

# CLINICAL FEATURES, MICROBIOLOGY, AND VANCOMYCIN REGIMENS IN SEPSIS PATIENTS: A RETROSPECTIVE STUDY CONDUCTED AT A SINGLE INFECTIOUS DISEASES CENTER

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Despite increasing antibiotic resistance, vancomycin remains the first choice to treat severe infections due to drug-resistant gram-positive bacteria. This study aimed to summarise the clinical, microbiological, and vancomycin treatment outcomes in bacteremia patients. From July to December 2019, a retrospective cohort analysis was conducted on patients with bacteremia treated with vancomycin at a tertiary hospital in Hanoi, Vietnam. Patients without vancomycin concentrations were excluded from the study. Patients had a median age of 54 years (IQR, 41.8 - 63.3), with a male/female ratio of 1.86. Renal complication was markedly different;  $Cl_{cr} < 60$ , 60 - 130, and  $> 130$  mL/min was 29%, 60%, and 11%, respectively. The median Charlson score was 3.0 (2-4.3), the qSOFA score was 1 (1-2), and the NEWS score was 76%, with a median of 6 (5-8). Twenty-one cases had positive blood culture where 85.7% were gram-positive. 93% of patients with sepsis were treated with vancomycin as the first antimicrobial, of which 72% used vancomycin in combination with other antibiotics. Renal complications occurred in 12% of all patients, with grades R, I, and F accounting for 4%, 5%, and 3%, respectively. The median duration of treatment was 12 days (IQR, 7-17), with a success rate of 82% and a failure rate of 18%, respectively.

**Conclusions:** In most patients with bacteremia, microbiological tests reveal no detectable bacteria. When sepsis is suspected, a vancomycin regimen should be initiated.

**Keywords:** Vancomycin, Treatment Outcome, Bacteremia, Anti-Bacterial Agents, AUC/MIC.

## I. INTRODUCTION

Bloodstream infection (BSI) is a leading cause of morbidity and mortality in patients worldwide.<sup>1,2</sup> Antimicrobial resistance (AMR) rates, pathogen distribution, demographics, and medical care delivery can influence BSI epidemiology.<sup>3</sup> A growing number of bacteria, such as Methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-

resistant *Streptococcus pneumoniae* (PRSP), and ampicillin-resistant *Enterococcus sp.* (*E. sp.*), can cause nosocomial infections.<sup>4,5</sup> Furthermore, *S. aureus* with intermediate sensitivity to vancomycin (VISA), vancomycin resistance (VRSA), or vancomycin sensitivity (hVISA) presents a therapeutic challenge. Sepsis caused by *Staphylococcus aureus* (*S. aureus*) occurs at a rate of 38.2 to 45.7 cases per 100,000 individuals per year, with a 30-day death rate of up to 20%, imposing a significant financial burden on the health system economics of a country.<sup>4,5,6</sup>

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As a result, it is critical to regularly monitor BSI pathogens' microbiology developments worldwide. Examining microbiological trends can aid in the development of diagnostic procedures, treatment plans, and preventative programs. Vancomycin is the first-line antibiotic for treating sepsis caused by Gram-positive bacteria resistant to other antibiotics. However, there is a tendency for the minimum inhibitory concentration (MIC) to increase, and long-term use of high vancomycin dosages has several adverse effects, including liver and renal failure. Thus, monitoring vancomycin blood levels using pharmacokinetic parameters such as AUC/MIC and  $C_{\text{trough}}$  is critical in clinical practice to obtain therapeutic concentrations while minimizing drug toxicity.<sup>4,5,7</sup>

Bach Mai is one of the largest tertiary referral hospitals in northern Vietnam, with over 3000 beds and 20 clinical and subclinical departments. Sepsis caused by Gram-positive bacteria occurs at a relatively high rate of over 30%.<sup>8</sup> This study aimed to summarise the clinical, microbiological, and vancomycin treatment outcomes in bacteremia patients in the Infectious Diseases Ward. The findings will improve the management and treatment of severe bacteria patients and control multidrug-resistant infections.

## II. METHOD AND MATERIAL

We conducted a retrospective study. All patients were treated at the Center for Tropical Diseases - Bach Mai Hospital from July 2019 to December 2019.

Written informed consent was obtained from all patients before participation. Ethics approval was obtained from the Human Subjects Protection Committee of Bach Mai Hospital: Code BM-2015-103, number 785/QĐ – BM, signed by the Director of Bach Mai Hospital on September 30th, 2015. This study is in line with the STROCSS 2019 criteria.<sup>9</sup>

*Inclusion criteria:* Diagnosis of sepsis is based on bloodstream infections with bacteria or a SOFA score  $\geq 2$ .<sup>10</sup> The patient was treated for sepsis with a regimen that included vancomycin.

*Exclusion criteria:* Patients who have taken vancomycin for less than 48 hours. Patients who are under the age of 18 years old. Pregnant and breastfeeding woman.

The general characteristics of patients in the study sample include age, gender, weight, and creatinine clearance. Percentage of patients hospitalized within 90 days, urine catheter, nasogastric tube, and central venous catheter. Patients' severity grade on the qSOFA scale, NEWS.<sup>11,12</sup> Microbiological characteristics obtained from blood samples include the rate of positive blood cultures and the frequency of bacterial strains. The number of bacterial strains used to estimate the vancomycin MIC and the matching MIC value are indicated.

### *Definitions:*

The diagnosis of sepsis was based on the 2017 US Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) diagnostic criteria for infectious diseases.<sup>13</sup> The Charson scale examines the patient's comorbid conditions;<sup>11</sup> the qSOFA score predicts mortality rates and hospital stay length. The NEWS score is used to assess the detailed medical status.<sup>12</sup>

The creatinine clearance (Clcr) of the patient was determined using the Cockcroft–Gault formula (14). Renal failure group (Clcr  $60 \leq$  mL/min); normal group ( $60 \text{ mL/min} < \text{Clcr} < 130 \text{ mL/min}$ ); increased clearance group (Clcr  $\geq 130 \text{ mL/min}$ ).<sup>15,16</sup>

The MIC value of bacteria is the lowest inhibitory concentration of bacteria with vancomycin that has been determined using the E-test method by standards at the Department of Microbiology.<sup>17</sup>

Renal complications were suspected to be vancomycin-related when creatinine clearance was reduced by more than 25% from pre-initiation values, prolonged for at least two days, and occurred after at least 24 hours of vancomycin administration. Severity according to RIFLE criteria with the following levels: "R-Risk", "I-Injury", "F-Failure", "L-Loss", and "E-End Stage Kidney Disease".<sup>16</sup>

#### Statistical Analyses:

Categorical data are summarised using the number and percentage of cases. Means and ranges, or rates, are used to convey values. Mean and standard deviation (SD) are used for continuous variables. All statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL).

### III. RESULTS

From July 2019 to December 2019, 100 patients with bacteremia were qualified and treated with vancomycin at the Center for Tropical Diseases, Bach Mai Hospital.

**Table 1. Patient characteristics (n = 100)**

Characteristics	
Age, median (IQR)	54.0 (41.8 – 63.3)
Sex, male/female	65/35
Weight (kg), median (IQR)	54.0 (49.0 – 62.3)
Creatinine clearance (Clcr) (mL/min), median (IQR)	76.0 (55.8 – 102.0)
Clcr < 60, n (%)	29 (29)
60 ≤ Clcr < 130, n (%)	60 (60)
Clcr ≥ 130, n (%)	11 (11)
30 days of immunosuppressive/chemotherapy, n (%)	15 (15)
Ventilator, n (%)	16 (16)
Urinary catheterization, n (%)	17 (17)
Nasogastric tube, n (%)	14 (14)
Central venous catheter placement, n (%)	1 (1)
Charlson scale, median (IQR)	3.0 (2.0 – 4.3)
qSOFA ≥ 2, n (%), median, IQR	49 (49)
Septic shock, n (%)	7 (7)
NEWS scale ≥ 5, n, %	76 (76)

Patients had a median age of 54 years (IQR, 41.8 - 63.3), with a male/female ratio of 1.86. Renal complication was markedly different; Clcr < 60, 60 – 130, and > 130 mL/min was respectively 29%, 60%, and 11%. Mechanical ventilation,

urine catheter, nasogastric tube, and central venous catheter were 16%, 17%, 14%, and 1% of patients. The median Charlson score was 3.0 (2–4.3), the qSOFA score was 1 (1–2), and the NEWS score was 76%, with a median of 6 (5–8).

**Table 2. Microbiological characteristics in blood**

<b>Factors</b>	<b>Patient, n (%)</b>
Number of patients with positive blood infection (n = 100)	21 (21)
Number of blood samples (n = 178)	32 (18)
Gram (+) bacteria	18 (85.7)
MSSA	3 (14.3)
MRSA	12 (57.1)
MIC vancomycin= 1 mg/L	3
MIC vancomycin= 1,5 mg/L	2
MIC vancomycin= 2 mg/L	1
Streptococcus sp	3 (14.3)
Streptococcus agalactiae	2
Streptococcus consellatus	1
Gram (-)	3 (14.3)
Burkholderia pseudomallei	1 (4.7)
E. coli	1 (4.7)
Enterobacter cloacae	1 (4.9)

The blood of 21 patients contained bacteria. There were 85.7% of Gram-positive and 14.3% of Gram-negative bacteria (Table 2).

**Table 3. Vancomycin-containing antibiotic regimen for the treatment of sepsis**

<b>Antibiotic regimen</b>	<b>N (%)</b>		
	Empiric treatment	Continuous treatment	
	100 (100)	Microbiology (-)	Microbiology (+)
		79 (79)	21 (21)
Contains vancomycin	93 (93,0)	79 (100,0)	19 (90,5)
Vancomycin monotherapy	21 (21.0)	14 (17.7)	11 (52.4)
Vancomycin + Cephalosporin 3	20 (20)	18 (22.7)	3 (14.3)
Vancomycin + Piperacilin-tazobactam	1 (1)	1 (1.3)	0 (0.0)
Vancomycin + Carbapenem	56 (56)	30 (38.1)	2 (9.5)
Vancomycin + Fluoroquinolone	9 (9)	9 (11.3)	2 (9.5)
Vancomycin + Aminoglycoside	5 (5)	6 (7.6)	1 (4.8)
Vancomycin + Sulfamethoxazol/trimethoprim	1 (1)	1 (1.3)	0 (0)
None vancomycin	7 (7)	0 (0)	2 (9.5)

93% of patients with sepsis were treated with vancomycin as the first antimicrobial, of which 72% used vancomycin in combination with other antibiotics (Table 3).

**Table 4. Renal complications and therapeutic outcomes**

Variable		
Number of patients with complications, n (%)	12 (12)	
Time of occurrence of events (day), mean $\pm$ SD	9.7 $\pm$ 4.5	
Classification, n (%)	R- Risk	4 (4)
	I - Injury	5 (5)
	F - Failure	3 (3)
Duration of treatment (day), median (IQR)	12.0 (7.0 - 17.1)	
Outcomes, n (%)	Symptomatic relief/healing	82 (82)
	Mortality	18 (18)

Renal complications occurred in 12% of all patients, with grades R, I, and F accounting for 4%, 5%, and 3%, respectively. The mean time to event onset was 9.7 days. The median

duration of treatment was 12 days (IQR, 7-17), with a success rate of 82 % and a failure rate of 18%, respectively (Table 4).

#### IV. DISCUSSION

Gram-positive bacteria-caused sepsis is rising in hospitals worldwide.<sup>1,2</sup> From 38.2 to 45.7 per 100,000 people per year, *staphylococcus aureus*-associated necrotizing fasciitis (*S. aureus*-associated bacteremia) is reported.<sup>3</sup> At Bach Mai Hospital, the rate of bacteremia caused by Gram-positive bacteria and *S. aureus* was 23.4% and 11.9%, respectively.<sup>8</sup> However, the trend toward raising the vancomycin MIC on these bacteria strains, combined with the development of VISA, VRSA, and hVISA strains, offers numerous challenges in assuring therapy success in patients.

The patients have a median age of 54 years, with more males than females. Renal function varies significantly in different categories; numerous diseases are related with a Charlson score of 3.0 (2–4.3), qSOFA score of 49%, and NEWS score of 76% (Table 1). In Yong Pil Chong's study, the patients had a median age

of 59 years, ranging from 49.5 to 68 years of age; males accounted for 64%, and the median Charlson score (interquartile range) was 3 (2–5) points.<sup>6</sup> In the study of Kovach (2019), the patients had a median age of 52 years; men accounted for 70%, and qSOFA had a median of 1 (qSOFA  $\geq$  2 accounted for 45%).<sup>1</sup> The proportion of patients who undergo invasive procedures and interventions is deficient. This finding is consistent with Jonathan Seah's study, which included most patients (64%) who had previously been hospitalized and 18.4% of patients on mechanical ventilation.<sup>18</sup>

Due to the low probability of positive blood infection, Gram-positive bacteria accounted for most isolates (32.9 - 50.4%), while *S. aureus* strains accounted for 16.7 - 16.8%, consistent with several published investigations.<sup>8</sup> Vancomycin susceptibility testing should be performed using the MIC approach, as

recommended by CLSI 2019.<sup>17</sup> However, only six individuals with MRSA isolates got vancomycin MICs out of twelve. This result partly demonstrates that the vancomycin MIC's determination has not received sufficient attention. The MIC values of 1 mg/L, 1.5 mg/L, and 2 mg/L for MRSA strains were 3, 2, and 1 patient. Similar findings were obtained in a study conducted by Yong Pil Chong using the vancomycin ratio MIC = 1.5 and MIC = 2 (mg/L) against MRSA strains up to 53.3 % and 20%, respectively.<sup>6</sup>

To date, vancomycin is the first-choice treatment for sepsis caused by Gram-positive bacteria resistant to other antibiotics.<sup>4,5,7,19</sup> In our study, vancomycin was indicated in the initial antibiotic regimen for empiric treatment of sepsis in most patients (93%). Because most patients have multi-resistant hospital-acquired infections, it is essential to combine antibiotics to achieve the disease's etiology. After microbiological results are obtained, antibiotic regimens are continued in patients who cannot isolate bacteria from blood to ensure that the agent continues to be covered as advised by treatment guidelines. The antibiotic regimen adopted in patients with positive blood tests (21 individuals) changed considerably into bacterial target therapy. The proportion of patients receiving vancomycin monotherapy jumped to 52.4%. However, three patients had their bacteria detected as MSSA but were still treated with vancomycin due to available antibiotics in the hospital. This is not consistent with current recommendations when de-escalation with antibiotics with a spectrum of action on MSSA can be considered.<sup>19,20</sup>

According to research conducted at Cho Ray Hospital, 50% of kidney damage was caused by septic shock, and vancomycin was a significant risk factor.<sup>21</sup> In this trial, only 12 %

reported renal complications, with the majority of those at risk (R) and injury (I). In the study of Yong Pil Chong (2013), Siegbert Rieg with recorded mortality rates of 20.7% and 22%, respectively.<sup>2,6</sup>

Limitations remain in our study. Firstly, a retrospective study with small sample size is likely to have bias. Secondly, we have not been responsible for observing the patient's recovery or any other side effects that may develop after leaving the hospital.

## CONCLUSION

In most patients with sepsis, microbiological tests reveal no detectable bacteria. When sepsis is suspected, a vancomycin regimen should be initiated.

### Abbreviations:

IQR Interquartile range., qSOFA quick Sequential Organ Failure Assessment; NEWS National Early Warning Score; BSI Bloodstream infection; AMR Antimicrobial resistance; MIC Minimum Inhibitory Concentration.

### Conflicts of interest:

The authors declare that they have no competing interests.

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**Author contribution:** TTH study concept, data collection, data analysis, writing the paper; TQS, THH writing the article, and final editing manuscript; NCC review literature, final editing manuscript.

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