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RESEARCH PROTOCOL

# Continuous vancomycin infusion versus intermittent infusion in critically Ill patients: The research protocol

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The authors declare no conflicts of interest associated with this manuscript.

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## ABSTRACT:

**Background:** Methicillin-resistant Staphylococcal and Enterococcal infections are important problems in intensive care units (ICUs). Vancomycin is a drug of choice, and continuous administration has long been proposed as an alternative method with better therapeutic benefits. This study aims to examine information on the benefits of continuous vancomycin infusion (CVI) compared with the intermittent vancomycin infusion (IVI) method.

**Methods:** A quasi-experimental study with a propensity score-matched historical control involves adult patients in medical or surgical ICUs. In the experimental group, 31 patients for whom vancomycin is indicated will be enrolled to receive CVI for at least 48 hours with therapeutic drug monitoring according to the study protocol. For the historical control group, data of patients who received IVI between January 2018 and October 2020 will be retrospectively reviewed. Capability to achieve serum vancomycin therapeutic target within 48 hours, 96 hours, the incidence of supra- and subtherapeutic level, treatment successfulness, mortality, and incidence of acute kidney injury (AKI) between the two infusion methods will be analyzed before and after one-to-two propensity score matching.

**Ethics and dissemination:** The study was approved by the institutional review boards of Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 027/2021). We plan to disseminate the results in peer-reviewed critical care medicine or infectious disease-related journals and national and international conferences.

**Trial registration:** TCTR20210122005. Registered on January 22, 2021, with Thai Clinical Trials Registry

**Keywords:** Continuous infusion, Pharmacodynamic, Vancomycin

## INTRODUCTION

Nosocomial gram-positive pathogens such as Methicillin-resistant Staphylococcus aureus (MRSA) and Enterococci are important hospital-acquired infections. Vancomycin, a glycopeptide antibiotic, is considered the first-line agent. Due to poor oral bioavailability, vancomycin needs to be administered intravenously. Serum vancomycin will be in the distribution phase 30-60 minutes after infusion, given the volume of distribution (Vd) of 0.4-1 L/Kg. The drug is not metabolized and is excreted mainly via the renal route. The half-life of vancomycin is 6-12 hours in patients with normal renal function. In those with renal impairment patients, the excretion will become slower and need a dose adjustment [1].

The antimicrobial activity of vancomycin varies directly with the area under the concentration curve divided by the minimal inhibitory concentration (AUC/MIC) [1-4]. In a human pharmacodynamic study, the 24-hour area under the concentration curve (AUC24) divided by the minimal inhibitory concentration (AUC24/MIC) value of ≥ 400 is associated with a successful treatment outcome [4-6]. If the drug level is maintained constantly low, the resistant organism can be developed [2, 6]. Thus, vancomycin therapeutic drug monitoring (TDM) is crucial to treatment success.

The infectious disease society of America (IDSA) launched therapeutic guidelines in 2009, recommending TDM using "trough level" before the fourth dose between 15-20 mg/L in serious MRSA infection. With this range, the AUC24/MIC should achieve a level of > 400 in most MRSA infected patients if the minimum inhibitory concentration (MIC) ≤ 1. For non-serious MRSA infections, the vancomycin trough level range can be lower, between 10-15 mg/L [6]. Later, evidence showed that "trough level" was not a promising therapeutic target because it might imply AUC24/MIC of > 400 but was unable to tell the exact value of AUC24/MIC and risk for overdoses. In 2020 the new recommendation from IDSA suggested using AUC24/MIC between 400-600 as TDM target for MRSA infection [7]. On the other hand, there is a lack of evidence to determine the TDM target for Enterococcal and other gram-positive pathogens infection [8-10].

TDM with AUC for IVI is not practical because of the need for multiple vancomycin levels for calculation or using Bayesian-derived AUC monitoring. Thus, TDM with trough level measurement remains the standard method in Thailand.

Recently, CVI was introduced. This method has been shown to achieve the therapeutic target more rapidly [11-14], provide a steadier drug level [11], and tend to reduce renal toxicity [15, 16]. The TDM is less complicated, the serum concentration measurement can be performed at any time in the steady stage, and AUC can be easily calculated with fewer samples and without complex statistics. CVI still has some concerns, phlebitis, and compatibility with other drugs [17].

In critically ill patients, we need rapid achievement and regular maintenance in the therapeutic target and avoiding adverse drug reactions. Hence, we conduct a study to compare the capability of achieving the therapeutic target between CVI and IVI.

### KEY MESSAGES:

- This study compares the capability of the experimental continuous vancomycin infusion (CVI) in attaining the therapeutic target within 48 hours to the conventional intermittent vancomycin infusion (IVI).
- We hypothesize that the CVI method should be better in attaining the therapeutic target and be considered an alternative method for critically ill patients.

## OBJECTIVES

### Primary Objective

• The primary objective is to compare the capability of achieving vancomycin therapeutic target within 48 hours between CVI and IVI methods.

### Secondary Objectives

• Secondary objectives are to compare the capability of achieving vancomycin therapeutic target within 96 hours, the number of subtherapeutic and supratherapeutic serum vancomycin concentrations within 96 hours, and the adverse drug reactions between the two infusion methods. The rate of successful treatment, mortality, and AKI will be assessed for those who received vancomycin as a definite treatment.

## MATERIAL AND METHODS

### Study Design and setting

This study is quasi-experimental with propensity score-matched historical control, conducted in the medical and surgical ICUs, Faculty of Medicine, Siriraj hospital, Mahidol University, Thailand.

### Eligibility Criteria for the experimental (CVI) group

### Inclusion criteria

1. Adults (18 years and older)
2. Infection or suspected infection from Staphylococcus aureus or methicillin-resistant coagulase-negative Staphylococci
3. Vancomycin is anticipated to be continued for at least 48 hours
4. Creatinine clearance by Cockcroft-Gault formula more than 30 ml/min/1.73m$^2$ [18]

### Exclusion criteria

1. History of receiving vancomycin within 48 hours before the enrollment
2. History of vancomycin allergy
3. Pregnant or lactating woman
4. Patient with AKI according to acute kidney injury network (AKIN) classification at the time of enrollment [19]
5. Body mass index below 15 kg/m$^2$
6. Receiving renal replacement therapy or extracor-

poreal membrane oxygenator

7. The treating physician considers the patient inappropriate for CVI
8. Do-not-resuscitation and terminally ill condition
9. Denials the consent

### Withdrawal criteria

1. Does not receive CVI
2. Receiving vancomycin less than 48 hours after being enrolled in the study
3. Dose not be measured serum vancomycin concentration at least two times after the enrollment
4. Receiving renal replacement therapy or extracorporeal membrane oxygenator within 48 hours after the enrollment
5. Withdraws the consent

### Eligibility Criteria for the historical control IVI group

### Inclusion criteria

1. Adults (18 years and older)
2. Receiving vancomycin for treatment of infection or suspected infection from Staphylococcus aureus or methicillin-resistant coagulase-negative Staphylococci
3. Creatinine clearance by Cockcroft-Gault formula more than 30 ml/min/1.73m$^2$ [18]
4. Receiving IVI according to Siriraj hospital protocol (loading dose of 25-30 mg/kg and maintenance with 15-20 mg/kg every 8-12 hours)
5. Being measured vancomycin trough level within 48 hours

### Exclusion criteria

1. History of receiving vancomycin within 48 hours before the enrollment
2. History of vancomycin allergy
3. Pregnant or lactating woman
4. Patient with AKI according to acute kidney injury network (AKIN) classification at the time of inclusion [19]
5. Body mass index below 15 kg/m$^2$
6. Receiving renal replacement therapy or extracorporeal membrane oxygenator
7. Documented do-not-resuscitation and terminally ill condition

### Recruitment and consent

Investigators will directly contact the physicians who are in service at medical and surgical ICUs and ask them to notify the investigators if they are going to give vancomycin to the patient.

The investigator will check for inclusion and exclusion criteria. If the patient is eligible, the investigator will visit the patient or relatives (if the patient cannot make the informed consent) at the ward during the loading period to inform and ask for the consent. If the relative is not present at the ward or not available at that time, the investigator will call to inform, ask for initial consent, and make an appointment to make the formal informed consent later.

### Intervention

The patient who is infected or suspected of infection from Staphylococcus aureus or methicillin-resistant coagulase-negative Staphylococci, diagnosed by the treating physician and needs vancomycin for treatment, will be loaded with vancomycin 25-30 mg/kg (actual body weight, maximum loading dose of 3,000 mg) as soon as possible.

After the consent is given, the maintenance dose of vancomycin will be continuously infused according to the study protocol. In contrast, if no consent is given, the method of administration is considered by the treating physician, and the patient will be excluded from the study.

Other treatments such as other antibiotics, vasoactive agents, ventilatory management, or nutritional support are directed by the treating physician according to the standard of care.

### Research procedures

### Continuous vancomycin infusion protocol (Figure 1, 2)

Every patient will be tested for complete blood count, serum creatinine, and total bilirubin if there is no previous result. The therapeutic serum vancomycin concentration range for CVI in this study is 15-20 mg/L.

### Drug preparation and administration

- Vancomycin will be diluted in normal saline solution to the concentration of 10 mg/ml.
- The daily dose of vancomycin [20] continuous infusion (mg/day) = (17 × CrCl) + 100
- The drug will be 24-hour continuously infused with an infusion pump
- Creatinine clearance (CrCl) is calculated using Cockcroft-Gault formula [18]

### Vancomycin TDM and adjustment

- Serum vancomycin concentration will be measured 24 hours after continuous infusion.
    - o If serum vancomycin concentration is within 15-20 mg/L, the current dose will be continued.
    - o If serum vancomycin concentration is below 15 mg/L, the daily dose will be increased 480 mg/day.
    - o If serum vancomycin concentration is over 20 mg/L, the daily dose will be decreased 480 mg/day.
- After the first measurement, serum vancomycin concentration will be measured every 24 hours and adjusted according to the protocol until serum vancomycin concentration is maintained within 15-20 mg/L for two consecutive times. Then the serum concentration will be measured every five days. If there are any critical clinical changes or treating physician concerns, an additional serum vancomycin test is applicable.
- The maximum daily dose of vancomycin for continuous infusion is 3,000 mg/day.
- After 48 hours of continuous infusion, the treating physician will be encouraged to continue using the CVI method until the end of treatment, but the treating physician can switch to IVI as appropriate.

### Vancomycin discharge

- Vancomycin can be discharged if there is no indication left or for other appropriate reasons.

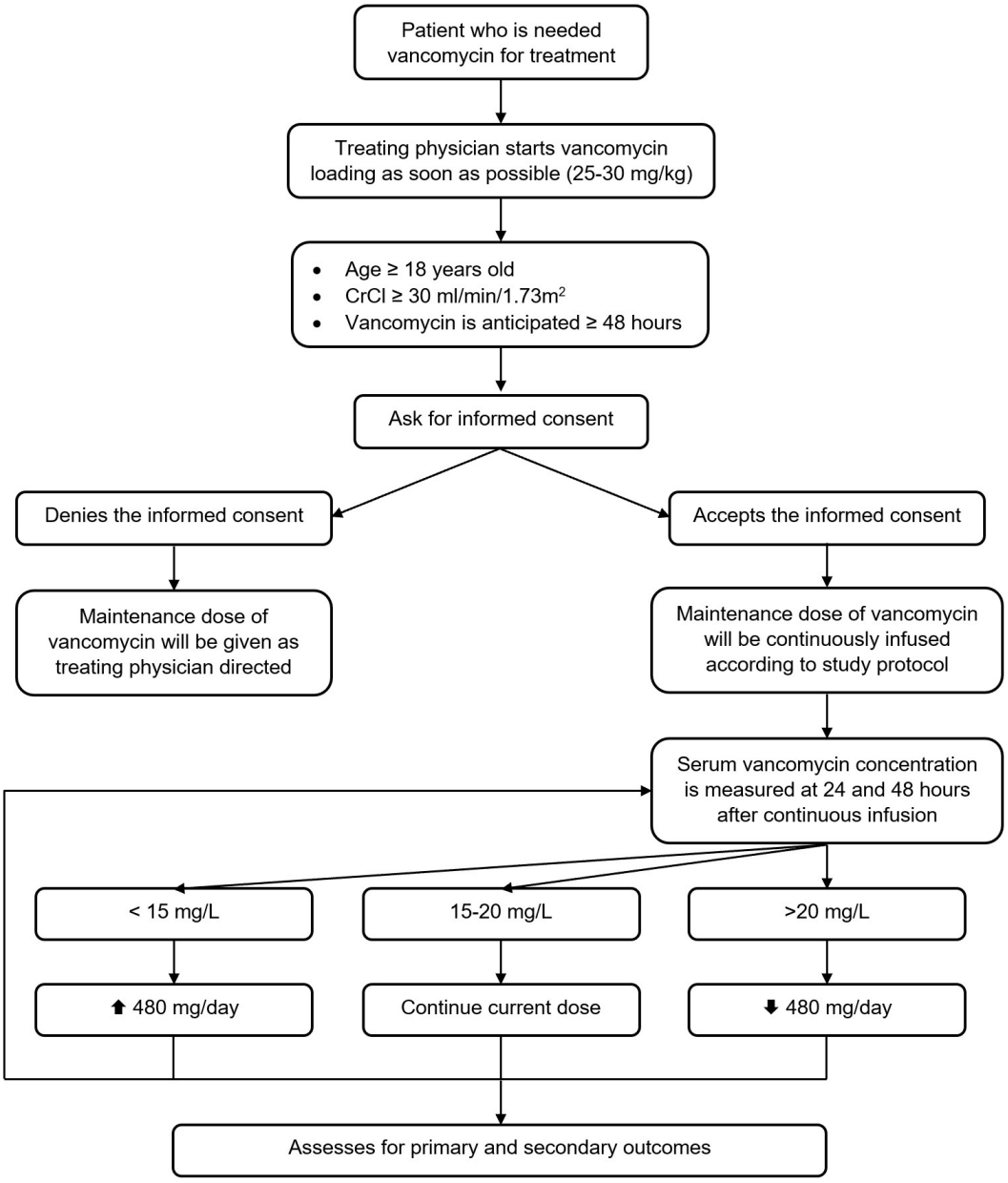


**Figure 1.** Continuous vancomycin infusion protocol.
Abbreviation: CrCl, creatinine clearance

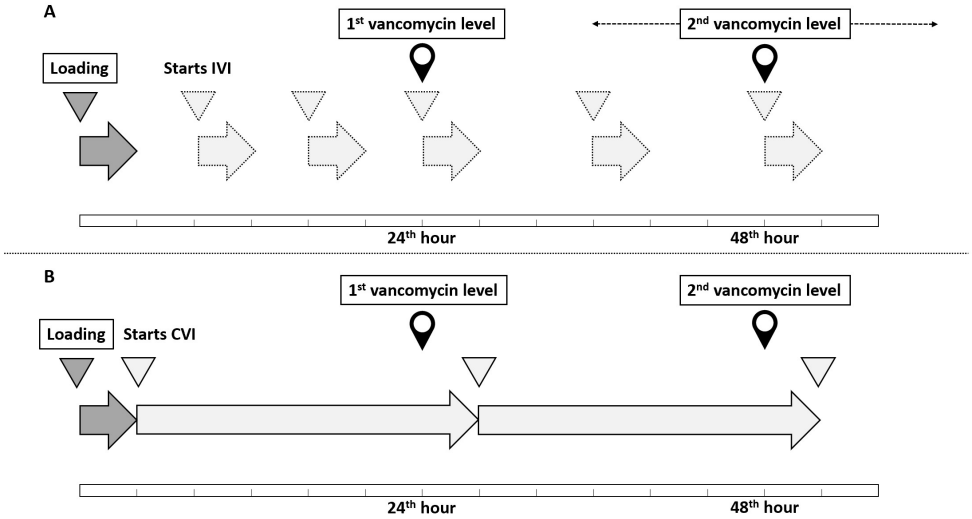


**Figure 2.** Comparing intermittent infusion and continuous infusion protocol.
Abbreviation: IVI, intermittent vancomycin infusion; CVI, continuous vancomycin infusion

### Safety monitoring

- The patient will be tested for complete blood count and serum creatinine on days 2 and 7 to monitor AKI and drug-induced cytopenia.
- If vancomycin is administered via a peripheral vein, the nurse will assess phlebitis at the beginning of every shift.
- Every patient will be assessed for tinnitus and alteration of hearing after the end of vancomycin treatment, and if there are any changes compared with before, the patient will be sent for an otoacoustic emissions test and further otolaryngologist visit.

### Intermittent vancomycin infusion protocol (Figure 2)

In our institution, the protocol for IVI consists of a 25-30 mg/kg (actual body weight) loading dose and 15-20 mg/kg maintenance every 8 to 12 hours. TDM will be made by measuring vancomycin trough level 30 minutes before the fourth dose. The treating physician will direct the dosage adjustment to keep the trough level between 15 to 20 mg/L.

Medical records of patients in medical and surgical ICUs who received vancomycin from January 2018 to October 2020 will be retrospectively reviewed. All the patients who met the inclusion criteria will be included in the study.

Only serum vancomycin levels intended for trough level measurement will be counted in this study.

### Outcome Measurement

### Primary outcomes

- Incidence of any serum vancomycin levels, steady stage for the CVI group or trough for the IVI group, between 15 and 20 mg/L within 48 hours

### Secondary outcomes

For all included patients

- Incidence of serum vancomycin level, steady stage for the CVI group or trough for the IVI group, between 15 and 20 mg/L within 96 hours
- Number of subtherapeutic and supratherapeutic serum vancomycin concentrations within 96 hours
- Incidence of treating physician documented vancomycin related adverse drug reactions, namely drug-induced cytopenia, phlebitis, and ototoxicity

For those who receive vancomycin as a definite treatment, defined by culture positive for pathogen susceptible to vancomycin and the drug is given for at least 96 hours.

- Incidence of successful treatment, defined by resolving of infection assessed clinically by any of defervescence, improvement of prior signs and symptoms, or vanishing of the pathogen from the source of infection.
- 14-day mortality and hospital mortality
- Incidence of AKI, defined by serum creatinine raising ≥ 0.3 mg/dL or 1.5 times from baseline [19]

### Study flow diagram

(Figure 3)

### Sample Size Estimation

The primary objective of this study is to compare the capability to achieve vancomycin therapeutic target within 48 hours between CVI and IVI methods.

From the literature review, 41% of patients using the CVI method have the serum vancomycin level within the therapeutic target compared with 11% in the IVI method [21].

For a 95% confident interval (Z = 1.96) with a power of 90% (β = 0.1), the sample size was calculated using the "Test for two independent proportion formula (without continuity correlation)."

$$n = \left[\frac{Z_{1-\alpha/2}\sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)}+Z_{\beta}\sqrt{p_1q_1+\left(\frac{p_2q_2}{r}\right)}}{\Delta}\right]^2$$

$$n = \left[\frac{1.96\sqrt{0.21\times0.79\left(1+\frac{1}{2}\right)}+1.28\sqrt{0.41\times0.59+\left(\frac{0.11\times0.89}{2}\right)}}{0.3}\right]^2$$

$$n = 31$$

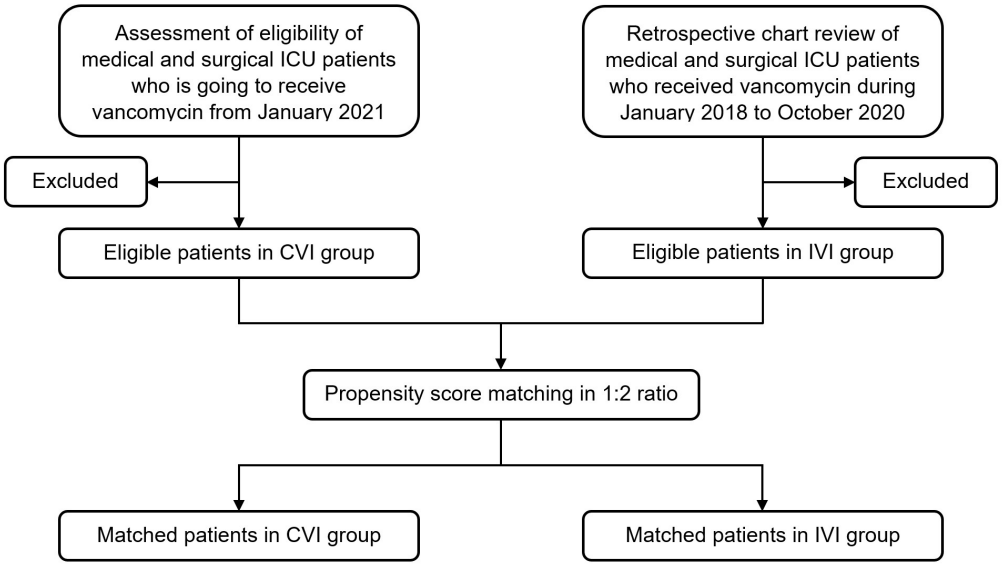


**Figure 3.** Study flow diagram

Abbreviation: ICU, intensive care unit; IVI, intermittent vancomycin infusion; CVI, continuous vancomycin infusion

where $\bar{p}=\frac{p_1+p_2 r}{1+r}=\frac{0.41+(0.11\times 2)}{1+2}=0.21$

$\bar{q}=1-\bar{p}=1-0.21=0.79$

$r=\frac{n_2}{n_1}=2$ (ratio)

$\Delta=p_1-p_2=0.41-0.11=0.3$

$q_1=1-p_1=1-0.41=0.59$

$q_2=1-p_2=1-0.11=0.89$

From the calculation, at least 31 subjects are needed in the CVI group. A 20% increment (7 subjects) is added in the CVI group to prevent missing data. We plan to use one-to-two propensity score matching for the patients in the IVI group, and thus 62 subjects are needed.

## DATA MANAGEMENT AND DATA MONITORING

### Data Collection

The case report form is used to collect baselines, interventions, and outcomes. All data will be imported into the study database by the investigators.

### Data Management

The principal investigator is responsible for managing the study data to ensure the data's authenticity, integrity, and privacy during the research process.

### Statistical Method

In order to balance key characteristics, propensity scores estimated by using a logistic regression model with one-to-two matching will be used.

Demographic parameters are presented descriptively for the two groups. The normal quantitative variables will be described using mean and standard deviation. The remaining data will be described using the median and interquartile range.

The primary outcome, qualitative data, will be analyzed using Chi-square or Fisher's exact test. Other qualitative outcomes will be analyzed using Chi-square or Fisher's exact test, and for quantitative data, an independent t-test or Mann-Whitney U test will be used.

### Interim analyses

The interim analysis will occur after 30% of progression or one year after the enrollment starts.

## DISCUSSION

CVI has shown some benefits over IVI, such as earlier target attainment [11-14], less serum concentration variability [11], ease in TDM, and less renal toxicity [15, 16]. To date, we still have limited evidence supporting the CVI method, and therefore a robust recommendation cannot be made. This study aims to compare the capability to achieve vancomycin therapeutic target within 48 hours between the two-infusion method and fill this knowledge gap.

Some studies focused on better target attainment between both methods. However, most of them were retrospective and did not mention how the two groups were properly compared [13, 14, 22, 23]. A few randomized controlled trials were conducted, but patients in the IVI group did not receive a loading dose, which has raised a concern that the better target attainment in the CVI group may be influenced by the loading dose, not the infusion method itself [11, 12]. The CVI regimen in this study is derived from Waineo et al. [20], which targeted a steady concentration of 17.5 mg/L, which is equal to AUC24 of 420 mg·24h/L; thus, we decided to use the same target concentration of 15-20 mg/L for both groups, but we use 480 mg/day dosage adjustment instead of 500 mg/day due to ease in adjustment by decreasing or increasing the rate of infusion by 2 ml/hour.

The strength of this study includes the study design, the adequate dosage regimen, and the clear pharmacological outcome. The study design includes a recent historical control in which the IVI protocol is currently in use in our institution, and propensity-score matching helps balance key characteristics between the group, making it more comparable. We provide an adequate loading dose for both groups, eliminating many previous studies' main confounder of concern. The serum concentration is a robust outcome that is most related to the infusion method and less affected by other concomitant treatments.

Nevertheless, this study also has some limitations. First, the primary outcome of this study is evaluated at 48 hours, which is the average time that the patient usually receives vancomycin before a microbiological result arrives. This may be too early to adjust the drug to the target range. For this reason, we will encourage the treating physician to continue the CVI method until the end of treatment. Second, the CVI protocol has the serum concentration tested at 24 and 48 hours; in contrast, the IVI protocol will have the first serum concentration tested before the fourth dose, which will be at 24 or 36 hours, and the latter test will base on treating physician decision. So, serum concentration tends to be tested more regularly and frequently in the CVI group. However, the investigators have plans to evaluate the achievement of the therapeutic target at 96 hours and the number of dose adjustments as secondary outcomes. Lastly, propensity-score matching also has its limitation; it adjusts only observed confounding variables but does not eliminate bias due to unobserved confounding variables.

If the results are satisfying, the CVI protocol will be considered an attractive alternative method of vancomycin administration, especially in critically ill patients whose vancomycin should be closely monitored and optimized based on pharmacokinetic/pharmacodynamic principles for a better outcome with less adverse effects.

## ETHICS

The study was approved by the institutional review boards of Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 027/2021) and has been registered with Thai Clinical Trials Registry (TCTR20210122005).

## CONFIDENTIALITY

A unique number represents the subject's information, and the coded data is stored at the department of critical care medicine, Faculty of Medicine Siriraj Hospital. The results of this study will be published in peer-review journals without specific information on each subject. The study data will be retained for two years after the study is finished, after that, the study data will all be disposed.

## DISSEMINATION POLICY

The results of this study will be presented at national and international conferences and published in peer-review journals. The dataset that supports the findings of this study is available from the principal investigator upon reasonable request.

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## AUTHORS' CONTRIBUTIONS

Chairat Permpikul provided study conceptualization and funding acquisition. Chailat Maluangnon contributed to data curation, formal analysis, and methodology. Both authors were responsible for project administration, visualization, manuscript writing, and editing.

## SUPPLEMENTARY MATERIALS

none

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