# EPIDEMIOLOGY OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* BLOODSTREAM INFECTION AT MAHARAJ NAKORN CHIANG MAI HOSPITAL, CHIANG MAI UNIVERSITY, CHIANG MAI, THAILAND (2013-2017)

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**Abstract.** Bloodstream infection (BSI) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with significant high prevalence of morbidity and mortality. In order to determine mortality risk factors, clinical characteristics of nosocomial MRSA BSI at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Thailand from January 2013 to December 2017 were gathered including minimal inhibitory concentration (MIC) of vancomycin against MRSA isolates. Of 84 patients, 63% were male, median age (interquartile range) was 68.5 years (56, 79 years) and 69% had MRSA bloodstream infection together with other co-morbidities, namely (in decreasing order of frequency), pneumonia (43%), skin and soft tissue infections (25%), osteomyelitis (11%), arterial graft infection (6%), infective endocarditis (6%), septic arthritis (6%), and urinary tract infection (3%). Percent patients with vancomycin MIC ≥1.5 mg/l were 68, 62, 47, 27, and 75% in 2013, 2014, 2015, 2016, and 2017, respectively. Overall mortality rate was 64%, with significant associated factors being ≥40 years of age (odds ratio (OR) = 11.35, 95% confidence interval (CI): 1.35-95.78), alteration of consciousness (OR = 11.19, 95% CI: 2.83-44.18) and concurrent pneumonia (OR = 4.44, 95% CI: 1.09-18.14), but there is no significant difference in mortality between those infected with MRSA with vancomycin MIC <1.5 and ≥1.5 mg/l. In conclusion, pneumonia was the most common concurrent infection and increased mortality. As half of the patients had clinical isolates with vancomycin MIC≥1.5 mg/l, careful monitoring of vancomycin MIC creep is crucial for appropriate antibiotic and dose selection.

**Keywords:** methicillin-resistant *Staphylococcus aureus*, bloodstream infection, epidemiology, minimum inhibitory concentration, mortality risk factor, vancomycin

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## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) is associated with significant morbidity and mortality (Cosgrove *et al*, 2003). Of 191,460 *S. aureus* isolates from 427 global centers collected by SENTRY antimicrobial surveillance program from 1997 to 2016, prevalence of MRSA *S. aureus* ranges from 26.8% in Europe and 47.0% in North America, while in the Asia-Pacific region, including Thailand, prevalence is 39.6% (Diekema *et al*, 2019). Among nosocomial *S. aureus* BSI, frequency of MRSA ranged from 37.8 to 45.3% (Diekema *et al*, 2019); in Thailand, during 2005-2006 prevalence of MRSA *S. aureus* in university hospitals (King Chulalongkorn Memorial Hospital, the Thai Red Cross Society and Siriraj Hospital, Mahidol University, Bangkok) is 57% (Song *et al*, 2011) and in Chiang Mai University Hospital from 2007 to 2011 prevalence is 23-43% (Chaiwarith *et al*, 2014).

Vancomycin is the mainstay treatment for MRSA; patients with MRSA BSI have successful treatment outcome if vancomycin MIC is ≤0.5 mg/l (Sakoulas *et al*, 2004) but have poor clinical outcome when vancomycin MIC is ≥1.5 mg/l (Lodise *et al*, 2008; van Hal *et al*, 2012; Jacob and DiazGranados, 2013). However, infections of MRSA with reduced susceptibility to vancomycin have been reported worldwide (Hiramatsu *et al*, 1997; Tenover *et al*, 1998; Van Griethuysen *et al*, 2003; Spagnolo *et al*, 2014), including in Thailand (Trakulsomboon *et al*, 2001). Treatment failure involving vancomycin with MIC ≤2 mg/l have been increasingly reported (Moise and Schentag, 2000; Howden *et al*, 2004; Soriano *et al*, 2008)

Here, in order to identify mortality risk factors of nosocomial MRSA BSI at Maharaj Nakorn Chiang Mai Hospital, we collected clinical characteristics of nosocomial MRSA BSI, mortality rate, and vancomycin MIC during 2013-2017. The findings should assist in developing appropriate treatment strategy to reduce mortality of MRSA BSI in face of reduced susceptibility of the organism to vancomycin.

## MATERIALS AND METHODS

### Study design and population

A retrospective study was conducted at the Maharaj Nakorn Chiang Mai Hospital, a 1400-bed, Chiang Mai University affiliated hospital in northern Thailand between January 2013 and

December 2017. Inclusion criteria were patients ≥18 years of age with nosocomial MRSA BSI. Nosocomial infection is defined as that in patients who received antimicrobial therapy in the preceding 90 days, hospitalized for ≥2 days in the preceding 90 days and underwent chronic dialysis in the preceding 30 days (American Thoracic Society and Infectious Diseases Society of America, 2005).

Study protocols were approved by the Faculty of Medicine Ethical Committee, Chiang Mai University (approval no. MED-2561-05488). Prior written informed consent was not obtained as existing data were collected retrospectively.

**Microbiological assays**

Bacterial identification and antimicrobial susceptibility testing were performed at the Microbiology Unit, Diagnostic Laboratory, Maharaj Nakorn Chiang Mai Hospital. *S. aureus* was identified by conventional biochemical tests (Bannerman and Peacock, 2007). *S. aureus* isolates were tested using a disk diffusion method following the Clinical and Laboratory Standards Institute (CLSI) guidelines, M02-A12 (CLSI, 2015) against four antibiotics, namely, erythromycin (15 μg), clindamycin (2 μg), oxacillin (30 μg cefoxitin as a surrogate drug), with a zone diameter ≥22 mm interpreted as methicillin-susceptible (MS) and ≤21 mm as methicillin-resistant (MR), and trimethoprim/sulfamethoxazole (1.25μg/23.75μg), (Becton, Dickinson and Company, Franklin Lakes, NJ). Vancomycin MIC of MRSA isolates from blood cultures was determined by E-test strip (BioMerioux, Marcy l'Etoile, France). MRSA can be categorized into three groups, namely, vancomycin-susceptible SA (VSSA) (MIC ≤2 mg/l), vancomycin-intermediate resistant SA (VISA) (MIC 4-8 mg/l), and vancomycin-resistant SA (VRSA) (MIC ≥16 mg/l) (CLSI, 2015).

**Statistical analysis**

Data are presented as number (%), mean ± SD), or median and interquartile range (IQR) as appropriate. Characteristics among groups were compared using Student's t-test, Mann-Whitney U test, Chi-square test or Fisher's exact test as appropriate. Factors associated with mortality were analyzed using a univariate logistic regression model and those with a *p*-value <0.10 were then tested using a multivariate logistic regression model employing a backward stepwise procedure. A two-sided test with a *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using a Stata statistical software version 10.0 (Stata Corp, College Station, TX).

## RESULTS

**Demographics and clinical history of patients**

Among BSI patients ($n$ = 84) at Maharaj Nakorn Chiang Mai Hospital

enrolled in the study from 2013 to 2017, 63% were male, median age (interquartile range (IQR)) was 68 years (56, 79) and over three quarters had underlying diseases, mainly hypertension and chronic kidney disease (Table 1). The number of patients enrolled in each calendar year was 22, 16, 19, 15, and 12, respectively. Patients were mainly admitted to general internal medicine ward ($n$ = 26) but 24 patients were in intensive care units (ICUs) when the blood samples were taken for culture (Table 1). In the preceding three months a little over half of the patients had been admitted to a hospital and over three quarters had been prescribed antibiotics, meropenem being the most frequent, followed by piperacillin/tazobactam, then ceftriaxone, and colistin.

**Clinical characteristics**

Prevalence of nosocomial MRSA was 33, 23, 27, 19, and 15% in 2013, 2014, 2015, 2016, and 2017, respectively. Each enrolled patient had single episode of MRSA BSI, 69% of whom with concurrent infection at other sites, most frequent being pneumonia, followed by skin and soft tissue infections (Table 2). There were five patients with concurrent infection at two sites: two patients with skin and soft tissue infection and infective endocarditis, and one patient each with skin and soft-tissue infection and osteomyelitis, septic arthritis and arterial graft infection, and pneumonia and urinary tract infection. Over three-quarters of the patients were fitted with medical devices, mostly central venous catheter (Table 2). Nearly three-fourths of the patients experienced fever (≥38.0°C), ~10% with hypotension (<90/60 mm Hg) and over half presenting with alterations of consciousness. Results of blood laboratory tests are described in Table 2.

**MRSA drug susceptibility**

All MRSA isolates were susceptible to vancomycin with the MIC ranging from 0.5-2 mg/l (Table 2). Percent of patients with vancomycin MIC ≥1.5 mg/l was 67, 62, 44, 27, and 72% from 2013 to 2017, respectively (Fig 1). Three patients had missing vancomycin MIC, one in year 2013, 2015 and 2017, respectively. Sixty-three (75%) MRSA isolates were susceptible to trimethoprim/sulfamethoxazole, four (5%) to erythromycin and 3 (4%) to clindamycin.

**Treatment, outcome and mortality risk factors of MRSA BSI patients**

MRSA BSI patients ($n$ = 79) received antibiotics treatment for a median (IQR) of 13 days (12, 21): 72 (86%) treated with vancomycin intravenously to maintain vancomycin trough concentration of 15-20 mg/l, five (6%) with linezolid 1200 mg/day intravenously in 2 divided doses, and two (2%) with fosfomycin 12 g/day in 3 divided doses with dose adjustment according to creatinine clearance. Median time (IQR) from positive blood culture to receipt of antibiotic was one day (0, 3 days).

Table 1

Demographics, prior medical history and outcome of patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai, Thailand (January 2013 - December 2017)

| Characteristic | Out of a total 84 patients *n* (%)* | Out of 30 patients recovered *n* (%)* | Out of 54 mortalities *n* (%)* | *p*-value |
|---|---|---|---|---|
| Gender, male | 53 (63) | 19 (63) | 34 (63) | 0.973 |
| Age, years, median (interquartile range) | 68 (56, 79) | 63 (54, 72) | 74.5 (61, 83) | 0.004 |
| Presence of underlying disease | 72 (86) | 25 (83) | 47 (87) | 0.748 |
| Hypertension | 32 (38) | 11 (37) | 21 (39) | 0.841 |
| Chronic kidney disease | 31 (37) | 16 (53) | 15 (28) | 0.020 |
| Diabetes mellitus | 16 (19) | 9 (30) | 7 (13) | 0.062 |
| Dyslipidemia | 14 (17) | 6 (20) | 8 (15) | 0.541 |
| Malignancy | 14 (17) | 4 (13) | 10 (19) | 0.541 |
| Chronic obstructive pulmonary disease | 8 (9) | 2 (7) | 6 (11) | 0.705 |
| Cerebrovascular accident | 8 (9) | 3 (10) | 5 (9) | 1.000 |
| Valvular heart disease | 6 (7) | 1 (3) | 5 (9) | 0.414 |
| Dilated cardiomyopathy | 5 (6) | 1 (3) | 4 (7) | 0.651 |
| Coronary artery disease | 5 (6) | 1 (3) | 4 (7) | 0.651 |
| History of surgery of aortic arterial aneurysm | 4 (5) | 2 (7) | 2 (4) | 0.614 |
| Bronchiectasis | 1 (1) | 0 (0) | 1 (2) | 1.000 |
| Human immunodeficiency virus | 1 (1) | 0 (0) | 1 (2) | 1.000 |

Table 1 (cont)

| Characteristic | Out of a total 84 patients *n* (%)* | Out of 30 patients recovered *n* (%)* | Out of 54 mortalities *n* (%)* | *p*-value |
|---|---|---|---|---|
| Prior hospitalization during previous three months | 45 (54) | 15 (50) | 30 (56) | 0.625 |
| Antibiotic treatment during prior three months | 73 (87) | 25 (83) | 48 (89) | 0.511 |
| Beta-lactam antibiotic | | | | |
| Cloxacillin | 5 (6) | 4 (13) | 3 (6) | 0.242 |
| Ampicillin | 3 (4) | 1 (3) | 2 (4) | 1.000 |
| Amoxicillin/clavulanate | 3 (4) | 1 (3) | 3 (6) | 1.000 |
| Piperacillin/tazobactam | 25 (30) | 3 (10) | 22 (41) | 0.003 |
| Cefazolin | 3 (4) | 2 (7) | 1 (2) | 0.289 |
| Ceftriaxone | 23 (27) | 6 (20) | 17 (32) | 0.258 |
| Ceftazidime | 6 (7) | 3 (10) | 3 (6) | 0.662 |
| Cefoperazone/sulbactam | 2 (2) | 0 (0) | 2 (4) | 0.286 |
| Ertapenem | 7 (8) | 4 (13) | 3 (6) | 0.242 |
| Imipenem/cilastatin | 5 (6) | 2 (7) | 3 (6) | 1.000 |
| Meropenem | 37 (44) | 11 (37) | 26 (48) | 0.310 |

Table 1 (cont)

| Characteristic | Out of a total 84 patients *n* (%)* | Out of 30 patients recovered *n* (%)* | Out of 54 mortalities *n* (%)* | *p*-value |
|---|---|---|---|---|
| Other | | | | |
| Azithromycin | 7 (8) | 2 (7) | 5 (9) | 1.000 |
| Ciprofloxacin | 14 (17) | 7 (23) | 7 (13) | 0.222 |
| Clindamycin | 11 (13) | 5 (17) | 6 (11) | 0.511 |
| Colistin | 19 (23) | 3 (10) | 16 (30) | 0.056 |
| Fosfomycin | 2 (2) | 0 (0) | 2 (4) | 0.535 |
| Levofloxacin | 1 (1) | 1 (3) | 0 (0) | 0.357 |
| Metronidazole | 2 (2) | 2 (7) | 7 (13) | 0.480 |
| Trimethoprim/sulfamethoxazole | 1 (1) | 0 (0) | 1 (2) | 0.453 |
| Vancomycin | 12 (14) | 4 (13) | 8 (15) | 1.000 |
| Hospital admission unit | | | | |
| General internal medicine | 36 (43) | 13 (43) | 23 (43) | 0.948 |
| Intensive care of internal medicine | 15 (18) | 3 (10) | 12 (22) | 0.161 |
| General surgery | 20 (24) | 6 (20) | 14 (26) | 0.541 |
| Intensive care of surgery | 8 (9) | 4 (13) | 4 (7) | 0.448 |
| General orthopedics | 4 (5) | 3 (10) | 1 (2) | 0.128 |
| Intensive care of orthopedics | 1 (1) | 1 (3) | 0 (0) | 0.357 |

*Unless otherwise stated

Table 2

Clinical characteristics, laboratory data and outcome of patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection (BSI), Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai, Thailand (January 2013 - December 2017)

| Characteristic | Out of a total 84 patients *n* (%)* | Out of 30 patients recovered *n* (%)* | Out of 54 mortalities *n* (%)* | *p*-value |
|---|---|---|---|---|
| Presence of medical device | 65 (77) | 20 (67) | 45 (83) | 0.080 |
| Central venous catheter | 45 (54) | 14 (47) | 31 (57) | 0.344 |
| Urinary catheter | 43 (51) | 8 (27) | 35 (65) | 0.001 |
| Nasogastric tube | 40 (48) | 6 (20) | 34 (63) | <0.001 |
| Endotracheal tube | 39 (47) | 6 (20) | 33 (61) | <0.001 |
| Sign and symptom | | | | |
| Alteration of consciousness | 48 (57) | 8 (27) | 40 (74) | <0.001 |
| Body temperature ≥38.0°C | 61 (73) | 23 (77) | 38 (70) | 0.616 |
| Blood pressure <90/60 mm Hg | 10 (12) | 2 (7) | 8 (15) | 0.483 |
| Tachycardia (heart rate ≥120/minute) | 26 (31) | 8 (27) | 18 (33) | 0.626 |
| Tachypnea (respiratory rate >20/minute) | 55 (65) | 16 (53) | 39 (72) | 0.097 |

Table 2 (cont)

| Characteristic | Out of a total 84 patients *n* (%)* | Out of 30 patients recovered *n* (%)* | Out of 54 mortalities *n* (%)* | *p*-value |
|---|---|---|---|---|
| Site of infection | | | | |
| Primary BSI | 26 (31) | 14 (47) | 12 (22) | 0.020 |
| BSI with pneumonia | 28 (33) | 3 (10) | 25 (46) | 0.001 |
| BSI with skin and soft tissue infection | 16 (19) | 6 (20) | 10 (18) | 0.868 |
| BSI with osteomyelitis | 7 (8) | 5 (17) | 2 (4) | 0.092 |
| BSI with infective endocarditis | 4 (5) | 0 (0) | 4 (7) | 0.292 |
| BSI with septic arthritis | 4 (5) | 2 (7) | 2 (4) | 0.614 |
| BSI with arterial graft infection | 4 (5) | 2 (7) | 2 (4) | 0.614 |
| BSI with urinary tract infection | 2 (2) | 0 (0) | 2 (4) | 0.535 |

Table 2 (cont)

| Characteristic | Out of a total 84 patients *n* (%)* | Out of 30 patients recovered *n* (%)* | Out of 54 mortalities *n* (%)* | *p*-value |
|---|---|---|---|---|
| Laboratory finding | | | | |
| Hemoglobin, g/dl, mean ± SD | 9.1 ± 1.5 | 9.1 ± 1.6 | 9.1 ± 1.5 | 0.978 |
| White blood cell count, cell/μl, median (IQR) | 11,850 (7,935, 18,250) | 10,950 (7,700, 12,800) | 12,355 (8,100, 19,100) | 0.170 |
| Percent neutrophils, median (IQR) | 84.8 (78.5, 89.7) | 83.3 (78.8, 88.2) | 87.1 (78.6, 90.0) | 0.130 |
| Platelet, platelets per 1,000 μl, median (IQR) | 207 (110, 272) | 234 (189, 306) | 156.5 (72, 266) | 0.024 |
| Serum creatinine, mg/dl, median (IQR) | 2.1 (0.9, 4.4) | 2.0 (0.7, 6.6) | 2.1 (0.9, 3.5) | 0.493 |
| Serum albumin, mg/dl, mean ± SD | 2.5 ± 0.6 | 2.6 ± 0.5 | 2.5 ± 0.6 | 0.477 |
| Serum alanine aminotransferase, IU/l, median (IQR) | 32 (21, 74) | 6 (12, 27) | 21 (13, 58) | 0.186 |
| Vancomycin MIC, mg/l, median (IQR) | 1.5 (1, 1.5) | 1.5 (1, 2) | 1 (1, 1.5) | 0.085 |
| Received antibiotic against MRSA | 76 (91) | 30 (100) | 46 (85) | 0.027 |

*Unless otherwise stated

BSI: bloodstream infection; IQR: interquartile range; IU/l: international unit/liter; mg/dl: milligram/deciliter; MIC: minimum inhibitory concentration; mm Hg: millimeter of mercury; MRSA: methicillin-resistant *Staphylococcus aureus*: μl: microliter; SD: standard deviation

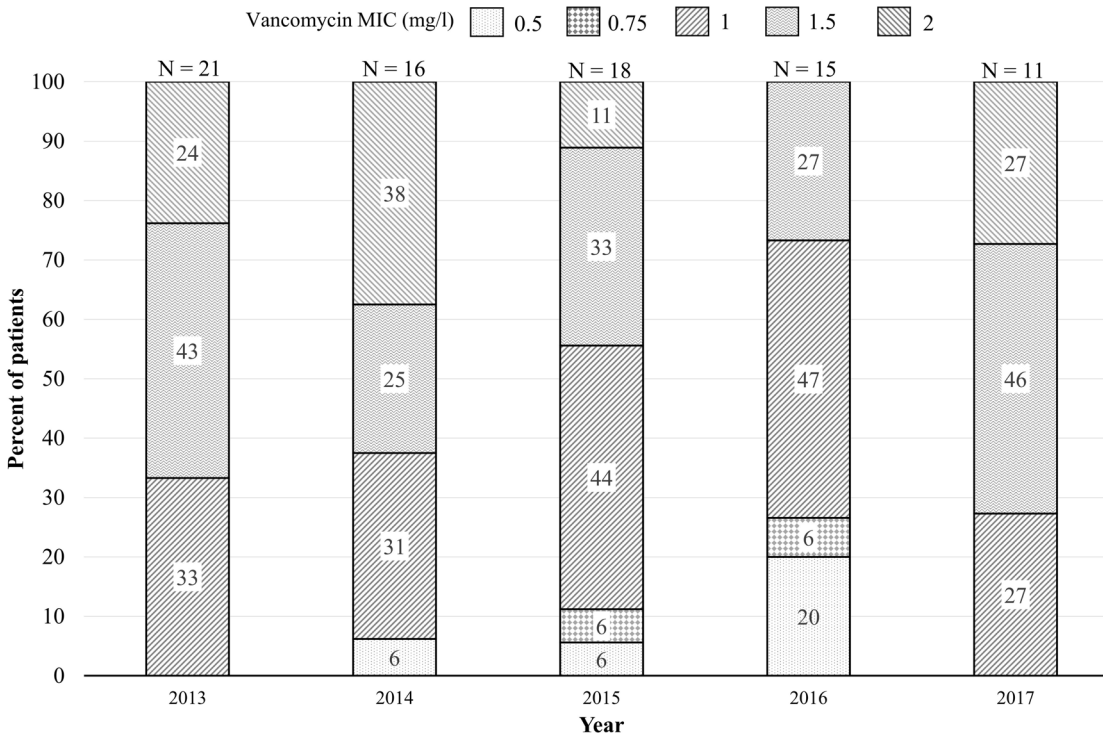


Fig 1 - Distribution of vancomycin minimum inhibitory concentrations of methicillin-resistant *Staphylococcus aureus* isolates from bloodstream infection of patients, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai, Thailand according to calendar year

Note: No MIC value for one patient each in 2013, 2015 and 2017

The other five patients died prior to antibiotic treatment against MRSA.

After a median (IQR) of 38 days (20, 80) post-admission, overall mortality of patients was 64% ($n$ = 54), with 26% ($n$ = 22) attributable to MRSA BSI. Median time (IQR) from diagnosis of MRSA BSI to death was 21 days (7, 42 days) and 5 days (2, 8 days) among whose death was attributable to MRSA BSI. Mortality is significantly associated with the older population of patients, those with history of use of piperacillin/tazobactam during three months prior to admission (Table 1), presence of alteration of consciousness, tachypnea, introduction of medical devices (endotracheal tube, nasogastric tube and urinary catheter), concurrent

pneumonia, and lower platelet counts (Table 2) ($p$-value <0.10). Patients' positive outcome is significantly associated with an underlying chronic kidney disease (Table 1) and antibiotic treatment against MRSA (Table 2) ($p$-value <0.10).

When the abovementioned factors were subjected to multivariate analysis, independent factors significantly associated with overall mortality are ≥40 years of age (odds ratio (OR) = 11.35, 95% confidence interval (CI): 1.35-95.78, $p$-value =0.026), presence of alterations of consciousness (OR = 11.19, 95% CI: 2.83-44.18, $p$-value = 0.001) and concurrent pneumonia (OR = 4.44; 95% CI: 1.09-18.14, $p$-value = 0.038). Independent factor significantly associated with patients' positive outcome is an underlying chronic kidney disease (OR = 8.00, 95% CI: 1.92-33.29, $p$-value = 0.004). However, there is no significant difference in mortality between those infected with MRSA strains with vancomycin MIC <1.5 and ≥1.5 mg/l. Independent factor significantly associated with mortality attributable to MRSA BSI is development of shock (OR = 9.31, 95% CI: 1.45-59.9, $p$-value =0.019), while significant association with positive outcome is antibiotic treatment against MRSA (OR = 22.53, 95% CI: 2.28-222.37, $p$-value = 0.008).

## DISCUSSION

Demographic, medical history and clinical characteristics of the patients in our study are comparable to those in previous reports from different countries and time periods (Nickerson *et al*, 2009; Chaiwarith *et al*, 2014; Simor *et al*, 2016). Our study demonstrates prevalence of MRSA among *S. aureus* BSIs remained relatively constant during 2013-2017, while during 2007-2011 at the same hospital there is an increasing prevalence, doubling from 23% to 43% (Chaiwarith *et al*, 2014). A SENTRY study reported a prevalence of 37.8% in the period 1997-2000, reaching a peak of 45.3% in 2005-2008 and slightly declining to 40.0% during 2013-2016 (Diekema *et al*, 2019). Surveillance of antimicrobial resistance in Europe in 2018 revealed a large difference among countries, with a range of 0-43% MRSA, almost one-third of European countries reporting a significant decrease in resistance rate during 2015-2018 (ECDC, 2019). The decreasing trend in many countries might be attributed to the introduction of new technologies enabling early detection of MRSA, *eg*, CRISPR-mediated DNA FISH method (Guk *et al*, 2017) and PCR-based point-of-care tests Parcell and Phillips, 2014; Hubner *et al*, 2015), leading to prompt initiation of appropriate antibiotic treatment in reducing colonization opportunities and improvement in infection control measures.

Vancomycin has been the mainstay of treatment for MRSA infections for several years, but it has a narrow therapeutic index, a requirement of 15-20 mg/l for treatment success

of MRSA BSIs, with a too high-level causing toxicity and a too low level resulting in treatment failure (Rybak *et al*, 2009; Kabbara *et al*, 2018). In the past, vancomycin MIC is mainly <0.5 m/l (Wang *et al*, 2006; Chang *et al*, 2015); however, there are reports of an increase in vancomycin MIC (Wang *et al*, 2006; Pitz *et al*, 2011; Joana *et al*, 2013; Chang *et al*, 2015). For example, in China, percent vancomycin MIC of 1 mg/l increases from 37.0% in 2006 to 75.7% in 2010 (Kabbara *et al*, 2018). Nearly one-fifth of the patients in our study had vancomycin MIC of 2 mg/l. There are conflicting data with regard to the association between treatment failure and MIC ≥1.5 mg/l (van Hal *et al*, 2012; Yeh *et al*, 2012; Jacob and DiazGranados, 2013; Song *et al*, 2017). Our study demonstrates no association between mortality and MIC of ≥1.5 mg/l. Given that a vancomycin MIC of <1.5 mg/l is still considered effective for treating MRSA infection at Maharaj Nakorn Chiang Mai Hospital, the detection of MRSA strains with MIC of 2.0 mg/l in our study should be a reminder to clinicians at the Hospital to maintain an updated antibiogram profiles of common microbial pathogens. In the face of rising vancomycin MICs, higher drug levels may be required to achieve the required pharmacokinetics/ pharmacodynamics (PK/PD) parameter. New drugs, *eg*, ceftaroline, daptomycin and linezolid, have become available (John, 2020), but these antibiotics are not yet widely accessible for the majority of patients in Thailand.

A systematic review and meta-analysis reported mortality rate of MRSA BSI ranging 14.2-41.8% during 2006-2011 (van Hal *et al*, 2012). From 2007 to 2011 mortality of MRSA BSI at Maharaj Nakorn Chiang Mai Hospital is 53.1% (Chaiwarith *et al*, 2014). van Hal *et al* (2012) observed an overall mortality rate of treatment with vancomycin of MIC <1.5 and ≥1.5 mg/l ranges 9-39% and 5-66% respectively, and not all studies demonstrated a higher mortality rate among those who received vancomycin of MIC ≥1.5 mg/l.

Our study using multivariate analysis of factors independently associated with MRSA BSI death identified older age, presence of alteration of consciousness and concurrent pneumonia, but no association with vancomycin MIC. Aging is associated with low immunity (Sadighi Akha, 2018), alteration of consciousness may represent signs of sepsis (Cotena and Piazza, 2012; Adam *et al*, 2013), and concurrent pneumonia might be associated with prolonged hospitalization, frequent use of medical devices and broad-spectrum antimicrobials, which may directly or indirectly lead to fatal outcome (Sakamoto *et al*, 2021). In addition, patients receiving corticosteroids and/ or requiring mechanical ventilation have sepsis or septic shock, and those failing to receive antibiotic treatment against MRSA within 24 hours of MRSA identification have a higher rate of fatality (Forstner *et al*, 2013;

Lee *et al*, 2015; Kim *et al*, 2019). We observed chronic kidney disease is an independent factor for good outcome as these patients, particularly those receiving renal replacement therapy, are acknowledged to be at risk of infection caused by MRSA or coagulase-negative staphylococci and are given early antibiotic therapy against MRSA. In addition, receiving antibiotics against MRSA is the only independent factor associated with good outcome from solely MRSA BSI.

However, the study had two major limitations. Firstly, being a retrospective study, some data may be missing, leading to misinterpretation of the results, *eg*, the leading cause of death might be due to MRSA infection itself or from other causes. And secondly, the number of patients recruited was limited and other factors associated with MRSA BSI mortality might have been apparent.

In conclusion, concurrent MRSA bloodstream infection and pneumonia lead to increased risk of mortality. Although vancomycin MIC is not significantly associated with fatal outcome, in view of reported increase in vancomycin MIC, attending physicians should monitor vancomycin MIC used in treating MRSA to allow selection of more appropriate alternative drugs and thereby reduce treatment failure.

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