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Effect of low vs. high vancomycin trough level on the clinical outcomes of adult patients with sepsis or gram-positive bacterial infections: a systematic review and meta-analysis

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Abstract

Background & objective The Infectious Disease Society of America guidelines recommend vancomycin trough levels of 15–20 mg/L for severe methicillin-resistant Staphylococcus aureus. However, recent consensus guidelines of four infectious disease organizations no longer recommend vancomycin dosing using minimum serum trough concentrations. Therefore, this study aimed to evaluate the impact of low (< 15 mg/L) vs. high (≥ 15 mg/L) vancomycin trough levels on clinical outcomes in adult patients with sepsis or gram-positive bacterial infections.

Method A systematic literature review from inception to December 2022 was conducted using four online databases, followed by a meta-analysis. The outcomes of interest included clinical response/efficacy, microbial clearance, length of ICU stay, treatment failure, nephrotoxicity, and mortality.

Results Fourteen cohort studies met the inclusion criteria from which vancomycin trough concentration data were available for 5,228 participants. Our analysis found no association between vancomycin trough levels and clinical response [OR = 1.06 (95%CI 0.41–2.72], $p = 0.91$], microbial clearance [OR = 0.47 (95% CI 0.23–0.96), $p = 0.04$], ICU length of stay [MD=-1.01 (95%CI -5.73–3.71), $p = 0.68$], or nephrotoxicity [OR = 0.57 (95% CI 0.31–1.06), $p = 0.07$]. However, low trough levels were associated with a non-significant trend towards a lower risk of treatment failure [OR = 0.89 (95% CI 0.73–1.10), $p = 0.28$] and were significantly associated with reduced risk of all-cause mortality [OR = 0.74 (95% CI 0.62–0.90), $p = 0.002$].

Conclusion Except for a lower risk of treatment failure and all-cause mortality at low vancomycin trough levels, this meta-analysis found no significant association between vancomycin trough levels and clinical outcomes in adult patients with sepsis or gram-positive bacterial infections.

Keywords Sepsis, Septic shock patients, Vancomycin, Trough levels, MRSA

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Introduction

Despite a decline in incidence since 1990, an estimated 48.9 million cases of sepsis and 11 million sepsis-related deaths were reported worldwide in 2017 [1]. Even in low-burden countries such as the United States [1], sepsis accounts for 15.6% of deaths among all hospitalized patients [2], while it is the immediate cause of death in about a third of patients admitted to acute care hospitals [3]. Furthermore, 40% of patients with sepsis have a microbiologically documented infection [4]. The most common causative organism in adults with severe sepsis includes gram-negative bacteria such as *Klebsiella pneumoniae* (13.1–19.8%) and *Escherichia coli* (11.7–37.3%) and gram-positive bacteria such as *Staphylococcus aureus* (8.2–14.1%) [5, 6]. Among those with *Staphylococcus aureus* infection, 42% are culture-positive for methicillin-resistant *Staphylococcus aureus* (MRSA) [5], which is highly associated with significant mortality and morbidity due to limited treatment options [7–10].

Vancomycin is the gold standard treatment for MRSA infections, with the highest cumulative clinical experience for various invasive clinical syndromes, including endocarditis, bacteremia, osteomyelitis, and pneumonia [11, 12]. However, its efficacy is currently questioned and criticized owing to its slow bactericidal activity, emerging resistant strains, and serious adverse effects such as hypersensitivity, ototoxicity, and nephrotoxicity [13]. Additionally, several studies have noted a gradual increase in minimal inhibitory concentrations (MICs) of vancomycin against MRSA [14–16], although this finding remains controversial [17–19]. Moreover, there is evidence for altered metabolism, distribution, and elimination of antimicrobial drugs, mainly hydrophilic drugs such as vancomycin, in septic shock or sepsis due to changes in renal clearance and volume of distribution [20].

The AUC/MIC (area under the concentration-time curve to minimum inhibitory concentration) ratio has gained recognition as a more precise predictor of vancomycin efficacy compared to trough levels alone, especially in MRSA infections. Studies have shown that targeting an AUC/MIC ratio of ≥ 400 is associated with improved clinical outcomes, including higher rates of microbial clearance and reduced treatment failure in MRSA infections [21–23]. These findings support the clinical relevance of AUC/MIC-guided vancomycin dosing, aligning with safety data and recommendations outlined in recent guidelines [24]. The 2011 guidelines of the Infectious Diseases Society of America (IDSA) for MRSA infection treatment recommend vancomycin trough concentrations below 15 mg/L for mild infections and 15–20 mg/L for severe infections [12]. The lower trough concentration threshold of 15 mg/L for patients with severe infections is supported by later studies. For instance, a meta-analysis of 4 prospective and 12 retrospective studies by Steinmetz et al. [11] showed that vancomycin concentration below 15 mg/L in patients with severe MRSA infection was associated with higher treatment failure, microbiologic failure, and mortality rates.

However, prolonged therapy and higher serum vancomycin trough concentrations have been associated with nephrotoxicity [11, 25, 26], possibly leading to increased acute kidney injury (AKI), compromising its safety at higher levels [27]. Lodise et al. [28] reported a vancomycin-associated AKI risk of 5% with the initial administration of low trough levels (< 10 mg/L), 21% for moderate (10–15 mg/L) trough levels, 20% for trough levels of 15–20 mg/L, and 33% for trough levels > 20 mg/L which is consistent with findings of other studies [29–31]. Consequently, the most recent consensus guidelines of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists (2020) no longer recommends vancomycin dosing using minimum serum trough concentrations due to efficacy and nephrotoxicity concerns [32]. Instead, it recommends assuming the vancomycin MIC as 1 mg/L and adopting AUC-guided vancomycin monitoring for MRSA infections [32].

Although MIC/AUC-guided vancomycin dosing and monitoring may be more effective in achieving time to and time in the therapeutic range [33] and possibly a better safety profile, the latest consensus guidelines also underscore the need for caution with this approach while treating mild noninvasive infections and infections caused by non-MRSA species responsive to vancomycin as the guidelines predominantly rely on pharmacological and toxicological data from patients treated for serious for severe MRSA infections [23]. Moreover, recent studies comparing AUC/MIC and trough-only dosing approaches have yielded inconsistent results in terms of safety. For instance, Folkers et al. [33] did not find any significant difference in the incidence of AKI with the two dosing approaches modality, while McClure et al. [34] reported a 23% lower risk of incident AKI with the AUC/MIC-guided approach versus trough-only approach. In addition, the AUC/MIC-guided approach is associated with a marginally higher cost of vancomycin dosing and monitoring [35], which may be limiting in resource-strapped settings or facilities with large caseloads.

Given that the data with that AUC/MIC-guided approach is still emerging and the trough-based approach will continue to be relevant for mild or non-MRSA infection and in limited resource settings, continuously evaluating emerging literature on vancomycin dosing and monitoring is essential. Therefore, this systematic

review and meta-analysis aimed to assess the impact of low (< 15 mg/L) vs. high (15–20 mg/L) trough concentration of vancomycin on the clinical response/efficacy, microbial clearance, length of intensive care unit (ICU) stay, treatment failure, nephrotoxicity, and mortality in patients with sepsis or gram-positive bacterial infections including MRSA.

Methods

This systematic review and meta-analysis conformed to the guidelines provided by the Cochrane Collaboration Search Strategy and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [36, 37].

Search strategy

Scopus (Medline), PubMed, Cochrane Central Register of Controlled Trials (Central), and Google Scholar databases were searched using a varied mix of search terms that included keywords and MeSH terms (vancomycin, pharmacokinetics, critically ill, ICU, efficacy, safety, AUC/area under the curve, MIC, trough, and AKI). Additionally, the reference lists of all potential articles were screened and manually retrieved for additional articles.

Inclusion criteria

Our inclusion criteria were guided by the PICOTS framework as follows:

- *Population*: Adult patients (> 18 years) with sepsis (including septic shock as a subset of sepsis) or gram-positive bacterial infections.
- *Intervention*: Vancomycin.
- *Comparison* Low (< 15 mg/L or 10-15 mg/L) vs. (15-20 mg/L or ≥ 15 mg/L) trough levels of vancomycin. We did not include troughs of > 20 in our analysis due to the very high risk of toxicity.
- *Outcomes* Treatment success/failure, clinical response, microbial clearance, mortality, ICU stay, bacterial recurrence, and/or nephrotoxicity.
- *Timing* Since inception to December 2022.
- *Setting & design* Controlled trials (randomized and nonrandomized) and cohort (retrospective and prospective) studies published in English.

Study screening, selection, and data extraction

Articles identified from the database search were electronically retrieved for screening. Two authors (SC and RK) screened, selected, and extracted data from articles meeting our inclusion criteria. The process involved identifying duplicate entries, title and abstract screening, and full-text screening while removing articles not meeting our inclusion criteria at each step. All disagreements were resolved by discussion and consensus between the two reviewers. However, the two authors independently conducted the data extraction process using a standard data extraction form comprising study setting and location, design, study duration, sample size, age and gender of participants, infection type, defined breakpoint, objectives, and relevant findings.

Outcomes and definitions

The primary study outcomes were clinical response/efficacy, microbial clearance, ICU length of stay, and all-cause mortality. All-cause mortality was defined as 30-day, in-hospital, or ICU mortality.

Secondary study outcomes included treatment failure and nephrotoxicity. Treatment failure was defined as a composite endpoint including at least one of the following: death from any cause within 30 days of treatment, microbiologic failure/bacterial persistence after seven days of vancomycin therapy, or recurrence of the bacterial infection within 60 days of discontinuing vancomycin therapy.

For the meta-analysis, vancomycin trough levels from the included studies were dichotomized into low, defined by serum trough of < 15 mg/L, and high, defined by serum trough of 15–20 mg/L.

Risk of bias and study quality assessment

Two reviewers (RK and SC) independently evaluated the risk of bias in the included articles that fulfilled the inclusion criteria. Most studies selected for this review were retrospective and prospective cohorts, so the quality assessment was evaluated based on the Newcastle-Ottawa Scale [38]. The following items were assessed: (a) study selection criteria, including representativeness of the exposed cohorts, selection of the non-exposure group, and ascertaining the exposure levels; (b) comparability of the study groups; and (c) outcomes, including assessment of various clinical outcomes (independent blind assessment/record linkage/self-report/no description), and follow-up duration for outcomes to occur.

Statistical analysis

All statistical analyses were conducted using R software (Version 2024.04.2 + 764). Odds ratios (ORs) and 95% confidence intervals (CI) were used to calculate the effect sizes of individual studies by producing forest plots. Heterogeneity in the results of the analyzed studies was assessed using the chi-square test for study heterogeneity and the I^2 statistic to measure inconsistency and heterogeneity degree [39, 40]. If no inter-study heterogeneity was detected, a meta-analysis was conducted using the Mantel-Haenszel fixed-effects model approach.

Otherwise, if the studies showed significant heterogeneity, the meta-analysis was performed using the Mantel-Haenszel random-effects model approach. Funnel plots were generated to assess the degree of asymmetry tested by Egger's [41] and Begg's test. A p-value < 0.05 was considered statistically significant.

Results

Literature search and selection results

Our search strategy yielded 817 articles from databases and 16 from the reference list screening, of which 412 were eliminated as duplicate studies. The remaining 421 records were screened based on titles and abstracts in conformity with the inclusion criteria, eliminating 356 studies. Seventy studies were eligible for full-text screening, of which 14 articles met the inclusion criteria and were included in this meta-analysis. The study screening and selection process is illustrated in Fig. 1.

Characteristics of included studies

The characteristics of the 14 included articles are listed in Table 1. Eleven included studies were retrospective observational cohorts [42–52], and three were prospective studies [53–55]; we did not identify any randomized controlled trials meeting our inclusion criteria. Regarding regional distribution, six studies were from the United States [42–46, 53], two from China [47, 48], and each from Korea [54], Japan [49], Israel [50], Iran [51], France [55], and Slovakia [52]. All the included studies were published between 1997 and 2023. Twelve studies included patients with laboratory-documented MRSA infections and two with documented gram-positive infections (including MRSA).

The 14 included studies provided a pool of 5,228 adult participants with vancomycin trough levels: two studies had four categories of vancomycin trough levels (< 10, 10-14.9, 15–20, and > 20 mg/L), three had three categories of trough levels (< 15, 15–20, and > 20 mg/L), and the remaining studies had two trough concentration levels (< 15 and ≥ 15 mg/L). The studies reported varied data for investigating the association between various vancomycin trough levels and clinical and drug resistance outcomes.

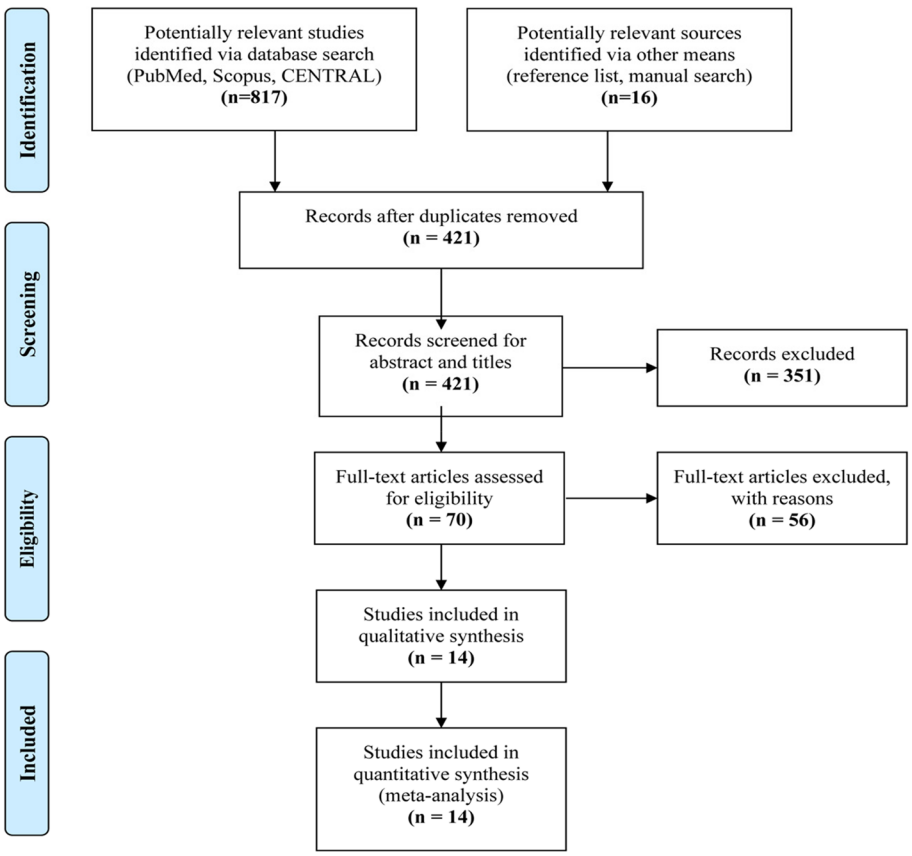

Fig. 1 PRISMA Flow Diagram of Study Selection Process

Table 1 Summary and characteristics of included studies

Author (Year) Country	Study duration	Study setting	Sample size	Age	Infection type	Outcomes	Key findings
Retrospective cohort studies							
Jeffres et al. [42] (2006) USA	Jan 1999 - Jun 2005	Inpatient including ICU	102	Mean age 59.4 ± 15.3 years	MRSA	Mortality, ICU length of stay	Aggressive dosing strategies for vancomycin (e.g., trough concentrations of > 15 g/mL) may not offer any advantage over traditional dose targets (range, 5 to 15 g/mL).
Hermsen et al. [43] (2010) USA	Jun 2005 - Jun 2007.	Inpatient including ICU	55	Mean age 60 years	MRSA	Clinical response, mortality, length of stay, and nephrotoxicity	-Mortality risk was not significantly different between the high (19%) and low (5%) trough group patients ($p = 0.1$). -LOS did not differ significantly between groups ($p = 0.7$). -Nephrotoxicity occurred in the low and high groups, respectively, for 10% and 31% ($p = 0.04$). -There was no significant difference between high and low trough levels on clinical outcomes for MRSA infections. However, nephrotoxicity was higher in the high trough group.
Kullar et al. [44] (2011) USA	Jan 2005 - Apr 2010	N/R	320	IQR 46–64 years	MRSA	Clinical outcome, treatment failure, and nephrotoxicity.	Vancomycin 10-14.9 mg/l reported more treatment failure (57.8%) and nephrotoxicity (17.1%) than 15–20 mg/l trough levels (39.5%) and nephrotoxicity (13%).

Table 1 (continued)

Author (Year) Country	Study duration	Study setting	Sample size	Age	Infection type	Outcomes	Key findings
Clemens et al. [45] (2011) USA	Apr 2008 - Aug 2009	Inpatient including ICU	118	Mean age 53 years (range: 18–89)	MRSA	Treatment failure, clinical efficacy	Treatment outcomes were similar regardless of VAN MIC, although there was a non-statistically significant trend towards decreased clinical efficacy among patients with VAN MIC = 2 mg/L. Optimization of VAN pharmacokinetic indices did not appear to correlate with clinical responses.
Hou et al. [46] (2021) USA	2014 to 2015	ICU	3,603	45.6% ≤ and 53.5% > 60 years	MRSA	ICU and hospital mortality	The mean vancomycin trough concentration (VTC) did not influence reduced ICU/ hospital mortalities, thus suggesting that VTC does not guarantee treatment efficacy for ICU patients.
Wang et al. [47] (2021) China	Jan 2017 -Dec 2019	Inpatient	349	Mean age 88 years	Complicated Gram-positive infection	Clinical response, 30-day mortality rates, persistent bacteremia, nephrotoxicity	-For patients with VTCs at < 10, 10–15, 15–20, and ≥ 20 μg/mL, the clinical response rates were, respectively, 77.8, 77.0, 80.5, and 61.0%; the 30-day mortality rates were 2.8, 15.0, 15.3, and 37.8%; and the rates of persistent bacteremia were 16.7, 12.4, 11.9, and 11.0%. -Higher VTC level was not associated with favorable treatment outcomes.

Table 1 (continued)

Author (Year) Country	Study duration	Study setting	Sample size	Age	Infection type	Outcomes	Key findings
Huang et al. [48] (2018) China	Jan 2007 - Jun 2014	ICU	50	Mean age 85.0 ± 3.9 years	Gram-positive infection	Mortality, clinical outcome, and nephrotoxicity	The 28-day mortality was 26.0% (13/50). Of the patients, 24% (12/50) had nephrotoxicity during the vancomycin treatment. The clinical efficacy was 60%, 86.7%, 58.3%, and 33.3%, and the 28-day mortality rate was 20%, 23.3%, 33.3%, and 33.3%, respectively, when the trough concentrations were ≤ 10 μg/mL, 10–15 μg/mL, 15–20 μg/mL, and ≥ 20 μg/mL.
Chuma et al. [49] (2018) Japan	Between 2005 and 2015	ED and ICU	109	Mean age 67 years	MRSA, Coagulase-negative Staphylococcus spp, Enterococcus spp	Nephrotoxicity	Nephrotoxicity incidence rate was 14.3% in patients with initial trough levels of 15–20 mg/L, higher than 12.5% in patients with initial trough levels of 10 < 20 mg/L.
Yahav et al. [50] (2019) Israel	Jan 2013 – Dec 2015	Inpatient excluding ICU	285 patients	Mean age 67 ± 15.8 years	MRSA	30-day all-cause mortality, clinical success, microbiological success, or nephrotoxicity	-There were no significant differences between patients achieving high and low vancomycin levels in mortality (46/131, 35.1% vs. 41/154, 26.6%), clinical success, microbiological success, or nephrotoxicity. -The study found no association between vancomycin levels > = 15 mg/L and clinical outcomes in patients with MRSA infection.

Table 1 (continued)

Author (Year) Country	Study duration	Study setting	Sample size	Age	Infection type	Outcomes	Key findings
Arasteh et al. [51] (2019) Iran	NR	ICU	39	42.18 ± 3.84 for low trough and 48.09 ± 9.54 for high trough patients	MRSA	Clinical response and microbiological clearance	-There was no difference between the groups on clinical response ($p = 0.677$) and microbiological clearance ($p = 1.00$) -Both patients' groups had comparable outcomes regardless of trough levels of vancomycin.
Kralovicova et al. [52] (1997) Slovakia	Jan 1990 to Dec 1995	Inpatient including ICU	198	NR	MRSA	Treatment failure, nephrotoxicity	A high trough level reported more nephrotoxicity (33.3% vs. 11.1%) than a low trough level.
Prospective cohort studies							
Bosso et al. [53] (2011) USA	Feb 2008 - Jun 2010	Inpatient including ICU	288	Mean age 55 ± 17 years	MRSA	Nephrotoxicity, ICU length of stay	Vancomycin trough concentrations of > 15 mg/ml associated with a 3-fold increased risk of nephrotoxicity and ICU length of stay.
Chung et al. [54] (2011) Korea	Aug 2005 - Jul 2007	ICU	141 (Intention-to-treat analysis of 68 patients with MRSA)	Mean age 62.7 ± 14 years	MRSA	Treatment success rate, length of ICU stays, and ICU mortality rate	No significant differences were observed in the treatment success rate, length of ICU stay, and ICU mortality rate between patients with vancomycin trough concentrations of > 20 mg/l, 15 to 20 mg/l, and < 15 mg/l.
Arshad et al. [55] (2012) France	Jul 2005 - Mar 2007	N/R	104	N/R	MRSA	Clinical response, mortality, and nephrotoxicity	A low trough level reported less nephrotoxicity, mortality, and medication failure than a high trough level.

ICU Intensive care unit, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant Staphylococcus aureus, *N/R* Not reported

Quality of included studies

Although the methodological quality of the fourteen included articles varied, it did not influence their inclusion for analysis. The scores of studies ranged from 8 to 9 on the Newcastle-Ottawa Scale. None of the articles attained a score of ≤ 7, indicating that the overall quality of the included studies was high. The details of the risk of bias assessment are shown in Table 2.

Primary outcomes

Clinical response/efficacy

Data for patient clinical outcomes were available from four cohort studies [47–51], which collectively provided a study sample of 203 participants with low and 210 with high vancomycin trough levels. A random effect model was used for the meta-analysis since the studies reported significant heterogeneity ($I^2 = 70\%$). The results showed no significant difference in the clinical response

Table 2 Newcastle Ottawa Scale (NOS) for Quality Assessment

Study	Selection			Comparability		Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Duration of follow-up enough for outcomes to occur	Adequate follow-up	
Full score	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**
Jeffres et al. [42] (2006)	1	1	1	1	1	1	0	1	7
Hermsen et al. [43] (2010)	1	1	1	1	2	1	0	1	8
Kullar et al. [44] (2011)	1	1	1	1	2	0	1	1	8
Clemens et al. [45] (2011)	1	1	1	1	1	1	1	1	8
Hou et al. [46] (2021)	1	1	1	1	2	1	1	1	9
Wang et al. [47] (2021)	1	1	1	1	2	1	1	1	9
Huang et al. [48] (2018)	1	1	1	1	2	1	0	1	8
Chuma et al. [49] (2018)	1	1	1	1	2	1	0	1	8
Yahav et al. [50] (2019)	1	1	1	1	2	1	1	1	9
Arasteh et al. [51] (2019)	1	1	1	1	2	1	1	1	9
Kralovicova et al. [52] (1997)	1	1	1	1	2	1	0	1	8
Bosso et al. [53] (2011)	1	1	1	1	2	1	1	1	8
Chung et al. [54] (2011)	1	1	1	1	2	1	0	1	8
Arshad et al. [55] (2012)	1	1	1	1	2	1	1	1	9

of patients with low or high trough levels of vancomycin [OR = 1.06 (95%CI 0.41–2.72], $p = 0.91$] (Fig. 2). A sensitivity analysis was performed to investigate the source of high heterogeneity detected in this meta-analysis. The exclusion of two studies [47, 50] demonstrated no heterogeneity; hence, it was presumed that the representativeness of the participants, i.e., possible selection bias of participants and ascertainment of the exposure, could confound the high heterogeneity.

Microbial clearance

Two studies reported microbial clearance with low ($n = 65$) or high ($n = 67$) trough levels of vancomycin [50, 51]. A fixed effect model was used for meta-analysis as the studies had no heterogeneity ($I^2 = 0\%$). The analysis indicates significantly lower odds of microbial clearance [OR = 0.47 (95% CI 0.23–0.96), $p = 0.04$] with low vancomycin trough concentrations (Fig. 3).

ICU length of stay

Two studies reported ICU length of stay with low ($n = 77$) or high ($n = 32$) trough levels of vancomycin [43, 54]. A fixed effect model was used for the meta-analysis since the studies reported no heterogeneity ($I^2 = 0\%$). Trough levels of vancomycin were not associated with ICU length of stay [MD= -1.01 (95%CI -5.73–3.71), $p = 0.68$] (Fig. 4).

All-cause mortality

Mortality data with low ($n = 1{,}572$) or high ($n = 1{,}637$) trough levels of vancomycin were available from 9 studies [42, 43, 45–48, 50, 54, 55] with no inter-study heterogeneity ($I^2 = 0\%$). Low vancomycin trough level was associated with a significantly lower mortality risk in the fixed effect model [OR = 0.74 (95%CI 0.62–0.90], $p = 0.002$] (Fig. 5).

Secondary outcomes

Treatment failure

Treatment failure was reported in six studies [43–46, 52, 55] with a large sample size of 2,918 patients (n for < 15 mg/L = 1,393 and for ≥ 15 mg/L = 1,525) and significant inter-study heterogeneity ($I^2 = 66\%$). In the fixed effect model, low vancomycin trough levels were associated with non-significant trend toward a lower risk of treatment failure compared with higher trough levels [OR = 0.89 (95% CI 0.73–1.10), $p = 0.28$] (Fig. 6).

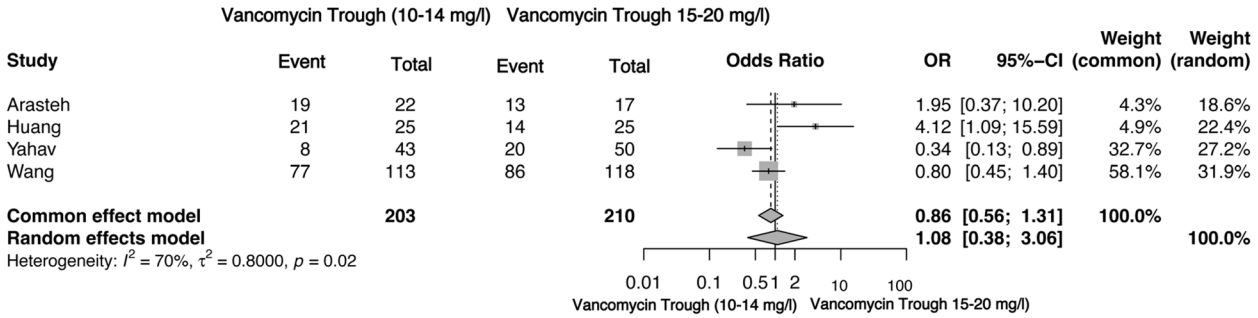

Fig. 2 Forest plot of comparison: clinical response/efficacy

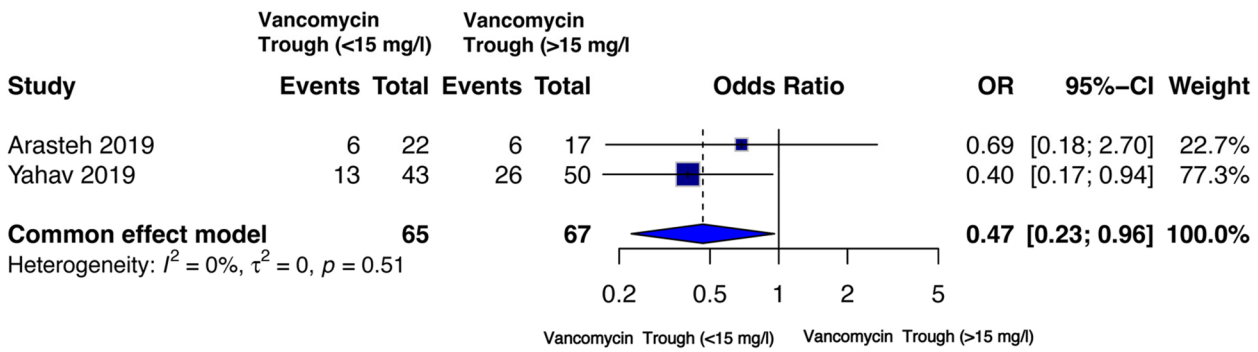

Fig. 3 Forest plot of comparison: microbial clearance

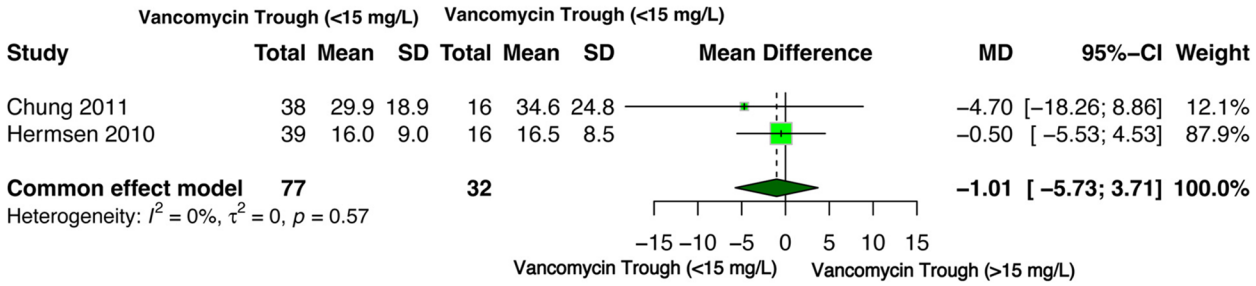

Fig. 4 Forest plot of comparison: ICU length of stay

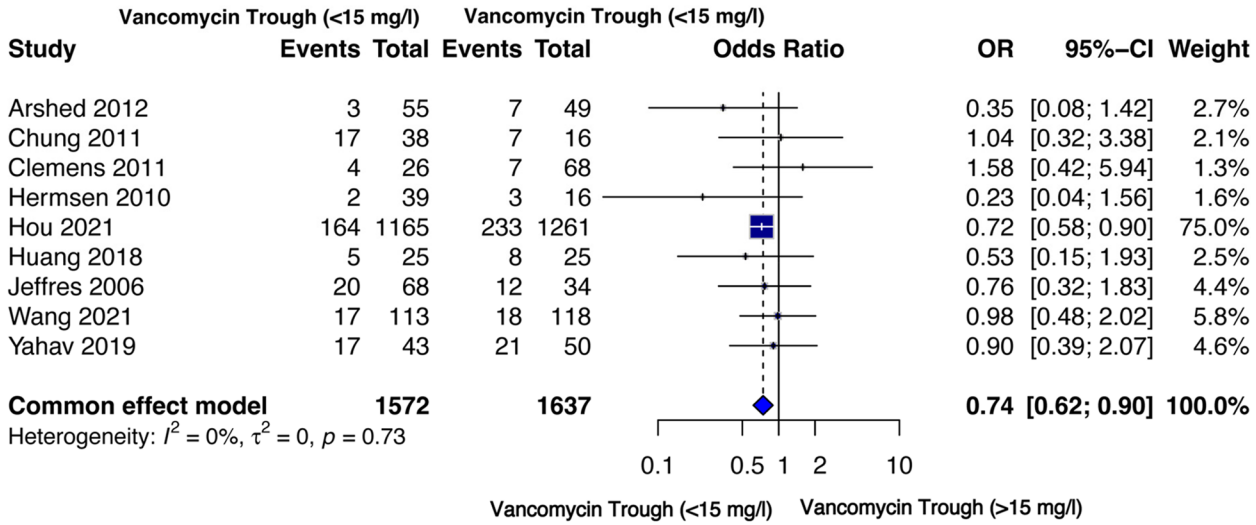

Fig. 5 Forest plot comparison: All-cause mortality

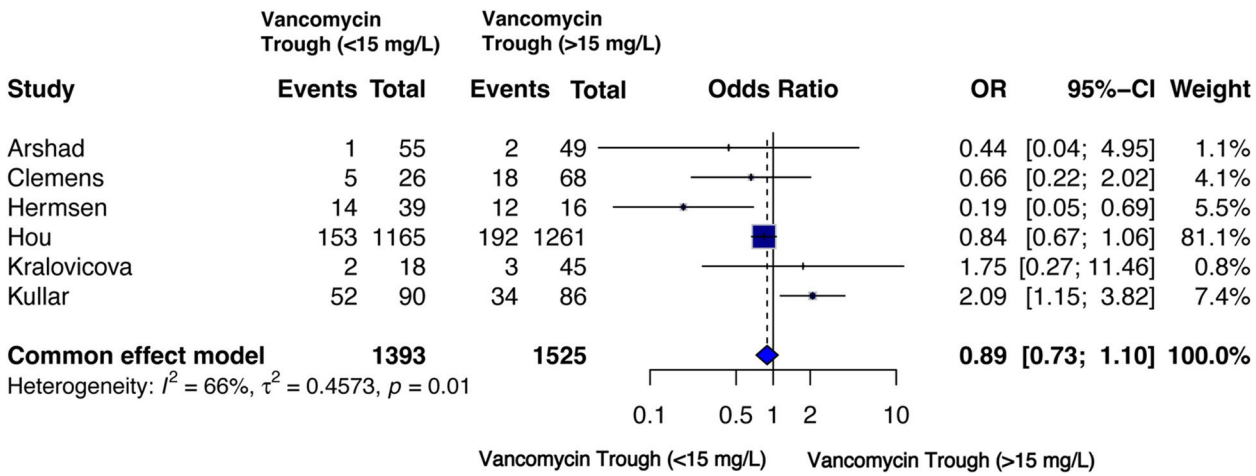

Fig. 6 Forest plot of comparison: Treatment failure

Nephrotoxicity

Nephrotoxicity was reported in eight studies [43, 44, 47, 49, 52–55], providing a sub-population of 502 patients with low trough and 420 patients with high trough levels of vancomycin with significant inter-study heterogeneity (I^2 = 62%). In the random effects model, trough levels

of vancomycin were not associated with nephrotoxicity [OR = 0.57 (95% CI 0.31–1.06), $p = 0.07$] (Fig. 7). However, due to the significantly high heterogeneity detected, a sensitivity analysis was done to determine the possible cause of the variability. An analysis by excluding three studies [44, 49] showed no heterogeneity among the other studies, implying that the high heterogeneity could be due to the high variability of patient data, i.e., serum creatine levels, receiving first vancomycin therapy a few days before the study and any other possible covariates.

Discussion

This meta-analysis evaluated the clinical and drug resistance outcomes associated with low and high vancomycin trough levels in adult patients with sepsis or gram-positive bacterial infections, including MRSA. Our analysis found no significant association between vancomycin trough levels and clinical response, microbial clearance, ICU length of stay, or nephrotoxicity. However, low trough levels were associated with a non-significant trend toward a lower risk of treatment failure and a significantly reduced risk of all-cause mortality.

Our findings contradict previous meta-analyses in this domain. For instance, Tongsai et al. [56] reported a higher risk of nephrotoxicity with high vancomycin trough levels while noting a null association between trough levels and clinical success or all-cause mortality. Similarly, Prybylski [29] showed that vancomycin trough levels were not associated with treatment failure, persistent bacteremia, or mortality. Furthermore, Steinmetz et al. [11] found no significant difference between low and high vancomycin trough levels and all-cause mortality or treatment failure rates. However, low and high vancomycin levels were associated with higher microbiologic failure rates and nephrotoxicity, respectively. Finally, Meng et al. [57] reported an increased risk of nephrotoxicity with high vancomycin trough concentrations, although trough concentrations were not associated with the risk of treatment failure and all-cause mortality.

These inconsistencies may be attributable to methodological differences. Our study population comprised patients with sepsis, gram-positive bacterial infection, or MRSA, the three most common indications for the vancomycin regime [13]. In contrast, Tongsai et al. [56] sampled studies reporting nephrotoxicity in patients with MRSA irrespective of infection site, Prybylski [29] specifically sampled patients with MRSA bacteremia, and Meng et al. [57] sampled patients with gram-positive bacterial infections including MRSA. Moreover, Tongsai et al. [56] and Prybylski [29] excluded patients with vancomycin trough levels > 20 mg/L in their meta-analysis. Although Steinmetz et al. [11] sampled patients with MRSA infections and sepsis, they excluded studies that only reported nephrotoxicity without efficacy outcomes.

Nonetheless, these inconsistencies support the notion that vancomycin trough level may not be a reliable predictor of clinical outcomes, in line with the latest consensus guidelines of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists not to use minimum serum trough concentrations for vancomycin therapeutic drug monitoring (TDM) [32]. Moreover, though monitoring vancomycin trough levels has been suggested to improve efficacy and safety of clinical outcomes and reduce nephrotoxicity and drug failure in gram-positive

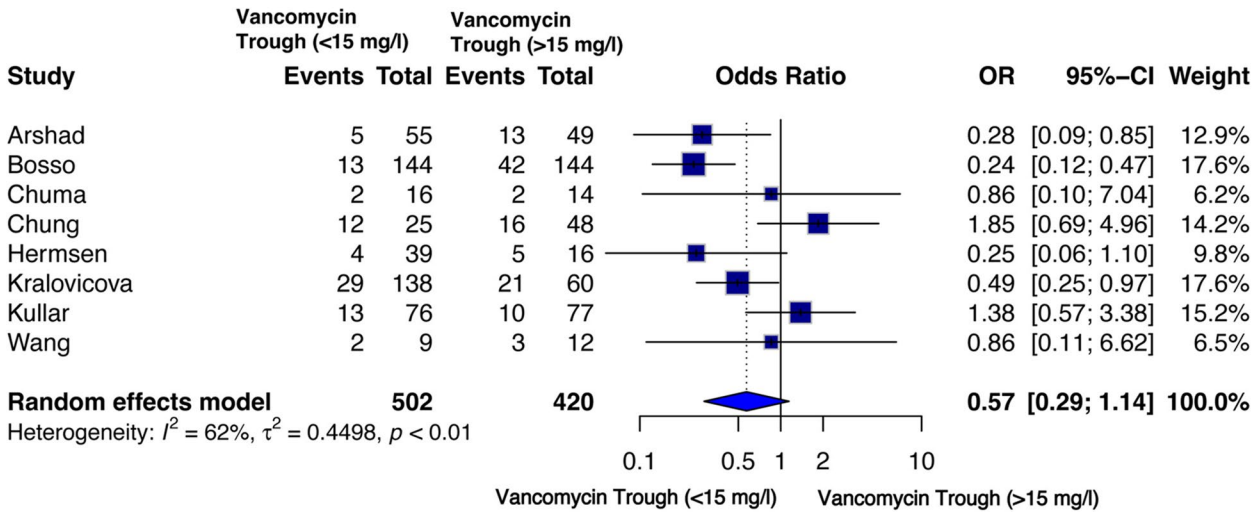

Fig. 7 Forest plot of comparison: Nephrotoxicity

patients, an effective target trough level is still not defined since the recommendations of 15–20 mg/L trough levels do not guarantee better outcomes.

As previously noted by Chung et al. [54] and Clemens et al. [45], our study indicates that patients would probably exhibit poor clinical success when administering high trough vancomycin levels. Furthermore, we observed a lower risk of treatment failure, defined as bacterial persistence with low trough levels. In agreement with this finding, Prybylski [29], Hale et al. [58] also showed that persistent bacteremia was higher in patients with high vancomycin trough levels.

Although several studies have previously demonstrated vancomycin-induced nephrotoxicity [25, 28, 59, 60], the non-significant reduction in the risk of vancomycin-induced nephrotoxicity at low trough levels observed in the current study warrants further investigation as this could indicate nephrotoxicity even at low trough levels or high variability in nephrotoxicity at high trough levels. In support of the latter, a meta-analysis by van Hal et al. [61] noted that nephrotoxicity incidence rates varied between 7% and 67% in patients exposed to elevated trough levels compared to 0 to 33% in the low serum trough level group. Additionally, Pan et al. [62] recently demonstrated that vancomycin-associated nephrotoxicity was associated with trough concentration ≥ 20 mg/L, and given that most studies included in the current meta-analysis report trough concentration < 20 mg/L, the incidence among low and high trough groups may not be sufficiently large to achieve statistical significance. It is also important to note that although Steinmetz et al. [11] demonstrated a higher risk of nephrotoxicity with vancomycin levels of ≥ 15 mg/L, irreversible renal damage was not reported in any of the cases of vancomycin-induced nephrotoxicity.

Limitations

Several limitations prevent the generalization of our findings. First, all studies included in this systematic review and meta-analysis were observational cohort studies, most with small sample sizes. These studies may be subject to selection bias for the participant impacting the quality of the study results. Moreover, most of the studies included were conducted in ICU settings, suggesting a higher potential for bias related to overall mortality and renal dysfunction. This bias could stem from vancomycin itself, septic shock, or nephrotoxicity from other medications.

Second, not all studies reported the initial trough value or only reported the average trough value. The successful treatment of MRSA infections could also be confounded by factors unrelated to vancomycin trough levels, such as adequate drainage and appropriate duration of therapy. These are difficult to isolate in this study. Additionally, vancomycin dosing is influenced by renal function and the severity of the disease, indicating that target trough levels may vary among different patient populations. Third, we could not consider vancomycin MIC as 8 of the 14 included studies were from over a decade ago, which did not allow the extraction of the distribution of MIC values. Fourth, there is an inherent risk of publication bias since positive studies were more likely to be published than negative ones. Fifth, targeted analysis was not possible due to the presence of confounding factors, limiting the ability of this study to establish a definite causal association between the study variables.

Finally, baseline patient characteristics such as disease severity and underlying comorbidities may have influenced our results. For instance, among the six studies included in our meta-analysis for treatment failure, three reported significantly high Acute Physiology and Chronic Health Evaluation (APACHE) scores among patients in ≥ 15 mg/L trough group [43, 46, 55], and one reported higher prevalence of heart failure and ICU admission [45] indicative of severe clinical status at baseline. APACHE score was not significantly different between the two trough groups in Kullar et al. [44], while Kralovicova et al. [52] did not report baseline clinical characteristics of the study population. Similarly, three out of nine studies included in our meta-analysis for all-cause mortality reported higher APACHE scores in the ≥ 15 mg/L trough group [43, 46, 55], one reported higher prevalence of heart failure and ICU admission [45], while two reported non-significant differences in APACHE scores [42, 54] and one reported non-significant differences in Charlson comorbidity index [50] between the two trough groups. Two studies did not report baseline APACHE scores for different trough groups [47, 48]. Incidentally, the four studies that reported a more severe clinical status at baseline in the ≥ 15 mg/L trough group contributed 92% of our pooled study population (and 81% of events) for treatment failure and 83% of our pooled study population (and 75% of events) for all-cause mortality. It is crucial to note that including infections caused by pathogens other than MRSA, such as enterococci and Streptococcus, in the current study may add additional variability in disease severity and outcomes.

Nevertheless, the current study provides a comprehensive analysis of the impact of low and high vancomycin trough levels on clinical outcomes, including two studies since the publication of the consensus guidelines of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists recommending MIC/AUC-guided vancomycin dosing and monitoring for MRSA infections [32]. Of these, the study by Hou et al.

[46] is one of the biggest to date in terms of participant size ($n = 3,603$) to report the association between vancomycin trough levels and mortality.

Conclusion

With the exception of a non-significant trend toward a lower risk of treatment failure and a significant reduction in all-cause mortality at low vancomycin trough levels, this meta-analysis did not detect any significant association between vancomycin trough levels and clinical outcomes in adult patients with sepsis or gram-positive bacterial infections. As demonstrated by studies published since the consensus guidelines, future observational studies with large sample sizes and randomized controlled trials are needed to determine if trough-guided vancomycin dosing and monitoring remain clinically relevant in specific patient populations. Maintaining a vancomycin trough level of < 15 mg/L may continue to be a viable option, particularly among patients with non-severe clinical status, but may not be appropriate for patients with severe infections.

Abbreviations

AKI	Acute Kidney Injury
AUC	Area Under Curve
ICU	Intensive Care Unit
IDSA	The Infectious Diseases Society of America
MRSA	Methicillin Resistant Streptococcus Aures
MICs	Minimal inhibitory concentrations
VIN	Vancomycin Induced Nephrotoxicity

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Authors' contributions

All authors had access to the data and contributed significantly to writing the manuscript. Subhash Chander, Roopa Kumari: Generated the hypothesis, analyzed the data, and wrote the first draft of the manuscript. Sheena Shiwlani, Sindhu Luhana, FNU Sadarat, Om Parkash: Literature review and help in table and figure development. Hong Yu Wang, Yaqui Nadeem Mohammed, FNU Sorath, Abhi Chand Lohana: Literature review and data gathering. SC: Supervise and review the final draft.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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