EPIDEMIOLOGY, CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES OF HEALTHCARE-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* BLOODSTREAM INFECTIONS AT CHIANG MAI UNIVERSITY HOSPITAL: A RETROSPECTIVE STUDY

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Abstract. The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) varies widely by region and healthcare setting. The prevalence of MRSA among *S. aureus* bloodstream infections increased from 23% in 2007 to 43% in 2011 at our hospital. We conducted this retrospective study among patients with MRSA to determine mortality rate of MRSA bloodstream infections (BSIs) and the risk factors for death in those patients at Chiang Mai University Hospital from January 1, 2007 to December 31, 2011. One hundred seventy-nine patients with 184 episodes of MRSA BSIs were enrolled. Ninety-eight patients (54.8%) were male and the mean age was 53.4±25.3 years. The median length of time from admission to diagnosis was 27.5 days (IQR 15, 43.5). One-hundred six patients had BSI with other sites of infection: pneumonia (78 episodes, 42.4%), skin and soft tissue infections (15 episodes, 8.2%), urinary tract infections (13 episodes, 7.1%) and infective endocarditis (4 episodes, 2.2%). The mortality rate was 53.1% (95 patients). Risk factors for death on multivariate analysis were: concurrent pulmonary infection (OR 2.65; 95% CI: 1.27-5.51, p=0.009), having a central venous catheter (OR 8.85; 95% CI: 2.31-33.88, p=0.001), having a urinary catheter (OR 8.52; 95% CI: 2.60-27.89, $p < 0.001$) and having a prothrombin time longer than 1.5 times the upper limit of normal (OR 3.85; 95% CI: 1.68-8.81, p=0.001). MRSA bloodstream infections caused significant mortality particularly among those patients with concurrent pulmonary infections.

Keywords: healthcare-associated infection, methicillin-resistant *Staphylococcus aureus*, bloodstream infections, epidemiology, outcome

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important drug-resistant gram-positive organism in the healthcare setting. Similar to methicillin-sensitive *Staphylococcus aureus* (MSSA), the

clinical manifestations can range from localized infections, such as skin and soft tissue infections, to serious bloodstream infections (Moreillon *et al*, 2005). The prevalence of healthcare-associated MRSA (HA-MRSA) infection varies widely and depends on the region and healthcare setting. The prevalence ranges from 34.2% in the US to 70% in Japan and Hong Kong (Washio *et al*, 1997; O'Donoghue *et al*, 2004; Ferry and Etienne, 2007; Goff and Dowzicky, 2007; Nimmo *et al*, 2007; Kramer *et al*, 2010; Santos *et al*, 2010). Data from the US shows invasive MRSA infections in the healthcare setting are declining, particularly bloodstream infections between 2005 and 2008 (Landrum *et al*, 2012). In Thailand, the National Antimicrobial Resistance Surveillance Center Thailand (NARST) has reported the prevalence of MRSA among bloodstream infections (BSIs) caused by *Staphylococcus aureus* to be between 16.0% and 25.0% during 2006-2010 (NARST, 2013). At Chiang Mai University Hospital, the proportion of MRSA infections among *S. aureus* BSIs increased from 23% in 2007 to 43% in 2011 (unpublished data).

The mortality rate from MRSA BSIs ranges from 32% to 70% (Naves *et al*, 2012; Gasch *et al*, 2013). Some studies have reported significant higher mortality rates compared to MSSA bloodstream infections (Laupland *et al*, 2008; de Kraker *et al*, 2011) while others reported no difference (Ponce-de-Leon *et al*, 2010; Naves *et al*, 2012). The objective of this study was to determine the mortality rate due to HA-MRSA bloodstream infections at Chiang Mai University Hospital and to determine the risk factors for death in those patients.

MATERIALS AND METHODS

This retrospective study was conducted among patients who had positive blood cultures for MRSA between January 1, 2007 and December 31, 2011 at Chiang Mai University Hospital, a 1,500 bed tertiary-care hospital in northern Thailand. A MRSA bloodstream infection was considered healthcare-associated if the patient met one of the following criteria: 1) hospitalized for ≥48 hours with current admission, 2) hospitalized for ≥48 hours during the preceding 90 days, 3) having undergone chronic dialysis during the previous 30 days, 4) being a resident in a nursing home or extended care facility or 5) having been colonized with MRSA (American Thoracic Society and Infectious Diseases Society of America, 2005; CDC, 2013).

Clinical data were collected from the hospital medical records using a preprinted data collection form.

Microbiological methods

All bacterial identification and susceptibility procedures were performed at the diagnostic laboratory, Chiang Mai University Hospital. *S. aureus* was identified by routine biochemical tests. Antimicrobial susceptibility tests were performed by agar disk diffusion method according to the Clinical and Laboratory Standard Institute (CLSI) (CLSI, 2007). Susceptibility testing to oxacillin, vancomycin, trimethoprim-sulfamethoxazole, erythromycin and clindamycin was performed. The MIC for vancomycin was not routinely performed at our hospital during the study period.

Cases were counted as episodes of infection. Blood cultures obtained from the same patient at different times were counted twice if a second episode of bacteremia occurred at least 4 weeks after the initial infection and MRSA clearance was documented after the first episode.

This study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University.

Statistical analysis

Clinical data were presented in numbers (%), means, standard deviations (SD), medians and interquartile ranges (IQR) where appropriate. Comparisons of demographic data and clinical characteristics between those who survived and those who died were made using the Student's *t*-test, Mann-Whitney *U* test, chi-square test or Fisher's exact test where appropriate. Univariate logistic regression analysis was performed to determine predictors of fatal outcomes. Variables with a *p*-value <0.10 on univarate analysis were then tested in a multivariate model. A two-tailed test with a significance level of $p < 0.05$ was used to determine statistical significance. All statistical analyses were performed using Stata statistical software version 10.0 (Stata Statistical Software: Release 10.0, Stata Corporation, College Station, TX).

RESULTS

Demographic data

One-hundred seventy-nine patients having 184 episodes of HA-MRSA infection were identified during the 5-year study period; the numbers of episodes during 2007, 2008, 2009, 2010 and 2011 were 24, 33, 38, 40, and 49, respectively. The prevalences of MRSA among *S. aureus* bacteremia isolates were 23%, 32%, 40%, 36% and 43% during 2007, 2008, 2009, 2010 and 2011, respectively (*p*-value for trend=0.072). Of the 179 patients, 98 (54.8%) were male and the mean age was 53.4±25.3 years (range 4 months-93 years). One hundred thirty-eight patients (77.1%) had underlying diseases or conditions including malignancy (41 patients, 22.9%), cardiovascular disease (40 patients, 22.3%), neurological disease (36 patients, 20.1%), chronic kidney disease (32 patients, 17.9%), current corticosteroid use (30 patients, 16.8%), diabetes (28 patients, 15.6%), chronic obstructive pulmonary disease (12 patients, 6.7%), connective tissue disease (10 patients, 5.6%) and cirrhosis (7 patients, 3.9%).

Clinical data

Patients were admitted to a medical unit (96 episodes, 51.2%), surgical unit (64 episodes, 34.8%), pediatrics unit (15 episodes, 8.2%), orthopedics unit (4 episodes, 2.2%), otolaryngology unit (4 episodes, 2.2%) and a gynecology unit (1 episode, 0.5%). One hundred thirty-seven patients (74.5%) were admitted to intensive care units (ICUs). One-hundred fifty-six patients had been hospitalized for ≥ 48 hours, 27 patients had a history of being hospitalization for ≥ 48 hours during the previous 90 days and 1 patient had a history of MRSA colonization. The median duration of hospitalization of the 156 patients with blood cultures before they became positive was 27.5 days (IQR 15, 43.5).

One-hundred six episodes of HA-MRSA BSIs (58.6%) also had infections at other sites: pneumonia (78 episodes, 42.4%), skin and soft tissue infections (15 episodes, 8.2%), urinary tract infections (13 episodes, 7.1%), infective endocarditis (4 episodes, 2.2%) and 2 episodes (1.1%) each for bone and joint infections, peritonitis and cholangitis. At the time of diagnosis, all patients had one or more medical devices inserted: a peripheral intravenous catheter (184 episodes, 100%), a central venous catheter (140 episodes, 76.1%), an arterial line (41 episodes, 22.3%), a double lumen venous catheter (39 episodes, 21.2%), an umbilical arterial

Table 1
The distribution of site of infections by survival status.

Site of infections	Survive (*n*=84) *n* (%)	Death (*n*=63) *n* (%)	Refused treatment (*n*=32) *n* (%)
Primary bloodstream infections (BSIs)	47 (56.0)	17 (27.0)	12 (37.5)
BSIs and pneumonia	21 (25.0)	39 (61.9)	16 (50.0)
BSIs and skin and soft tissue infections	9 (10.7)	4 (6.4)	1 (3.1)
BSIs and urinary tract infections	8 (9.5)	3 (4.8)	2 (6.3)
BSIs and spontaneous bacterial peritonitis	0	1 (1.6)	1 (3.1)
BSIs and infective endocarditis	1 (1.2)	2 (3.2)	1 (3.1)
BSIs and cholangitis	1 (1.2)	1 (1.6)	0 (0)
BSIs and bone and joint infections	2 (2.4)	0	0

catheter (9 episodes, 4.9%), an orogastric or nasogastric tube (160 episodes, 87.0%), a jejunostomy tube (12 episodes, 6.5%), an endotracheal or tracheostomy tube (151 episodes, 82.1%) or a urinary catheter (151 episodes, 82.1%). In the majority of episodes (181 patients, 98.4%), an antimicrobial agent had been prescribed during the 72 hours prior to obtaining the positive blood culture.

The clinical manifestations of patients with HA-MRSA BSIs included: fever (184 episodes, 98.9%), cough or dyspnea (77 episodes, 41.9%), myalgias (34 episodes, 18.5%), back pain (27 episodes, 14.7%), altered consciousness (24 episodes, 13.0%), headache (20 patients, 10.7%), and arthritis (3 episodes, 1.6%).

MRSA isolates were sensitive to vancomycin (181/181, 100%), erythromycin (6/184, 3.3%), clindamycin (6/176, 3.4%) and trimethoprim/sulfamethoxazole (27/179, 15.1%).

Mortality

Of the five patients with two episodes of MRSA bloodstream infection, mortality during the second episode was counted. In total, 63 patients died, giving an all-cause in-hospital mortality of 35.2%. Thirty-two patients had no clinical improvement and finally refused treatment, 84 patients had clinical improvement, defined as defervescence of fever and resolution of signs and symptoms of infection. The sites of infection by survival status are shown in Table 1. The median times to death or discharge after the diagnosis of MRSA were 25.5 days (IQR 11, 43.5), 11 days (IQR 3, 30), and 14.5 days (IQR 6, 20), in those who survived, died and refused treatment, respectively.

Factors predicting a fatal outcome

Sixty-three patients died. Another 32 patients refused further treatment and requested discharge in a terminally ill state against medical advice. Therefore, a total of 95 patients are assumed to have died from MRSA BSIs. Comparisons of the characteristics among patients who survived and who died are shown in Tables 2 and 3. Patients who died were more likely to be older, had more frequent concurrent pulmonary infections, lower platelet counts, higher creatinine levels and longer prothrombin times. Those who died were also more likely to have a medi-

Table 2
Comparison of demographic characteristics among patients who survived and who died.

Variables	Patients who survived (*n*=84) *n* (%)	Patients who died (*n*=95) *n* (%)	*p*-value
Male	48 (57.1)	50 (52.6)	0.552
Age in years (median, IQR)	50 (24,69)	65 (48,76)	<0.001
Presence of underlying disease	60 (71.4)	78 (82.1)	0.109
Medical instruments in place			
Central venous catheter/ arterial lines	60 (71.4)	93 (97.9)	<0.001
Enteral feeding	63 (75.0)	94 (99.0)	<0.001
Endotracheal or tracheostomy tube	58 (69.1)	89 (93.7)	<0.001
Urinary catheter	56 (66.7)	90 (94.7)	<0.001
Intensive care unit admission	50 (59.5)	84 (88.4)	<0.001
Units			<0.001
Medicine	36 (42.9)	58 (61.1)	
Surgery	31 (36.9)	32 (33.7)	
Gynecology	0	1 (1.1)	
Pediatrics	12 (14.3)	3 (3.2)	
Orthopedics	3 (3.6)	0	
Otolaryngology	2 (2.4)	1 (1.1)	
Hospitalization within previous 3 months	79 (94.1)	85 (89.5)	0.295
Median (IQR) duration of hospitalization prior to positive blood cultures (hours)	20 (8.5,33.5)	22 (10,43)	0.205

Data are presented in number (%), mean±standard deviation, and median (IQR).

cal device in place (*eg*, a central venous catheter, enteral tubing, endotracheal or tracheostomy tube or urinary catheter), to be admitted to an ICU or medical unit, and to be receiving β-lactams within 72 hours prior to diagnosis.

Multivariate analysis showed factors associated with mortality included concurrent pulmonary infections (OR 2.65; 95% CI: 1.27-5.51 p=0.009), having a central venous catheter (OR 8.85; 95% CI: 2.31-33.88, p=0.001), 3), having a urinary catheter in place (OR 8.52; 95% CI: 2.60-27.89, p<0.001), and having a prothrombin time greater than 1.5 times the upper limit of normal (OR 3.85; 95% CI: 1.68-8.81, p=0.001).

DISCUSSION

HA-MRSA is a serious drug-resistant bacteria causing morbidity and mortality worldwide, but the incidence of HA-MRSA has decreased since 2005 in the US, Scotland, and Spain (Freixas *et al*, 2012; Landrum *et al*, 2012; Lawes *et al*, 2012). This study highlights the significant morbidity and mortality of HA-MRSA at a tertiary care hospital in northern Thailand. The prevalence of HA-MRSA among *S. aureus* BSIs increased during the study period, although this increase did not reach statistical significance. As people live longer in the era of more sophisticated medical technologies and

Table 3
Comparison of clinical characteristics and laboratory data among patients who survived and who died.

Variables	Patients who survived (*n*=84) *n* (%)	Patients who died (*n*=95) *n* (%)	*p*-value
Signs and symptoms			
Body temperature > 38°C	83 (98.8)	94 (99.0)	1
Headache	8 (9.5)	9 (9.5)	1
Muscle ache	14 (16.7)	19 (20.0)	0.7
Cough/dyspnea	27 (32.1)	47 (49.5)	0.023
Alteration of consciousness	9 (10.7)	14 (14.7)	0.505
Other concurrent infections			
Skin and soft tissue infections	9 (10.7)	5 (5.3)	0.264
Urinary tract infections	8 (9.5)	5 (5.3)	0.388
Pneumonia	21 (25.0)	55 (57.8)	<0.001
Laboratory findings			
Hemoglobin (g/dl)	11.0 ± 3.1	10.5 ± 2.9	0.214
White blood cell count (x 1,000 cells/mm^3)	11.2 (7.5, 17.7)	11.1 (7.4, 16.0)	0.483
Platelet (x1,000/mm^3)	262 (172, 398)	220 (93, 318)	0.012
Creatinine (mg/dl)	1.1 (0.7,1.6)	1.4 (0.9,2.9)	0.003
Albumin (mg/dl)	2.6 (1.9, 2.9)	2.6 (1.9,3.1)	0.529
Alanine Aminotransferase (U/l)	22 (14,43)	31 (15, 54)	0.076
Prothrombin time (min)	12.9 (11.7,14.5)	15.0 (12.9,18.8)	<0.001
Antimicrobials within 72 hours of positive hemocultures	69 (82.1)	81 (85.3)	0.685
β-lactams	69 (82.1)	63 (66.3)	0.018
Clindamycin	7 (8.3)	5 (5.3)	0.552
Vancomycin	3 (3.6)	3 (3.2)	1
Received vancomycin therapy	62 (73.8)	69 (72.6)	0.868
Median (IQR) duration after positive hemoculture until receiving appropriate antibiotics (hours)	2 (1,3)	1 (0,3)	0.228
Median (IQR) length of hospital stay after diagnosis of MRSA BSIs (days)	25.5 (11, 43.5)	13 (4, 25)	<0.001

Data are presented in number (%), mean±standard deviation, and median (IQR).

broad-spectrum of antimicrobials, more people are at risk for infection caused by multidrug-resistant pathogens while hospitalized.

The demographic data of patients with HA-MRSA BSI in this study are similar to those of previous reports (Law and Gill, 1988; Mekviwattanawong *et al*, 2006; Bishara *et al*, 2012; Casey *et al*, 2013). All our patients had a medical device present, such as a peripheral intravenous catheter, urinary catheter, enteral tubing, endotracheal/tracheostomy tube or a central venous catheter.

Sixty percent of patients had a concurrent infection at another site, of which pneumonia was the most common (41.9%). However, since this was a retrospective study it was not possible to clearly define whether pneumonia was secondary to bacteremia or if bacteremia followed pneumonia. The majority of patients in this study were admitted to a medical ward. They had underlying medical conditions and medical procedures performed, which may have put them at increase risk for infection (Mekviwattanawong *et al*, 2006). All the clinical isolates in this study were sensitive to vancomycin, however the MIC for vancomycin is not routinely performed.

The mortality rate from this study (53.1%) is similar to that of other reports which range from 40.2 to 63.4% (Mekviwattanawong *et al*, 2006; Bishara *et al*, 2012; Castillo *et al*, 2012). Similar to other reports, risk factors for death included concurrent pneumonia, having a central venous or urinary catheter or having a prothrombin time > 1.5 times the upper limit of normal (Carnicer-Pont *et al*, 2006; Bishara *et al*, 2012). Other factors related to fatal outcome reported in other studies but not in this study included female sex (Bishara *et al*, 2012; Castillo *et al*, 2012), old age (Bishara *et al*, 2012; Castillo *et al*, 2012), receiving corticosteroids (Bishara *et al*, 2012), ICU admission (Castillo *et al*, 2012), mechanical ventilation (Law and Gill, 1988), hypoalbuminemia (Bishara *et al*, 2012), high blood urea nitrogen (Bishara *et al*, 2012), and receiving inappropriate antimicrobial therapy (Castillo *et al*, 2012). In conclusion, HA-MRSA bloodstream infections caused high morbidity and mortality in this study, particularly in patients with concurrent pneumonia. Appropriate, timely treatment might help decrease morbidity and mortality in these patients.

This study had several limitations. First, this was a retrospective study which might have missing data, such as the vital status and cause of death of patients who refused treatment against medical advice, which may lead to misinterpretation of the results. Secondly, there is no data of the severity of illnesses, such as an APACHE II score. This may also lead to misinterpretation of the results. However, it may be assumed patients admitted to the ICU had higher severity scores than those who were not. Thirdly, MICs for vancomycin and serum vancomycin trough levels were not determined. This made it difficult to interpret whether mortality was associated with underdosing of the antibiotic. Lastly, the number of patients may not have been large enough to capture all the risk factors for death.

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