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Clinical and Economic Outcomes for Patients with Health Care-Associated *Staphylococcus aureus* Pneumonia▽

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While the increasing importance of methicillin-resistant *Staphylococcus aureus* (MRSA) as a pathogen in health care-associated *S. aureus* pneumonia has been documented widely, information on the clinical and economic consequences of such infections is limited. We retrospectively identified all patients admitted to a large U.S. urban teaching hospital between January 2005 and May 2008 with pneumonia and positive blood or respiratory cultures for *S. aureus* within 48 h of admission. Among these patients, those with suspected health care-associated pneumonia (HCAP) were identified using established criteria (e.g., recent hospitalization, admission from nursing home, or hemodialysis). Subjects were designated as having methicillin-resistant (MRSA) or methicillin-susceptible (MSSA) HCAP, based on initial *S. aureus* isolates. Initial therapy was designated "appropriate" versus "inappropriate" based on the expected susceptibility of the organism to the regimen received. We identified 142 patients with evidence of *S. aureus* HCAP. Their mean (standard deviation [SD]) age was 64.5 (17) years. Eighty-seven patients (61%) had initial cultures that were positive for MRSA. Most (~90%) patients received appropriate initial antibiotic therapy (86% for MRSA versus 91% for MSSA; $P = 0.783$). There were no significant differences between MRSA and MSSA HCAP patients in mortality (29% versus 20%, respectively), surgery for pneumonia (22% versus 20%), receipt of mechanical ventilation (60% versus 58%), or admission to the intensive care unit (79% versus 76%). Mean (SD) total charges per admission were universally high ($98,170 [$94,707] for MRSA versus $104,121 [$91,314]) for MSSA [$P = 0.712$]). Almost two-thirds of patients admitted to hospital with *S. aureus* HCAP have evidence of MRSA infection. *S. aureus* HCAP, irrespective of MRSA versus MSSA status, is associated with significant mortality and high health care costs, despite appropriate initial antibiotic therapy.

Traditionally, infections have been categorized as either community associated or nosocomial in origin. The theory supporting this dichotomy arose from observations that pathogens causing these two types of infections were distinct. However, with the spread of health care delivery beyond the confines of acute-care hospitals, patients increasingly may present to emergency departments (ED) with infections caused by organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). This trend has led to the evolution of the concept of health care-associated infection (HCAI). Recent studies have validated the concept of HCAI for a number of types of infection, ranging from endocarditis to pneumonia (1, 4, 10, 12). Many such reports, however, have provided scant microbiologic information and have focused more on distinctions in patient types and risk factors for resistant infection. The situation regarding limited microbiologic data is particularly acute with respect to *S. aureus*. Although Fridkin and colleagues, in an assessment of the national burden of MRSA, underscored the growing prevalence of this pathogen in health care-associated pneumonia (HCAP) (3), they presented little information regarding outcomes of such infections.

S. aureus in general—and MRSA in particular—remains a growing challenge for both hospitals and physicians. Good infection prevention practices necessitate isolation precautions for patients with MRSA, which has made early identification of these persons a time-sensitive endeavor. Beyond infection prevention issues, which may complicate the care of patients at risk for MRSA HCAP, patients with HCAP due to either methicillin-sensitive *S. aureus* (MSSA) or MRSA may consume substantial resources. Further complicating management of HCAP due to *S. aureus* is the shift in strain types and antimicrobial resistance implicated in pneumonia (3). The USA300 strain of MRSA, for example, may produce significant toxins and may not respond well to anti-MRSA antimicrobials that are routinely employed (11). Because of these issues, physicians require data regarding the microbiology, epidemiology, and outcomes associated with HCAP due to *S. aureus* (both MSSA and MRSA).

To address these issues, we conducted a retrospective observational study of patients in a large urban hospital with HCAP due to culture-proven *S. aureus.* Our aims were to describe outcomes and resource utilization among patients with *S. aureus* HCAP and to understand possible differences between patients with MSSA versus MRSA pneumonia. We also sought to examine differences in outcomes and resource utilization as a function of pathogen susceptibility to vancomycin and the specific strain type involved.

(Preliminary findings from this study were presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC]-Infectious Diseases Society of America [IDSA] 46th Annual Meeting and the 2008 annual

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meeting of the American College of Chest Physicians [ACCP] [1a, 10a, 11a].)

MATERIALS AND METHODS

Data source. This retrospective study was conducted at Henry Ford Hospital, a 903-bed tertiary care center in Detroit, MI. Data were obtained from the Henry Ford CarePlus electronic medical record database, the Henry Ford Infectious Diseases Research Laboratory database, and the cost component of the Corporate Data Store, which is a central repository of data on patient encounters at Henry Ford Hospital and all Henry Ford Health System (HFHS) ambulatory care sites. In addition to the analyses presented herein, data collected in this study have been used to characterize the epidemiology of *S. aureus* pneumonia and the clinical and economic outcomes of community-acquired *S. aureus* pneumonia.

Sample selection. The source population for the study consisted of all admissions to Henry Ford Hospital between January 2005 and May 2008 ("study period"). Patients were included in the study sample if they had (i) a discharge diagnosis (principal or secondary) of pneumonia (*International Classification of Diseases*, *9th ed.*, *Clinical Modification* [ICD-9-CM] [9a], diagnosis codes 481.X to 486.X) on their discharge summary or in their medical record; (ii) a positive chest X-ray (i.e., infiltrate, consolidation, or pleural effusion) within 48 h of hospital admission; (iii) an abnormal temperature (>38.3°C [101.0°F] or <36°C [96.8°F]), an abnormal white blood cell count (>12,000/mm^3 or <4,000/mm^3), or increased sputum production on their day of hospital admission; (iv) a positive blood or respiratory culture for *S. aureus* within 48 h of hospital admission; and (v) evidence of (*a*) hospitalization for ≥2 days during the 90-day period preceding the index admission, (*b*) admission to hospital from a nursing home or long-term care facility, (*c*) hemodialysis ≤30 days prior to hospital admission, (*d*) receipt of cancer chemotherapy, intravenous antibiotic therapy, or wound care ≤30 days prior to hospital admission, or (*e*) receipt of an immunosuppressant at the time of hospital admission. Patients admitted to hospital with MRSA infection were identified based on the results of *S. aureus* cultures obtained within the first 48 h of admission.

Data extraction. For each admission in the study sample, selected demographic and clinical information was extracted from inpatient and outpatient medical records, beginning 1 year prior to the date of the index admission and ending 30 days following hospital discharge or discontinuation of antibiotic therapy, whichever occurred later. All data were extracted by trained medical abstractors, using a set of case report forms developed specifically for this study.

Study measures. Baseline demographic and clinical characteristics of study subjects were examined, including age, sex, race, presence of positive *S. aureus* culture during the 1-year period prior to hospital admission, history of selected disease conditions, clinical status at admission (e.g., comorbidities, vital signs, white blood count, and platelet count), and receipt of appropriate initial antibiotic therapy. A CURB-65 score (confusion, urea nitrogen, respiratory rate, blood pressure, 65 years of age and older) was calculated for each patient, based on clinical information at hospital admission (6). (A CURB-65 score of 0 indicates a low [<1%] risk of death from pneumonia, while a score of 5 indicates a very high [57%] risk of death.)

Patients were designated as having MSSA or MRSA HCAP based on the results of blood or respiratory cultures within 48 h of hospital admission. All respiratory isolates at the study center undergo initial microscopic screening by the clinical microbiology laboratory for specimen quality. Sputum specimens with <25 polymorphonuclear leukocytes and >10 squamous epithelial cells per low-powered field are reported as inadequate and are not further evaluated or cultured (9). MRSA isolates were initially identified using automated dilution testing, in accordance with the guidelines of the Clinical and Laboratory Standards Institute (13). The genotypic and phenotypic characteristics of MRSA isolates were examined, including susceptibility to vancomycin and presence of the Panton-Valentine leukocidin (PVL) gene. MICs for vancomycin were ascertained using Etest (AB Biodisk, Solna, Sweden) (14). Isolates were tested for the heterogeneous vancomycin-intermediate *S. aureus* phenotype by the macrodilution Etest method (bio-Merieux, Durham, NC). Detection of the PVL gene was based on PCR detection (7).

Initial antibiotic therapy was defined to consist of all antibiotics received within the first 48 h in hospital, regardless of sequence. Appropriateness of initial antibiotic therapy was ascertained based on the susceptibility of the organism to the initial regimen received. Patients with MRSA isolates were designated as having received appropriate initial therapy if they were treated with vancomycin, linezolid, or tigecycline. All *S. aureus* isolates were tested by the clinical microbiology laboratory for *in vitro* susceptibility to linezolid (13). Patients with MSSA isolates were designated as having received appropriate initial therapy if they were treated with a beta-lactam, vancomycin, linezolid, or tigecycline. For patients with MRSA or MSSA infection who received doxycycline, clindamycin, or sulfamethoxazole-trimethoprim, each culture was evaluated individually to determine appropriateness, defined as *in vitro* susceptibility of the organism to the antimicrobial received.

Clinical and economic outcomes of interest included (i) thoracic surgery for pneumonia anytime prior to hospital discharge; (ii) receipt of mechanical ventilation anytime prior to hospital discharge; (iii) admission to an intensive care unit (ICU), irrespective of reason, anytime prior to hospital discharge; (iv) length of stay in hospital; (v) total hospital charges for all services provided between hospital admission and hospital discharge; and (vi) in-hospital death ("case fatality").

Statistical analyses. We examined the baseline demographic and clinical characteristics of patients in the study sample, on an overall basis and for those with MRSA versus MSSA isolates. Categorical measures were summarized using frequency distributions and percentages; means, standard deviations (SD), and medians were employed for continuous measures.

Clinical and economic outcomes were examined similarly, on an overall basis and for patients with MSSA versus MRSA isolates. For patients with MRSA infection, we also examined outcomes in relation to selected genotypic and phenotypic characteristics of MRSA isolates, including vancomycin MICs (1.0 μg/ml, 1.5 μg/ml, and 2.0 μg/ml) and the presence of the gene for PVL toxin.

The statistical significance of differences between patients with MRSA versus MSSA isolates was assessed using *t* tests for continuous measures and chi-square tests for categorical measures; statistical significance was assessed similarly for patients with the PVL toxin gene versus those without it. Because the distribution of vancomycin MICs was highly skewed, the statistical significance of differences in outcomes was not assessed in relation to this measure.

All analyses were conducted using SAS proprietary software, release 9.1 (SAS Institute Inc., Cary, NC). Missing and/or incomplete case report form data were not imputed, as observations were presumed not to be missing at random.

RESULTS

Between January 2005 and May 2008, there was a total of 282 patients with positive blood or respiratory cultures for *S. aureus* within 48 h of admission. Twelve patients had a negative chest X-ray or negative clinical findings for pneumonia on the day of hospital admission and were excluded from the study sample. Among the remaining 270 patients, 142 (53%) patients met criteria for HCAP and were included in the analysis; 61% of these patients had positive MRSA cultures within 48 h of hospital admission. Among the 142 patients, 18 were identified by positive blood culture, 109 were identified by positive respiratory culture, and 15 were identified by both. The demographic and clinical characteristics of study subjects are presented in Table 1.

The mean (SD) age of study subjects was 64.5 (16.6) years; 65% were nonwhite, and 51% were males. Chronic comorbidities were quite prevalent, including cancer, acute renal failure, coronary artery disease, cerebral vascular disease, congestive heart failure, chronic renal failure, chronic obstructive pulmonary disease, diabetes, myocardial infarction, and peripheral vascular disease (all present in >20% of patients). Approximately 20% of patients had positive *S. aureus* cultures in the year prior to admission. There were few notable differences between patients with MRSA versus MSSA, with the only notable exceptions being a higher prevalence of positive cultures for MRSA in the year preceding hospital admission (23.0% versus 3.6%; $P = 0.002$) and more diagnoses of heart failure (49.4% versus 30.9%; $P = 0.037$) for patients with MRSA.

Overall, the population was quite ill at hospital admission, and more than three-quarters were admitted to ICU (Table 2). Nearly 60% of patients presented with respiratory failure re-

TABLE 1. Characteristics of patients with health care-associated *S. aureus* pneumonia

Characteristic	No. (%) of patients		
	MSSA patients (n = 55)	MRSA patients (n = 87)	All patients (n = 142)
Age (yr)			
17–34	4 (7.3)	4 (4.6)	8 (5.6)
35–49	5 (9.1)	12 (13.8)	17 (12.0)
50–64	20 (36.4)	24 (27.6)	44 (31.0)
≥65	26 (47.3)	47 (54.0)	73 (51.4)
Mean (SD)	62.7 (16.5)	65.7 (16.7)	64.5 (16.6)
Sex			
Male	33 (60.0)	40 (46.0)	73 (51.4)
Female	22 (40.0)	47 (54.0)	69 (48.6)
Race			
African American	30 (54.5)	54 (62.1)	84 (59.2)
Caucasian	20 (36.4)	30 (34.5)	50 (35.2)
Other/unknown	5 (9.1)	3 (3.4)	8 (5.6)
Prior positive *S. aureus* culture[a]			
MSSA	5 (9.1)	2 (2.3)	7 (4.9)
MRSA[c]	2 (3.6)	20 (23.0)	22 (15.5)
Both	0 (0.0)	1 (1.1)	1 (0.7)
Comorbidities[b]			
Active malignancy	18 (32.7)	17 (19.5)	35 (24.6)
Acute renal failure	26 (47.3)	46 (52.9)	72 (50.7)
CABG	2 (3.6)	2 (2.3)	4 (2.8)
CAD	14 (25.5)	35 (40.2)	49 (34.5)
Cerebral vascular disease	13 (23.6)	19 (21.8)	32 (22.5)
CHF[c]	17 (30.9)	43 (49.4)	60 (42.3)
Chronic renal failure	14 (25.5)	26 (29.9)	40 (28.2)
COPD	10 (18.2)	25 (28.7)	35 (24.6)
Diabetes	18 (32.7)	42 (48.3)	60 (42.3)
DM with organ damage	3 (5.5)	11 (12.6)	14 (9.9)
ESRD on HD or PD	8 (14.5)	7 (8.0)	15 (10.6)
HIV/AIDS	1 (1.8)	2 (2.3)	3 (2.1)
Myocardial infarction	8 (14.5)	23 (26.4)	31 (21.8)
Peripheral vascular disease	17 (30.9)	40 (46.0)	57 (40.1)
CURB-65 score			
0	6 (10.9)	6 (6.9)	12 (8.5)
1	16 (29.1)	15 (17.2)	31 (21.8)
2	9 (16.4)	33 (37.9)	42 (29.6)
3	16 (29.1)	17 (19.5)	33 (23.2)
4	4 (7.3)	11 (12.6)	15 (10.6)
5	4 (7.3)	5 (5.7)	9 (6.3)
Mean (SD)	2.1 (1.4)	2.3 (1.3)	2.2 (1.3)

[a] During 1 year prior to admission.
[b] History of comorbidity or presence of comorbidity at clinical presentation. CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CURB, confusion, urea nitrogen, respiratory rate, blood pressure, age of ≥65 years; DBP, diastolic blood pressure; DM, diabetes mellitus; ESRD, end-stage renal disease; HD, hemodialysis; HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; PD, peritoneal dialysis.
[c] The P value for the difference between MSSA and MRSA is <0.05.

quiring mechanical ventilation, and 21% required some kind of surgical intervention (e.g., chest tube placement) during hospitalization. Most (~90%) patients received appropriate initial antibiotic therapy. Among the 87 patients with MRSA, the majority (84%) received vancomycin as initial therapy. As a reflection of disease severity, the rate of in-hospital mortality was 25.4%. The median length of stay was 12 days, and median total hospital charges were $70,000.

TABLE 2. Comparison (unadjusted) of clinical and economic outcomes between patients with MRSA and MSSA HCAP

Study outcome	No. (%) of patients[a]		
	MSSA[b] (n = 55)	MRSA[b] (n = 87)	All patients (n = 142)
Case fatality	11 (20.0)	25 (28.7)	36 (25.4)
Surgery for pneumonia	11 (20.0)	19 (21.8)	30 (21.1)
Receipt of mechanical ventilation	32 (58.2)	52 (59.8)	84 (59.2)
ICU admission	42 (76.4)	69 (79.3)	111 (78.2)
Length of stay (days)			
Mean (SD)	14 (9.1)	14 (11.2)	14 (10.4)
Median	14.0	12.0	12.0
Total charges ($)			
Mean (SD)	104,121 (91,314)	98,170 (94,707)	100,475 (93,126)
Median	71,186	70,028	70,397

[a] Unless indicated otherwise.
[b] Differences in outcomes between patients with MSSA and MRSA were not statistically significant.

Table 2 also reports differences in severity of illness and outcomes between patients with MSSA and MRSA HCAP. In general, there were few differences between the two groups; the needs for ICU care and mechanical ventilation, for example, were similar. Although a larger number of MRSA patients died in hospital, the case fatality rates were not significantly different (28.7% for MRSA versus 20% for MSSA patients). Resource utilization rates were also similar.

Fourteen subjects with MRSA HCAP (14.3%) had PVL-producing isolates. As with the comparison between MRSA and MSSA HCAP, rates of ICU admission and respiratory failure were comparable between patients with and without the PVL gene (for ICU, 71% versus 81% [P = 0.475]; and for mechanical ventilation, 64% versus 59% [P = 0.774]). Rates of surgery for pneumonia (21% versus 22%; $P > 0.99$) and lengths of stay (13 versus 14 days; P = 0.635) were almost identical. While the mortality rate was twice as high among HCAP patients with PVL$^-$ infections (odds ratio, 2.76; 95% confidence interval [95% CI], 0.571 to 13.35), this difference was not statistically significant. Total charges were nominally lower for patients with the PVL gene ($84,810 versus $100,732 for PVL$^-$ infections; P = 0.425).

Only 8.2% of MRSA patients who received vancomycin as initial antibiotic therapy showed MICs of ≤1.0 μg/ml. The most common MIC was 1.5 μg/ml, while a MIC of 2.0 μg/ml was noted for approximately 15% of MRSA isolates. There was no significant relationship between vancomycin MICs and illness severity, mortality, or resource use (data not presented). Seven (9.6%) MRSA patients who received vancomycin as initial antibiotic therapy were heteroresistant to vancomycin.

DISCUSSION

In this retrospective study of HCAP due to *S. aureus*, we found that a large number of such infections are caused by MRSA. We also found that a number of cases of MRSA HCAP are associated with PVL-producing strains and that vancomycin MICs are sometimes elevated. Patients with *S. aureus* HCAP are often severely ill and face substantial short-term mortality. Nonetheless, we failed to observe differences in outcomes in relation to methicillin resistance, PVL status, or vancomycin MIC.

Prior studies of HCAP have reported that such infections are associated with a unique distribution of pathogens and that outcomes are generally worse than those noted for community-acquired pneumonia (CAP). In an analysis of an administrative database, Kollef and colleagues found that the microbiology of HCAP was distinct from that of CAP and that MRSA was a frequent cause of HCAP (4). In a review of patients admitted via the ED with pneumonia, Micek and colleagues confirmed that the microbiology of HCAP differed from that of CAP and that patients with HCAP were more likely to be infected with a resistant pathogen, to receive inappropriate antibiotic therapy, and to die (8). International reports from both Japan and Italy confirm that HCAP, as defined by the current American Thoracic Society/Infectious Diseases Society of America's position statement on nosocomial pneumonia, captures a cohort of patients more likely to be infected with MRSA, *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamases.

Our observations add to these earlier reports by providing more detailed information about the prevalence of MRSA versus MSSA in HCAP. Our finding that MRSA is a more frequent cause of infection than MSSA indicates that the criteria we applied to identify HCAP do in fact capture patients with ongoing interaction with the health care system, which in turn increases their risk for infection with MRSA. In other words, we provide indirect evidence confirming that HCAP seems to be unique from CAP, where MRSA is thought not to be an important pathogen. Moreover, we also show that MSSA may remain an important pathogen in HCAP and thus highlight that physicians treating patients with HCAP should continue to consider this organism when making treatment decisions.

There are several notable findings in our study. First, we showed that PVL^+ strains of MRSA may cause HCAP. Until recently, PVL-producing strains of MRSA were reported essentially from skin infections or in rare cases of patients presenting to hospital with pneumonia (5). Earlier descriptions of pneumonia due to PVL-producing strains have stressed that this may be an aggressive and rapidly fatal syndrome. In our study, however, patients with PVL^+ MRSA pneumonia had a mortality rate that was nominally (albeit not significantly) lower than the rate among patients with PVL^- strains. This suggests that PVL production, in and of itself, may not be a marker of poor clinical outcomes and that PVL-producing strains likely cause a range of illnesses not limited to severe disease only. Second, although many patients with MRSA HCAP had vancomycin MICs of >1.0 μg/ml, we did not observe a correlation between vancomycin MIC and either morbidity or mortality. Others have reported that MICs for MRSA infections are strongly linked to outcomes. For example, Soriano et al. previously described a clear increase in mortality from MRSA bacteremia as the vancomycin MIC increased (10b). Hidayat and colleagues also reported a lower response rate among patients with vancomycin MICs of ≥ 1.0 μg/ml than among those with MICs of <1.0 μg/ml (2). Our failure to confirm such a relationship may have arisen, at least in part, because of our small sample size, coupled with the large clustering of pathogens with a MIC of 1.5 μg/ml. Most patients in our study also received appropriate initial antibiotic therapy. In this setting, the impact of higher MICs may be more limited. Alternatively, given how severely ill the patients in our study cohort were, it may be that MICs are a less important driver of outcome when patients are critically ill and face a high risk for death (2). Third, we showed that the cost of both MRSA and MSSA HCAP is high, showing that resistance to methicillin is not the sole contributory factor to high cost.

Our analysis has several significant limitations. First, as with all retrospective studies, it is subject to various potential forms of bias. While we attempted to limit their impact as much as feasible (e.g., by ensuring that all cases had radiologic evidence of pneumonia), the extent to which we were successful in these efforts is unknown. Second, the fact that our study was conducted at a single center undoubtedly limits the generalizability of our findings. As such, physicians must explore their local data to determine if our results are applicable in their institutions. Third, we included in our study only patients with culture evidence of infection. Cultures can often be negative for patients with bacterial infections. However, given our emphasis on microbiology, it was necessary to limit the population to these individuals. Cultures are oftentimes not obtained for patients with pneumonia on general practice units, and accordingly, we may have missed those with milder disease caused by *S. aureus*.

Finally, we used only one method of MIC testing to determine vancomycin susceptibility. It would have been interesting to have used automated dilution testing also and to have compared both methods. Comparison of laboratory methods was not among our study objectives, and most earlier studies examining epidemiology and outcomes used a single laboratory testing method only.

In summary, our study confirms that in *S. aureus* HCAP, MRSA may be a more prevalent pathogen than MSSA. HCAP due to either MRSA or MSSA is associated with significant morbidity, mortality, and health care costs, even when initial antibiotic therapy is appropriate. Both PVL-producing strains of MRSA and those with elevated vancomycin MICs may be seen in MRSA HCAP. The impact of these factors on clinical and economic outcomes, however, seems limited.

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