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Risk Factors for 30-Day Mortality in Patients with Methicillin-Resistant Staphylococcus aureus Bloodstream Infections

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SUMMARY

Objectives: Methicillin-resistant *Staphylococcus aureus* (MRSA) blood stream infections (BSI) are a major health care problem accounting for a large percentage of nosocomial infections. The aim of this study was to identify risk factors associated with 30-day mortality in patients with MRSA BSI.
Methods: This was a retrospective study performed in Southeast Michigan. Over a 9- year period, a total of 1,168 patients were identified with MRSA BSI. Patient demographics and clinical data were retrieved and evaluated using electronic medical health records.
Results: 30-day mortality during the 9-year study period was 16%. Significant risk factors for 30-day mortality were age, cancer, heart disease, neurologic disease, nursing home residence and Charlson score >3 with Odds Ratio (OR) of 1.03 (CI 1.02–1.04), 2.29 (CI 1.40–3.75), 1.78 (CI 1.20–2.63), 1.65 (CI 1.08–2.25), 1.66 (CI 1.02 – 2.70) and 1.86 (CI 1.18 – 2.95) correspondingly. Diabetes mellitus, peripheral vascular disease (PVD), and readmission were protective factors for 30-day mortality with OR of 0.53 (CI 0.36–0.78), 0.46 (CI 0.26–0.84) and 0.13 (CI0.05 – 0.32) respectively.
Conclusions: Our study identified significant risk factors for 30-day mortality in patients with MRSA BSI. Interestingly, diabetes mellitus, PVD and readmission were protective effects on 30-day mortality. There was no statistically significant variability in 30-day mortality over the 9-year study period.

Introduction

MRSA infection was first described in 1961 and continues to be a major public health concern, accounting for significant nosocomial and increasing community-acquired infections (Barber, 1961; Pastagia et al., 2012). From 1993 to 2009, septicemia related hospitalizations increased to 153 percent, adding to healthcare cost, up to 15.4 billion dollars (Elixhauser et al., 2011). Recent data show that the incidence is still increasing (Elixhauser et al., 2011). In the 2013 National Center for Health Statistics Report showed an overall decrease in mortality but an increase in bloodstream related deaths by 17% (Hall et al., 2013). In the 2010 National Healthcare Safety Network (NHSN) report on antimicrobial-resistant pathogens associated with healthcare infections, *S. aureus* was the most common pathogen reported, of which 54.6% were methicillin-resistant (Sievert et al., 2013). MRSA BSI can cause devastating complications with mortality reported up to 39% (Pastagia et al., 2012; Keynan and Rubinstein, 2013; Mansur et al., 2012; Wi et al., 2012; Lee et al., 2013; Gasch et al., 2013a). Identifying risk factors associated with mortality is essential to improving patient outcomes. Studies have shown that the most important factors determining patient outcomes in MRSA BSI are age, presence of comorbidities, and appropriate initial antibiotic treatment (Pastagia et al., 2012; Keynan and Rubinstein, 2013; Ok et al., 2013). This study aims to identify possible predictors of 30-day mortality in MRSA BSI patients and to evaluate changes in mortality rate over a 9 year period.

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Methods

Study Design and Patient Identification

This was a retrospective study performed at an integrated 4-hospital health system in southeast Michigan. The primary outcome of this study was 30-day all-cause mortality in patients with MRSA BSI. All patients ≥ 18 years of age with confirmed MRSA BSI were identified over a 9-year period, from July 2005 to June 2014, via review of microbiology laboratory records. Electronic medical health records were utilized to obtain clinical information, patient demographics and 30-day mortality. Thirty-day all cause mortality was defined as death within 30 days of index blood culture. Patient demographics and comorbidities included: age, gender, presence of immunosuppressive disease, cancer, heart disease, gastrointestinal (GI) disease, neurological disease, renal disease, diabetes mellitus, human immunodeficiency virus (HIV), neutropenia, solid organ transplant recipient, intravenous drug use (IVDA), peripheral vascular disease (PVD) and connective tissue disease. The following healthcare exposures were analyzed: prior hospitalization including admission to intensive care unit (ICU), recent surgery within the past 1 year, nursing home residence (NHR), and presence of indwelling central venous catheter (CVC). Source of acquisition was categorized as follows: CVC related, osteomyelitis, endocarditis, graft infection, skin or wound infections, intra-abdominal (IA), respiratory, urinary tract (UTI) or undetermined source. Duration of bacteremia and recurrence were evaluated. Recurrence was defined as positive blood culture within 30 days of completing treatment; duration of bacteremia was divided in 3 groups: ≤3 days, 4–6 days and ≥ 7 days. Patients with recurring positive blood cultures during one admission were included once. Readmission was defined as any infection-related readmissions within 30 days of completing therapy. The Charlson Comorbidity Index was calculated to compare patients' comorbidities and 30-day mortality (Charlson et al., 1987).

Statistical Analysis

Continuous data were described using means and standard deviations, while all categorical data were presented as counts and percentages. Five patients were excluded from the analysis because of incomplete data. Univariate two-group tests were performed to compare clinical and demographic data between patients who expired within 30 days from index blood culture with alive patients. All predictors of mortality with univariate P-value <0.2 were included in a multivariable logistic regression model. A final model was produced using manual backwards selection, meaning non-significant predictors were removed one by one in descending P-value order and the model re-run each time until each predictor remaining was significant. Variability in 30-day all-cause mortality over the 9-year study period was determined using

Table 1
Univariate and Multivariate Logistic Regressionn Analysis.

Predictor	Demographics and Clinical Characteristics	Univariate Logistic Regression			Multivariate Logistic Regression		
		Unadjusted OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
Age, years, mean(SD)	60.3 (17.6)	1.04	1.03-1.05	<**0.001**	1.03	1.02-1.04	<**0.001**
Gender, male	689 (59%)	1.13	0.83-1.55	0.4417			
Race							
African American	694 (60%)						
Caucasian	407 (35%)						
Other	56 (5%)						
Cancer	140 (12%)	2.73	1.84-4.07	<**0.0001**	2.29	1.40-3.75	**0.001**
Connective tissue	23 (2%)	1.12	0.38-3.36	0.8341			
CVC	127 (11%)	0.61	0.34-1.08	0.0913			
Diabetes	467 (40%)	0.75	0.54-1.04	0.0800	0.53	0.36-0.78	**0.0015**
Duration of bacteremia, days (SD)	3.9	1.32	0.78-2.23	0.3099			
GI disease	238 (20%)	1.06	0.73-1.55	0.7486			
Heart disease	329 (28%)	2.25	1.64-3.10	**0.0001**	1.78	1.20-2.63	**0.0039**
HIV	35 (3%)	0.30	0.07-1.26	0.1009			
Immunosuppressive disease	75 (6%)	1.83	1.06-3.15	**0.0306**			
IV drug use	206 (18%)	0.40	0.24-0.68	**0.0006**			
Neurologic disease	236 (20%)	2.44	1.73-3.43	**0.0001**	1.65	1.08-2.52	**0.02**
Neutropenia	13 (1%)	3.20	1.04-9.89	**0.0432**			
Nursing home resident	129 (11%)	2.67	1.77-4.02	<**0.0001**	1.66	1.02-2.70	0.0421
Prior hospitalization	597 (51%)	1.25	0.92-1.70	0.1599			
Prior ICU stay	183 (16%)	1.31	0.88-1.96	0.1876			
Prior surgery	102 (9%)	1.10	0.65-1.89	0.7165			
PVD	149 (13%)	0.66	0.39-1.11	0.1191	0.46	0.26-0.84	**0.0106**
Readmit infection	169 (14%)	0.13	0.05-0.33	<**0.0001**	0.13	0.05-0.32	<**0.001**
Recurrence 30d	84 (7%)	0.24	0.09-0.65	**0.0055**			
Renal disease	550 (47%)	1.29	0.95-1.76	0.1077			
Respiratory disease	208 (18%)	2.10	1.47-3.01	<**0.0001**			
Solid organ transplant	31 (3%)	1.79	0.79-4.05	0.1655			
Source: Graft	31 (3%)	1.22	0.49-3.01	0.6675			
Source: CVC	244 (21%)	0.63	0.41-0.96	**0.0316**	0.39	0.24-0.63	0.0001
Source: IE	0	N/A		N/A			
Source: IA	10 (1%)	2.18	0.56-8.52	0.2609			
Source: None	247 (21%)	1.91	1.36-2.70	**0.0002**			
Source: Respiratory	97 (8%)	2.26	1.41-3.62	**0.0007**			
Source: Skin/Wound	370 (32%)	0.51	0.35-0.75	**0.0005**	0.48	0.31-0.71	0.001
Source: GU	61 (5%)	1.14	0.58-2.24	0.6986	0.40	0.18-0.88	0.022
Source: Osteomyelitis	7 (1%)	0.00	0.001- > 999	0.9838			
Source: Endocarditis	106 (9%)	0.89	0.51-1.55	0.6779			
Charlson Score, N, mean (SD)	1154, 3.2 (2.4)	1.77	1.11-1.25	<**0.001**			
Charlson Score Category (> = 3 vs <3)		2.40	1.69-3.40	<**0.001**	1.86	1.18-2.95	**0.0079**

a chi-square test. All statistical analyses were completed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Over the 9-year period there were 1,168 individual patients with MRSA BSI, of which 193 (16%) expired within 30 days of index blood culture. Over the 9-year period there was no significant variability in 30-day mortality (p = 0.1934).

Results from univariate and multivariate logistic regression models evaluating the association between risk factors and 30-day mortality are shown in Table 1. The following risk factors were associated with increased risk of 30-day mortality: cancer OR 2.29 (CI 1.40-3.75 p value 0.001), heart disease OR 1.78 (CI 1.20-2.63 p-value 0.0039), neurologic disease OR 1.65 (CI 1.08-2.52 p-value 0.02), nursing home residence OR 1.66 (CI 1.02-1.70 p value 0.0421), and Charlson score >3 OR 1.88 (CI 1.19-2.97 p value 0.0068). Age was a statistically significant risk factor (p-value <0.001). The odds of 30-day mortality increased by 2.9% for every year increase in age when controlling for other variables. Diabetes, PVD, and readmission were protective factors for 30-day mortality with OR of 0.60 (CI 0.42-0.86 p-value 0.0056), 0.53 (CI 0.30 −0.93 p-value 0.0277), 0.12 (CI 0.05–0.30 p- value <0.001) respectively. There was a relationship between lower mortality and infection sources including CVC OR 0.39 (CI 0.24-0.63 p value 0.0001), skin/wound OR 0.48 (CI 0.31-0.71 p value 0.001) and GU OR 0.40 (CI 0.18-0.88 p value 0.022).

Discussion

Consequences of MRSA bacteremia are devastating with increase in hospital stay, morbidity, and mortality. Therefore, early identification of MRSA BSI is important to optimize patient outcomes (Lee et al., 2013; Gasch et al., 2013a; Bassetti et al., 2011; Hernandez et al., 2015; Gasch et al., 2013b). Prior studies have shown two modifiable risk factors for 30-day mortality: 1) appropriate empiric antimicrobial therapy, 2) prompt removal of focus (Keynan and Rubinstein, 2013; Lee et al., 2013; Gasch et al., 2013a; Ok et al., 2013). Notably, with time we found no improvement in overall mortality over time despite advancement in antimicrobial treatment. Thus far, the role of different antimicrobial agents against MRSA infection in clinical setting is uncertain.

The strength of this study is a large sample size with comprehensive clinical data over an extended period of time. Despite advances in medical therapy, use of newer antibiotics, and changes in patient characteristics and strains, we did not find any statistically significant change in the rate of 30-day mortality over the 9-year study period. Our study found 16.5% all cause 30-day mortality in MRSA BSI; this is lower than rates reported in other studies, which vary between 21–39% (Sievert et al., 2013; Wi et al., 2012; Gasch et al., 2013a; Ok et al., 2013; Gasch et al., 2013b).

Our study showed age and cardiac disease as risk factors for 30-day mortality which is consistent with findings in other studies (Pastagia et al., 2012; Mansur et al., 2012; Ok et al., 2013; Gasch et al., 2013b). A study evaluating outcomes in patients over 65 year of age with community onset bacteremia found 52 out of 2,065 (2.51%) patients with MRSA BSI. Although the most common pathogen isolated was *Escherichia coli*, MRSA had the highest mortality (28%). Mortality was significantly higher in patients over 75 year of age, and administration of inappropriate antibiotic treatment (Gasch et al., 2013b). This stresses the importance of identifying these patients early in order to improve their outcomes. Our analysis found that nursing home residence increased the risk of 30 day mortality, which is likely due to advanced age and increased number of comorbidities.

Contrary to other studies, we found that cancer was a significant risk factor for 30-day mortality with an OR of 2.84 (1.82–4.44 p-value <0.001). Various studies have reported that the presence of a previous rapid fatal underlying disease is an important risk factor, but only one study analyzed cancer as an independent risk factor which was not statistically significant (Lee et al., 2013; Ok et al., 2013; Gasch et al., 2013b). Cancer, as well as other conditions, is included in the Charlson weighted index of comorbidity score. Although it can be a good tool that can help clinicians identify patients who are at increased risk for early mortality due to MRSA BSI, other factors such as source of acquisition are not included (Retamar et al., 2012; Lesens et al., 2003; Charlson et al., 1987).

Another study found that persistent bacteremia (defined as positive blood cultures >7 days) had greater mortality than non-persistent bacteremia 58.1% vs. 16.2% (p-value <0.001) (Hernandez et al., 2015). However, our study did not find duration of bacteremia to be a statistically significant risk factor for 30-day mortality. All other risk factors that were evaluated including presence of immunosuppressive disease, GI disease, renal disease, diabetes, HIV status, neutropenia, solid organ transplant recipient, IVDA, connective tissue disease, ICU stay, and prior surgery were not significantly associated with 30-day mortality. Continuous observation of patients with MRSA BSI is essential to improve our understanding of risk factors associated with 30-day mortality.

In our study diabetes and PVD were protective factors for 30-day mortality in patients with MRSA BSI. Other studies included diabetes in their evaluation of risk factors, finding them to be protective factors, though only one found it to be statistically significant (Pastagia et al., 2012; Lee et al., 2013; Gasch et al., 2013a). This is an unexpected finding, but we believe that it can be associated with the source of infection. Patients with PVD and diabetes are usually less acutely ill and present with skin/wound infections which are more easily managed, and started earlier on appropriate antibiotic treatment. There has been recent research on hypoxia inducible factor 1 (HIF-1) playing an important role in the innate response to infections (Bento and Pereira, 2011; Shalova et al., 2015). HIF-1 is a transcription factor that is involved in energy metabolism, cellular adaptation to hypoxia, and immune response. Recent studies have shown that hyperglycemia destabilizes HIF-1, which could contribute to diabetic complications such as infections (Bento and Pereira, 2011; Howangyin and Silvestre, 2014). T. Bhandari et al and other groups are conducting research into the possibility of having HIF-1 as a therapeutic target, which would provide increased treatment options to patients with BSI (Bhandari and Nizet, 2014; Okumura et al., 2012; Zeitouni et al., 2016; Li et al., 2014).

We also found that readmission due to infection is a protective factor. The reason of this was not determined, however, patients who were readmitted because of MRSA infection would have probably received an earlier and better management, which may have prevented progression of disease, resulting in a decreased mortality. Source of infection is an important mortality risk factor. Our study found that skin/wound, GU, and CVC source of infection are protective factors for 30-day mortality. Further studies are needed in order to understand the causality of these relationships.

A limitation of this study was that we did not have access to information regarding ID consultation. All patients with MRSA bacteremias were treated with vancomycin or daptomycin, but we do not have information regarding timing of initial treatment. Further studies are needed to evaluate the effects of appropriate initial antibiotic treatment in high risk patients such as patients with cancer, heart and neurologic disease. We did not include MRSA strain types and vancomycin MICs as factors in our analysis.

Conclusions

During the 9-year study period we did not find any statistically significant variability in 30-day mortality. Our study showed that age, cancer, heart disease, neurologic disease, nursing home residence and Charlson score greater than 3 are risk factors for 30-day mortality in patients with MRSA BSI. These findings can help clinicians correlate patient risk factors with poor outcomes and provide early optimal management, including removal of devices, focus or other modifiable risk factors. Further prospective studies are needed to examine this subset of patients, in order to design interventions that can improve outcomes. We found that diabetes, PVD and readmission were statistically significant protective factors for 30-day mortality, though we believe that this is due to the source and severity of infection. Continuous surveillance of patients with multidrug resistant organism infections is essential for our health care system.

Conflicts of interest

M. Z. has received research grants from Pfizer, Cerexa, Cubist, Merck, Tetraphase, Melinta, Paratek and Rempex and Cempra. K.R. has received research grant from Cubist, Merck and Theravance. All other authors have nothing to declare.

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