The Impact of Early Achievement of Therapeutic Levels of Vancomycin in Critically Ill Patients With Confirmed Gram-Positive Infection: A Retrospective Cohort Study

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Abstract

Background

Vancomycin is a commonly used antibiotic in critically ill patients for various indications. Critical illness imposes pharmacokinetic-pharmacodynamics challenges which makes optimizing vancomycin in this population cumbersome. Data are scarce on the clinical impact of time to therapeutic trough levels of vancomycin in critically ill patients.

Objective (s)

The aim of this study to evaluate the timing to achieve therapeutic trough level vancomycin on 30-day mortality in critically ill patients.

Setting

Adult critically ill patients admitted to intensive care units (ICUs) between January 1st, 2017 and December 31st, 2018 at a tertiary teaching hospital.

Method

A retrospective cohort study for all adult critically ill patients aged 18 years or older with confirmed gram-positive infection and received vancomycin. We compared early (<48 hours) versus late (≥ 48 hours) attainment of vancomycin therapeutic trough levels.

Main outcomes

Primary outcome was the 30-day mortality in critically ill patients. Secondary outcomes were development of resistant organisms, eradicating microorganisms within 4-5 days of vancomycin initiation, vancomycin-induced acute kidney injury (AKI), and ICU LOS.

Results

Two hundred and nine patients were included. No significant differences between comparative groups in baseline characteristics. Achieving therapeutic levels were associated with better survival at 30 days (OR: 0.48; 95% CI [0.26-0.87]; p<0.01). Additionally, patients who achieved therapeutic levels of vancomycin early were less likely to develop resistant organisms (OR=0.08; 95% CI [0.01-0.59]; p=0.01). Acute kidney injury (AKI) and ICU length of stay (LOS) were not significant between the two groups.

Conclusion

Early attainment of vancomycin therapeutic levels was associated with possible survival benefit.

Impacts On Practice

- Early achieving of therapeutic level vancomycin in patients with confirmed gram-positive infection associated with survival benefit.
- Attainment of therapeutic levels early may decrease the development of vancomycin-resistant organisms.

Introduction

Infections may induce sepsis/septic shock, which is common in critically ill patients [1]. Mainly, gram-positive infections are a growing concern given their resistant patterns, including methicillin-resistant Staphylococcus aureus (MRSA) with a reported mortality rate of up to 55% in critically ill patients [2, 3]. Vancomycin is still commonly used for suspected or confirmed gram-positive infections in critically ill patients, despite having newer antimicrobial therapies with MRSA coverage [3–8]. The optimal dosing for vancomycin in critically ill patients is still unclear, despite being in the market for over 60 years [6, 7, 8].

Vancomycin requires a deep understanding of its pharmacokinetic-pharmacodynamic (Pk-PD) properties in various patient populations, and due to its narrow therapeutic index, vancomycin requires frequent therapeutic drug monitoring (TDM) to determine its safety and efficacy [4, 9]. Critically illness may significantly impact patients' volume of distribution, metabolism, and excretion, which adds another hurdle in promptly achieving therapeutic levels [9]. Several factors associated with failure to achieve initial therapeutic vancomycin trough levels in critically ill patients include male gender, young patients, not receiving loading dose, augmented renal clearance (ARC), and high albumin levels [3–5]. The recent recommendation suggested that the area under the curve (AUC)-guided vancomycin monitoring strategy should be utilized in patients with MRSA infections due to superiority in efficacy as well as nephrotoxicity data [7, 8]. However, due to the complexity of AUC-guided vancomycin monitoring in clinical practice, the vancomycin trough level remains the most common and practical method for monitoring vancomycin efficacy and safety [8].

Vancomycin-induced acute kidney injury remains the most common adverse drug reaction (ADR) with the current TDM strategy that carries an increased risk of prolonged hospitalization [3, 4, 7, 8]. The fear of this ADR may cause some practitioners to be hesitant in dosing vancomycin, which may be predisposing patients to have more resistant organisms [3, 5]. Time to check therapeutic vancomycin trough levels was recommended to be drawn immediately before the fourth dose, which would be within two days per the previous TDM consensus from the American society of health-system pharmacists (ASHP), the infectious diseases society of America (IDSA), and the society of infectious diseases pharmacists (SIDP) [7, 8].

According to our knowledge, no study evaluates the timing to reach the therapeutic trough level in correlation with critically ill patients' clinical outcomes. Therefore, we aimed to study the correlation of early achievements of therapeutic trough levels of vancomycin on 30-day ICU mortality in critically ill patients.

Methods

Study design

A retrospective, observational study of critically ill patients admitted to intensive care units (ICUs) with confirmed Gram-positive infections (e.g., MSSA, MRSA) and received intravenous vancomycin. All patients who met our inclusion criteria during the study period from 01/01/2017 to 31/12/2018 were included. Patients were divided into two groups based on the timing of achieving therapeutic vancomycin trough level during their ICU stay to an early and late group. We defined the early group as achieving therapeutic vancomycin trough levels within 48 hours of the first intravenous vancomycin exposure. The initial therapeutic trough target levels were determined according to infection types as 15–20 mg/L for severe infections (sepsis, pneumonia, meningitis, osteomyelitis, bacteremia, and endocarditis) and 10–15 mg/L for other infections. Vancomycin trough levels were obtained 30 minutes before the fourth dose (without a loading dose) and the third dose (with loading dose) in all patients included. Clinical pharmacy is a consulting service at KAMC. Critical care pharmacists are responsible for vancomycin therapeutic drug monitoring (TDM) in their respected critical care units. No specific nomogram was followed.

Bacteria were identified in the blood, urine, wound, drainage, cerebrospinal fluid (CSF), and respiratory specimens. Gram stain is used to differentiate between gram-positive and negative bacteria. Blood and MacConkey agar are used to culture microorganisms; after 24 hours of incubation, a single colony is selected and smeared directly as a thin film on a Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) biomerieux for pathogen identification, then VITEKR 2 is used thereafter to determine susceptibility.

Confirmed infection defined as sputum or endotracheal aspiration shows growth ≥ of 100,000 CFU/ml; bronchoalveolar lavage (BAL) shows growth ≥ of 10,000 CFU of single organism/ml for protected specimen brushes (PSBs), and ≥ 100,000 CFU of single organism/ml for BAL fluid. Additionally, urinary cultures were considered significant if showing a growth of ≥ 100,000 CFU/ml of no more than two species of microorganisms [30]. Cultures were excluded if the laboratory reported them as a "contaminant sample."

Eligibility criteria

Patients were enrolled in the study if they were critically ill, aged 18 years or older with confirmed gram-positive infection, and received IV vancomycin between 01/01/2017 to 31/12/2018. Exclusion criteria include using vancomycin empirically without continued treatment (Duration < 3 days) and no available vancomycin trough reading. Besides, patients with ICU length of stay (LOS) ≤ 1 day or > 60 days and/or labeled as "Do-Not-Resuscitate" status within the first 24 hours of ICU admission were excluded due to futility of care (Fig. 1).

Setting

This study was conducted in the adult medical, neuro, transplant, surgical, trauma, and burn ICUs at the National Guard Health Affairs - King Abdulaziz Medical City (KAMC), a tertiary-care academic referral hospital in Riyadh, Saudi Arabia.

Ethics approval and consent to participate

The study was approved in November 2020 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Reference No: RC20/587/R). Participants' confidentiality was strictly observed throughout the study using the anonymous unique serial number for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per the governmental and local research center's policy.

Data collection

Demographic data, Acute Physiology And Chronic Health Evaluation II (APACHE II) score, comorbidities, laboratory tests, cultures (Blood, Skin, Respiratory, Urine, CSF), microorganism (s), vancomycin date of administration, duration of vancomycin, vancomycin trough concentrations, time to reach the therapeutic levels, development of resistant organisms (e.g., Vancomycin Intermediate Staphylococcus Aureus (VISA), Vancomycin-Resistant Staphylococcus Aureus (VRSA) or Vancomycin-Resistant Enterococcus (VRE)), vancomycin induced acute kidney injury(VIN), the needs of dialysis, ICU mortality, ICU LOS were collected from an electronic record system (Best Care system). All variables have been compiled in an electronic data collection sheet. Patients were followed during ICU stay until death or discharge, whichever occurred first.

Endpoint (s)

The primary endpoint was to evaluate the association between timing of achieving therapeutic levels of vancomycin (early vs. late) in critically ill patients and mortality at 30 days from ICU admission. Secondary endpoints include developing a vancomycin-resistant organism, eradicating microorganisms within 4–5 days of vancomycin initiation, vancomycin-induced acute kidney injury (AKI), and ICU LOS.

Acute kidney injury was defined using AKIN definition [10].

Definition (s)/Procedure (s)

1. Susceptibility of gram-positive bacteria based on Clinical Laboratory Standards Institute (CLSI) [11]:

- Methicillin-Sensitive Staphylococcus Aureus (MSSA): Clinical isolate of *Staphylococcus aureus* sensitive to oxacillin; Minimal inhibitory concentration (MIC) < 2 μg/mL.
- Methicillin-Resistant Staphylococcus Aureus (MRSA): Clinical isolate of *Staphylococcus aureus* resistant to oxacillin; Minimal inhibitory concentration (MIC) > 4 μg/mL.
- Vancomycin Intermediate resistant *Staphylococcus aureus* (VISA): Clinical isolate of *Staphylococcus aureus* resistant to vancomycin; MIC 4–8 μg/mL.
- Vancomycin-resistant *Staphylococcus aureus* (VRSA): Clinical isolate of *Staphylococcus aureus* that is resistant to vancomycin; MIC > 8 μg/mL.
- Vancomycin-Resistant Enterococcus (VRE): Clinical isolate of Enterococcus resistant to vancomycin; MIC > 8 μg/mL.

Data management and Statistical analysis

Data were entered in Microsoft Excel 2010. Categorical variables were reported using numbers and percentages. Continuous variables were reported using mean with standard deviation (SD) or median with interquartile range (IQR) when appropriate. We compared normally distributed numerical variables with the t-test and other continuous variables with the Mann-Whitney U test and categorical variables using the chi-square / Fisher exact test. The normality assumptions were assessed for all continuous variables using graphical representation (i.e., histograms and Q-Q plots) and statistical test (i.e., Shapiro–Wilk test). The baseline and clinical characteristics were compared between early and late initiation groups. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection.

Multivariate logistic and generalized linear regression analyses were used to determine the relationship between therapeutic levels' timing and the different outcomes considered in this study. Variables that are clinically relevant were included in the model if they were different between study groups and associated with the primary outcome with a p-value of < 0.2 and did not overlap with another variable. The odds ratios (OR) estimates with the 95% confidence intervals (CI) were reported for the associations. We considered a P value of < 0.05 statistically significant and used SAS version 9.4 for all statistical analyses.

Sample size calculation

The sample size was calculated using Power Analysis and Sample Size (PASS) software (PASS 15 Power Analysis and Sample Size Software (2017). From a pilot study of 30 patients, the ICU mortality was estimated to be 25% in the late group, and we were expecting a reduction in 30-day ICU mortality by 13.3% in the early group (i.e., 11.7%). With 80.003% power to detect a difference in ICU mortality between the two groups of 13.3 and one-sided Z-test statistics with pooled variance. A total sample size of 209 was considered to assess the study's primary endpoint.

Results

Result Section

Of 209 patients included in this study, 99 (47.4%) patients' characteristics were included in the analysis of early achieving therapeutic levels of vancomycin compared to110 (52.6%) patients included in late achievement.

Demographic and Clinical Characteristics

Characteristics of the patients are presented in Table 1. The mean age for patients was 65 years-old and 59 years-old in the early and late therapeutic levels attainment of vancomycin, respectively. In the study, 63 (63.6%) of the patients were males in early and 70 (63.6%) in the late achievement of vancomycin's therapeutic levels. More obese patients in the late group 24 out of 110 (21.8%) versus 13 out of 99

(13.1%); p = 0.157. The median APACHE II score was 15 in both groups, p = 0.661. Also, the median modified sequential organ failure assessment (mSOFA) score was 5 in early, compared with 6 in the late achievement, which was not statistically significant (p = 0.144). Moreover, no major differences were observed between groups in their baseline characteristics (Table 1). More patients received vancomycin loading dose in the late group; 22.7% vs. 16.2%, respectively. However, this difference was not statistically significant (p = 0.233).

Table 1
Baseline characteristics

	Early (N = 99)	Late (N = 110)	P-value
Age (years) □	65.21 (± 16.88)	59.52(± 20.29)	0.324*
Male □	63(63.6%)	70(63.6%)	> 0.999**
Weight (kg) □	71.39 (± 23.36)	68.45(± 19.62)	0.324 **
Obese (body mass index > 30 kg/m2), □	13 (13.1%)	24 (21.8%)	0.157**
Admission category			
Medical □	69 (69.7%)	57 (51.8)	0.008
Surgical □	11 (11.1%)	19 (17.2%)	0.204
Trauma □	6 (6.06%)	14 (12.7%)	0.101
Burn □	4 (4.04%)	1 (0.90)	0.192^^^
Neuro □	8 (8.08%)	19 (17.2 %)	0.047
Others □	1(1.01%)	0 (0%)	0.473 ^^^
Diabetes mellitus □	57(57.6%)	55 (50.0%)	0.273**
Hypertension □	66 (667%)	64(58.2%)	0.207**
Liver disease □	9 (9.1 %)	14 (12.7%)	0.402**
Chronic kidney disease □	13 (13.1%)	16 (14.5%)	0.768**
Heart failure □	17(17.2%)	17 (15.5%)	0.737**
Acute coronary syndrome □	24(24.2%)	23 (20.9%)	0.564**
mSOFA score, Δ	5 (3–7)	6 (4–8)	0.144***
APACHE II Score, Δ	15 (11–19)	15 (10–22)	0.661*
Admission GCS, □	9.30 (± 4.63)	9.25 (4.77)	0.932*
Intubated on mechanical ventilation □	68 (49.3%)	70 (50.7%)	0.147**
Lactic acid (mmol/L), □	2.57(± 2.24)	2.71(3.33)	0.757*
Serum creatinine (μmol/L), □	105.82(± 71.34)	119.11(100.75)	0.280*
eGFR (ml/min/1.73 m2), □	80.35 (± 44.66)	73.01 (41.76)	0.223*
Albumin (g/L), □	28.63 (± 5.50)	31.46 (6.61)	0.002*

	Early (N = 99)	Late (N = 110)	P-value
Platelets count (1000 × 10^6/L), □	296.82(± 176.23)	251.18(141.32)	0.042*
Loading dose, *	16 (16.2%)	25(22.7%)	0.233**
Maintenance dose (mg/kg/day), □	26.02 (± 11.7)	25.9 (± 11.7)	0.140**

* Data analyzed using independent samples t-test;

** Data analyzed using Chi-square

*** Data analyzed using Mann–Whitney U test (Significant at α = 0.05)

(□) Data presented as n, (%)

(□) Data presented as Mean, standard deviation (SD)

(Δ) Data presented as Median, 25th percentile (Q1) – 75th percentile (Q3)

Severity and sources of infection /Microorganism (s)

Among 209 patients admitted to ICU, the primary source of infection in our population was bacteremia, followed by pneumonia. The most common species detected were Staphylococcus Spp., followed by Enterococcus Spp. and Streptococcus Spp. respectively (Table 2).

Table 2
Severity/Source of infection and microorganism (s)

		Early (N = 99)	Late (N = 110)	P-value
Sources of gram-positive infection	Bacteremia	63(63.6%)	69(62.7%)	0.891*
	o MSSA Bacteremia	2 (3.1%)	7 (10.1%)	0.168**
	o MRSA Bacteremia	11(17.4%)	13 (18.8%)	0.837*
	o Others	50 (79.3%)	49 (71.0%)	0.268*
	Pneumonia	18(18.2%)	26(23.6%)	0.334*
	Skin/wound infection (s)	8(8.1%)	6(5.5%)	0.448**
	Other source of infection	10(10.1%)	9(8.2%)	0.629**
Organism	Staphylococcus aureus	37(37.4%)	43(39.1%)	0.133*
	Staphylococcus (Non-aureus)	49(49.5%)	44(40.0%)	
	Streptococcus Spp	2(2.0%)	9(8.2%)	
	Enterococcus Spp	6(6.1%)	10(9.1%)	
	Others	5(5.1%)	4(3.6%)	

*Data analyzed using Chi-square

**Data analyzed using Fischer exact

() Data presented as n, (%)

Study outcome (s)

The descriptive and regression analysis of outcomes shows that patients who achieved therapeutic levels of vancomycin early have 18.2% ICU mortality within 30 days compared with 19.1% for those who achieve therapeutic levels after 48 hours (OR: 0.48 (0. 26, 0.87); p-value = 0.0151) (Table 3).

Table 3
Regression analysis for the outcomes of vancomycin early achieving as compared with late achieving therapeutic level

Outcomes	**Early (N = 99)**	**Late (N = 110)**	**P-value**	**Odds ratio (95%CI)**	**P-value**
ICU mortality within 30 days □	18 (18.2%)	21 (19.1%)	0.866^*	0.48 (0. 26, 0.87)	0.015*
Developing of vancomycin resistance □	1 (1%)	2 (1.8%)	> 0.999^**	0.08 (0.01, 0.59)	0.013*
Eradication of microorganism within 4–5 days of vancomycin initiation. □	51 (51.5%)	66 (60.6%)	0.189^*	0.74 (0.46, 1.22)	0.236*
Vancomycin induced acute kidney injury (AKI) □	23 (23.2%)	24 (22.0%)	0.834^*	0.60 (0.34, 1.04)	0.068*
Continuous Outcome				**beta coefficient (Estimates) (95%CI)**	
ICU length of stay Δ	17 (8.0, 31.0)	22 (9.5, 36.0)	0.150^	0.28(-0.01, 0.57)	0.058**

^** Fisher exact test/^* Chi-square test used to calculate p-value.

^ Mann-Whitney-U test was used to calculate p-value.

*P-value was calculated using multivariate logistic regression after adjusting for patients mSOFA scores.

**P-value was calculated using negative binomial regression after adjusting for patients mSOFA scores.

(□) Data presented as n, (%)

(Δ) Data presented as Median, 25th percentile (Q1) – 75th percentile (Q3)

Table 4
Concomitant use with other intravenous nephrotoxic medications

Medication (s)	Early (N = 99)	Late (N = 110)	P-value
Flucloxacillin	0 (0%)	4 (3.6%)	0.123
Amikacin	8 (8.0%)	4 (3.63%)	0.235
Gentamicin	9 (9.09%)	7 (6.36%)	0.603
Colistin	11(11.11 %)	8 (7.27%)	0.348
Piperacillin/tazobactam	43 (43.4%)	42 (38.1%)	0.440
Sulfamethoxazole/trimethoprim	4 (4.04%)	0 (0%)	0.048
Furosemide	36 (36.3%)	28 (25.4%)	0.087
Contrast	16 (16.1%)	14 (12.7%)	0.479
All data presented as n, (%)			

Moreover, one patient (1%) developed a vancomycin-resistant organism in the early achievement group compared with two patients (1.8%) in late (Table 3). On the other hand, 23.2 % of the patients developed an acute kidney injury when achieving the therapeutic target level of vancomycin within 48 hours of initiation (Early group), compared with 22.0 % in the late group; however, it was not statistically significant.

Among 47 patients who developed acute kidney injury, eight patients (17%) required dialysis during ICU stay, of which six patients (12.7 %) in the early group required dialysis compared to 2 patients (4.26%) in the late group. The most common concomitant nephrotoxic intravenous medications were piperacillin/tazobactam followed by furosemide (Table 4). Ten patients on the early group developed an AKI with the combination of vancomycin and piperacillin/tazobactam compared to 13 patients in the late group.

Discussion

Our results show that in a broad population of adult ICU patients treated with vancomycin, the early attainment of therapeutic drug levels within 48 hours was associated with a reduced risk of 30-day ICU mortality. Several studies have correlated optimizing pharmacokinetic-pharmacodynamics (PK-PD) with better clinical outcomes in infections due to Staphylococcus aureus treated with vancomycin. Compared to methicillin-susceptible S. aureus (MSSA), MRSA is independently associated with an increased risk of hospital mortality; thus, early attainment of MRSA therapeutic levels is crucial [2, 4, 6, 12].

Several studies have evaluated different nomograms or dosing strategies for vancomycin; however, limited data provided an insight into the correlation between time to achieve vancomycin therapeutic levels and significant clinical outcomes [12–16]. The median time to reach a therapeutic level for vancomycin in previously reported data was three days, which would be considered late in our study definition [13–16] However, a prospective multicenter study that validated the vancomycin consensus guideline nomogram published in 2009 had a median time of two days [17]. Many strategies are suggested to achieve earlier trough levels using continuous vancomycin infusion [18–20]. The timing to achieve therapeutic trough levels for vancomycin earlier in our study was associated with lower 30-day ICU mortality when compared to the late group. Our reported mortality was different between groups with (18 (18.2%) vs. 21 (19.1%)); however, the early attainment of vancomycin therapeutic levels was associated with a statistically significant difference when plotting the regression analysis (OR: 0.48; 95% CI [0.26–0.87]; $p < 0.01$). We believe that this outcome is a good hypothesis-generating finding, as it makes sense to have better survival when treating infections appropriately in a timely fashion.

We observed a low incidence of vancomycin associated resistance patterns in the early group (one patient) than in the late group (two patients). This finding aligns with a few studies that reported an increased risk of developing resistance patterns of vancomycin with subtherapeutic vancomycin levels (< 10 mg/L) and inability to reach an appropriate minimum inhibitory concentration (MIC) to optimize PK-PD targets [21, 22]. A study by Hidayat et and colleagues reported higher infection-related mortality in patients with MRSA infections with high MIC (24% vs. 10%) [23]. We cannot claim a clear correlation for this outcome due to our small numbers and the fact that we did not report pathogen-specific MICs in our study. However, we reported the resistance patterns documented by our microbiology lab based on the electronic medical records based on the CLSI criteria [10].

Higher rates of AKIs were reported in studies that applied the AKIN criteria for nephrotoxicity as it reached 35%-37% when using intermittent vancomycin infusions when compared to our study (21–25%) [24–26]. High vancomycin trough levels, among other factors such as concurrent nephrotoxic agents, concurrent vasopressor therapy, and/or undergone a procedure, are common risk factors for developing acute kidney injury (AKI) in critically ill patients (Table 4) [24–30]. A recent systematic review suggested higher risk of AKI with the co-administration of piperacillin/tazobactam, however in our data its use was similar between groups [31].

An important observation was the difference between groups population in terms of their admission categories. More medical patients were included in the early group compared to the late group. Additionally, this may explain the ability to achieve early therapeutic vancomycin levels despite a similar mean maintenance dose between groups. Recently, more data have discussed the prevalence of augmented renal clearance (ARC) in patients with trauma-surgical and/or neuro admission category, which may lead to the inability to reach earlier therapeutic levels of vancomycin [32–34].

Our study has several limitations that include the retrospective nature of this study and the sample size. Our patient population's heterogeneity (medical, surgical, burn, and trauma ICU patients) might have

affected our outcomes. Additionally, we reported mortality for a small sample size study with many potential confounders; however, none of these variables was shown to impact our outcome based on our univariate regression analysis. Additionally, we were able to report nephrotoxic medication co-administration and contrast use. We acknowledge the revised consensus guidelines for vancomycin monitoring in MRSA infections to use individualized target area under the curve (AUC) over MIC, however many clinicians are still using the previous recommendation for targeting trough levels of 15–20 mg/L in day-to-day practice [7, 8]. Adopting AUC/MIC consensus guidelines in the developed countries may need more time and education [7]. Future studies are needed to confirm our findings.

Conclusion

Early attainment of vancomycin therapeutic levels may be associated with plausible survival benefits. More studies are needed to provide an insight into these correlations.

Declarations

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Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the manuscript's final version.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

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Figures

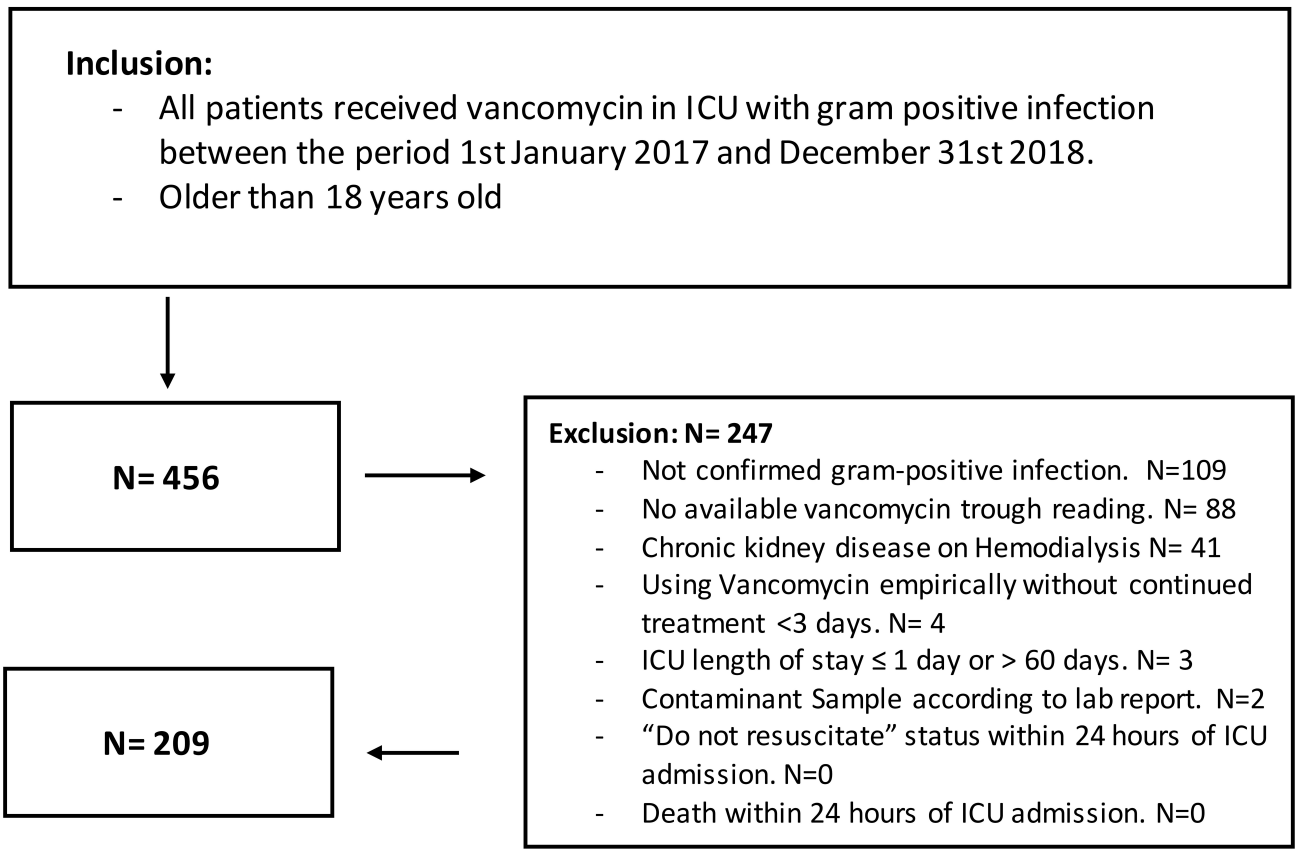

Figure 1

Flow diagram of inclusion/exclusion criteria, and for eligible patients who underwent analysis.