Research Article

ความสัมพันธ์ระหว่างค่าความเข้มข้นต่ำสุดที่สามารถยับยั้งการเจริญเติบโตของเชื้อของยาแวนโคมัยซินและผลลัพธ์การรักษาในผู้ป่วยที่มีการติดเชื้อ Methicillin-Resistant *Staphylococcus aureus* ในกระแสเลือด: การศึกษาย้อนหลังสี่ปี

ธีระพงษ์ มนต์มธุรพจน์[1,*], วริศรา จินาทองไทย[2], คนึงนิตย์ เซมรัมย์[3]

[1] อาจารย์ กลุ่มวิชาเภสัชกรรมปฏิบัติ คณะเภสัชศาสตร์ มหาวิทยาลัยอุบลราชธานี อุบลราชธานี
[2] เภสัชกร กลุ่มงานเภสัชกรรม โรงพยาบาลสรรพสิทธิประสงค์ อุบลราชธานี
[3] อายุรแพทย์สาขาโรคติดเชื้อ กลุ่มงานอายุรกรรม โรงพยาบาลสรรพสิทธิประสงค์ อุบลราชธานี
*** ติดต่อผู้นิพนธ์**: ธีระพงษ์ มนต์มธุรพจน์ อาจารย์ กลุ่มวิชาเภสัชกรรมปฏิบัติ คณะเภสัชศาสตร์ มหาวิทยาลัยอุบลราชธานี อุบลราชธานี 34190
โทรศัพท์ +6645353626 อีเมล์: phteermo@gmail.com

บทคัดย่อ

ความสัมพันธ์ระหว่างค่าความเข้มข้นต่ำสุดที่สามารถยับยั้งการเจริญเติบโตของเชื้อของยาแวนโคมัยซินและผลลัพธ์การรักษาในผู้ป่วยที่มีการติดเชื้อ Methicillin-Resistant *Staphylococcus aureus* ในกระแสเลือด: การศึกษาย้อนหลังสี่ปี

ธีระพงษ์ มนต์มธุรพจน์[1,*], วริศรา จินาทองไทย[2], คนึงนิตย์ เซมรัมย์[3]

ว. เภสัชศาสตร์อีสาน 2559; 12(4) : 83-94

รับบทความ : 3 ตุลาคม 2559 **ตอบรับ :** 23 พฤศจิกายน 2559

ความล้มเหลวในการรักษาโรคติดเชื้อแบคทีเรีย Methicillin-resistant *Staphylococcus aureus* (MRSA) ด้วยยา vancomycin เริ่มมีรายงานเพิ่มมากขึ้นเรื่อยๆ ทั้งนี้ เนื่องจากมีการเพิ่มขึ้นของอัตราการดื้อยาซึ่งได้แก่ การเพิ่มขึ้นของค่าความเข้มข้นต่ำสุดที่สามารถยับยั้งการเจริญเติบโตของเชื้อ (minimum inhibitory concentration; MIC) MRSA ต่อยา vancomycin ถึงแม้ว่าค่า MIC จะอยู่ในช่วงที่เชื้อยังคงไวต่อยาก็ตาม การศึกษานี้จึงมีวัตถุประสงค์เพื่อหาความสัมพันธ์ระหว่าง vancomycin MIC และความล้มเหลวในการรักษาผู้ป่วยที่มีการติดเชื้อ MRSA ในกระแสเลือดที่รักษาด้วยยา vancomycin **วิธีดำเนินการวิจัย:** การศึกษาย้อนหลัง ณ โรงพยาบาลสรรพสิทธิประสงค์ อุบลราชธานี โดยเก็บข้อมูลย้อนหลังในช่วงปี พ.ศ. 2555 ถึง พ.ศ. 2558 ในผู้ป่วยที่มีการติดเชื้อ MRSA ในกระแสเลือดและได้รับการรักษาด้วยยา vancomycin เป็นระยะเวลาอย่างน้อย 48 ชั่วโมง แบ่งผู้ป่วยออกเป็นสองกลุ่ม กลุ่มที่หนึ่งคือกลุ่มผู้ป่วยที่ติดเชื้อ MRSA ในกระแสเลือดที่มีค่า vancomycin MIC น้อยกว่าหรือเท่ากับ 1 มิลลิกรัมต่อลิตร และกลุ่มที่สองคือ vancomycin MIC มากกว่า 1 มิลลิกรัมต่อลิตร ผลลัพธ์หลักของการศึกษาคือความล้มเหลวในการรักษารวมซึ่งได้แก่ การเสียชีวิตภายในระยะเวลา 30 วัน ความล้มเหลวในการกำจัดเชื้อและหรือการติดเชื้อ MRSA ซ้ำ **ผลการวิจัย:** ผู้ป่วยทั้งหมด 121 คนที่เข้าเกณฑ์การศึกษา แบ่งเป็นผู้ป่วยจำนวน 50 คน (ร้อยละ 41.3) และ 71 คน (ร้อยละ 58.7) ในกลุ่มที่หนึ่งและกลุ่มที่สองตามลำดับ ข้อมูลพื้นฐานของผู้ป่วยทั้งสองกลุ่มแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ ผลการศึกษาพบว่าความล้มเหลวในการรักษารวมในกลุ่มที่มีค่า vancomycin MIC มากกว่า 1 มิลลิกรัมต่อลิตรมีค่าสูงกว่ากลุ่มที่มีค่า vancomycin MIC น้อยกว่าหรือเท่ากับ 1 มิลลิกรัมต่อลิตร ซึ่งแตกต่างกันอย่างมีนัยสำคัญทางสิถิติที่ p-value น้อยกว่า 0.001 ผู้ป่วยจำนวน 27 คน ซึ่งคิดเป็นร้อยละ 22.3 ของผู้ป่วยทั้งหมดมีการเสียชีวิตภายในระยะเวลา 30 วัน โดยมีจำนวน 5 คนในกลุ่มที่มีค่า vancomycin MIC น้อยกว่า 1 มิลลิกรัมต่อลิตรและ 22 คนในกลุ่มที่มีค่า vancomycin MIC มากกว่า 1 มิลลิกรัมต่อลิตร ซึ่งมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติเช่นเดียวกัน (OR 4.04, 95%CI: 1.33-14.67, p-value 0.008) สำหรับความล้มเหลวในการกำจัดเชื้อและการติดเชื้อ MRSA ซ้ำพบว่าให้ผลสอดคล้องกับการเสียชีวิตภายในระยะเวลา 30 วัน ผู้ป่วยในการศึกษานี้ร้อยละ 65 มีความเข้มข้น

ของยา vancomycin ในเลือดที่สภาวะคงที่อย่างน้อย 15 มิลลิกรัมต่อลิตรซึ่งอยู่ในช่วงของการรักษาและไม่มีความแตกต่างกันของความเข้มข้นของยาในเลือดระหว่างสองกลุ่ม **สรุปผลการวิจัย:** การศึกษานี้แสดงให้เห็นชัดเจนว่าผู้ป่วยที่ติดเชื้อ MRSA ในกระแสเลือดที่มีค่า vancomycin MIC มากกว่า 1.0 มิลลิกรัมต่อลิตรส่งผลให้ประสิทธิภาพในการรักษาด้วยยา vancomycin ลดลงและมีความสัมพันธ์อย่างมีนัยสำคัญกับการเพิ่มขึ้นของความล้มเหลวในการรักษา ดังนั้น บุคลากรทางการแพทย์ควรตระหนักและให้ความสำคัญในการป้องกันการติดเชื้อและการใช้ยา vancomycin อย่างเหมาะสมเพื่อป้องกันการเพิ่มขึ้นของเชื้อดื้อยาในอนาคต

คำสำคัญ: ยาแวนโคมัยซิน, เชื้อ Methicillin-resistant *Staphylococcus aureus,* ภาวะติดเชื้อในกระแสเลือด, ค่าความเข้มข้นต่ำสุดที่สามารถยับยั้งการเจริญเติบโตของเชื้อ

Relationship of Vancomycin Minimum Inhibitory Concentration and Treatment Outcomes among Patient with Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Four Year Retrospective Study

Teerapong Monmaturapoj[1,*], Warisara Jinathongthai[2], Khanungnit Semram[3]

[1] Lecturer, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani

[2] Pharmacist, Department of Pharmacy, Sunpasitthiprasong Hospital, Ubon Ratchathani

[3] Medical Doctor in Infectious Diseases, Department of Medicine, Sunpasitthiprasong Hospital, Ubon Ratchathani

***Corresponding author**: Teerapong Monmaturapoj, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani, Thailand, 34190, Tel: +6645353626, E-mail address: phteermo@gmail.com

Abstract

Relationship of Vancomycin Minimum Inhibitory Concentration and Treatment Outcomes among Patient with Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Four Year Retrospective Study

Teerapong Monmaturapoj[1,*], Warisara Jinathongthai[2], Khanungnit Semram[3]

IJPS, 2016; 12(4) : 83-94

Received : 3 October 2016 **Accepted :** 23 November 2016

Therapeutic failures with vancomycin in Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been increasingly reported. There is growing evidence that infection with an organism with an increased vancomycin minimum inhibitory concentration (MIC) that is still within the susceptible range may also be associated with increased rates of vancomycin failure. This study aimed to determine the association between vancomycin MIC and treatment failures among patient with MRSA bloodstream infection in Thailand. **Methods:** This retrospective study was conducted at Sunpasitthiprasong hospital, a tertiary care and academic hospital. All medical records of the patients who had MRSA bacteremia and were treated with vancomycin between January 2012 and 2015 were reviewed. Patients were categorized into two groups; MIC≤1 mg/L (low) and MIC>1 mg/L (high). The primary outcome was overall failure (thirty-day mortality, microbiological failure and recurrence of MRSA infection). **Results:** During the study period, 121 patients met the inclusion criteria. Of these, 50 (41.3%)

and 71 (58.7%) patients had vancomycin MIC ≤ 1 mg/L and MIC > 1 mg/L respectively. Demographic data were generally similar between the two groups. Overall failure was statistically significantly different between low and high vancomycin MIC with p-value <0.001. Twenty seven patients (22.3%) in both groups had thirty day mortality. Of these, 5 (10%) patients were in the low vancomycin MIC group and 22 (31%) patients were in the high vancomycin MICs group. There was a significant difference (OR 4.04, 95%CI: 1.33-14.67, p-value 0.008). Microbiological failure and recurrence MRSA infection were also high and consistent with thirty day mortality in high vancomycin MICs group. Approximately 65% of all patients achieved vancomycin level at steady state of at least 15 mg/L and there were no differences of trough vancomycin level between two groups. **Conclusion:** The present study strongly suggests that patients with MRSA bloodstream infections with vancomycin MICs of >1.0 mg/L respond poorly to vancomycin therapy and were significantly associated with overall failure. Therefore, healthcare professionals should concern and take a consideration by preventing this infection and optimal use of vancomycin in order to prevent the increasing of antimicrobial resistance.

Keywords: Vancomycin, Methicillin-resistant *Staphylococcus aureus*, Bacteremia, Minimum Inhibitory Concentration

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are serious and associated with significant mortality and health-care costs (Chuamuangphan *et al.*, 2014; Cosgrove *et al.*, 2003). In most hospitals, MRSA has become the most common gram-positive bacterial species associated with serious hospital-acquired infections. Until recently vancomycin has remained the mainstay of therapy for serious Gram-positive infections, particularly MRSA bloodstream infection for many years (Rybak *et al.*, 2009). Associated with an increase in vancomycin use, there is growing concern that it has diminished activity for MRSA infections (Hidayat *et al.*, 2006; Sakoulas *et al.*, 2004), with vancomycin MICs at the high end of the 2015 Clinical and Laboratory Standards Institute (CLSI) susceptibility range (MICs of 2 mg/L) (CLSI, 2015). Despite this growing concern, there are limited clinical data to support this notion. From standard treatment guideline, vancomycin in doses adjusted to achieve serum trough concentrations of 15 to 20 mg/L has been recommended when empirically or definitely covering MRSA infection (Liu *et al.*, 2011; Rybak *et al.*, 2009). It is recommended that AUC/MIC ratio be kept between 350 and 400 to achieve trough concentration 15 to 20 mg/L provide a greater clinical response and microbiological eradication against MRSA with MIC values ≤ 1 mg/L (Kullar *et al.*, 2011). Therefore, probability of achieving a target AUC/MIC which is widely regarded as the best predictor of successful vancomycin therapy is nearly zero percent if vancomycin MIC 2 mg/L with low or high dose of vancomycin. (Jeffres *et al.*, 2006; Moore *et al.*, 2011)

Several studies demonstrated the association between higher vancomycin MIC and poor vancomycin therapeutic outcome even within the susceptible range in MRSA bacteremia (Lodise *et al.*, 2008; Soriano *et al.*, 2008). A retrospective study at Siriraj hospital, a large teaching hospital of Thailand found that vancomycin MICs of more than 1.0 mg/L from MRSA bloodstream isolates were approximately 69.4% (Sitthananun *et al.*, 2014). The relationship between vancomycin MIC and treatment outcomes of MRSA bacteremia in Thailand have not been reported. The purpose of this study was to investigate the association between vancomycin MIC and treatment

failures among patient with MRSA bloodstream infections treated with vancomycin.

1.1 Patients and Methods

1.1.1 Study design A retrospective study was performed at Sunpasitthiprasong hospital, a tertiary care and academic hospital with 1,200-beds located in Ubon Ratchathani, Thailand. The study protocol was approved by the appropriate ethics committee of the institutional review board of Sunpasitthiprasong hospital (Ubon Ratchathani, Thailand) based on the Declaration of Helsinki, study protocol number 036/2558.

1.1.2 Patients All patients with MRSA blood-stream infections between January 2012 and May 2015 were eligible. MRSA bacteremia was defined as occurring in a patient with at least one blood culture positive for MRSA and clinical signs and symptoms of sepsis based on a previous definition. Patients were included in the study if they were (i) at least 18 years old, (ii) non-neutropenic patient (an absolute neutrophil count more than of 1,000 cells/mm^3), (iii) with an MRSA culture that met the Centers for Disease Control and Prevention (CDC) criteria for bloodstream infection (Garner *et al.*, 1988), (iv) had received vancomycin therapy within 48 hour of the index blood culture collection, and (v) had survived more than 24 hour after vancomycin administration. If a patient had more than one episode during a study period, only the first episode was considered for eligibility. For patients with multiple MRSA blood cultures, the vancomycin MIC of the index bloodstream isolate was considered in the analysis.

Data were extracted from inpatient patients' medical records and electronic database. Data elements included the following conditions: age, sex, weight, medical history and comorbidity, receipt of antibiotics in the 30 days prior to the index blood culture collection, requiring surgery or invasive procedure within the 30 days prior to admission. Length of hospitalization prior to collection of blood culture, hospital, creatinine clearance (CrCl) estimated by the Cockcoft-Gault formula prior vancomycin treatment, source of MRSA bloodstream infection, presence of infective endocarditis, vancomycin trough concentrations (date, time, and temporal relationship to vancomycin dose), concomitant antimicrobial administered during vancomycin therapy (date, time, dosing regimen, and duration), microbiologic data, and outcome. The glomerular filtration rate in acute renal failure, acute kidney injury and ESRD patients were calculated by using serum creatinine before the initial vancomycin treatment.

The presence of the following comorbid conditions was documented: diabetes mellitus, history of cardiovascular diseases (congestive heart failure, acute coronary syndrome, myocardial infarction), history of cerebrovascular accident (ischemic or hemorrhagic stroke), malignancy, chronic obstructive pulmonary disease, renal failure (as indicated by the necessity for dialysis), human immunodeficiency virus (HIV) infection, chronic ulcers (bed sore, diabetic foot), administration of immunosuppressive drugs (corticosteroid or any antineoplastic chemotherapy).

Treatment data included those for all antibiotics (date, time, dose, route, and duration) administered to the patient to treat the MRSA bloodstream infections. Vancomycin concentrations were collected at pharmacokinetic and Therapeutic Drug Monitoring Unit of the Pharmacy Department. For patients who had vancomycin concentrations, prediction and real trough vancomycin concentrations were calculated by using short infusion pharmacokinetic model at steady state condition. All date, time, and relationship to next dose were collected. For patient who did not have drug level, predicted trough vancomycin concentrations at steady state and calculated pharmacokinetics for definitive treatment were determined based on dose, interval, infusion time and serum creatinine of population pharmacokinetic parameters. Trough vancomycin concentrations 15-20 mg/L were categorized as therapeutic range. Antibiotics administered in combination with vancomycin (concomitant antibiotics) were also recorded.

The source of the MRSA bloodstream infection was determined from an assessment of other positive *S. aureus* cultures at the time of *S. aureus* bacteremia and the physician's clinical description in the medical records. When clinical and microbiological criteria precluded determination of the source, the data were considered as unknown. The presence of infective endocarditis was also documented.

1. 1. 3 Microbiologic data All clinical MRSA isolates from blood cultures were collected at the site of Microbiological Laboratory during the study period. The date and time of the MRSA cultures were recorded, as well as the time of the last MRSA blood culture and first negative blood culture. All isolates were identified as *S. aureus* according to standard methods. Initial susceptibility testing for oxacillin resistance was performed according to CLSI 2015 guidelines. The vancomycin MICs were determined by using E-test (0.016 to 256 mg/L) for the index bloodstream isolate. Other microorganisms during MRSA bacteremia and vancomycin treatment were also noted.

1.1.4 Outcomes An objective, easily reproducible assessment of treatment failure that included only readily measurable study end points was used in the study due to its retrospective, observational nature. Primary outcome in our study was treatment or overall failure. Treatment failure was defined as any of the following: (i) death within 30 days from any causes of index MRSA blood culture (30-day mortality); (ii) microbiological failure, defined as a blood culture growing MRSA obtained 5-7 days after the initiation of vancomycin therapy and before the completion of antimicrobial therapy; or (iii) recurrence of MRSA bacteremia within 30 days of the discontinuation of vancomycin therapy. If a patient met more than one criterion, the outcome was classified only as a failure one time. If vancomycin was started prior to collection of the index MRSA blood culture specimen, the index MRSA blood culture date was considered as the first day in calculating days of bacteremia. The secondary outcome was the length of hospital stay after the index blood culture was collected. Lastly, the proportion of patients who were switched to an alternative anti-MRSA antibiotic such as linezolid or tigecycline, was calculated.

1. 1. 5 Statistical analyses Categorical variables were compared by the Pearson Chi square test or Fisher's exact test, and continuous variables were compared by Student's *t* test or the Mann-Whitney U test. The values were presented as the mean ± SD for the continuous variables or as the percentage of the group from which they were derived for the categorical variables. A p-value less than 0.05 was considered significant for two-tailed tests. All results were analyzed by using the SPSS and STATA statistical programs version 23.0 and 12.0 respectively.

2. Results

2.1 Patients

A total of 148 patients with MRSA bloodstream infection were screened for inclusion. The primary reason for exclusion that they had been treated with vancomycin within less than 48 hours of presentation, incomplete of medical record, and/or lacked of vancomycin MIC data. A total of 121 patients were considered eligible in the analyses. Baseline demographics of both groups were generally similar. There are presented in Table 1. Overall, the majority of the population was male (71.1%), with a mean age of 57.6±10.7 years. Diabetes (44.6%), cardiovascular diseases (42.1%) and end stage renal disease (28.1%) were common comorbidities, and 19% of the population had been treated with antibiotics in the previous month. The mean hospital length of stay before blood culture collection was 2.6±1.6 days. The Catheter-related blood stream infections (CRBSIs) (59.5%) and hospital-acquired pneumonia (19%) were common source of MRSA bacteremia. Approximately sixty percent of CRBSIs causing MRSA bacteremia which most common

source of bacteremia were associated with end stage renal disease (ESRD) in dialysis patients. Vancomycin trough concentration was available for 81 patients (66.9%). The mean vancomycin trough concentrations in both groups were 15.1±12.2 mg/L. Approximately 65% of all patients achieved a vancomycin trough concentration of at 15-20 mg/L and there were no differences of vancomycin levels at steady state between the two groups (p-value 0.486). The distribution of vancomycin MIC for MRSA is presented in *Figure 1*. The majority of vancomycin MIC (38%) was 1.5 mg/L. MRSA bacteremic patients with vancomycin MICs more than 1.0 mg/L accounted for more than 58% of all isolates. The most common of concomitant infections with MRSA bacteramia were Gram negative pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. There were no significant differences between the two groups. Concomitant antimicrobial agents for both empirical and specific therapy administered during vancomycin treatment were generally similar in both groups.

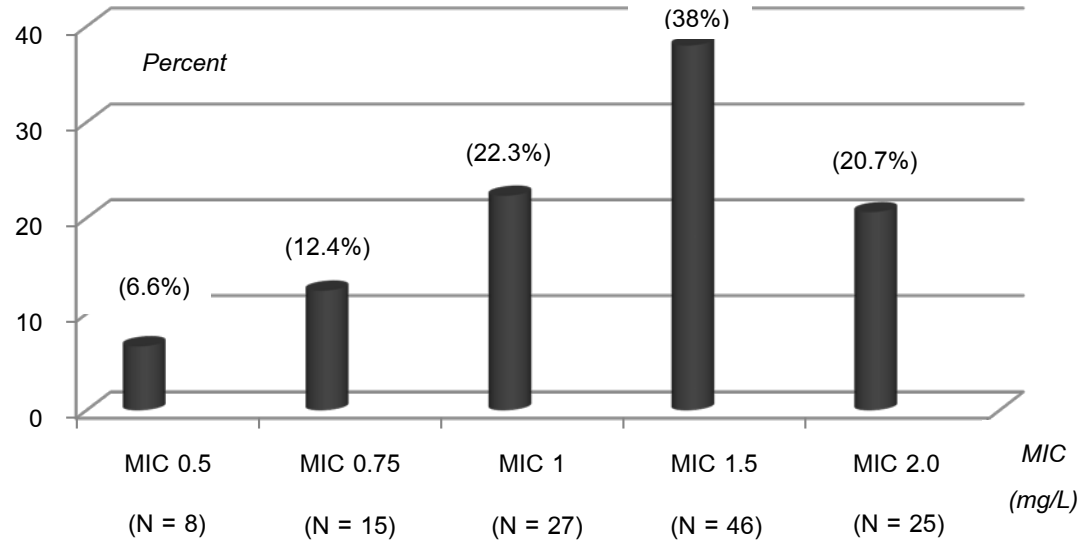

Figure 1 Distribution of vancomycin MIC among patients with MRSA bloodstream infection (n=121)

Table 1 Baseline characteristics between low (≤1 mg/L) and high (>1 mg/L) vancomycin MIC

Characteristic	Vancomycin MIC		P-value
	≤ 1 mg/L (n=50)	> 1 mg/L (n=71)	
Age in year (mean±SD)	57.2±10.7	58.1±11.2	0.658
Male gender	36 (72)	50 (70.4)	0.848
Weight in Kg (mean±SD)	58.2±7.1	60.3±5.2	0.063
Underlying or history of			
Diabetes mellitus	24 (48)	30 (42.2)	0.527
Cardiovascular disease	17 (34)	34 (47.9)	0.127
Cerebrovascular disease	6 (12)	13 (18.3)	0.348
Malignancy	4 (8)	9 (12.7)	0.411

Characteristic	Vancomycin MIC		P-value
	≤ 1 mg/L (n=50)	> 1 mg/L (n=71)	
COPD	2 (4)	4 (5.6)	0.689
ESRD on dialysis (HD or PD)	12 (24)	22 (31)	0.399
HIV	3 (6)	2 (2.8)	0.383
Chronic ulcer	5 (10)	11 (15.5)	0.379
Immunocompromise condition	10 (20)	9 (12.7)	0.277
Antibiotics in previous 30 days	7 (14)	16 (22.5)	0.240
Invasive procedure in previous 30 days	10 (20)	17 (23.9)	0.612
Length of hospitalization before blood culture collection (day) (mean±SD)	3.2±2.2	3.7±1.4	0.129
Baseline creatinine clearance (ml/min) (mean±SD)	46.2±11.6	44.2±9.3	0.296
Source of bacteremia			
Intravenous catheter (CRBSI)	28 (56)	44 (62)	0.508
Skin and soft tissue/bone/joint	6 (12)	7 (9.9)	0.714
Respiratory tract	10 (20)	13 (18.3)	0.814
Multiple	3 (6)	4 (5.6)	0.926
Undetermined	3 (6)	3 (4.2)	0.653
Infective endocarditis	1 (2)	3 (4.2)	0.504
Vancomycin trough concentration at steady state (mg/L) (mean±SD)	16.2±12.1	14.6±12.6	0.486
Concomitant infections with MRSA bacteremia	16 (32)	22 (31)	0.907
Concomitant IV antimicrobial administered during vancomycin therapy			
Meropenem	16 (32)	18 (25.4)	0.427
Ertapenem	0	3 (4.2)	0.142
Imipenem/cilastatin	9 (18)	17 (23.9)	0.436
Piperacillin/tazobactam	16 (32)	22 (31)	0.907
Cefoperazone/sulbactam	11 (22)	18 (25.4)	0.666
Colistin	10 (20)	20 (28.2)	0.304
Fosfomycin	2 (4)	4 (5.6)	0.689
Aminoglycoside	4 (8)	3 (4.2)	0.377

Abbreviations: COPD; Chronic Obstructive Pulmonary Disease, HD; Hemodialysis, PD; Peritoneal Dialysis, IV; Intravenous

2.2 Assessment of treatment outcome and failure

Overall failure (thirty day mortality, microbiological failure, and recurrent MRSA infection) was significantly different between low and high vancomycin MIC groups (18% vs 47.9%; 95% CI: 1.67-11.17; P<0.001). A comparison of treatment failure between low and high vancomycin MICs can be found in Table 2. Outcome assessments conducted at 30 days from acquisition of the

index blood culture found a mortality rate of 27 patients (22.31%), 5 patients (10%) of low MIC and 22 patients (31%) of high MIC. There was a statistically significant difference between the two groups (P= 0. 008) . Furthermore, microbiological failure and recurrence MRSA infection were significantly higher in high vancomycin MIC than those with low vancomycin MIC with p-value of 0.004 and 0. 014 respectively. Thirty-day mortality was also higher among patients that had a microbiological failure than among those that did not. The mean total hospital length of stay was significantly longer for patients with high vancomycin MIC than those with low vancomycin MIC (23.1±6.4 days vs 11.6±8.2 days; p-value <0.001). This study analyzed a large subgroup analysis of vancomycin MICs between 1.5 and 2.0 mg/L to identify the impact of treatment failure in the high range of vancomycin MIC group. The result revealed that in the high vancomycin MIC, overall failure and thirty days mortality were generally similar (43.5 vs 56.0; p-value 0.33 and 26.1 vs 40.0; p-value 0.28 respectively).

During the study period, approximately 85% of all patients were repeated blood culture after vancomycin treatment. Of 18 patients (14.9%) that had persistent of MRSA bacteremia after 5-7 day of vancomycin treatment which was categorized as micribiological failure, 16 patients (88. 9%) were switched to an alternative anti-MRSA agents; 12 to linezolid and four to tigecycline. These 16 patients received vancomycin for a mean 6.4±2.4 days before switching to the alternative agents.

Table 2 Comparison of treatment failure between low (≤ 1 mg/L) and high (> 1 mg/L) vancomycin MIC

Outcome	Vancomycin MIC		OR	95% CI	P-value
	≤ 1 mg/L (n = 50)	> 1 mg/L (n = 71)			
Primary outcome					
Overall failure	9 (18)	34 (47.9)	4.19	1.67-11.17	<0.001
Thirty-day mortality	5 (10)	22 (31)	4.04	1.33-14.67	0.008
Microbiological failure	2 (4)	16 (22.5)	6.98	1.50-64.84	0.004
Recurrent MRSA infection	2 (4)	14 (19.7)	5.89	1.24-55.35	0.014
Secondary outcome					
Switched to alternative anti-MRSA drugs	2 (4)	14 (19.7)	5.89	1.24-55.35	0.014
Total hospital length (day) (mean±SD)	11.6±8.2	23.1±6.4			<0.001

All data presented are number (percent) of patients.

Abbreviations: OR = Odd Ratio, CI = Confidence Interval

3. Discussion and conclusion

MRSA is a common cause of bloodstream infection and is often associated with invasive infections and high rates of mortality (Chuamuangphan *et al.*, 2014; Cosgrove *et al.*, 2003; Liu *et al.*, 2011). Vancomycin has been the standard of treatment since the emergence of MRSA infection. The failure of treatment with vancomycin has been attributed to its slow bactericidal activity, the presence of subtherapeutic concentrations, and the reduced susceptibility of organisms (Cosgrove *et al.*, 2004; Mohr *et al.*, 2007; Song *et al.*, 2004). Recently, a debate has arisen over its continued utility for this purpose

(Deresinski, 2007), fueled by a steady stream of reports linking a worse clinical outcome of MRSA infected patients and a higher vancomycin MIC of the infecting pathogen. Several studies found that the vancomycin MIC can have important prognostic value for vancomycin treated patients (Moise-Broder *et al.*, 2004). In the present study, the prevalence of MRSA bacteremia with vancomycin MIC > 1.0 mg/L was found to be 58.7% among hospitalized patients in Sunpasitthiprasong Hospital between 2012 to 2015, and this finding was similar to a previous study in Thailand (Sitthananun *et al.*, 2014). The present study examined the relationship between vancomycin MICs and treatment outcomes among MRSA bacteremic patients treated appropriately with vancomycin. The major outcome in this study was overall failure.

The results of the present study were generally consistent with those of recent studies that evaluated the relationship between vancomycin MICs and outcomes among patients with MRSA bacteremia infections. Higher treatment failure or higher mortality was associated with high vancomycin MIC group (Kullar *et al.*, 2011; Maclayton *et al.*, 2006; Neoh *et al.*, 2007). A 30% difference in the overall failure between high and low vancomycin MICs group was seen in the present study. Similar to the result from Lodise et al, the difference of overall mortality was 21% between high and low vancomycin MICs group (Lodise *et al.*, 2008). In addition, Hidayat et al found a 23% difference of treatment failure in patients infected with MRSA with high MIC (≥2 mg/L) compared with low MIC (1 mg/L) (Hidayat *et al.*, 2006). A 28.2% of difference in mortality between low (1.0 mg/L) and high MIC (2.0 mg/L) groups of bacteremic patients was reported by Musta et al (Musta *et al.*, 2009) similar to the present study which was 21.0%. Patients with persistent MRSA bacteremia in the present study were associated with high vancomycin MIC group similar to a study by Yoon et al (Yoon *et al.*, 2010). Therefore, clinicians or healthcare professionals should respond to this association by either increasing or adjusting the vancomycin dose or switching to an alternative anti-MRSA antibiotics, especially in MRSA with vancomycim MIC more than 1.0 mg/L. Novel alternative drugs for MRSA infection such as linezolid, daptomycin and tigecycline which are now available in Thailand might be considered especially in patient with treatment failure from vancomycin. However, recent practice guidelines from the Infectious Diseases Society of America for treatment of MRSA infections did not recommend using a vancomycin alternative treatment based on an elevated MIC alone, provided that the isolate has an MIC in the susceptible range (Liu *et al.*, 2011). The clinical sign and symptoms of infection should also be considered.

The present study is the first report in Thailand to demonstrate the association between vancomycin MIC and treatment outcome in MRSA bacteremic patients. The strength of the study is in its include robust sample size and clearly defined outcomes. All enrolled subjects in the study had only MRSA bloodstream infection. With over 120 patients, it is the largest sample size of retrospective study in Asia. The present study provides further evidence to support the association between higher vancomycin MIC and worse patient outcome in MRSA infected patients. Another interesting feature was seen in the patients who switched to tigecycline treatment. Seventy five percent of patient (3 cases) had recurrent MRSA infection. This medication has not been approved for MRSA bacteremia due to the limitation of pharmacokinetic properties (Meagher *et al.*, 2005). Given concerns regarding achieving adequate tigecycline serum drug concentrations, caution should be used with it for the treatment of patients with bacteremia even for treatment of susceptible pathogens (Cai *et al.*, 2011).

However, there are several limitations of this study that need to be considered when interpreting the results. First, this was a retrospective study and data were subject to inherent biases. Some required information was not available such as the proportion of patient with intravenous catheter removal or adequacy of surgical debridement of skin and soft tissue infection sites which influenced to persistence of MRSA bacteremia after vancomycin administration. These factors might be

affected to the treatment outcomes. Second, all MRSA blood culture data were collected from a single center in North-Eastern Thailand, therefore institutional differences in prescribing patterns, antibiotic resistance patterns, and patient populations may affect the application of these results to other regions. Third, this study excluded neutropenic, so the results may not be generalizable to this patient group. Finally, sixty seven percent of all patients had vancomycin trough concentration availability and sixty five percent achieved vancomycin level at steady state of at least 15 mg/ L, hence application and interpretation of results from this study should be concerned.

The results of the present study strongly suggested that MRSA bloodstream infections with vancomycin MICs > 1.0 mg/L had a higher likelihood of treatment failure. These patients had a significantly high rate of mortality, longer duration of MRSA bacteremia, a higher likelihood of recurrence MRSA infection, and a longer hospital length of stay. Higher vancomycin troughs of more than 15-20 mg/L to achieve optimal AUC/MIC ratio were not found to improve the treatment success rates (Lodise *et al.*, 2008). Moreover, a higher trough vancomycin concentration was also associated with nephrotoxicity (Hidayat *et al.*, 2006; Lodise *et al.*, 2008). For this reason, the practice of systematically switching patients infected with MRSA exhibiting vancomycin MIC > 1.0 mg/L from vancomycin to an alternative antibiotic is probably often necessary. Moreover, the CLSI 2015 of vancomycin susceptibility breakpoint for MRSA bloodstream infections should be decreased from $\leq$ 2.0 mg/L to $\leq$ 1.0 mg/L. At present, daptomycin is the only drug approved by the FDA for MRSA bloodstream infections and is associated with a better outcome with higher vancomycin MIC (Bennet *et al.*, 2008; McDaneld *et al.*, 2013). Daptomycin is associated with a higher probability of survival at 60 days and indicated for patients who are not improving during vancomycin therapy (Moore *et al.*, 2012). In conclusion, we ultimately demonstrated that overall failure associated with MRSA bacteremia was significantly higher when vancomycin was used for treatment of infection with strains with vancomycin MIC>1.0 mg/L.

Funding

This work was partially supported by research funds of Faculty of Pharmaceutical Sciences, Ubon Ratchathani University (Grant number: 0529.11/11567)

Conflict of interest

None declared

Acknowledgments

The authors thank the Unit of Microbiology, Sunpasitthiprasong Hospital, Ubon Ratchathani, Thailand for providing hospital vancomycin MIC data and staff of the Office of International Relations at Ubon Ratchathani University for assistance with English.

References

Bennett JW, Murray CK, Holmes RL, *et al.* Diminished vancomycin and daptomycin susceptibility during prolonged bacteremia with Methicillin-resistant *Staphylococcus aureus*. *Diagn Microbiol Infect Dis* 2008; 60:437-40.

Cai Y, Wang R, Liang B, *et al.* Systematic Review and Meta-Analysis of the Effectiveness and Safety of Tigecycline for Treatment of Infectious Disease. *Antimicrob Agents Chemother* 2011; 55:1162-72.

Chuamuangphan T, Chongtrakool P, Sungkanuparph S. Predicting Factors of Methicillin-resistant *Staphylococcus aureus* Bacteremia among Hospitalized Patients in a Tertiary-care Hospital: A Case-control Study. *J Infect Dis Antimicrob Agents* 2014; 31:79-89.

Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. Wayne:CLSI; 2015.25th Informational Supplement, M100-S25.

Cosgrove SE, Carroll KC, Perl TM. *Staphylococcus aureus* with reduced susceptibility to vancomycin. *Clin Infect Dis* 2004; 39:539-45.

Cosgrove SE, Sakoulas G, Perencevich EN, *et al.* Comparison of Mortality Associated with Methicillin-Resistant and Methicillin-Susceptible Staphylococcus aureus Bacteremia: A Meta-analysis. *Clin Infect Dis* 2003; 36:53-9.

Deresinski S. Counterpoint: Vancomycin and *Staphylococcus aureus*-An antibiotic enters obsolescence. *Clin Infect Dis* 2007; 44:1543-8

Garner JS, Jarvis WR, Emori TG, *et al.* CDC definitions for nosocomial infections. *Am J Infect Control* 1988; 16:128-40.

Hidayat LK, Hsu DI, Quist R, *et al.* High dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med 2006*; 166:2138-44.

Jeffres MN, Isakow W, Doherty JA, *et al.* Predictors of mortality for Methicillin-resistant *Staphylococcus aureus* health-care-associated pneumonia: specific evaluation of vancomycin pharmacokinetic indices. *Chest* 2006; 130:947-55.

Kullar R, Davis SL, Levine DP, *et al.* Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis* 2011; 52:975-81.

Liu C, Bayer A, Cosgrove SE, *et al.* Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children. *Clin Infect Dis* 2011; 51:1-38.

Lodise TP, Graves J, Evans A, *et al.* Relationship between Vancomycin MIC and Failure among Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia Treated with Vancomycin. *Antimicrob Agents Chemother* 2008; 52:3315-20.

Lodise TP, Lomaestro B, Graves J, *et al.* Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother* 2008; 52(4):1330-6.

Maclayton DO, Suda KJ, Coval KA, *et al.* Case-control study of the relationship between MRSA bacteremia with a vancomycin MIC of 2 microg/mL and risk factors, costs, and outcomes in inpatients undergoing hemodialysis. *Clin Ther* 2006; 28:1208-16.

McDaneld PM, Spooner LM, Mohr JF, *et al.* Use of daptomycin to treat infections with methicillin-resistant *Staphylococcus aureus* isolates having vancomycin minimum inhibitory concentrations of 1.5 to 2 ug/mL. *Ann Pharmacother* 2013;47: 1654-65.

Meagher AK, Ambrose PG, Grasela TH. The Pharmacokinetic and Pharmacodynamic Profile of Tigecycline. *Clin Infect Dis* 2005; 41:333-40.

Mohr JF, Murray BE. Point: Vancomycin Is Not Obsolete for the Treatment of Infection Caused by Methicillin-Resistant *Staphylococcus aureus. Clin Infect Dis* 2007; 44:1536-42.

Moise-Broder PA, Sakoulas G, Elipopoulos GM, *et al.* Accessory gene regulator group II polymorphism in methicillin resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. *Clin Infect Dis* 2004; 38:1700-5.

Moore CL, Lu M, Cheema F, *et al.* Prediction of Failure in Vancomycin-Treated Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection: a Clinically Useful Risk Stratification Tool. *Antimicrob Agents Chemother* 2011; 55:4581-8.

Moore CL, Osaki-Kiyan P, Haque NZ, *et al.* Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. *Clin Infect Dis* 2012; 54:51-8.

Musta AC, Riederer K, Shemes S, *et al.* Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: Trends over 11 years. *J Clin Microbiol* 2009; 47:1640-4.

Neoh HM, Hori S, Komatsu M, *et al.* Impact of reduced vancomycin susceptibility on the therapeutic outcome of MRSA bloodstream infections. *Ann Clin Microbiol Antimicrob* 2007; 6:1-6.

Rybak M, Lomaestro B, Rotschafer JC, *et al.* Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 2009; 66:82-98.

Rybak MJ, Leonard SN, Rossi KL, *et al.* Characterization of vancomycin-heteroresistant *Staphylococcus aureus* from the metropolitan area of Detroit, Michigan, over a 22-year period (1986 to 2007). *J Clin Microbiol* 2008; 46:2950-4.

Sakoulas G, Moise-Broder PA, Schentag J, *et al.* Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004; 42:2398-402.

Sitthananun C, Keratisin P, Tongsai S, *et al.* Association Between the MIC Level of Vancomycin and Outcome of the Patient with MRSA Septicemia (Abstract). *J Infect Dis Antimicrob* 2014; 31(2):133.

Song JH, Hiramatsu K, Suh JY, *et al.* Emergence in Asian countries of *Staphylococcus aureus* with reduced susceptibility to vancomycin. *Antimicrob Agents Chemother* 2004; 48:4926-8.

Soriano A, Marco F, Martinez JA, *et al.* Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008; 46:193-200.

Yoon YK, Kim JY, Park DW, *et al.* Predictors of persistent methicillin resistant *Staphylococcus aureus* bacteraemia in patients treated with vancomycin. *J Antimicrob Chemother* 2010; 65:1015-8.