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Clinical and Economic Analysis of Methicillin-Susceptible and -Resistant *Staphylococcus aureus* Infections

Brian J Kopp, David E Nix, and Edward P Armstrong

BACKGROUND: The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased significantly over the last decade. Previous cohort studies of patients with MRSA bacteremia have reported higher mortality rates, increased morbidity, longer hospital length of stay (LOS), and higher costs compared with patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia. The clinical and economic impact of MRSA involving other sites of infection has not been well characterized.

OBJECTIVE: To determine the clinical and economic implications of MRSA compared with MSSA infections across a variety of infection sites and severity of illnesses.

METHODS: A retrospective, case–control analysis comparing differences in clinical and economic outcomes of patients with MRSA and MSSA infections was conducted at an academic medical center. Case patients with MRSA infection were matched (1:1 ratio) to control patients with MSSA infection according to age, site of infection, and type of care.

RESULTS: Thirty-six matched pairs of patients with *S. aureus* infection were identified. Baseline characteristics of patients with MSSA and MRSA infection were similar. Patients with MRSA infections had a trend toward longer hospital LOS (15.5 vs 11 days; p = 0.05) and longer antibiotic-related LOS (10 vs 7 days; p = 0.003). Median hospital cost associated with treatment of patients with MRSA infections was higher compared with patients with MSSA infections ($16 575 vs $12 862; p = 0.11); however, this difference was not statistically significant. Treatment failure was common in patients with MRSA infection. Among patients with MSSA infections, treatment failure was associated with vancomycin use.

CONCLUSIONS: Patients with MRSA infections had worse clinical and economic outcomes compared with patients with MSSA infections.

KEY WORDS: methicillin resistance, *Staphylococcus aureus*.

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Antimicrobial resistance has increased steadily over the last decade, especially in intensive care units (ICUs).[1,2] Among hospitals participating in the Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance system, the incidence of *Staphylococcus aureus* infections found to be methicillin-resistant (MRSA) increased from approximately 43% in 1995–1999 to 55.3% in 2000. Similar patterns of increasing resistance were noticed for other nosocomial organisms.[3]

Author information provided at the end of the text.

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The factors associated with increasing antimicrobial resistance include suboptimal antibiotic dosages, cross-transmission, and high utilization of antimicrobial agents.[1,4] Inappropriate and excessive use of antimicrobial agents is perhaps the most important variable associated with the development of resistance.[1] Between 70% and 92% of patients who are admitted in an ICU receive antibacterial agents during their stay due to the belief that the drugs are relatively safe, the difficulty in assessing infection in critically ill patients, and concerns about potential litigation.[5] Previous studies have found that between 20% and 80% of antibacterial courses are inappropriately used due to a variety of reasons, which is concerning given the correlation between antibiotic use and development of resistance.[1,6,7]

The potential implications of increasing rates of bacterial resistance include increased mortality and morbidity, longer hospital length of stay (LOS), and use of more expensive and/or broader-spectrum antibacterial agents.[1,5,8-10] Hospital LOS is commonly two- to threefold higher for patients with resistant infections.[2,8,10,11] Since LOS is the most important factor in determining total hospital costs, the development of antimicrobial resistance places a tremendous financial burden on the healthcare industry.[5,12]

The clinical impact of MRSA infections has not been established across a wide variety of patient populations and sites of infection. Mortality rates in cohort studies comparing MRSA and methicillin-susceptible *S. aureus* (MSSA) bacteremia have been inconsistent and conflicting after controlling for confounding data.[13-21] Observational studies comparing the impact of MRSA infections with that of MSSA infections on hospital LOS have also reported inconsistent results.[20,22,23] The observed higher mortality among patients with MRSA could be related to underlying disease rather than the MRSA itself.[13] However, a recent meta-analysis concluded that the mortality rate after controlling for confounding variables was higher in patients with MRSA bacteremia compared with MSSA bacteremia.[24] Most studies that evaluated economic outcomes have reported higher costs associated with treating MRSA infections compared with MSSA infections.[20,22,25]

The purpose of this study was to determine the clinical and economic implications of MRSA compared with MSSA across a variety of infection sites and severity of illnesses. To our knowledge, as of June 30, 2004, this is the only case–control study comparing clinical and economic outcomes of patients with MRSA and MSSA across a variety of infection sites.

Methods

PATIENTS

Patients admitted to the study institution between January 1, 1999, and December 31, 2000, with a diagnosis of *S. aureus* infection who received appropriate antimicrobial therapy for at least 24 hours were eligible for inclusion. Appropriate antimicrobial treatment included any regimen containing vancomycin for MRSA and any regimen containing nafcillin, a first- or second-generation cephalosporin, or vancomycin for MSSA. The appropriate use of vancomycin for MSSA was limited to an allergic reaction to a β-lactam antibiotic that was documented in the medical record.

All patients with an MRSA isolate obtained during an inpatient visit were evaluated. Potential candidates were identified using microbiology reports, ICD-9 codes, computerized discharge notes, and infectious disease consultations. The inpatient medical records of patients with MRSA cultures were reviewed to confirm eligibility. Patients were excluded from the study if there was evidence of a polymicrobial infection, diagnosis of the index infection was made at another institution, there was lack of evidence suggesting infection, or age was <2 years.

Control patients with MSSA infections were identified in a similar manner as patients with an MRSA infection. Case and control patients were matched according to site of infection, type of care, and age. Patients were matched according to site of infection based on the primary site (bacteremia, endocarditis, pneumonia, skin/skin structure, skeletal, or urinary tract). Patients with a primary site infection and secondary bacteremia were matched to a control patient with a similar primary source infection and bacteremia when an appropriate match could be identified. In the event that a match could not be made using these criteria, the case was matched to a control patient with bacteremia before matching to the primary source infection since the clinical implications of bacteremia were felt to be more severe. Patients who could not be matched were excluded from the study.

Type of care was established by whether the patient was receiving treatment in an ICU or non-ICU area when the initial positive culture for *S. aureus* was obtained. Patients were classified as having ICU care if they were transferred to an ICU within 48 hours after isolation of the first positive culture for *S. aureus*.

Age matching of control patients was completed according to the protocol in Table 1.

DESIGN

This was a retrospective, case–control, matched chart review comparing patients with infections due to MRSA and MSSA. The local institutional review board approved the project through the expedited review process.

A single reviewer using a standard data collection form collected outcome data on patients who met the inclusion criteria. Baseline data collected on all patients included gender, date of birth, allergies, type of care, and site of infection. A sequential organ failure assessment (SOFA) score was calculated using data obtained within 24 hours of initiating treatment for the index infection to characterize severity of illness.[26] The SOFA score is comprised of 6 different organ-specific subscores, each with a maximum of 4 points. Higher SOFA scores indicate greater severity of illness. When data were unavailable to calculate the SOFA score during this time period, pertinent data collected during the same hospital admission were used. Subscores relating to respiratory, central nervous system, and liver dysfunction were commonly unavailable in patients receiving non-ICU care. Progress notes were reviewed in these patients to help determine whether there was information that would indicate the presence of organ dysfunction. Patients who did not appear to have significant organ dysfunction based on the progress notes received subscores of 0.

The primary economic analysis was conducted from the perspective of the hospital, and information was obtained from computerized databases at the study institution. Hospital cost represents the amount required to medically manage the patient. The hospital cost takes into account both direct and indirect costs to account for non–revenue-generating departments and overhead. These indirect costs are allocated proportionally to each patient care unit based on the expense to the hospital. The hospital charge represents the amount the institution charges the patient for medical management. The charge master is submitted to a state agency on an annual basis to ensure that the charges are consistent with other institutions.

ENDPOINTS

The primary study endpoints were inpatient LOS, antibiotic LOS (defined as the duration of antibiotic treatment for the index infection), and hospital cost. Secondary endpoints included ICU LOS, duration of mechanical ventilation, hospital charge, and number of treatment failures. Treatment failure was defined as addition or alteration of treatment more than one week after the start of treatment (not including streamlining or intravenous to oral switch), persistent infection, need for prosthetic device removal after >4 weeks of antimicrobial treatment, recurrent infection within 30 days after the end of treatment, or death. Treatment for at least 5 days with an appropriate antibacterial agent was required before failure of treatment could be declared unless the patient died. Patients who received at least 5 days of appropriate treatment were also designated as a clinical failure if the physician(s) documented this outcome in the chart.

Table 1. Age-Matching Criteria for Control Patients

Age (y)	Criteria
2–16	same age group as case patient and within ± 5 y
17–40	same age group as case patient
41–65	same age group as case patient and within ± 10 y
>65	same age group as case patient and within ± 10 y

STATISTICS

Nominal data were analyzed using χ^2 or Fisher's exact test. Primary and secondary endpoints were evaluated to determine whether the data were normally distributed using the Shapiro-Wilke test. Comparison of interval data was performed using the unpaired *t*-tests if normally distributed and the Wilcoxon sign-rank test if not normally distributed. All analyses were 2-tailed, using an α of 0.05. Microsoft Excel was utilized for data entry, and statistical analysis was completed using SAS 8.1 (SAS Institute, Cary, NC).

Results

Thirty-six matched pairs of patients with *S. aureus* infections were identified. A total of 11 MRSA cases and 12 MSSA cases were excluded from the study due to the lack of a suitable match. Baseline characteristics and demographics were similar between the 2 groups (Table 2). All of the data required to determine the SOFA score were available for 24 of 30 patients classified as receiving ICU care and 2 of 42 patients receiving non-ICU care. The overall percentage of patients with missing SOFA data was similar in the MRSA (33%) and MSSA groups (39%). There were 18 patients (2 ICU pts.) in the MRSA group and 15 patients (1 ICU pt.) in the MSSA group who had no blood gas determinations and were assigned a SOFA respiratory subscore of 0. Ten patients (1 ICU pt.) in the MRSA group and 10 patients (2 ICU pts.) in the MSSA group had not had a serum bilirubin concentration determined. None of these patients had documented jaundice or liver impairment and all received liver subscores of 0. A neurologic subscore in the form of a Glascow Coma Score was not documented in 20 patients (2 ICU pts.) in the MRSA group and 19 patients (0 ICU pts.) in the MSSA group. A Glasgow Coma Score was assigned based on physician and nursing notes. The number of matched cases by type of infection were bacteremia (n = 14), pneumonia (n = 9), skin/skin structure infection (n = 7), skeletal/skeletal structure infection (n = 4), and urinary tract infection (n = 2).

Clinical and economic outcomes of patients with MRSA and MSSA infections are shown in Table 3. There was a trend toward longer hospital LOS in patients with MRSA infections compared with patients having MSSA infections. Antibiotic LOS was significantly longer in patients with MRSA infections. Hospital costs associated with treating patients with MRSA infections were not significantly higher than those associated with treating patients with MSSA infections.

Subgroup analysis of ICU patients revealed nonsignificant trends toward longer ICU LOS in the MRSA group and similar durations of mechanical ventilation.

There was a trend toward higher rates of treatment failure in patients with MRSA infections compared with MSSA infections. The most common reasons for treatment failure in both groups were death and recurrent infection (Table 4). One patient in each group died prior to receiving 5 days of antibiotic treatment. Four of 5 MSSA patients who failed treatment received vancomycin for prolonged periods of time for treatment of the index infection. Vancomycin was prescribed in 3 of these patients due to penicillin allergy. The other patient who received vancomycin was converted to cefazolin more than one week after the diagnosis of the MSSA infection and had clinical improvement at the time of discharge.

Discussion

The majority of studies evaluating differences in clinical outcomes between patients with MRSA and MSSA infections have enrolled patients with bacteremia. The results

Table 2. Demographics and Baseline Characteristics

Parameter	MRSA (n = 36)	MSSA (n = 36)	p Value
Age, y (mean ± SD)	54.3 ± 21.3	55.8 ± 18.9	0.74[a]
Gender, n (%)			
male	21 (58.3)	23 (63.9)	0.63[b]
female	15 (41.7)	13 (36.1)	
SOFA score, median (IQR)	3.5 (0–6)	2.5 (0–6.5)	0.93[c]
Type of care, n (%)			
non-ICU	21 (58.3)	21 (58.3)	1.00[b]
ICU	15 (41.7)	15 (41.7)	
Pts. with mechanical ventilation, n (%)	14 (38.9)	16 (44.4)	0.63[b]
Days from admission to infection, median (IQR)	1 (0–7.5)	2 (0–4)	0.94[c]
Empiric antibiotic active against organism, n (%)	21 (58.3)	26 (72.2)	0.22[b]
Secondary infection, n (%)	7 (19.4)	10 (27.8)	0.25[b]
Mortality, n (%)[d]	4 (11.1)	2 (5.6)	0.67[b]

ICU = intensive care unit; IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus;* SOFA = sequential organ failure assessment.
[a]Two-sample *t*-test.
[b]χ^2 analysis.
[c]Wilcoxon sign-rank test.
[d]Fisher's exact test.

from these studies have been inconsistent and have not clearly established the clinical impact of MRSA infections.[13-21] This is the first case–control study evaluating differences between patients with MRSA and MSSA infections across a variety of sites of infection.

Patients with MRSA infections had a median hospital LOS 4.5 days longer than matched control patients with MSSA infections. Since the duration of stay prior to the index infection was similar between the 2 groups, it is more likely that the additional hospital LOS was the result of complications relating to MRSA infection. Also, there was no evidence that MRSA, rather than MSSA, was more likely to occur with increasing hospital duration.

A case–control study of nosocomial *S. aureus* primary bacteremia found that patients with MRSA infections had a median excess hospital LOS of 8 days and approximately threefold higher median total hospital costs compared with patients with MSSA infections.[20] The differences in hospital LOS and costs were greater in the previously published study than in our analysis, although it is unclear why the differences occurred. Potential explanations include differences in patient population, severity of illness, study design, and methods for determining hospital costs.

Duration of antimicrobial treatment for the index infection was significantly longer in patients with MRSA infections compared with MSSA infections. Patients in the MSSA group tended to receive an empiric antimicrobial agent with activity against the infecting organism more often than the patients with MRSA infections; however, the difference was not statistically significant ($p = 0.22$). By day 3 of treatment for the index infection, 30 of 36 patients in the MRSA group and 31 of 36 patients in the MSSA group were receiving appropriate therapy ($p = 0.74$). This suggests that the increased duration of antimicrobial treatment was related to MRSA infection rather than the result of inappropriate antimicrobial treatment.

There was a trend toward higher rates of therapeutic failure in patients with MRSA infections compared with patients with MSSA infections. Four of 5 patients in the MSSA group who had treatment failure received prolonged courses of vancomycin therapy. Despite the fact that our study was not designed to evaluate the endpoint of treatment failure associated with vancomycin use, the higher rate of failure was striking. Several authors have suggested that vancomycin is less effective than β-lactam antibiotics for treatment of *S. aureus* infections and have found associations between the use of vancomycin and treatment failure.[20,27,28] Bacteriologic data of *S. aureus* determined in vitro suggests that vancomycin is less rapidly bactericidal than nafcillin, and slower clearance of bacteremia has been described with vancomycin.[27,28] These studies may help explain the increased duration of antimicrobial treatment observed in the MRSA group and the higher rates of treatment failure in patients treated with vancomycin. Additional research is required to better establish a direct cause-and-effect relationship.

Subgroup analysis of patients receiving care in the ICU at any time during hospitalization demonstrated a trend toward longer ICU LOS, while duration of mechanical ventilation in the groups was similar. Additional study is warranted since these subgroup analyses involved small numbers of patients and limited data regarding these endpoints exist.

The limitations of this study include the retrospective design and its reliance on the accuracy of documentation. The method used for matching patients was designed to minimize the chance that the patients were different at the time the index infection was diagnosed. The patients were well matched according to baseline characteristics. It may be possible that unbalanced differences in comorbid conditions existed that might have altered the study findings. Although the sample size was small, the number of subjects was comparable to or exceeded that of prior studies. Matched pa-

Table 3. Clinical and Economic Outcomes of Patients with *Staphylococcus aureus* Infections

Parameter	MRSA (n = 36)	MSSA (n = 36)	p Value
Clinical outcomes, median (IQR)			
hospital LOS, days	15.5 (7.5–35.5)	11 (2–18.5)	0.054[a]
antibiotic-related LOS, days	10 (2–19.5)	7 (1–12.5)	0.003[a]
ICU LOS, days	19 (6–32) n = 18	13 (5–20) n = 19	0.094[a,b]
duration of mechanical ventilation, days	13.5 (1–27) n = 14	10 (4–17) n = 16	0.487[a,c]
Economic outcomes, median (IQR)			
hospital cost, $	16 575 (7275–89 157)	12 862 (5292–36 471)	0.11[a]
hospital charge, $	50 059 (22 200–215 752)	40 102 (14 775–112 278)	0.162[a]
Treatment failure, n (%)	10 (27.8)	5 (13.9)	0.164[d]

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.
[a]Wilcoxon sign-rank test.
[b]Comparison with subset admitted to ICU.
[c]Comparison with subset that required mechanical ventilation.
[d]χ^2 analysis.

tients were examined for 2 years. While the inclusion dates could have been extended to increase the population available, results could be more affected by shifts in practice or costs over a longer period. Finally, data necessary for calculation of SOFA scores were commonly lacking in patients receiving non-ICU care. The associated error in the respiratory or liver subscores in these patients was felt to be minor, as many patients were breathing room air and had >95% oxygen saturation by pulse oximeter and did not have clinically apparent jaundice.

Data for this study were collected from patients admitted to the hospital during 1999–2000. The only changes notable in recent years include an increasing number of cases of MRSA relative to MSSA in some institutions and increasing prevalence of community-acquired MRSA infections. Treatment of MRSA versus MSSA infections has remained relatively constant; however, there are a few additional options including quinupristin/dalfopristin, linezolid, and daptomycin. These agents are generally used for salvage therapy or in cases where patients do not tolerate first-line drugs.

Summary

Infections due to MRSA were associated with longer hospital LOS, longer antibiotic-related LOS, and higher hospital costs compared with MSSA infections. Although these results did not demonstrate statistical significance, the trends suggest that there are important clinical and economic implications for preventing the spread of antimicrobial resistance. Several agencies have been involved in developing guidelines for the prevention of antimicrobial resistance and isolation of patients with documented resistant organisms.[29-31] Implementation of these recommendations could help manage the problem. Physicians, pharmacists, and other healthcare workers have the opportunity to affect the emergence of antimicrobial resistance by minimizing the use of inappropriate antimicrobial use, selecting the most appropriate antimicrobial agent when needed, and optimizing dosage regimens based on pharmacodynamic principles.

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Table 4. Causes of Treatment Failure in Patients with *Staphylococcus aureus* Infections

Reason for Failure	MRSA[a]	MSSA
Alteration of therapy	3	1
Persistent infection	3	0
Recurrent infection	4	2
Death	4	2

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.
[a]Four patients in the MRSA group had 2 documented reasons for treatment failure.

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EXTRACTO

TRASFONDO: La taza de infecciones debido al *Staphylococcus aureus* resistente a la meticilina (MRSA) ha aumentado considerablemente durante la ultima década. Estudios anteriores de un cohorte de pacientes con bacteremia de MRSA han divulgado índices más altos de mortalidad, morbilidad creciente, una longitud más larga de días hospitalarios, y costos más altos comparados a aquellos con bacteremia debido al *Staphylococcus aureus* susceptible a la meticilina (MSSA). El impacto clínico y económico de otros sitios de infección no han sido bien caracterizado.

OBJETIVO: Determinar las implicaciones clínicas y económicas de MRSA comparado a MSSA a través de una variedad de sitios de infección y severidad de enfermedades.

MÉTODOS: Un análisis retrospectivo de caso control que compara diferencias en resultados clínicos y económicos de pacientes con infecciones de MRSA y de MSSA en un centro médico académico. Se emparejó a pacientes de caso con la infección de MRSA (razón de 1:1) a pacientes control con la infección de MSSA según edad, sitio de infección, y tipo de cuidado.

RESULTADOS: Se identificó a 36 pares de pacientes emparejados con infección a *Staphylococcus aureus*. Las características de base de los pacientes con infección a MSSA y MRSA fueron similares. Pacientes con infecciones a MRSA tenían una tendencia a tener una hospitalización más prolongada (15.5 versus 11 días; $p = 0.05$) y una estadía prolongada que estaba asociada al uso de antibióticos (10 versus 7 días; $p = 0.003$). El costo hospitalario mediano asociado al tratamiento de pacientes con infecciones a MRSA era más alto comparado a pacientes con infecciones de MSSA ($16 575 vs $12 862, $p = 0.11$); sin embargo, esta diferencia no alcanzo ser estadísticamente significativo. La falla del tratamiento era común en pacientes con infección a MRSA. Entre pacientes con infecciones a MSSA, la falla de tratamiento fue asociada con el uso de vancomicina.

CONCLUSIONES: Los pacientes con infecciones de MRSA tenían peores resultados clínicos y económicos comparados a los pacientes con infecciones de MSSA.

Carlos da Camara

RÉSUMÉ

MISE EN CONTEXTE: L'incidence des *Staphylocoques aureus* résistants à la méthicilline (SARM) a significativement augmentée au cours de la dernière décennie. Des études de cohortes ont rapportés des taux plus élevés de mortalité et de morbidité ainsi que des durées d'hospitalisation plus longues et des coûts plus élevés pour des patients bactériémiques à SARM par rapport aux *S. aureus* sensibles à la méthicilline (SASM). Toutefois, l'impact clinique et économique des autres infections à SARM est moins connue.

OBJECTIF: Déterminer les implications cliniques et économiques des infections à SARM dans divers sites et niveaux de sévérité.

MÉTHODES: Étude cas-témoin rétrospective comparant les résultats cliniques et l'impact économique des infections à SARM et à SASM dans une centre hospitalier universitaire. Les patients sont appariés 1:1 selon l'age, le site d'infections et les soins requis.

RÉSULTATS: Trente-six paires de patients sont identifiées. Les caractéristiques de départ sont similaires entre SARM et SASM. Les patients atteints d'infections à SARM ont une durée d'hospitalisation plus longue (15.5 vs 11 jours; $p = 0.05$) et des traitements antibiotiques hospitalier plus longs (10 vs 7 jours; $p = 0.003$) Les coûts d'hospitalisation sont plus importants pour le SARM (médiane $16 575 vs $12 862; $p = 0.11$), mais n'est toutefois pas significatif. Les échecs thérapeutiques sont communs chez les SARM.

CONCLUSIONS: Les patients atteint d'une infection à SARM présentent des résultats cliniques et des impacts économiques moins bons qu'avec des SASM.

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