 0–3				
MRSA infection	0.53 (0.27–0.79)	0.13	<.001	70
Charlson index	0.24 (0.12–0.36)	0.06	<.001	27
Death	−0.19 (−0.69 to 0.30)	0.25	.45	−18
Age	−0.01 (−0.01 to 0.00)	0.00	.22	−0.6
Infection site[b]				0.0
Skeletal	0.82 (0.44–1.20)	0.20	<.001	127
Respiratory system	1.70 (1.26–2.14)	0.22	<.001	448
Blood and cardiovascular system	1.91 (1.43–2.39)	0.24	<.001	575
Urban residency	−0.16 (−0.43 to 0.12)	0.14	.26	−14
Charlson index ⩾4				
MRSA infection	0.35 (0.08–0.63)	0.14	.01	43
Charlson index	0.05 (−0.01 to 0.12)	0.03	.13	5.3
Death	0.03 (−0.28 to 0.35)	0.16	.83	3.5
Age	−0.02 (−0.03 to 0.00)	0.01	.01	−1.6
Infection site[b]				0.0
Skeletal	0.96 (0.51–1.41)	0.23	<.001	161
Respiratory system	0.97 (0.59–1.34)	0.19	<.001	163
Blood and cardiovascular system	0.96 (0.60–1.32)	0.18	<.001	162
Urban residency	0.13 (−0.15 to 0.42)	0.14	.36	14

NOTE. R^2 for the Charlson comorbidity index 0–3 multivariate model was 0.2965. R^2 for the Charlson comorbidity index ⩾4 multivariate model was 0.1887. CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Effect on cost was calculated by exponentiating the estimate and subtracting 1, that is, exp (estimate) − 1.

[b] Skin, mucosal, and soft tissue was the reference infection site category.

patient interviews and from providers outside the VA system was less accurate than VA data, but it showed that non-VA costs were insubstantial. Several features of our study population and design maximized our ability to capture costs associated with recurrences, complications, and long-term morbidity, which are common after *S. aureus* infections.[27,28] Like others,[9,11,13,28] we found that it was not possible to separate cleanly services provided to diagnose and treat *S. aureus* infection from services for concurrent conditions, so the costs of these conditions were included in our analysis. Multivariate analysis showed that much of the excess cost associated with methicillin resistance was independent of conditions reflected in the Charlson index. The approach that we used to quantify costs can be easily replicated or compared with future studies or used to predict costs in other populations.

Patients infected with MRSA spent more days in intensive care units and other wards than did patients infected with MSSA, as reported previously.[29] Patients infected with MRSA received more laboratory tests, imaging tests, and rehabilitation during hospitalization. Inpatient costs for antimicrobial agents were greater for patients infected with MRSA, and outpatient costs for antimicrobial agents were greater for patients infected with MSSA, but total costs for antimicrobial agents were less than 1% of overall healthcare costs and contributed only marginally to differences between the 2 groups. Mental, social, and spiritual costs were greater for patients infected with MRSA, which probably reflected their more numerous comorbidities and the frailties that accompanied these comorbidities. Overall outpatient costs and utilization were similar between the 2 groups.

Excess costs associated with methicillin resistance add to the substantial costs of *S. aureus* infections in general. In one study of *S. aureus* bacteremia associated with prosthetic devices from 1994 through 2002, mean hospital and outpatient services for the 12-week period after onset cost $67,439 for nosocomial infections and $37,868 for community-acquired infections in 2002 US dollars.[28] That study emphasized that recurrence is common with *S. aureus* infection: 15% of patients with device-related *S. aureus* infections were discharged and then rehospitalized to treat recurrent infection.[28] Recurrences were common for our patients and added to overall costs. In a population-based study, the total cost of all nonobstetrical *S. aureus* infections in hospitals in New York, New York, for 1995 was estimated to be $435.5 million, with a per-patient average cost of $32,100.[8] In the United States, hospitalizations during which *S. aureus* infection was diagnosed and treated increased 62% from 294,570 during 1999 to 477,927 during 2005.[5,30]

In several studies, medical costs associated with MRSA infection have been greater than for MSSA infection, but methods and results have been variable and difficult to generalize.[8-15] In one study, the average daily inpatient costs for MRSA bacteremia during the period from 1997 through 1999 were 2.8 times the costs for MSSA bacteremia. Excess costs

TABLE 5. Unadjusted Median Healthcare Utilization

Utilization category	Patients infected with MRSA (n = 335)		Patients infected with MSSA (n = 390)		P [b]
	Median (range)	No. (%)[a]	Median (range)	No. (%)[a]	
Inpatient utilization					
Inpatient days	15 (4–54)	268 (80)	5 (0–20)	245 (63)	<.001
Intensive care unit–days	0 (0–2)	104 (31)	0 (0–0)	77 (20)	<.001
Other hospital ward–days	11 (2–42)	257 (77)	4 (0–18)	239 (61)	<.001
Laboratory tests	104 (22–288)	267 (80)	32 (0–128)	243 (62)	<.001
Imaging tests	5 (0–19)	242 (72)	1 (0–8)	208 (53)	<.001
Surgical procedures	0 (0–1)	87 (26)	0 (0–0)	105 (27)	.07
PMR	0 (0–9)	153 (46)	0 (0–1)	105 (27)	<.001
Outpatient utilization					
Clinic visits	6 (2–12)	287 (86)	7 (3–12)	363 (93)	.03
Laboratory tests	19 (0–46)	246 (73)	26 (9–52)	339 (87)	.006
Imaging tests	1 (0–3)	172 (51)	1 (0–3)	236 (61)	.05
Surgical procedures	0 (0–0)	26 (8)	0 (0–0)	35 (9)	.56
PMR	0 (0–0)	53 (16)	0 (0–0)	59 (15)	.77

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; PMR, Physical Medicine and Rehabilitation.

[a] No. (%) refers to the number and percentage of patients with at least 1 utilization for the given category.

[b] Calculated with use of the Wilcoxon-Mann-Whitney test.

for MRSA infection occurred in patients with more severe underlying illnesses.[11] In a second study, median costs for treatment of patients with MRSA bacteremia were $14,655, compared with $10,655 for patients with MSSA bacteremia.[13] In a third study, the adjusted mean cost associated with MRSA bacteremia was $21,577, compared with $11,688 for MSSA bacteremia.[14] In patients with end-stage kidney disease who were dependent on hemodialysis and who developed MRSA bacteremia, mean adjusted costs were $25,518, compared with $17,354 for patients with end-stage kidney disease who were dependent on hemodialysis and who developed MSSA bacteremia.[15] In a study of *S. aureus* surgical-site infections, median charges were $92,363 for MRSA infections, compared with $52,791 for MSSA infections, and after adjustment for other variables, estimated costs for MRSA infection were 19% greater.[9]

Our study had some limitations. It was performed at a single hospital; all VA patients were adults, and most were male. Because out-of-pocket expenses were excluded, this analysis presents costs from the VA perspective, but out-of-pocket expenses were small compared with VA costs. During the study period, patients infected with MRSA were placed in isolation, which incurred extra costs for private rooms, gowns, gloves, and labor. These costs were not assigned to individual patients in the DSS and could not be included in costs attributed to MRSA infection. Patients were not screened systematically during the study period for MRSA carriage. Other researchers have documented that costs of screening, isolation, and in some cases eradication in response to outbreak or endemic MRSA infection are substantial. During an MRSA outbreak in Finland in 2003, control measures, infection-related treatment costs for 168 cases, and lost revenue from closed hospital beds were estimated to cost €1,569,830 (US $1,899,871).[31] Estimated costs of infection prevention practices in Germany in 2000 for MRSA infections or carriage in surgical patients were at least €9622 (US $9,509) per case.[32]

This study has important strengths. We included all cases of *S. aureus* infection instead of just certain infection types. The DSS is well suited for studies of healthcare costs and utilization, because the method is more accurate and subject to less distortion than that used in typical healthcare organization accounting systems.[17] Data from this project can be used to estimate excess costs associated with MRSA infection in other healthcare organizations or in populations with known rates of MRSA infection.

The results of this study demonstrate the substantial costs of MRSA infections, even after adjustment for comorbidities. Patients infected with MRSA are more likely to suffer complications of their infection and are more likely to die than are patients infected with MSSA.[27] MRSA infections are a major, growing public health threat[2-6] with no easy solution. Most US hospitals isolate known MRSA carriers, and some screen for MRSA carriage among high-risk patients or hospital-wide to identify and isolate a greater percentage of carriers. Screening and isolation, with or without efforts to eradicate carriage, have been associated with decreased MRSA secondary transmission and a decreased rate of MRSA bacteremia.[33] General infection prevention efforts also reduce the incidence of MRSA infection. For example, central line–associated MRSA bloodstream infections have decreased in US intensive care units during the period from 1997 through

2007, but decreases were also observed for bloodstream infections caused by MSSA and other pathogens.[34] The optimal balance between infection prevention efforts targeted to prevent MRSA infections and general infection prevention efforts has not been definitively established and should be individualized for each institution. In addition to assiduous infection prevention, careful use of antibiotics in the healthcare setting is crucial. Antibiotic use drives resistance to antimicrobial agents,[35] and there is substantial evidence that antimicrobial stewardship programs reduce costs by improving patient outcomes, reducing length of stay, and optimizing antibiotic drug costs.[36]

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