NIH Public Access
Author Manuscript
J Infect. Author manuscript; available in PMC 2014 January 01.

Published in final edited form as:
J Infect. 2013 January ; 66(1): 41–47. doi:10.1016/j.jinf.2012.09.001.

The Effect of Staphylococcal Cassette Chromosome *mec* (SCC*mec*) Type on Clinical Outcomes in Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Jennifer H. Han, MD, MSCE[a], **Paul H. Edelstein, MD**[b], **Warren B. Bilker, PhD**[c,d], and **Ebbing Lautenbach, MD, MPH, MSCE**[a,c,d]

[a]Division of Infectious Diseases, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

[b]Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

[c]Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

[d]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Abstract

Objectives—The impact of staphylococcal cassette chromosome *mec* (SCC*mec*) type on mortality in methicillin-resistant *Staphylococcus aureus* (MRSA) infections remains unclear. The objective of this study was to determine the association between SCC*mec* type and mortality in MRSA bacteremia.

Methods—A cohort study of patients who were hospitalized with MRSA bacteremia was conducted within a university health system. A multivariable logistic regression model was developed to evaluate the association of SCC*mec* type with 30-day in-hospital mortality.

Results—Thirty-four of a total of 184 patients with MRSA bacteremia died, resulting in a mortality rate of 18.5%. Adjusted risk factors for 30-day mortality included APRDRG Risk of Mortality score (odds ratio [OR], 5.33; 95% confidence interval [CI], 2.28-12.4; $P<0.001$), white blood cell count (OR, 1.09; 95% CI, 1.03-1.15; $P=0.002$), and malignancy (OR, 3.25; 95% CI, 1.17-9.02; $P=0.02$). On multivariable analyses, SCC*mec* II was not significantly associated with mortality in patients with MRSA bacteremia (OR, 1.85; 95% CI, 0.69-4.92; $P=0.22$).

Conclusions—Mortality in MRSA bacteremia was independent of SCC*mec* type. SCC*mec* type II is most likely a marker for disease severity rather than a direct mediator of mortality. Further research is needed to elucidate the factors associated with poor clinical outcomes in MRSA infections.

© 2012 The British Infection Society. Published by Elsevier Ltd. All rights reserved.

Corresponding author: Jennifer Han, MD, MSCE, Division of Infectious Diseases, Department of Medicine, Hospital of the University of Pennsylvania, 3400 Spruce Street, 3rd Floor, Silverstein Building, Ste E, Philadelphia, PA 19104, Telephone: +1-215-615-4725, Fax: +1-215-662-7611, jennifer.han@uphs.upenn.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Potential conflicts of interest. E.L. has received research grant support from AstraZeneca, Cubist, and 3M. All other authors: no conflicts.

$watermark-text
$watermark-text
$watermark-text

$watermark-text

$watermark-text

$watermark-text

Keywords

methicillin-resistant; *Staphylococcus aureus*; outcomes; bacteremia

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common causes of healthcare-associated infections worldwide and is associated with significant morbidity and mortality.[1] Methicillin resistance is mediated by acquisition of the *mecA* gene, which is located within the staphylococcal cassette chromosome *mec* (SCC*mec*) element.[2] In recent years, MRSA has also emerged as an important cause of infections in the community setting.[3] Despite the lack of a uniform definition of community-associated MRSA (CA-MRSA) in the literature, the term has usually been used to describe strains causing infections in patients without recent contact with the healthcare environment.[3] However, recent epidemiologic evidence indicates that CA-MRSA strains are increasingly causes of nosocomial infections,[4] and that traditional epidemiologic definitions and risk factors may no longer reliably differentiate between CA-MRSA and healthcare-associated MRSA (HA-MRSA).[5]

From a molecular standpoint, CA-MRSA has typically been distinguished from HA-MRSA by the SCC*mec* element, with SCC*mec* IV and V predominating in CA-MRSA strains and SCC*mec* I, II, and III in HA-MRSA strains.[3] Despite the increasing spread of CA-MRSA into the hospital setting, the impact of SCC*mec* type on mortality in MRSA infections remains unclear. Studies to date evaluating this association have demonstrated conflicting results, most likely due to differences in patient populations, geographic region (e.g., United States, Asia), anatomic site of infection, selection of reference groups, and lack of multivariable analyses.[6-14] Furthermore, only a proportion of these studies have focused specifically on bacteremia,[6, 8, 12-14] a major source of healthcare-associated infections due to MRSA and one associated with significant morbidity and mortality.[15] These studies have also demonstrated conflicting results, and the majority evaluated patient populations outside of the United States[6, 12, 14] where different SCC*mec* types predominate.

We conducted this cohort study to determine the association between SCC*mec* type and mortality in MRSA bacteremia. Specifically, we compared mortality in patients with *S. aureus* bacteremia with SCC*mec* II as opposed to SCC*mec* IV, the predominant SCC*mec* types in the United States.[4]

Patients and Methods

Study design and setting

This retrospective cohort study was conducted at two hospitals in the University of Pennsylvania Health System (UPHS) in Philadelphia: the Hospital of the University of Pennsylvania (HUP), a 725-bed academic tertiary care medical center, and Penn Presbyterian Medical Center (PPMC), a 344-bed urban community hospital. The study was approved by the institutional review board of the University of Pennsylvania.

Study population

All hospitalized patients with an episode of MRSA bacteremia occurring between 1 December 2007 and 31 May 2009 were identified through the HUP Clinical Microbiology Laboratory, which processes all specimens obtained from patients at HUP and PPMC. All of

$watermark-text

$watermark-text

$watermark-text

these patients were subsequently included in the study. For patients with multiple blood cultures positive for MRSA, only the first culture was included for analysis.

Microbiologic methods

Identification and susceptibility testing of *S. aureus* was performed and interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Standard susceptibility testing was performed using Vitek2. SCC*mec* typing was performed as previously described.[16] The vancomycin minimum inhibitory concentration (MIC) of all isolates was determined by the Etest using Mueller-Hinton agar (BBL, BD Diagnostic Systems, Franklin Lakes, NJ, USA)[17] with reduced vancomycin susceptibility defined as an Etest vancomycin MIC >1.0 μg/ml.[18, 19] Vancomycin hetero-resistance was screened for using the macro-Etest method using Etest GRD vancomycin/teicoplanin strips with brain heart infusion agar[17] and by growth on vancomycin-containing brain heart infusion agar;[20] a positive result for either screening test was confirmed by population analysis using a Spiral Plater (Advanced Instruments, Norwood, MA, USA) and inoculation onto vancomycin brain heart infusion agar (BBL).[21] Detection of the genes encoding Panton-Valentine leukocidin (PVL) was performed using real-time polymerase chain reaction using previously described methods.[22] Isolates were evaluated for accessory gene regulator (*agr)* dysfunction via delta-hemolysin production using a beta-hemolysin disk.[23]

Data collection

Data were abstracted from the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD),[24, 25] which includes demographic, laboratory, pharmacy, and billing information. The following data were collected for all patients: baseline demographics, origin at the time of hospital admission (i.e., physician referral, transfer from another facility, or admission through the Emergency Department), previous admission to UPHS in the 30 days prior to the culture date, hospital location at the time of infection (i.e., intensive care unit [ICU] or medical floor), nosocomial infection (date of the culture ≥48 hours after admission), white blood cell count (WBC) on the culture date, and All Patient Refined-Diagnosis Related Group (APRDRG) Risk of Mortality and Severity of Illness scores.[26] Infections were classified as healthcare-associated if the date of the first positive blood culture was ≥48 hours from the date of admission, or if the patient had been previously hospitalized at HUP or PPMC in the 30 days prior to the culture date or was admitted as a transfer from another institution. Otherwise, infections were classified as community-onset. Data on the following conditions was collected in relation to the positive blood culture date: diabetes mellitus, HIV infection, malignancy, renal insufficiency (creatinine ≥2.0 mg/dL or the requirement of dialysis), solid organ or hematopoietic stem cell transplantation, neutropenia (absolute neutrophil count <500/mm^3), and receipt of an immunosuppressive agent (e.g., corticosteroids, tacrolimus) in the prior 30 days. The Charlson comorbidity index was calculated for each subject.[27] Chart review was performed to collect data on the presence of complicated infection (i.e., endocarditis, osteomyelitis, septic arthritis, epidural and/or spinal abscess) and the presence of intravascular devices (i.e., intravascular catheter, pacemaker or defibrillator, arteriovenous fistula or graft) prior to the episode of bacteremia.

Information on all antimicrobial therapy administered during the same hospitalization was collected, including the time of receipt in relation to the culture date. Antibiotics were considered to be appropriate in relation to treatment of the episode of MRSA bacteremia if they were determined to be active *in vitro* against the isolate via standard susceptibility testing. The primary outcome was crude in-hospital 30-day mortality, defined as death in the hospital from any cause occurring in the 30 days after the date of the first positive blood culture.

$watermark-text

$watermark-text

$watermark-text

Statistical analysis

Continuous variables were compared using the Student's t-test or Wilcoxon rank-sum test and categorical variables were compared using the χ^2 or Fisher's exact test. Bivariable analyses were performed to determine the association between SCC*mec* type and 30-day in-hospital mortality, with the primary exposure of interest being SCC*mec* type II. Stratified analyses were conducted to elucidate where confounding and interaction were likely to exist in multivariable analyses, using the Mantel-Haenszel test for summary statistics.[28] In particular, location in the ICU, hospital of admission, and healthcare-associated infection were designated *a priori* as potential effect modifiers of interest. Effect modification was assumed to be present when the test for heterogeneity between the odds ratios (ORs) for different strata yielded a *P* value <0.05. The Mantel-Haenszel test for summary statistics[28] was used to evaluate the effects of each variable of interest as a possible confounder. Adjusted ORs with 95% confidence intervals (CI) were calculated using multiple logistic regression for the outcome of 30-day in-hospital mortality. A stepwise selection procedure was used for all multivariable analyses, with variables with *P* values <0.20 on bivariable analyses or noted to be confounders on stratified analyses considered as candidate variables and maintained in the final model if their inclusion resulted in a ≥15% change in the effect measure for the primary association of interest or were statistically significant on likelihood ratio testing.[29]

For all calculations, a 2-tailed *P* value <0.05 was considered to be significant. All statistical calculations were performed using commercially available software (STATA version 11.0; StataCorp LP, College Station, Texas, USA).

Results

Study population

A total of 184 unique patients with MRSA bacteremia were identified during the study period. The distribution of SCC*mec* type among isolates was as follows: 109 (59.2%) with SCC*mec* II and 75 (40.8%) with SCC*mec* IV. Baseline clinical and demographic characteristics of patients with MRSA bacteremia are shown in Table 1. Patients with bacteremia due to MRSA harboring SCC*mec* II compared to SCC*mec* IV were older (mean age 62.8 and 55.1 years, respectively; *P*=0.002), had a higher APRDRG Risk of Mortality score at the time of MRSA isolation (mean 2.6 and 1.8, respectively; *P*=0.004), and had a significantly longer length of stay prior to the culture date (11.1 and 2.49 mean days, respectively, *P*=0.02).

Microbiologic characteristics

Isolates with SCC*mec* II versus SCC*mec* IV were more likely to be characterized by reduced vancomycin susceptibility (51.4% and 22.7%, respectively; *P*<0.001)[30] and less likely to be PVL positive (0.9% and 68.0%, respectively, P<0.001). There were no significant differences in the proportion of isolates with SCC*mec* II and SCC*mec* IV that were characterized by vancomycin hetero-resistance (6.4% and 2.7%, respectively; *P*=0.36) or *agr* dysfunction (16.5% and 10.7%, respectively; *P*=0.29).

In regard to antimicrobial susceptibility rates, MRSA isolates with SCC*mec* IV compared to those with SCC*mec* II demonstrated significantly higher rates of susceptibility to clindamycin (86.7% and 4.6%, respectively; *P*<0.001) and levofloxacin (41.3% and 0.92%, respectively; *P*<0.001). However, there were no significant differences in susceptibility rates for isolates with SCC*mec* IV versus SCC*mec* II for tetracycline (94.7% and 98.2%, respectively; *P*=0.23) and trimethoprim-sulfamethoxazole (94.7% and 99.1%, respectively; *P*=0.16).

$watermark-text

$watermark-text

$watermark-text

Risk factors for 30-day in-hospital mortality

A total of 34 patients died while hospitalized for MRSA bacteremia, resulting in a crude mortality rate of 18.5%. The mortality rate was 23.9% and 10.7% for patients with MRSA isolates characterized by SCC*mec* II and SCC*mec* IV, respectively (P=0.03). Results of bivariable analyses of risk factors associated with in-hospital mortality are given in Table 2. The majority of patients received appropriate antibiotics, specifically 99.3% of patients who survived and 96.9% of patients who died during hospitalization, with vancomycin the most commonly administered initial antibiotic (86.7% and 91.2%, respectively; P=0.58).

On multivariable analyses of risk factors for 30-day in-hospital mortality (Table 3), there was no significant effect modification by location in the ICU (P=0.26), hospital of admission (P=0.21), or healthcare-associated infection (P=0.16). The unadjusted OR between SCC*mec* II and mortality was 2.62 (95% CI 1.06-7.12, P=0.03). On multivariable analyses, independent risk factors for in-hospital mortality included APRDRG Risk of Mortality score (OR 5.33, 95% CI 2.28-12.4, P<0.001), malignancy (OR 3.25, 95% CI 1.17-9.02, P=0.02), and WBC count on the culture date (OR 1.09, 95% CI 1.03-1.15, P=0.002). After controlling for confounders, SCC*mec* II was not significantly associated with greater 30-day in-hospital mortality (OR 1.85, 95% CI 0.69-4.92, P=0.22).

Discussion

In this cohort study of patients with MRSA bacteremia, we found that SCC*mec* type, specifically SCC*mec* II compared to SCC*mec* IV, was not significantly associated with mortality. Furthermore, isolates harboring SCC*mec* IV had higher susceptibility rates to clindamycin and levofloxacin compared to those with SCC*mec* II. The results of our study also demonstrated that a higher standardized mortality risk score, the presence of malignancy, and a higher white blood cell count were independent risk factors for mortality in MRSA bacteremia.

Previous studies have demonstrated conflicting results in regard to the role of SCC*mec* type on mortality in infections due to MRSA.[6-14] In a study evaluating patients with MRSA skin and soft tissue infections,[11] SCC*mec* II was associated with greater mortality compared to both MRSA with other SCC*mec* types (primarily IVa) and methicillin-susceptible *S. aureus* (MSSA). In a larger study of 465 MRSA isolates responsible for skin and soft tissue infections from a phase IV clinical trial,[10] clinical and microbiologic outcomes, including mortality, were independent of SCC*mec* type. A study evaluating 100 community-associated MRSA isolates from various sources (e.g., respiratory tract, bacteremia) demonstrated greater mortality in the SCC*mec* II/III group compared to the SCC*mec* IV group (i.e., two patients and one patient died during hospitalization, respectively), although there was no difference in clinical or microbiologic success rates.[7] However, all of these studies were limited to bivariable analyses. Finally, a study evaluating clinical outcomes in MRSA pneumonia[9] found that SCC*mec* II was associated with increased mortality on bivariable analysis; however, this association was not significant on subsequent multivariable analyses.

Studies evaluating the impact of SCC*mec* type on mortality exclusively in MRSA bacteremia,[6, 8, 12-14] as was the focus of our study, have also demonstrated conflicting results, as well as significant heterogeneity in regard to patient population, ascertainment of potential confounders, geographic region, and use of multivariable analyses. A few studies[6, 8] have found increased mortality with MRSA strains harboring SCC*mec* II, but these were limited by comparison to MSSA only,[6] failure to account for time to receipt of appropriate antimicrobial therapy,[8] and evaluation of only community-onset infections.[6] Other studies[12-14] have demonstrated no association between SCC*mec* type and mortality, although these were limited by use of bivariable analyses only,[12] or evaluated a patient

$watermark-text

$watermark-text

$watermark-text

population from a different geographic region than the present study (i.e., Asia versus the United States)[12, 14] where different SCC*mec* types predominate. Our study demonstrated no association between SCC*mec* II and mortality, and to our knowledge, is the largest to date evaluating the impact of SCC*mec* type on mortality in MRSA bacteremia using multivariable analyses. The results are further strengthened by the comprehensive capture of potential confounders, including time to receipt of appropriate antimicrobial therapy, standardized severity of illness and risk scores, and presence and/or removal of intravascular devices.

Factors that are likely to contribute to the relationship between MRSA infection and mortality include bacterial virulence and fitness, host factors including comorbidities and severity of illness, and the receipt of early and appropriate antimicrobial therapy.[31] It is possible that SCC*mec* II may be a marker of illness severity and/or greater exposure to the healthcare system rather than a direct mediator of mortality, and indeed, in our study and others,[4, 7, 14] SCC*mec* II compared to SCC*mec* IV was associated with significantly higher standardized severity of illness scores and longer hospital lengths of stay prior to isolation of MRSA. Therefore, in the hospitalized population, which is generally characterized by a greater severity of illness and the presence of more comorbidities compared to the community population, SCC*mec* II may not have a direct causal effect on mortality.Along these lines, in the present study, while SCC*mec* II was a risk factor for mortality on bivariable analyses compared to SCC*mec* IV, after adjustment for potential confounders including a standardized score for mortality risk, there was no association between SCC*mec* type and mortality.

The receipt of appropriate antimicrobial therapy (e.g., one or more agents that are active *in vitro* against the isolate), as well as timing of receipt, have been shown to decrease mortality in MRSA bacteremia.[32] Notably, in our study, the majority of patients with bacteremia due to MRSA with both SCC*mec* II and SCC*mec* IV received appropriate antimicrobial therapy (98.7% and 99.1%, respectively; $P>0.99$). Furthermore, there was no significant difference in time to administration of appropriate antimicrobial therapy in patients with bacteremia due to MRSA with either SCC*mec* II or SCC*mec* IV (mean of 16.1 and 15.8 hours, respectively, $P=0.31$).

In regard to organism factors, evidence suggests that MRSA strains with SCC*mec* IV may exhibit enhanced virulence and/or fitness compared to those harboring SCC*mec* II.[33, 34] Indeed, some studies have demonstrated an increased risk of metastatic infection with SCC*mec* IV,[8, 13] although this did not translate to an increased risk of persistent bacteremia.[13] Interestingly, SCC*mec* II was associated with elevated vancomycin MIC in our study,[30] although this did not increase mortality in the final multivariable model.

There are several potential limitations of our study. We were unable to ascertain pharmacologic data on therapeutic drug monitoring in patients receiving vancomycin. Selection bias is a potential concern; however, patients with MRSA bacteremia were identified through the Clinical Microbiology Laboratory which processed and cultured all specimens obtained at HUP and PPMC during the study period, thereby minimizing the likelihood of excluding potential microbiologic isolates. Finally, the present study was conducted in a single healthcare system, and these results may not be generalizable to other institutions or geographic locations.

In conclusion, we found that after adjustment for relevant confounders, mortality in MRSA bacteremia is independent of SCC*mec* type. It is clear that the epidemiology of MRSA is complex and evolving, and strains possessing SCC*mec* IV are an increasing cause of infections in the nosocomial setting, including invasive infections such as bacteremia.

Further research is needed to elucidate potentially modifiable host and organism factors associated with mortality in MRSA infections.

Acknowledgments

The authors thank Martha Edelstein for performing SCC*mec* typing and *agr* testing, Andrew Baltus for PVL testing and antimicrobial susceptibility testing, Baofeng Hu for assistance with SCC*mec* typing, and Jose Mediavilla and the Kreiswirth laboratory at the University of Medicine and Dentistry of New Jersey for their assistance with SCC*mec* typing of some isolates.

Funding. This work was supported by the National Institutes of Health (K24 AI080942 to E.L.), a Commonwealth Universal Research Enhancement Program grant from the Pennsylvania State Department of Health (to E.L.), and the Centers for Disease Control and Prevention Epicenters Program (U54-CK000163 to E.L.). The dataset on which this study was based was constructed as part of a study originally funded by Cubist Pharmaceuticals. However, Cubist had no role in the present study.

Role of the funding agency. The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

REFERENCES

1. Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. Emergence and resurgence of meticillin-resistant Staphylococcus aureus as a public-health threat. Lancet. 2006; 368:874–885. [PubMed: 16950365]
2. Katayama Y, Ito T, Hiramatsu K. A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in Staphylococcus aureus. Antimicrob Agents Chemother. 2000; 44:1549–1555. [PubMed: 10817707]
3. Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant Staphylococcus aureus infection. JAMA. 2003; 29:2976–2984. [PubMed: 14665659]
4. Maree CL, Daum RS, Boyle-Vavra S, Matayoshi K, Miller LG. Community-associated methicillin-resistant Staphylococcus aureus isolates causing healthcare-associated infections. Emerg Infect Dis. 2007; 13:236–242. [PubMed: 17479885]
5. Popovich KJ, Weinstein RA, Hota B. Are community-associated methicillin-resistant Staphylococcus aureus (MRSA) strains replacing traditional nosocomial MRSA strains? Clin Infect Dis. 2008; 46:787–794. [PubMed: 18266611]
6. Chen SY, Wang JT, Chen TH, et al. Impact of traditional hospital strain of methicillin-resistant Staphylococcus aureus (MRSA) and community strain of MRSA on mortality in patients with community-onset S aureus bacteremia. Medicine (Baltimore). 2010; 89:285–294. [PubMed: 20827105]
7. Davis SL, Rybak MJ, Amjad M, Kaatz GW, McKinnon PS. Characteristics of patients with healthcare-associated infection due to SCCmec type IV methicillin-resistant Staphylococcus aureus. Infect Control Hosp Epidemiol. 2006; 27:1025–1031. [PubMed: 17006808]
8. Ganga R, Riederer K, Sharma M, et al. Role of SCCmec type in outcome of Staphylococcus aureus bacteremia in a single medical center. J Clin Microbiol. 2009; 47:590–595. [PubMed: 19144813]
9. Haque NZ, Arshad S, Peyrani P, et al. Analysis of pathogen and host factors related to clinical outcomes in patients with hospital-acquired pneumonia due to methicillin-resistant Staphylococcus aureus. J Clin Microbiol. 2012; 50:1640–1644. [PubMed: 22337980]
10. Huang DB, Reisman A, Hogan P. Clinical outcomes by methicillin-resistant Staphylococcus aureus staphylococcal cassette chromosome mec type: isolates recovered from a phase IV clinical trial of linezolid and vancomycin for complicated skin and skin structure infections. Antimicrob Agents Chemother. 2010; 54:4036–4037. [PubMed: 20585131]
11. Jahamy H, Ganga R, Al Raiy B, et al. Staphylococcus aureus skin/soft-tissue infections: the impact of SCCmec type and Panton-Valentine leukocidin. Scand J Infect Dis. 2008; 40:601–606. [PubMed: 18979597]

$watermark-text
$watermark-text
$watermark-text

$watermark-text

$watermark-text

$watermark-text

12. Kuo SC, Chiang MC, Lee WS, et al. Comparison of microbiological and clinical characteristics based on SCCmec typing in patients with community-onset meticillin-resistant Staphylococcus aureus (MRSA) bacteraemia. Int J Antimicrob Agents. 2011; 39:22–26. [PubMed: 21982834]
13. Neuner EA, Casabar E, Reichley R, McKinnon PS. Clinical, microbiologic, and genetic determinants of persistent methicillin-resistant Staphylococcus aureus bacteremia. Diagn Microbiol Infect Dis. 2010; 67:228–233. [PubMed: 20542203]
14. Wang JL, Wang JT, Chen SY, Chen YC, Chang SC. Distribution of Staphylococcal cassette chromosome mec types and correlation with comorbidity and infection type in patients with MRSA bacteremia. PLoS One. 2010; 5:e9489. [PubMed: 20221428]
15. 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 charges. Infect Control Hosp Epidemiol. 2005; 26:166–174. [PubMed: 15756888]
16. Chen L, Mediavilla JR, Oliveira DC, Willey BM, de Lencastre H, Kreiswirth BN. Multiplex real-time PCR for rapid Staphylococcal cassette chromosome mec typing. J Clin Microbiol. 2009; 47:3692–3706. [PubMed: 19726600]
17. Fitzgibbon MM, Rossney AS, O'Connell B. Investigation of reduced susceptibility to glycopeptides among methicillin-resistant Staphylococcus aureus isolates from patients in Ireland and evaluation of agar screening methods for detection of heterogeneously glycopeptide-intermediate S. aureus. J Clin Microbiol. 2007; 45:3263–3269. [PubMed: 17687008]
18. Holland TL, Fowler VG. Vancomycin minimum inhibitory concentration and outcome in patients with Staphylococcus aureus bacteremia: pearl or pellet? J Infect Dis. 2011; 204:329–331. [PubMed: 21742827]
19. Yamaki J, Lee M, Shriner KA, Wong-Beringer A. Can clinical and molecular epidemiologic parameters guide empiric treatment with vancomycin for methicillin-resistant Staphylococcus aureus infections? Diagn Microbiol Infect Dis. 2011; 70:124–130. [PubMed: 21392923]
20. Satola SW, Farley MM, Anderson KF, Patel JB. Comparison of detection methods for heteroresistant vancomycin-intermediate Staphylococcus aureus, with the population analysis profile method as the reference method. J Clin Microbiol. 2011; 49:177–183. [PubMed: 21048008]
21. Walsh TR, Bolmstrom A, Qwarnstrom A, et al. Evaluation of current methods for detection of staphylococci with reduced susceptibility to glycopeptides. J Clin Microbiol. 2001; 39:2439–2444. [PubMed: 11427551]
22. Lina G, Piemont Y, Godail-Gamot F, et al. Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia. Clin Infect Dis. 1999; 29:1128–1132. [PubMed: 10524952]
23. Schweizer ML, Furuno JP, Sakoulas G, et al. Increased mortality with accessory gene regulator (agr) dysfunction in Staphylococcus aureus among bacteremic patients. Antimicrob Agents Chemother. 2011; 55:1082–1087. [PubMed: 21173172]
24. Barton TD, Fishman NO, Weiner MG, LaRosa LA, Lautenbach E. High rate of coadministration of di- or tri-valent cation-containing compounds with oral fluoroquinolones: risk factors and potential implications. Infect Control Hosp Epidemiol. 2005; 26:93–99. [PubMed: 15693415]
25. Lee I, Fishman NO, Zaoutis TE, et al. Risk factors for fluconazole-resistant Candida glabrata bloodstream infections. Arch Intern Med. 2009; 169:379–383. [PubMed: 19237722]
26. Iezzoni LI, Ash AS, Shwartz M, Daley J, Hughes JS, Mackiernan YD. Predicting who dies depends on how severity is measured: implications for evaluating patient outcomes. Ann Intern Med. 1995; 123:763–770. [PubMed: 7574194]
27. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43:1130–1139. [PubMed: 16224307]
28. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959; 22:719–748. [PubMed: 13655060]
29. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol. 1989; 129:125–137. [PubMed: 2910056]

30. Han JH, Edelstein PH, Lautenbach E. Reduced vancomycin susceptibility and staphylococcal cassette chromosome mec (SCCmec) type distribution in methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. Jul 3.2012 epublished ahead of print.

31. Cameron DR, Howden BP, Peleg AY. The interface between antibiotic resistance and virulence in Staphylococcus aureus and its impact upon clinical outcomes. Clin Infect Dis. 2011; 53:576–582. [PubMed: 21865195]

32. Paul M, Kariv G, Goldberg E, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2010; 65:2658–2665. [PubMed: 20947620]

33. Collins J, Rudkin J, Recker M, Pozzi C, O'Gara JP, Massey RC. Offsetting virulence and antibiotic resistance costs by MRSA. ISME J. 2010; 4:577–584. [PubMed: 20072161]

34. David MZ, Glikman D, Crawford SE, et al. What is community-associated methicillin-resistant Staphylococcus aureus? J Infect Dis. 2008; 197:1235–1243. [PubMed: 18422435]

$watermark-text

$watermark-text

$watermark-text

$watermark-text
$watermark-text
$watermark-text

Table 1

Clinical and demographic characteristics of patients with methicillin-resistant *Staphylococcus aureus* bacteremia

Characteristic	SCC*mec* II[a] (n=109)	SCC*mec* IV[a] (n=75)	*P* Value
Age, mean years (SD)	63 (15.7)	55 (17.4)	0.002
Female sex	44 (40.4)	29 (38.7)	0.82
White race	71 (62.7)	35 (45.9)	0.07
HUP	85 (78.0)	43 (57.3)	0.003
Emergency Department admission	43 (39.5)	48 (64.0)	0.001
Nosocomial onset	38 (34.9)	12 (16.0)	0.007
Healthcare-associated	76 (69.7)	36 (48.0)	0.003
APRDRG Risk of Mortality score[b], mean (SD)	2.3 (0.9)	1.8 (1.1)	0.004
HIV	2 (1.8)	7 (9.3)	0.03
Malignancy	32 (29.4)	13 (17.3)	0.06
Intravascular device	56 (51.4)	23 (30.7)	0.005
In-hospital length of stay prior to culture date, mean days (SD)	11.1 (52.9)	2.5 (8.8)	0.02
30-day in-hospital mortality	26 (23.9)	8 (10.7)	0.03

SD, standard deviation; HUP, Hospital of the University of Pennsylvania; APRDRG, All Patient Refined-Diagnosis Related Group.

[a]Data are presented as numbers (percentages) except where noted.

[b]Risk of patient death as based on DRG. The four subclasses are numbered sequentially from 1 to 4 indicating respectively, minor, moderate, major, or extreme risk of mortality.

$watermark-text
$watermark-text
$watermark-text

Table 2

Unadjusted risk factors associated with in-hospital mortality in methicillin-resistant *Staphylococcus aureus* bacteremia

Variable	No. (%) Survived (n=150)[a]	No. (%) Deceased (n=34)[a]	OR (95% CI)[b]	*P* Value
Age, mean years (SD)	58.7 (16.9)	64.1 (15.7)	N/A	0.10
Female sex	57 (38.0)	16 (47.1)	1.45 (0.63-3.28)	0.33
White race	87 (56.8)	19 (50.0)	0.64 (0.28-1.44)	0.26
PPMC admission	51 (34.0)	5 (14.7)	0.33 (0.10-0.95)	0.04
Physician referral on admission	27 (18.0)	3 (8.8)	0.44 (0.08-1.59)	0.30
Nosocomial infection	39 (26.0)	11 (32.4)	1.36 (0.55-3.23)	0.52
Total duration of bacteremia from culture date, mean days (SD)	3.5 (4.6)	3.6 (5.6)	N/A	0.52
Receipt of appropriate antibiotic(s)	147 (99.3)	31 (96.9)	0.21 (0.003-17.1)	0.33
Days to receipt of appropriate antibiotics, mean (SD)	0.70 (1.2)	0.48 (0.63)	N/A	0.60
APRDRG Risk of Mortality score[c], mean (SD)	1.9 (1.0)	2.8 (0.54)	N/A	<0.001
APRDRG Severity of Illness score[c], mean (SD)	2.4 (0.64)	2.9 (0.41)	N/A	<0.001
Charlson Comorbidity score, mean (SD)	4.4 (4.6)	4.1 (3.4)	N/A	0.97
Intravascular device	64 (42.7)	15 (44.1)	1.06 (0.46-2.39)	>0.99
Removal of intravascular device	47 (73.4)	12 (80.0)	1.45 (0.33-8.91)	0.75
Complicated infection	52 (34.7)	10 (29.4)	0.79 (0.31-1.86)	0.69
Diabetes mellitus	46 (30.7)	11 (32.4)	1.08 (0.44-2.54)	0.84
Malignancy	32 (21.3)	13 (38.2)	2.28 (0.94-5.38)	0.05
Renal insufficiency	42 (28.2)	13 (38.2)	1.58 (0.66-3.65)	0.30
Neutropenia	4 (11.8)	7 (4.7)	2.70 (0.54-11.4)	0.13
Transplant (solid organ or hematopoietic stem cell)	19 (12.7)	2 (5.9)	0.43 (0.05-1.95)	0.38
Receipt of any immunosuppression ≤30 days prior to the culture date	15 (10.0)	8 (23.5)	2.77 (0.91-7.79)	0.04
ICU location on culture date	31 (20.7)	15 (44.1)	3.03 (1.27-7.10)	0.01
WBC count, mean X 109/L (SD)	12.4 (7.8)	16.6 (12.0)	N/A	0.07
Reduced vancomycin susceptibility	61 (40.7)	12 (35.3)	0.80 (0.33-1.83)	0.56
hGISA	7 (4.7)	2 (5.9)	1.28 (0.12-7.13)	0.67
PVL	46 (30.7)	6 (17.7)	0.49 (0.15-1.31)	0.15
agr dysfunction	20 (13.3)	6 (17.7)	1.39 (0.42-4.03)	0.59

OR, odds ratio; CI, confidence interval; SD, standard deviation; N/A, not applicable; PPMC, Penn Presbyterian Medical Center; APRDRG, All Patient Refined-Diagnosis Related Group; ICU, intensive care unit; WBC, white blood cell count; hGISA, glycopeptide heterointermediate *Staphylococcus aureus*; PVL, Panton Valentine leukocidin; *agr*, accessory gene regulator.

[a] Data are presented as numbers (percentages) except where noted.

[b] ORs unavailable for continuous variables.

[c] Risk of patient death and severity of illness as based on DRG. The four subclasses are numbered sequentially from 1 to 4 indicating respectively, minor, moderate, major, or extreme risk of mortality or severity of illness.

$watermark-text

$watermark-text

$watermark-text

$watermark-text

$watermark-text

$watermark-text

Table 3

Final multivariable model of risk factors associated with in-hospital mortality in methicillin-resistant *Staphylococcus aureus* bacteremia

Variable	OR (95% CI)	*P* Value
APRDRG Risk of Mortality score[a]	5.33 (2.28-12.4)	<0.001
Malignancy	3.25 (1.17-9.02)	0.02
WBC count on culture date	1.09 (1.03-1.15)	0.002
SCC*mec* II	1.85 (0.69-4.92)	0.22
Neutropenia	4.52 (0.77-26.4)	0.09

OR, odds ratio; CI, confidence interval; APRDRG, All Patient Refined-Diagnosis Related Group; WBC, white blood cell count.

[a]Risk of patient death based on DRG. The four subclasses are numbered sequentially from 1 to 4 indicating respectively, minor, moderate, major, or extreme risk of mortality.