International Journal of Antimicrobial Agents 62 (2023) 107005

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Serum concentration of continuously administered vancomycin influences efficacy and safety in critically ill adults: a systematic review

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ARTICLE INFO

Article history:
Received 27 July 2023
Accepted 29 September 2023

Editor: Dr MH Scheetz

Keywords:
Acute kidney injury
Intensive care unit
Mortality
Continuous infusion
Sepsis
Vancomycin concentration

ABSTRACT

Objectives: Vancomycin is used to treat Gram-positive infections in critically ill adults. For vancomycin administered by continuous infusion (CI), various target ranges have been used, ranging from 15–20 mg/L to 30–40 mg/L. This systematic literature review was conducted to investigate the impact of steady-state serum concentration (C_{ss}) of CI on safety and efficacy of therapy in critically ill adults.
Methods: Relevant literature was identified by searching two electronic databases (PubMed, Cochrane Library) and Google Scholar from inception until July 2023, focusing on studies reporting measured C_{ss} and treatment outcomes (e.g. mortality, nephrotoxicity) with CI. Due to study heterogeneity, a narrative synthesis of the evidence was performed.
Results: Twenty-one publications were included with a total of 2949 patients. Mortality was higher (two studies, $n = 388$ patients) and clinical cure was lower (one study, $n = 40$ patients) with $C_{ss} < 15$ mg/L measured 24 h after initiation of CI (C_{24}). An adequate loading dose appeared most important for maintaining higher C_{24}. Generally, higher C_{ss} was associated with higher rates of acute kidney injury (AKI) (15 studies, $n = 2331$ patients). It was calculated that $C_{ss} < 25$ mg/L (versus ≥25 mg/L) was preferable for reducing nephrotoxicity (three studies, $n = 515$ patients).
Conclusions: Despite sparse data availability, the target range of 15–25 mg/L in CI may increase clinical cure and reduce mortality and AKI. In future research, vancomycin C_{ss} cohorts should be formed to allow evaluation of the impact of C_{ss} of CI on treatment outcomes.

1. Introduction

Infections in intensive care units (ICU) are highly prevalent. More than one-half of ICU patients may become infected during their ICU stay [1] and between 8–22% of infections are acquired nosocomially [1,2]. Infections with Gram-positive pathogens regularly occur in critically ill patients [3–5], causing one-third (range 21–67%) of all infections [6]. Available since the 1950s, the glycopeptide vancomycin remains an important antibiotic for the treatment of infections with Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci (CoNS) and *Enterococcus faecium* [7–11]. It is also frequently used in sepsis therapy as empirical treatment in combination with β-lactam antibiotics in areas with a high prevalence of MRSA [12]. Physiological changes caused by critical illness may alter drug excretion and lead to inappropriate drug levels, in particular renal insufficiency affects drug elimination [13–15]. In addition, vancomycin itself can impair renal function by inducing acute tubulointerstitial nephritis [16,17] or acute tubular necrosis [18] leading to acute kidney injury (AKI), which worsens the outcome of ICU stay [19,20]. The appropriate dosage of vancomycin has therefore been under discussion for some time. Vancomycin is administered via intermittent infusion or continuous infusion (CI). CI appears to hold several advantages over intermittent infusion,

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https://doi.org/10.1016/j.ijantimicag.2023.107005
0924-8579/

including a lower potential risk of AKI [21–25], earlier target achievement or higher rates of target attainment [24–35], less variability in serum concentrations [26,32,34,36], and easier and less expensive monitoring of drug levels [26,29,31,34]. Several studies have been published previously with CI using multiple target ranges of vancomycin steady-state serum concentration (C_{ss}). These were (indication-independent) 15–20 mg/L [17,31,37–40], 15–25 mg/L [29,30,32,41–47], 20–25 mg/L [33,34,48–50], 20–30 mg/L [26,51–61], 25–30 mg/L [62], 20–40 mg/L [61] and 30–40 mg/L [63]. As far as we are aware, there is a lack of a comprehensive comparative evaluation of the influence of vancomycin serum concentration during vancomycin CI on the therapeutic outcomes of efficacy (e.g. clinical and microbiological outcomes such as mortality or cure) and safety (e.g. nephrotoxicity such as AKI) in critically ill adult patients. Therefore, this review examines the current knowledge on the impact of C_{ss} on the efficacy and safety of vancomycin CI in critically ill adults in the ICU.

2. Materials and methods

A systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [64].

2.1. Selection criteria

According to the PICOS questions (population, intervention, comparison, outcomes and study design), enrolment of studies was performed as follows:

- population: adults (age ≥18 years) having been treated with vancomycin in an ICU;
- intervention: continuous infusion of vancomycin;
- comparison: vancomycin with or without intermittent infusion, chronic kidney disease (CKD), renal replacement therapy (RRT), obesity or different dosing regimens;
- outcomes: vancomycin steady-state serum level [~24 h after the start of therapy (C_{24}), average serum level during the entire duration of therapy or ≥3 days of therapy (C_{mean}), area under the serum concentration–time curve for 24 h (AUC_{24})] and efficacy or safety. Efficacy was defined as clinical or microbiological success or failure (e.g. survival or mortality, cure or relapse). Safety was defined as occurrence of nephrotoxicity (e.g. AKI); and
- study design: clinical trials and observational studies.

Studies with the following criteria were excluded: non-human data; paediatric patients (age <18 years); records without intravenous vancomycin application; records without CI; non-ICU setting; lacking efficacy or safety data; omitted vancomycin serum levels; case reports; comments; editorials; reviews; and meta-analyses. In addition, investigations with <30 patients with CI, studies with a duration of <1 year, and studies assessing fewer patient records than patients included in the study were excluded from the analysis. Exclusion based on the language of publication was not performed.

2.2. Data sources

A literature search from inception until 15 July 2023 in two electronic databases (MEDLINE through the PubMed interface, Cochrane Library) and Google Scholar was performed using the combined search terms ‘vancomycin’ and ‘continuous’ (PubMed: (vancomycin[Title]) AND (continuous); Cochrane Library: Title Abstract Keyword: vancomycin; AND All Text: continuous; Google Scholar: allintitle: vancomycin continuous).

2.3. Study selection

First, duplicate studies were excluded. Then, articles were selected based on the information obtained from the title and abstract according to the inclusion criteria. Pertinent articles or those not providing sufficient information via title or abstract were evaluated in full-text. Finally, the selected articles were critically read in full (Fig. 1).

2.4. Quality assessment

The quality of the studies selected for inclusion was rated using two tools: The Newcastle–Ottawa Scale (NOS) for non-randomised studies [65,66]; and the Cochrane risk-of-bias tool for randomised trials (RoB 2) [67]. Using the NOS, a ‘star system’ described the suitability of the selection of the study groups (one star maximum each), the comparability of the groups (two stars maximum) and the ascertainment of the exposure or outcome of interest (one star maximum each). The total number of stars of each study was interpreted as ‘good quality’ at 8–9 stars, ‘fair quality’ at 6–7 stars, ‘questionable quality’ at 4–5 stars, ‘poor quality’ at 2–3 stars and ‘serious risk of bias’ at 0–1 stars. With the RoB 2 scale, risk of bias was categorised as ‘low risk’, ‘high risk’ or ‘some concerns’, with ‘low risk’ of overall bias interpreted as ‘good quality’, ‘high risk’ as ‘serious risk’, and ‘some concerns’ as ‘questionable quality’. Due to the heterogeneity of the study designs (e.g. inclusion or exclusion of patients with CKD) and outcome measures (e.g. use of different definitions for AKI or mortality), it was not possible to summarise the results in a meta-analysis. In accordance with the Cochrane Consumers and Communication Review Group guideline [68], a narrative synthesis of the evidence was therefore performed. To minimise the influence of seasonal variations in infection type and frequency on study results (selection bias) [69–71], investigations with a duration of <1 year or a population number of <30 patients with CI were excluded from the analysis. Attrition bias from publications that analysed fewer patient records than were included in the study was prevented by excluding them from the evaluation. Because of the inhomogeneous coverage of potential factors affecting outcome, such as disease severity or concomitant nephrotoxin use, some degree of performance and reporting bias was to be expected. Language bias was avoided by including all languages of publication. The free internet translation programme DeepL (www.Deepl.com/Translator) was used for translation where necessary.

2.5. Data extraction

The main characteristics of the included studies were outlined in five tables, which are accessible online via the Supplementary material: design, type of study and main objective (Supplementary Table S1); characteristics of the study population (Supplementary Table S2); information regarding treatment with vancomycin (Supplementary Table S3); main findings in terms of efficacy (Supplementary Table S4); and main findings in terms of safety (Supplementary Table S5). ‘Efficacy’ indicates clinical or microbiological cure, improvement, persistence, progression, relapse or re-infection (further definitions displayed in Supplementary Table S11), mortality/survival and target attainment, while ‘safety’ indicates nephrotoxic and extrarenal adverse events (Table 1). Some of the values given have been calculated by us in the presence of sufficient numerical data.

2.6. Analysis

The reported average C_{ss} values were primarily divided into three categories: vancomycin serum level on the second day, i.e.

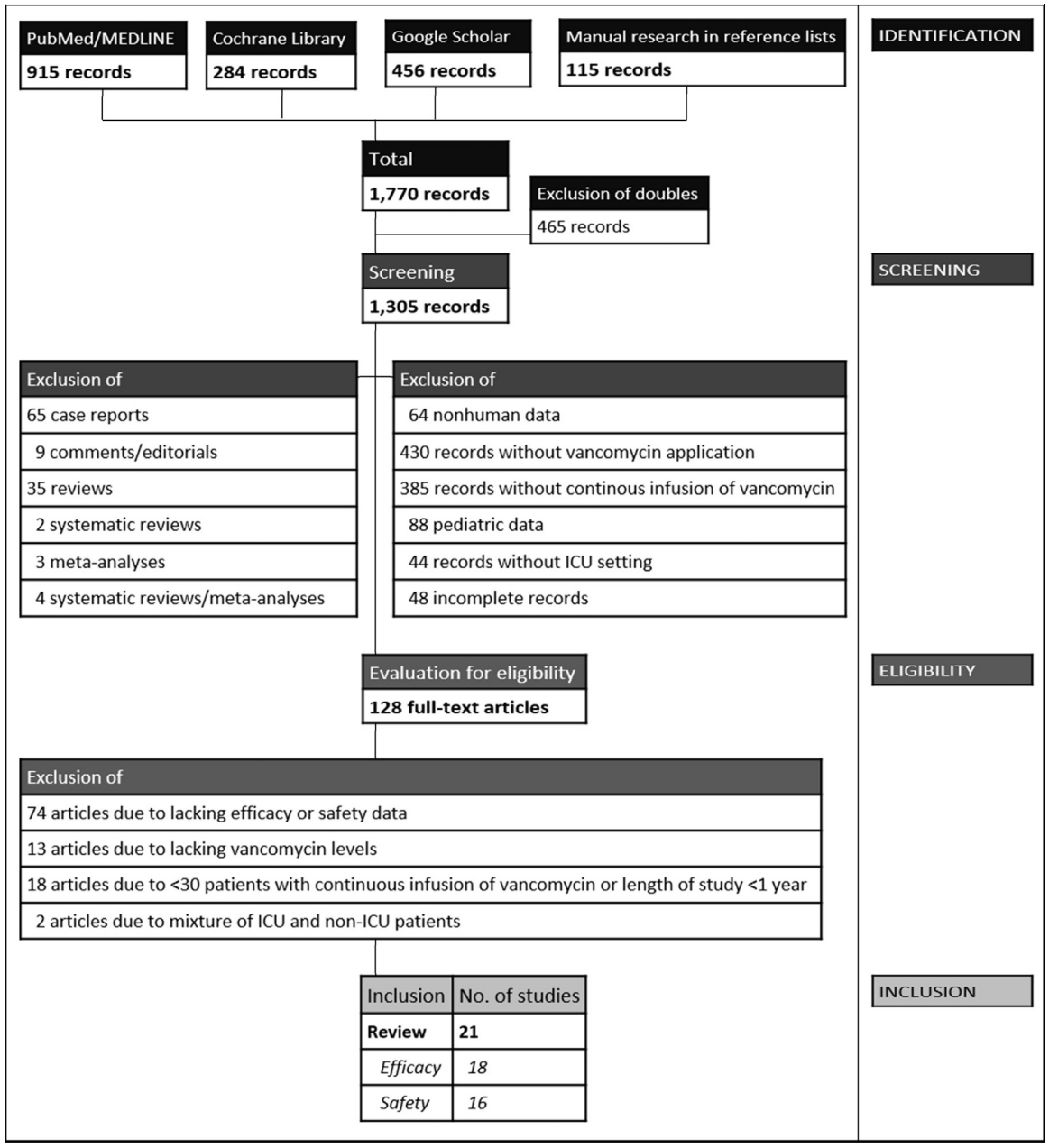

Fig. 1. Flowchart of study selection. ICU, intensive care unit.

~24 h after initiation of CI (C_{24}); mean vancomycin serum level during the entire duration of CI or ≥3 days of CI (C_{mean}); and area under the serum concentration–time curve for a period of 24 h during CI (AUC_{24}). The mortality rate was differentiated into 'in-hospital', 'ICU', 'infection-related', '*x* days' (e.g. 28 days), 'end of therapy' or 'not reported'. Likewise, nephrotoxicity in the form of AKI was classified according to Table 1 using 'AKIN', 'KDIGO', 'RIFLE', 'Rybak2009', 'Rybak2020', 'RRT' or 'other'. To compare the reported C_{ss} in cases where no mean but only the median was stated, the mean and standard deviation were calculated according to the method described by Wan et al. [72]: mean = (median + lower quartile + upper quartile)/3. In order to use only one value per study for the comparison, weighted means of serum concentration, mortality, nephrotoxicity or target attainment rates were calculated if values were given only for subgroups but not the entire CI population of a study. Because individual values of the study population were not available, no relationship between the variables could be tested by regression analysis. But to give an impression of interdependence, average C_{ss}, i.e. C_{24}, C_{mean}, AUC_{24}, were plotted against the corresponding percentage rates of clinical failure (mortality, persistence or progression of infection symptoms), clinical success (cure, improvement of infection symptoms), microbiological failure (persistence, escalation, relapse), microbiological success (cure), AKI or target attainment. Additionally, scatterplots were created comparing rates of mortality with AKI (Supplementary Figures S1–S3), target attainment with mortality or AKI (Supplementary Figures S4 and S5) and target attainment with target range (data not shown). For comparison of the different cohorts and based on the parameters identified as significant predictors for outcomes in the included studies (Table 2), the

Table 1
Compilation of all definitions of acute renal injury (AKI) used in the included publications

	Serum creatinine (SCr)		CL_{Cr}/$eGFR_{MDRD}$	Urine output		AKI (%)	Reference
Consensus recommendation from ASHP/IDSA/SIDP on therapeutic monitoring of vancomycin (2009) (Rybak2009) [113]						5	[43]
	SCr ↑ ≥1.5 × baseline SCr for ≥2 consecutive measurements after several days of vancomycin therapy and in absence of alternative explanation	*or* SCr ↑ ≥0.5 mg/dL					
KDIGO (2012) [101]						60	[48]
1	SCr ↑ 1.5–1.9 × baseline SCr (7 days)	*or* SCr ↑ ≥0.3 mg/dL (48 h)		<0.5 mL/kg/h for 6–12 h			
2	SCr ↑ 2.0–2.9 × baseline SCr			<0.5 mL/kg/h for ≥12 h			
3	SCr ↑ ≥3.0 × baseline SCr	*or* SCr ↑ ≥4.0 mg/dL	*or* initiation of RRT	<0.3 mL/kg/h for ≥24 h	*or* anuria for ≥12 h		
AKIN criteria (2007) [100]						20–50	[33,46,61,75]
1	SCr ↑ 1.5–2.0 × baseline SCr (7 days)	*or* SCr ↑ ≥0.3 mg/dL (48 h)		<0.5 mL/kg/h for >6 h			
2	SCr ↑ 2.0–3.0 × baseline SCr	*or* SCr ↑ ≥0.5 mg/dL		<0.5 mL/kg/h for >12 h			
3	SCr ↑ >3.0 × baseline SCr	*or* acute SCr ↑ ≥0.5 mg/dL if SCr is ≥4 mg/dL	*or* initiation of RRT	<0.3 mL/kg/h for ≥24 h	*or* anuria for ≥12 h		
RIFLE category (ADQI) (2004) [114]						25–37	[33,76]
Risk	SCr ↑ ≥1.5 × baseline SCr		*or* eGFR ↓ >25% from baseline	<0.5 mL/kg/h for 6–12 h			
Injury	SCr ↑ ≥2.0 × baseline SCr		*or* eGFR ↓ >50% from baseline	<0.5 mL/kg/h for ≥12 h			
Failure	SCr ↑ ≥3.0 × baseline SCr	*or* acute SCr ↑ ≥0.5 mg/dL if SCr is ≥4 mg/dL	*or* eGFR ↓ >75% from baseline	<0.3 mL/kg/h for ≥24 h	*or* anuria for ≥12 h		
Loss	Persistent acute renal failure (AFR): complete loss of kidney function for >4 weeks (requiring dialysis)						
ESRD	Complete loss of kidney function for >3 months (requiring dialysis)						
Other							
	Increase in SCr by >0.3 mg/dL on ≥2 consecutive days					6	[53]
	Increase in SCr by 50 from baseline until the end of treatment					16	[34]
	Increase in SCr by 0.5 mg/dL or ≥50 from baseline over two consecutive SCr values					0	[42]
	Increase in SCr by 0.5 mg/dL or ≥50 from baseline to end of treatment; CVVH: daily urine output <0.3 mL/kg					20	[49]
	Increase in SCr by 0.3 mg/dL or ≥50–100 from baseline over 2 consecutive days during and within 72 h after vancomycin discontinuation and/or daily urine output <0.5 mL/kg/h					24	[56]
	Increase of SCr					0	[47]
	Reduction of CL_{Cr}					0	[47]
	Haemodialysis upon discharge from hospital					0	[42]
	Start of RRT					7	[44]
	Alterations in renal function					0	[74]

ADQI, Acute Dialysis Quality Initiative; AKIN, Acute Kidney Injury Network; ASHP, American Society of Health-System Pharmacists; CL_{Cr}, creatinine clearance; CVVH, continuous venovenous haemofiltration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IDSA, Infectious Diseases Society of America; KDIGO, Kidney Disease: Improving Global Outcomes; MDRD, Modification of Diet in Renal Disease; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; RRT, renal replacement therapy; SIDP, Society of Infectious Diseases Pharmacists; ↑, increase; ↓, reduction.

dosing (planned loading dose, planned maintenance dose, actually applied loading dose and actually applied maintenance dose), length of therapy with vancomycin, age, sex distribution, body weight (BW), kidney status at baseline [serum creatinine (SCr), creatinine clearance (CL_{Cr})], number of patients with sepsis, severity of illness at start of CI [Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, Sepsis-related Organ Failure Assessment (SOFA) score], number of patients with mechanical ventilation and concomitant reported nephrotoxins were added to the scatterplots. The relative risk, its confidence interval, *z*-value and *P*-value for AKI at C_{ss} above or below 25 mg/L were calculated by the formulas described by Altman and Bland [73] and were displayed in a forest plot. The collected data were summarised and graphically plotted using Microsoft Excel (2016) (Microsoft Corp., Redmond, WA, USA) and the ggplot2 and epitools packages of the R Statistical Software v.4.2.0 (R Core Team 2021).

3. Results

3.1. Bibliographic search

Across the various databases, 1770 articles were identified (915 from PubMed, 284 from Cochrane Library, 456 from Google Scholar and 115 from a manual search in the reference lists of related publications). Subsequently, 465 duplicate studies were excluded, leaving 1305 records for further investigation. A total of 1177 publications were classified as inappropriate according to the PICOS criteria after inspection of the title and abstract, mainly because of the absence of intravenous or continuous use of vancomycin. Of the remaining 128 full-text articles, 21 were evaluated for data extraction and inclusion in this systematic review. Eighteen reported efficacy data and sixteen presented safety data. Fig. 1 shows the selection process.

Table 2
Significant predictors of the outcomes 'acute kidney injury', 'mortality' and 'target attainment' identified by univariate and multivariate regression analysis in the studies

Univariate analysis		Multivariate analysis	
Target attainment (TA) rate		*Target attainment (TA) rate*	
• Loading dose (↑ dose → ↑ TA)	[59]		
• Daily vancomycin dosage (↑ dosage → ↑ TA)	[58]	• Daily vancomycin dosage (↑ dosage → ↑ TA)	[58]
• Serum creatinine (↑ SCr → ↑ TA)	[59]		
• Creatinine clearance (↓ CL_{Cr} → ↑ TA)	[59]	• Creatinine clearance (↓CL_{Cr} → ↑ TA)	[52,59]
• CRRT intensity (↓ intensity → ↑ TA)	[55,58]	• CRRT intensity (↓ intensity → ↑ TA)	[58]
• Age (↓ age → ↑ TA)	[58]	• Age (↓ age → ↑ TA)	[58]
• Body weight (↑ body weight → ↑ TA)	[52,55]	• Body weight (↑ body weight → ↑ TA)	[52]
		• Body mass index (↑ BMI → ↑ TA)	[52]
• Sex (male → ↓ TA)	[59]	• Sex (male → ↓ TA)	[59]
• Prolonged ICU stay before initiation of vancomycin (↑ stay → ↓ TA)	[48]	• Prolonged ICU stay before initiation of vancomycin (↑ stay → ↓ TA)	[48]
• SOFA score (↑ score → ↑ TA)	[59]		
ICU mortality		*In-hospital mortality*	
• AKI (AKI → ↑ mortality)	[61]	• C_{24} < 15 mg/L (↓ C_{24} → ↑ mortality)	[43]
		• SAPS II (↑ score → ↑ mortality)	[43]
AKI		*AKI*	
• Diabetes mellitus (diabetes → ↑ AKI)	[46]	• C_{ss} of CI (esp. >30 mg/L) (↑ C_{ss} → ↑ AKI)	[46,56,76]
• Shock (shock → ↑ AKI)	[46]	• Duration of therapy [at time of highest SCr (risk/injury)] (↑ duration → ↑ AKI)	[56,76]
		• CL_{Cr} at ICU admission	[43]
		• Body weight (↑ lean body weight → ↑ AKI)	[46]
		• SAPS 3 score (↑ score → ↑ AKI)	[46]
		Early AKI	
		• Bacteraemia (bacteraemia → ↑ AKI)	[56]
		• C_{mean} day 1-3 (↑ C_{mean} → ↑ AKI)	[56]
		• Daily vancomycin dosage (day 1-3) (↓ dosage → ↑ AKI)	[56]
		Late AKI	[56]
		• Diabetes (diabetes → ↑ AKI)	[56]
		• Duration of therapy (↑ duration → ↑ AKI)	[56]

AKI, acute kidney injury; BMI, body mass index; C_{24}, mean steady-state vancomycin serum concentration ~24 h after initiation of therapy; C_{mean}, mean steady-state vancomycin serum concentration during the entire duration of therapy or ≥3 days of therapy; CI, continuous infusion of vancomycin; CL_{Cr}, creatinine clearance; CRRT, continuous renal replacement therapy; C_{ss}, steady-state serum concentration; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SCr, serum creatinine; SOFA, Sepsis-related Organ Failure Assessment; ↑, increase; ↓, reduction.

3.2. Quality of included studies

The methodological quality of the studies included in this review varied but did not influence inclusion in the analysis. The detailed results of the risk-of-bias assessment are shown in Supplementary Tables S8 and S9.

3.3. Characteristics of included studies

Only two randomised controlled trials (RCTs) met the inclusion criteria [34,47]. Two of the included studies were multicentre investigations [34,46]. Eight studies (38%) had a prospective design [34,41,47,52,53,55,74,75]. The studies were conducted between 2001 and 2020 and the majority (16/21) were performed in Europe [33,34,43,44,46–48,52,53,55,56,58,59,61,74,76]. In 13 studies (62%) different patient groups were compared [33,34,42–44,46,47,49,53,56,61,74,76]. Equally, in 13 studies (62%) only patients on CI were included [41–43,46,48,52,53,55–59,75]. In total, 2949 patients treated with CI were enrolled in the trials. In nine studies (43%) only patients with sepsis were included [43,52,53,55–59,74], where different definitions were used [77–80]. Positive cultures were described in almost one-half of the studies [46,48,52,55,56,58,59,61,74,75], which ranged from 6% to 100%. Two studies were focused on infections caused by β-lactam-resistant pathogens (i.e. MRSA, methicillin-resistant CoNS) [34,47]. Additional use of nephrotoxins was described in eight studies (38%) [33,34,43,46,48,56,61,76]. Aminoglycosides were listed most frequently (7/8) [33,34,43,46,48,56,61]. The heterogeneous characteristics of the included studies can be seen in Table 3 and in more detail in Supplementary Tables S1 and S2.

3.4. Characteristics of vancomycin treatment

In general, vancomycin therapy consisted of a loading dose (LD) and a maintenance dose (MD). The dosing regimen was differentiated according to a fixed or body weight-dependent protocol, if necessary with adaptation according to renal function. Mean LDs ranged from 500 mg [74] to 2894 mg [42] and from 8 mg/kg BW [74] to 35 mg/kg BW [52]. The average daily MDs ranged from 396 mg/day or 5 mg/kg BW/day [43] to 3039 mg/day or 42 mg/kg BW/day [42]. A total dose throughout the course of therapy was reported in five studies and ranged from 3.6 g to 14 g [43,47,56,61,76]. The average duration of vancomycin therapy was reported in 17 studies [33,34,41–44,46–49,55,56,58,59,61,75,76]. It ranged from 3 days [55] to 15 days [46] (mean 6 days, interquartile range 5–9 days). Different C_{ss} ranges were aimed for, but no indication dependence was evident: 20–30 mg/L (n = 7 [52,53,55–59]), 15–25 mg/L (n = 6 [41–44,46,47]), 20–25 mg/L (n = 4 [33,34,48,49]), 20–40 mg/L (n = 1 [61]) and 20 mg/L (n = 1 [74]). In approximately one-half of the studies, average C_{24} values were reported. They were distributed as follows: 15 to <20 mg/L (n =2 [56,74]) and 20 to <25 mg/L (n = 9 [41,42,48,52,53,55,57–59]). No study had an average C_{24} <15 mg/L or ≥25 mg/L (Supplementary Fig. S6a). In approximately two-thirds of the studies, C_{mean} values were stated or could be calculated. They were distributed as follows: 15 to <20 mg/L (n = 3 [44,47,76]), 20 to <25 mg/L (n = 6 [34,41,49,56,59,61]), 25 to <30 mg/L (n = 2 [33,58]) and ≥30 mg/L (n = 1 [75]) (Supplementary Fig. S6b). Different kinds of immunoassays were used for measurement, which measured the total vancomycin amount in serum. In seven studies an average AUC_{24} (total) value was presented [33,34,42,43,52,55,75], which was most often calculated by a (log-)trapezoidal rule (n = 4). Mean AUC_{24}

data ranged from 484 mg·h/L [42] to 788 mg·h/L [75] (Supplementary Fig. S6c). The parameters for treatment with vancomycin are depicted in Table 3 and Supplementary Table S3.

3.4.1. Target attainment

In approximately one-half of the studies a target attainment rate (TA) was reported (n = 1391 patients; 24–92%) (Table 3) [41–43,48,49,52,53,55,57–59]. In addition, in one-third each the rate of subtherapeutic and supratherapeutic levels was described [41,44,49,55,57–59]. In no study was a dependence of the TA on C_{SS} per se detected, but a higher vancomycin dose increased the TA (Table 2) [58,59]. We observed that a lower and wider target range was achieved more often (Fig. 2). In no study was the time within the target range reported, but in three studies a time required to reach the target C_{SS} was stated. Therefore, a link to efficacy would be questionable. It took 16 h (target range 20–25 mg/L, ICU mortality 21%) [33], 36 h (target range 20–25 mg/L, ICU mortality 37%) [34] and 48 h (target range 20–30 mg/L, ICU mortality 30%) [59] to reach target concentrations.

3.5. Characteristics of outcome parameters

C_{SS}-dependent efficacy and safety of CI were analysed. However, there was no single study whose primary objective was the target concentration range-dependent comparison of outcome parameters. Results are displayed in Table 3 and Supplementary Tables S4 and S5.

Table 3
Overview of the main characteristics of the 21 included studies with continuous infusion (CI) of vancomycin (VCM)

Reference	Country	Design	Time Course	ICU	Study Population with CI: Total Number of Patients	Study Population with CI: Comparison of Patient Groups	Specialty of study	Target Vancomycin Level: Definition Css [mg/L] AUC24/MIC	Target Vancomycin Level: Measured Value Css [mg/L] AUC24 [mg*h/L]	Outcome	Definition	Results
Akers 2012 [49]	USA	Retrospective single-center cohort study	2009/12-2006/01	Surgical (burn)	90		Burn patients (100%)	Css: 20-25 AUC24: ≥400	**Overall therapy**: 20.0±3.8 Gram-positive bacteremia: 19.3±3.2 Sepsis without proven gram-positive bacteremia: 21.2±4.2 Pneumonia: 22.0±3.9 Lack of postinfusion peak data prevented actual calculation of AUC	ECF	Mortality (in-hospital, 14-day, 28-day)	In-hospital mortality: All: 32.2% (29/90) Non-CVVH: 19.1% (13/68) Gram-positive bacteremia: 16 % (4/25) (4.4% (4/90)) Sepsis without gram-positive bacteremia: 70% (14/20) (15.6% (14/90)) Pneumonia: 35% (7/20) / 7.8% (7/90) 14-d mortality: All: 10% (9/90) 28-d mortality: All: 18.9% (17/90)
										EMF	Recurrence of gram-positive bacteremia after beginning of CI	MSSA: (2 of an unknown quantity) CI+II: 17.5% (10/57) MRSA: (2 of an unknown quantity) Enterococci: (3 of an unknown quantity)
										SR	Non-CVVH: Increase in SCr by ≥0,5 mg/dL or at least 50% increase from start to end of vancomycin therapy CVVH: Urine output <0.3 mL/kg/d	All (CVVH + Non-CVVH): ≥ 50% SCr increase: 7.8% (7/90) ≥0,5 mg/dL SCr increase at end of therapy: 6.7% (6/90) ≥0.5 mg/dL SCr increase at any time during therapy: 20% (18/90) Non-CVVH: ≥ 50% SCr increase: 10.4% (7/68) ≥0.5 mg/dL SCr increase at end of therapy: 8.8% (6/68) ≥0,5 mg/dL SCr increase at any time during therapy: 22.1% (15/68)
										SNR	Bone marrow toxicity: Difference in leukocytes, neutrophils and platelets at the beginning and end of CI	Leukocytes (x1000/uL): Start of CI 10.6 (8.4-17.5); End of CI: 12.2 (8.4-18.8) (p=0.22) Neutrophils (x1000/uL): Start of CI: 9.1 (6.7-14.8); End of CI: 9.9 (6.4-16.5) (p=0.33) Platelets (x1000/uL): Start of CI: 176 (101-271); End of CI: 236 (108-417) (p=0.001)
Baptista 2014 [53]	Portugal	Retrospective/ Prospective single-center cohort study	A (MD 30 mg/kg/d): 13 months; B (MD nomogram): ND	Medical: A: 39.2% B: 20.0% Surgical: A: 60.8% B: 80.0%	104	A (MD 30 mg/kg/d): 79 B (MD nomogram): 25	Augmented renal clearance (77%) Mechanical ventilation (100%) Sepsis (100%)	Css: 20-30	**24 h**: A: 21.5±6.4 B: 24.5±5.2	SR	Increase in SCr by >0.3 mg/dL on ≥2 consecutive days	A (MD 30 mg/kg/d): 6.3% (5/79) B (MD nomogram): 4.0% (1/25)
										SNR	Red-man-syndrome	ND
Beumier 2013 [55]	Belgium	Prospective/ Prospective single-center cohort study	2012/05-2011/01	Medical: 69% Surgical: 31%	32		CRRT (100%) Mechanical ventilation (78%) Sepsis (100%)	Css: 20-30 AUC24: >400	**24 h**: 24.3±9.3 679±150	ECF	Mortality (ICU)	57% (18/32)
										ECS	Target attainment	*Target:* **12 h**: 69% **24 h**: 63% *Subtherapeutic:* **12 h**: 3% **24 h**: 19% *Supratherapeutic:* **12 h**: 28% **24 h**: 19%
Cianferoni 2013 [56]	Belgium	Retrospective single-center cohort study	2009/12-2008/01	Medical: All: 59% No AKI: 59% AKI: 62% (Early AKI: 60% Late AKI: 63%) Surgical: All: 41% No AKI: 41% AKI: 38% (Early AKI: 40% Late AKI: 37%)	207	No AKI: 157 AKI: 50 (Early AKI: 28 Late AKI: 22)	Mechanical ventilation (69%) Sepsis (100%)	Css: 20-30	**Overall therapy**: All: 22.3±7.0 No AKI: 21.2±6.8 AKI: 25.8±6.6 (Early AKI: 27.2±5.1 Late AKI: 24.1±7.8) **24 h**: All: 19.7±8.5 No AKI: 18.7±7.0 AKI: 22.5±9.6 (Early AKI: 24.5±7.8 Late AKI: 20.2±11.1)	ECF	Mortality (ICU)	All: 23% (48/207) No AKI: 18% (28/157) AKI: 40% (20/50) Early AKI: 46% (13/28) Late AKI: 32% (7/22)
										SR	Daily urine output <0.5 ml/kg/h and/or increase of SCr ≥0.3 mg/dl or 50-100% increase from baseline (=VCM on first day of therapy) on at least two consecutive days during and within 72 h after VCM discontinuation Early AKI: Occurrence within first 2 days of therapy; Late AKI: Occurrence after 2 days of therapy; Severe AKI: Need for CRRT or HD within VCM therapy or up to 3 days after drug discontinuation	Total: 24% (50/207) VCM level <15 mg/L: 6% (2/34) 15-20 mg/L: 11% (5/47) 20-25 mg/L: 30% (18/60) 25-30 mg/L: 38% (15/39) >30 mg/L: 37% (10/27) Early AKI: 56% (28/50) Late AKI 44% (22/50) CRRT/HD: No AKI: 2% (3/157 patients needing CRRT 9/11/13 d after VCM discontinuation) AKI: 18% (9/50) during VCM therapy
Covajes 2013 [58]	Belgium	Retrospective single-center cohort study	2010/12-2008/01	Medical: 69% Surgical: 31%	85		CRRT (100%) Mechanical ventilation (84%) Sepsis (100%)	Css: 20-30	**24 h**: 24.7±9.0 **48 h**: 26.0±8.1 **72 h**: 27.7±9.3	ECF	Mortality (ICU)	59% (50/85)
										ECS	Target attainment	*Target:* **24 h**: 51% **48 h**: 56% **72 h**: 67% *Subtherapeutic:* **24 h**: 29% **48 h**: 22% **72 h**: 8% *Supratherapeutic:* **24 h**: 20% **48 h**: 21% **72 h**: 26%
Cristallini 2016 [52]	Belgium	Prospective single-center cohort study	2013/05-2012/01	Medical: 36% Surgical: 64%	107		Mechanical ventilation (54%) Sepsis (100%)	Css: 20-30 AUC24: ND	**12 h**: 26.0±8.3 **24 h**: 23.0±6.8 **48 h**: 26.0±6.0 780±180	ECF	Mortality (ICU)	22% (24/107)
										ECS	Target attainment	**12 h**: 56% **24 h**: 54% **48 h**: 73%
Hanrahan 2014 [76]	UK	Retrospective single-center cohort study	2009/06-2004/12	Medical Surgical	653		ND	Css: ND	**Overall therapy**: 18.4±4.2	ECF	Mortality (ICU all-cause; within 72 h of last recorded VCM dose)	ICU: 26.3% (172/653) Within 72 h of last VCM: 19.9% (130/653) Mortality or nephrotoxicity within 72 h of cessation: 38.7% (253/653)
										SR	AKI (RIFLE [114])	24.7% (161/653) Nephrotoxicity or mortality within 72 h of cessation: 38.7% (253/653)
Hutschala 2009 [33]	Austria	Retrospective single-center cohort study	2005/12-2001/01	Surgical (cardiosurgical)	119		Cardiosurgery (100%) CKD (0%; SCr >1.5 mg/dL))	Css: 20-25 AUC24: ND	**Overall therapy**: 25.0±4.0 Time to target: 16±8 h 529±98	ECF	Mortality (ICU, in-hospital)	ICU: 21% (25/119); In-hospital: 30.3% (36/119) Timing of death in course of VCM administration: 9±3.3 d (1-20)
										ECS	Improvement (= Reduction of CRP; leukocytes)	CRP: -66.4±41.6% ((before CS: 3,7±5,1 (0.5-25.1) at start of VCM: 22.64±10.1 (7.3-55); on 10th day of VCM: 7.6±5.69 (0.7-32.1))
										SR	AKI (AKIN [100] and RIFLE [114])	**AKIN**: 49.6% (59/119) RRT: 23.5% (28/119)

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Table 3 (*continued*)

												AKIN: 1: 29.4%; 2: 11.8 %; 3: 8.4 % **RIFLE**: 37% (44/119) RIFLE: R: 30.3%; I: 4.2 %; F: 2.5 %	Necessity to administer diuretics (furosemide): 12.6% (15/119)	
Lin 2016 [42]	USA	Retrospective single-center cohort study	2015/01-2013/01	Surgical	52	Obese (BMI >35 kg/m²): 26 Non-obese (BMI <30 kg/m²): 26	CVVH (35%) Differentiation obese/non-obese Mechanical ventilation (~100%)	Css: 15-25 AUC24: ND	**24 h**: All: 20.32±3.72 Obese: 20.3±3.81 Non-obese: 20.03±3.8 CVVH: Obese: 19.8±3.05 Non-obese: 21.6±3.02 Preserved renal function: Obese: 20.6±4.21 Non-obese: 19.6±4.41 Obese: 488±91.5 Non-obese: 480.9±91 CVVH: Obese: 474±73.2 Non-obese: 517±48.6 Preserved renal function: Obese: 496±101 Non-obese: 471±106	ECF ECS SR SNR	Mortality (in-hospital) Target attainment Not requiring CVVH: Increase in SCr by 0.5 mg/dL or at least 50 % increase from baseline over two consecutive SCr values Hemodialysis upon discharge from hospital Hearing loss	50% (7/14) **24 h**: Obese: 92.3% Non-obese: 88.5% AKI: 0%; Hemodialysis: 0% Hearing loss: 0%	CVVH Obese: 100% Non-obese: 100%
Mohammedi 2006 [74]	France	Prospective single-center cohort study	12 months	Medical	40	A (LD 500 mg): 20 B (LD 15 mg/kg): 20	Mechanical ventilation (90%) Sepsis (100%)	Css: 20	**24 h**: A: 14.9±5.4 B: 18.5±6.4	ECF ECS SR	Mortality (ICU) Cure (in patients with proven infection) Alterations in renal function	A (LD 500 mg): 50% (10/20) A (LD 500 mg): 56% (10/18) 0%	B (LD 15 mg/kg): 35% (7/20) B (LD 15 mg/kg): 93% (14/15)
Ocampos-Martinez 2012 [59]	Belgium	Retrospective single-center cohort study	2009-2008	Medical: 59.8% Surgical: 40.2%	261		Mechanical ventilation (71%) Sepsis (100%)	Css: 20-30	**24 h**: 20.4±8.9 **48 h**: 24.1±9.1 **72 h**: 25.5±10.1 Time to target: 2 d (1-3)	ECF ECS	Mortality (ICU) Target attainment	29% (77/261) *Target:* **24 h**: 47% **48 h**: 67% **72 h**: 86%	*Subtherapeutic:* **24 h**: 42% **48 h**: 14% **72 h**: ND	*Supratherapeutic:* **24 h**: 11% **48 h**: 19% **72 h**: ND
Omuro 2021 [61]	Germany	Retrospective single-center cohort study	2019-2012	Medical: 30.3% Surgical: 68.9% Neurolog.: 0.8%	119		CKD (8%) Mechanical ventilation (87%)	Css: 20-40	**Overall therapy**: 20.7±7.9	ECF SR	Mortality (ICU) AKI (AKIN [100])	CI: 25.2% (30/119) 20.2% (eventually higher rate of AKI in medical patients (CI/II: surgical: 25,7%; medical: 42,6%))	(VCM-AKI (CI+II): 48%	Non VCM-AKI (CI+II): 16.8%)
Perin 2020 [48]	France	Retrospective single-center cohort study	2018/12-2016/01	No data on type of ICU provided	179 Primary outcome: 176 Finished follow-up: 131 (follow-up = 15 consecutive days after VCM initiation)		Augmented renal clearance (4%) Mechanical ventilation (85%) RRT (27%)	Css: 20-25	**24–48 h**: 20.3±6.8	ECF ECS ECS EMF SR	Mortality (ICU, in-hospital, 28-day) Persistence or progression of baseline signs and symptoms of infection after ≥ 2 d of treatment, consistent with active infection Requirement for additional antibacterial treatment Target attainment Cure (= Resolution of clinical signs and symptoms compared with baseline, no requirement for antibiotic escalation) Relapse (= Finding of same pathogen); Reinfection (= Presence of another pathogen) AKI (KDIGO [101] (measured on D1-4; D10; D15))	**28-day**: All: 26% (46/178) Failure without identification: 13% (23/179) **24–48 h**: 24% 65% (116/179) (test of cure could not be assessed in 13% (23/179)) Relapse: 3% (5/179) Reinfection 7% (12/179) During VCM administration: 60% (107/179) With RRT: 27% (49/179)	D2/3 VCM level 20-25 mg/L: 19% (8/42) D2/3 VCM level <20/>25 mg/L: 28% (37/132) VCM >25 mg/L at d2/3: 77% (34/44) With RRT: 36% (16/44)	VCM <25 mg/L at d2/3: 55% (72/131) With RRT: 25% (33/131)
Saugel 2013 [44]	Germany	Retrospective single-center cohort study	2008/12-2004/01	Medical	164		Mechanical ventilation (54%) RRT (43%)	Css: 20-30	**Overall therapy**: 19.7±14.7	SR	Start of RRT	7.3% (12/164)		
Sin 2018 [41]	USA	Prospective single-center cohort study	2017/01-2014/11	Surgical: 65.4% Medical: 34.6%	52		CVVH (100%)	Css: 15-25	**24 h**: 20.1±4.7 **48 h**: 20.7±3.7 **72 h**: 21.9±3.5	ECF ECS SNR	Mortality (in-hospital) Target attainment Infusion reaction; Ototoxicity	63.5% (33/52) *Target:* **24 h**: 82.7% **48 h**: 81.8% **72 h**: 75.0% 0%	*Subtherapeutic:* **24 h**: 3.8% **48 h**: 6.1% **72 h**: 8.3%	*Supratherapeutic* **24 h**: 13.5% 48 h: 12.1% **72 h**: 16.7%
Spadaro 2015 [43]	Italy	Retrospective single-center cohort study	2013/07-2010/03	Medical: CrCl >50 mL/min: 57% ≤50 mL/min: 50% Surgical: CrCl >50 mL/min: 43% ≤50 mL/min: 50%	348	CrCl >50 mL/min: 210 CrCl ≤50 mL/min: 138	CKD (40% CrCl ≤50 mL/min) Differentiation in CrCl ≤/>50 mL/min	Css: 15-25 AUC24: >400	Not described CrCl >50 mL/min: 468±79 (AUC/MIC) CrCl ≤50 mL/min: 490±84 (AUC/MIC)	ECF ECS SR	Mortality (ICU) Target attainment AKI (Consensus Recommendation from ASHP/IDSA/SIDP on Therapeutic Monitoring of Vancomycin (2009) [113])	CrCl >50 mL/min: 21.4% (45/210) **24 h**: CrCl >50 mL/min: 44% CrCl ≤50 mL/min: 57% CrCL >50 mL/min: 2.4% (5/210) CrCL ≤50 mL/min: 9.4% (13/138)	CrCl ≤50 mL/min: 23.9% (33/138) **48 h**: CrCl >50 mL/min: 41% CrCl ≤50 mL/min: 40% VCM level 25-30 mg/L: 0% VCM level >30 mg/L: <8%	**72 h**: CrCl >50 mL/min: 41% CrCl ≤50 mL/min: 41%
Spapen 2011 [46]	Belgium	Retrospective two-center cohort study	2009/11-2008/01	No data on type of ICU provided	129	AKI: 38 No AKI: 91	CKD (0%; SCr >1.5 mg/dL))	Css: 15-25	**Overall therapy**: VCM level <25 mg/L: No AKI: 95.6% (65/68) (71.4%, 65/91)	ECF SR	Mortality (no differentiation between "infection-related" or "AKI-induced") AKI (AKIN [100] 1)	AKI: 53% (20/38) Total: 29.5% (38/129)	No AKI: 20% (18/91) VCM level 25-30 mg/L:	

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Table 3 (*continued*)

									AKI: 4.4% (3/68) (7.9%, 3/38) VCM level 25-30 mg/L: No AKI: 69.0% (20/29) (22.0%, 20/91) AKI: 31.0% (9/29) (23.7%, 9/38) VCM level >30 mg/L: No AKI: 18.8% (6/32) (6.6%, 6/91) AKI: 81.3% (26/32) (68.4%, 26/38)			Distribution according to VCM level: VCM level <25 mg/L: 7.9% (3/38) VCM level 25-30 mg/L: 23.7% (9/38) VCM level >30 mg/L: 68.4% (26/38) VCM level <25 mg/L: No AKI: 95.5% (65/68) (71.4% (65/91)) AKI: 4.5% (3/68) (7.9% (3/38))	No AKI: 69% (20/29) (22% (20/91)) AKI: 31% (9/29) (23.7% (9/38)) VMC level >30 mg/L: No AKI: 18.8% (6/32) (6.6% (6/91)) AKI: 81.3% (26/32) (68.4% (26/38)) Return of SCr to baseline at discharge (surviving): 66% (12/18)
Stepan 2009 [47]	Czeck Republic	Prospective single-center randomized controlled trial	2008/05-2004/05	Medical and Surgical	33		ND	Css: 15-25	**Overall therapy**: 19.0±4.3	ECF	Mortality (infection-related)	18% (6/33)	
										ECF	Persistence of symptoms; Increase of symptoms	Not described	
										ECS	Cure (= Vanishing of all symptoms of an infection); Improvement (= Reduction of symptoms of infection; LOS; LOV; LOT; Reduction of leukocytes; Reduction of CRP)	Cure/improvement: 64% (21/33) LOS: 26 d (12.8-40.3) LOV: 25 d (10.5-39.3)	LOT: 9 (7-10) Leukocytes: d0: 13.4 (9,7-18,9) end: 10.9 (8,6-17,9) (-18.7%) CRP: d0: 192.0±98.1 end: 123±83.1 (-35.9%)
										EMF	Persistency; Superinfection; Relapse	Not described	
										EMS	Cure (=Eradication; Suspected eradication)	76% (25/33)	
										SR	Increase of SCr; Reduction of CrCl	0%	
Tuon 2021 [75]	Brazil	Prospective single-center cohort study	2020/09-2018/01	No data on type of ICU provided	33		CNS infection (100%)	Css: ND AUC24: ND	**Overall therapy**: 33.8±16.0 788±384	SR	AKI (AKIN [100])	Total: 21% (7/33) AKIN 1: 3% (1/33)	AKIN 2: 6% (2/33) AKIN 3: 12% (4/33)
Udy 2013 [57]	Australia	Retrospective single-center cohort study	2010/12-2008/01	No data on type of ICU provided	81	CVVH: 41 CVVHDF: 40	CRRT (100%) Mechanical ventilation (85%) Sepsis (100%)	Css: 20-30	**24 h**: 24.6±9.2	ECF	Mortality (not specified)	58% (47/81)	
Wysocki 2001 [34]	France	Prospective multicenter cohort study	36 months	Medical and Surgical	61		Mechanical ventilation (79%)	Css: 20-25	**Overall therapy**: 24±8 Success: 23±4	ECF	Mortality (infection-related: 10-day; end of treatment; overall: 10-day; end of treatment; ICU)	**Infection-related**: D10: 8% (5/61) End of treatment: 10% (6/61)	**Overall**: D10: 8% (5/61) End of treatment: 18% (11/61) **ICU**: 37% (21/61)
								AUC24: ND	Failure: 25±5 Time to target: 36±31 h 577±120 Failure: 685±260 Success: 596±159	ECF	Persistency or impairment of clinical, laboratory, radiological statuses	D10: 21% (13/61)	End of treatment: 21% (13/61)
										ECS	Cure; Improvement	78.7% (48/61)	
										EMF	Presence of *Staphylococcus spp.* or other species in specimen on day 5	Staphylococcus: 39% (24/61)	Other species: 15% (9/61) Bacteremia: 28% (17/61)
										EMS	Cure (= Eradication of *Staphylococcus spp.* In specimen on d5)	46% (28/61)	
										SR	50% increase of SCr from D0 until end of treatment	16.4% (10/61) Dialysis: 9.8% (6/61)	
										SNR	Phlebitis/fever	3% (2/61)	

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ARC, augmented renal clearance; ASHP, American Society of Health-System Pharmacists; AUC_{24}, vancomycin area under the serum concentration–time curve over 24 h; BMI, body mass index; CI, continuous infusion of vancomycin; CKD, chronic kidney disease; CL_{Cr}, creatinine clearance; CNS, central nervous system; CRP, C-reactive protein; C_{ss}, steady-state serum concentration; CVVH, continuous venovenous haemofiltration; CVVHDF, continuous venovenous haemodiafiltration; d, days; D, Day after initiation of vancomycin therapy; ECF, failure of clinical effectivity; ECS, success of clinical effectivity; EMF, failure of microbiological effectivity; EMS, success of microbiological effectivity; HD, haemodialysis; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; II, intermittent infusion of vancomycin; KDIGO, Kidney Disease: Improving Global Outcomes; LD, loading dose; LOS, length of stay; LOT, length of therapy; LOV, length of ventilation; MD, maintenance dose; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; MV, mechanical ventilation ND, not described; Prosp., prospective; RCT, randomised controlled trial; Retrosp., retrospective; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; (C)RRT, (continuous) renal replacement therapy; SC, single-centre; SCr, serum creatinine; SIDP, Society of Infectious Diseases Pharmacists; SNR, non-renal safety; SR, renal safety.

3.5.1. *Efficacy*

Efficacy was mentioned in 18 studies and could be divided into clinical or microbiological treatment failure or success (n = 2648 patients with CI) (Table 3; Supplementary Tables S4, S10 and S11) [33,34,41–43,46–49,52,55–59,61,74,76]. Only for C_{24} < 15 mg/L could a significant association with in-hospital mortality or clinical cure be shown (n = 388 patients) [43,74]. No other statistically significant associations were found between C_{ss} and clinical or microbiological success or failure. Five studies compared cohorts with different C_{ss} and treatment effectiveness [34,42,43,49,74]. Mohammedi et al. (n = 40 patients) used a constant LD (500 mg = 7.5 ± 1.5 mg/kg) and a weight-based LD (15 mg/kg = 1147 ± 317 mg) [74]. This resulted in different C_{ss} of 14.9 ± 5 mg/L and 18.5 ± 6 mg/L. Differences in ICU mortality (50% vs. 35%; not significant) and clinical cure (56% vs. 93%; P < 0.02) were noticed, arguing for the higher dose and resulting higher C_{24} (Fig. 3a). Spadaro et al. (n = 348 patients) studied patients with CL_{Cr} (A) above and (B) below 50 mL/min [43]. They reported a significant correlation between subtherapeutic levels at first measurement (C_{24} target, 15–25 mg/L) and in-hospital mortality (odds ratio = 2.1; P = 0.003) (Table 2). Additionally, they found lower AUC_{24}/MIC with also numerically lower ICU mortality in group A (group A, AUC_{24}/MIC 468 ± 79, mortality 21.4%; group B, AUC_{24}/MIC 490 ± 84, mortality 23.9%). Lin et al. (n = 52 patients) distinguished between obese (o) [body mass index (BMI) > 35 kg/m^2] and non-obese (no) (BMI < 30 kg/m^2) patients [42]. No statistically significant differences were noticed between groups with respect to mean C_{ss} and mortality (C_{24}, o/no: 20 ± 4 mg/L; AUC_{24}, o: 488 ± 92 mg·h/L, no: 481 ± 91 mg·h/L; mortality, o: 19.2%, no: 15.4%). In a subset analysis, Akers et al. (n = 90 patients) distinguished between patients with Gram-positive bacteraemia (1), patients with sepsis without proven Gram-positive bacteraemia (2) and patients with pneumonia (3) (C_{mean}, 1: 19 ± 3 mg/L, 2: 21 ± 4 mg/L, 3: 22 ±4 mg/L) [49]. A slight numerical difference in serum levels was observed, which was not associated with in-hospital mortality (1: 16%, 2: 70%, 3: 35%) and was not studied in relation to the impact on microbiological failure (C_{mean} overall, 20 ± 4 mg/L; failure overall, 18%). Wysocki et al. (n = 61 patients) associated a C_{mean} of 23 ± 4 mg/L with treatment success and a C_{mean} of 25 ± 5 mg/L with treatment failure [34].

3.5.2. *Safety*

Safety was discussed in 16 studies (n = 2383 patients) (Table 3; Supplementary Table S5) [33,34,41–44,46–49,53,56,61,

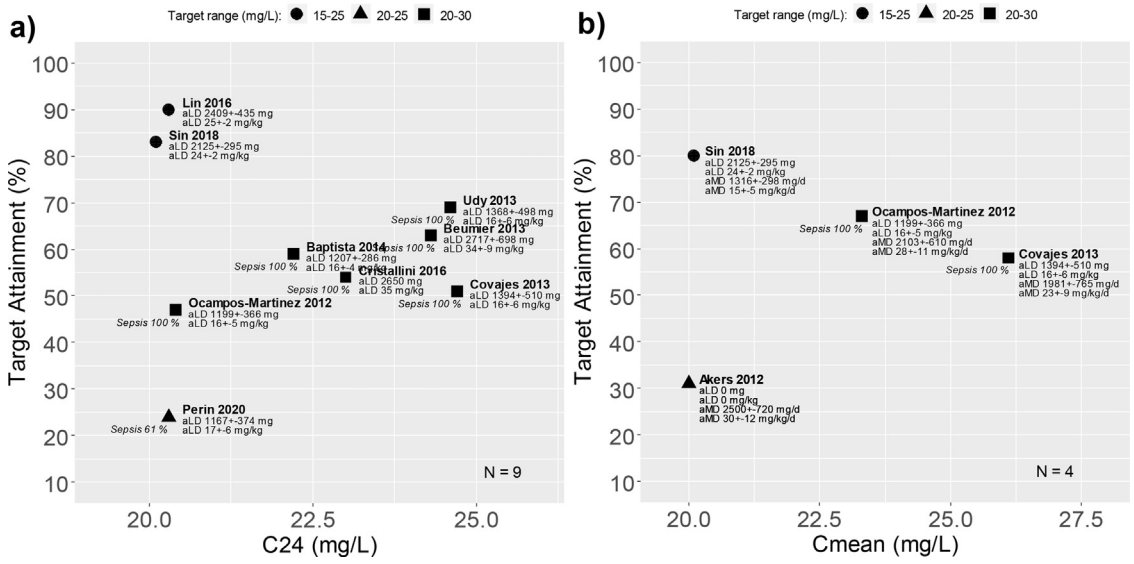

Fig. 2. Scatterplots of mean vancomycin steady-state serum concentrations (C_{ss}) plotted against each cohort's rate of target attainment. (a) Studies in which C_{ss} ~24 h after initiation of therapy with continuous infusion of vancomycin (C_{24}) was reported (n = 9 studies representing 953 patients). (b) Studies in which C_{ss} during the entire duration of therapy with continuous infusion of vancomycin or ≥3 days of therapy (C_{mean}) was reported (n = 4 studies representing 488 patients). Filled black square = C_{ss} target range of 20–30 mg/L; filled black circle = C_{ss} target range of 15–25 mg/L; filled black triangle = C_{ss} target range of 20–25 mg/L. aLD, applied average loading dose; aMD, applied average maintenance dose; Sepsis, proportion of patients with sepsis in the study population.

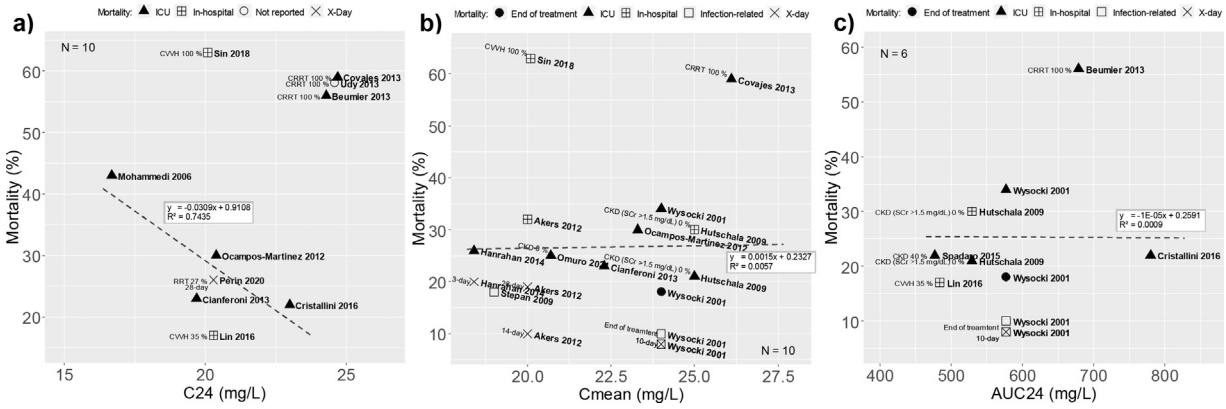

Fig. 3. Scatterplots of mean vancomycin steady-state serum concentrations (C_{ss}) plotted against each cohort's mortality rate. The dashed lines represent the regression lines (RL) of intensive care unit (ICU) mortality in studies without 100% dialysis patients. (a) Studies in which C_{ss} ~24 h after initiation of therapy with continuous infusion of vancomycin (C_{24}) was reported (n = 10). RL: n = 4 studies representing 615 patients; R^2 = 0.7435. (b) Studies in which C_{ss} during the entire duration of therapy with continuous infusion of vancomycin or ≥3 days of therapy (C_{mean}) was reported (n = 10). RL: n = 6 studies representing 1420 patients; R^2 = 0.0057. (c) Studies in which mean vancomycin area under the serum concentration–time curve for 24 h for continuously administered vancomycin (AUC_{24}) was reported (n = 6). RL: n = 4 studies representing 635 patients; R^2 = 0.0009. Filled black circle = mortality at the end of treatment with vancomycin; filled black triangle = ICU mortality; bordered cross = in-hospital mortality; X = x day mortality (e.g. 10 day, 28 day, 30 day); non-filled circle = mode of mortality not reported; non-filled square = infection-related mortality. CKD, chronic kidney disease; (C)RRT, (continuous) renal replacement therapy; CVVH, continuous venovenous haemofiltration; SCr, serum creatinine.

74–76], with 'nephrotoxicity' in the form of AKI being dealt with most often (15/16; n = 2331 patients) [33,34,42–44,46–49,53,56,61,74–76]. Different definitions were used to describe AKI (Table 1); the frequency varied from 0% [42,47,74] to 60% [48]. Higher C_{ss} (especially >30 mg/L) was identified as a significant predictor of AKI occurrence by multivariate regression analysis (Table 2) [46,56,76]. In contrast, Spadaro et al. found no relationship between AKI and C_{ss} [43]. In four studies (n = 863 patients), vancomycin serum concentration-dependent nephrotoxicity was described, the incidence of which varied widely [43,46,48,56]. Spadaro et al. (n = 348 patients) observed no nephrotoxicity at C_{ss} of 25–30 mg/L and an incidence <8% (<28/348) when the C_{ss} exceeded 30 mg/L [43]. Cianferoni et al. (n = 207 patients) described an increasing incidence the higher the C_{ss}, with a maximum of 38% (25/66) above a level of 25 mg/L [56]. They also established a link between C_{ss}, onset of AKI and ICU mortality, with rising mortality and AKI rate at higher C_{ss} (no AKI, C_{24} 18.7 mg/L, C_{mean} 21.2 mg/L, mortality 18%; early AKI, C_{24} 24.5 mg/L, C_{mean} 27.2 mg/L, mortality 46%). However, it could not be ruled out that the increased serum concentrations were only a marker for a declining glomerular filtration and did not cause AKI per se. Perin et al. (n = 179 patients) observed an AKI rate of 55% (72/131) with C_{ss} < 25 mg/L versus 77% (34/44) with C_{ss} > 25 mg/L [48]. Spapen et al. (n = 129 patients) demonstrated an increase in AKI the higher the C_{ss}: <25 mg/L, 4.5% (3/68), 25–30 mg/L, 31% (9/29), >30 mg/L, 81% (26/32) [46]. Additionally, mortality was higher in patients with AKI (no AKI, 20%; AKI, 53%; P = 0.01). Comparing the information from the latter three studies (the only ones that provided patient numbers

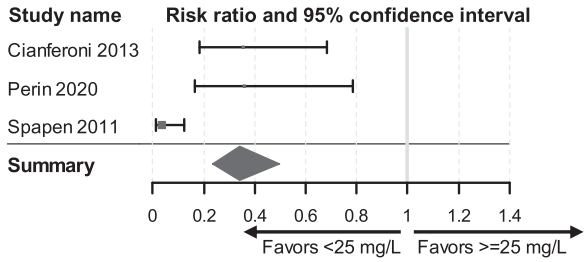

Fig. 4. Forest plot comparing the influence of vancomycin steady-state serum concentration below or above 25 mg/L on acute kidney injury (AKI) (n = 3 studies representing 515 patients). Overall risk ratio = 0.535 (95% CI 0.432–0.662; z = –5.745; P < 0.0001). Risk ratio <1 indicates a lower risk of AKI at a vancomycin serum concentration <25 mg/L as opposed to ≥25 mg/L. The dark grey diamond represents the overall risk ratio. CI, confidence interval.

with concentration-dependent AKI rates), there appeared to be an advantage in terms of AKI occurrence when the target concentration was <25 mg/L (Fig. 4; Supplementary Tables S6 and S7).

4. Discussion

Although vancomycin has been used for decades to treat infections with Gram-positive pathogens, and data on vancomycin concentration and therapeutic outcome have been published in numerous studies, this systematic review shows that there are few data on the target serum concentration range to achieve effective yet tolerable therapy during CI in critically ill adult patients.

4.1. Target attainment

The literature did not provide associations between TA and C_{ss}; achievement of target ranges was used to evaluate new dosing protocols [42,53,55] or different dosing modalities [24,25]. Based on differences in tissue penetration of vancomycin [81] or pathogen susceptibility [82], an indication-dependent target range selection would be likely. For example, Tsutsuura et al. showed that in MRSA bacteraemia, but not MRSA infections per se, higher trough concentrations resulted in significantly fewer treatment failures [83]. However, no correlation between the selected target range and the investigated indication was apparent to us in the synopsis. When plotting the TA and C_{ss} of each trial, higher TAs were observed with higher LDs without influence of MDs (Fig. 2). In studies with sepsis or burn patients, lower TAs were found. Physiological changes during sepsis or burns may have played a role (e.g. capillary leakage or oedema) [13–15]. However, it should be noted that different definitions of sepsis were used in the studies, making it difficult to compare patients and sepsis rates. Temporal differences (16–48 h) to reach target C_{ss} could be due to another dosing regimen (higher vancomycin doses equal faster target achievement) [33,34,59].

4.2. Efficacy

An assessment of the reported mortality data was difficult. Mortality appeared to depend on numerous factors and was not only influenced by C_{ss}. Furthermore, there was very little comparative concentration and mortality data. Higher C_{24} resulted in lower mortality rates, with a concentration >15 mg/L found to be favourable [43,74]. A target concentration for C_{mean} or AUC_{24} leading to lower mortality was not evaluated. Looking at the available datasets of each study's average C_{ss} and mortality rate, we also noticed an association of ICU mortality with C_{24} (R^2 = 0.7435), but not with C_{mean} (R^2 = 0.0057) or AUC_{24} (R^2 = 0.0009) (Fig. 3). In a consensus review published in 2020 by several societies on the dosing and monitoring of vancomycin, for CI a lower limit of the target C_{ss} range of 20 mg/L [=AUC_{24}/MIC ≥ 480 if MIC ≤ 1 mg/L; pharmacokinetic/pharmacodynamic (PK/PD) target not validated] was recommended [84]. This threshold was pharmacokinetically, microbiologically and clinically justified [34], was used in most studies considered [84], but was not derived from concentration comparative effectiveness studies. For intermittent infusion (II), the same practice guideline and meta-analyses recommended AUC_{total}/MIC-guided monitoring with a value ≥400 [if MIC ≤ 1 mg/L, determined by broth microdilution (BMD)] as the PK/PD target for efficacy [83–85]. For CI, this target would correspond to a concentration of 17 mg/L (if MIC = 1 mg/L) and is thus close to the lower limit of the target concentration range found in our research. Cristallini et al. calculated AUC_{24}/MIC ratios ≥400 (if MIC ≤ 1 mg/L) for C_{24} ≥ 15 mg/L [52]. The PK/PD threshold resulted from studies with infections with MRSA whose epidemiological cut-off value (ECOFF) of ≤2 mg/L is one-half that of methicillin-resistant CoNS or *Enterococcus faecalis* [82,84]. Studies on the optimal vancomycin PK/PD target for infections with these micro-organisms are lacking. However, Ampe et al. calculated AUC_{total}/MIC_{BMD} = 667, AUC_{free}/MIC_{BMD} = 452, AUC_{total}/MIC_{Etest} = 457 and AUC_{free}/MIC_{Etest} = 301 as the thresholds between clinical success or failure in ward patients with mono-infections with various Gram-positive pathogens and CI as the only effective agent [86]. A transfer of dose recommendations from II to CI is however uncertain. When comparing mortality during CI and II, meta-analyses have found no difference [22–25]. Nevertheless, the average measured C_{ss} values in the included studies were always higher for CI and additionally differed within the comparison groups. A meta-analysis on mortality of the same C_{ss} of CI versus II is missing so far. Additionally, for II, Dalton et al. demonstrated that the use of AUC/MIC to predict patient outcome was modest [87], and Tsutsuura et al. found no significant difference in mortality rates with trough- versus AUC-guided treatment monitoring [83]. For CI, the benefit of PK/PD-guided therapy remains completely unclear. Mohammedi et al. emphasised the need for sufficient LDs to maintain high C_{24} and to reduce mortality [74]. We also observed the importance of sufficient LDs (Supplementary Table S3). Additionally, higher MDs appeared to result in lower mortality in the C_{24} cohort (Supplementary Table S3). Reaching high therapeutic levels as early as possible at the beginning of anti-infective therapy is in accordance with general recommendations [15,88–93]. CI has advantages over II in this respect [26–29,32–34]. However, sufficient dosing in critically ill patients is challenging [15], partly due to the increased volume of distribution with impaired capillary barrier function and the probable losses through renal function and replacement procedures [14]. The difficulty of appropriate dosing could account for the heterogeneity of doses applied in the studies included in this review. From our diagrams (Fig. 3), it could be deduced that dialysis was a predictor of mortality, supported by the known higher mortality of dialysis patients [94]. The initial severity of illness, as measured by APACHE II, SAPS II or SOFA score, may also have influenced mortality (Supplementary Table S2). C_{ss} and clinical cure in two CI cohorts were only compared by Mohammedi et al. (higher C_{24} equals higher cure) [74], whereas C_{ss} and microbiological efficacy were not analysed comparatively in any study. For C_{mean} and clinical success, the comparison of results by Stepan et al. and Wysocki et al. coincided with the analysis of Mohammedi et al. (higher C_{mean} equals higher cure), but not for microbiological success (higher C_{mean} equals lower cure) (Supplementary Table S10) [34,47,74]. This may be related to different observation periods (5 days versus end of treatment), different definitions of 'success' and 'failure', or the chicken-and-egg question of what came first, (disease-related) renal failure or high vancomycin levels. For example, Wysocki et al. found a higher C_{mean} with treatment failure

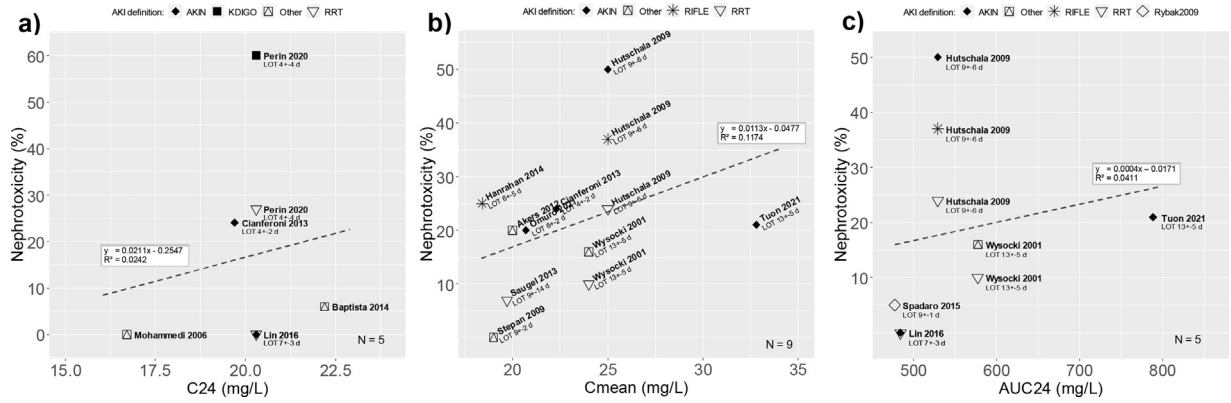

Fig. 5. Scatterplots of mean vancomycin steady-state serum concentrations (C_{ss}) plotted against each cohort's rate of acute kidney injury (AKI) (= nephrotoxicity). Dashed lines represent the regression lines calculated from the data of all cohorts of a respective C_{ss} class. (a) Studies in which C_{ss} ~24 h after initiation of therapy with continuous infusion of vancomycin (C_{24}) was reported (n = 5 studies representing 582 patients; R^2 = 0.0242). (b) Studies in which C_{ss} during the entire duration of therapy with continuous infusion of vancomycin or ≥3 days of therapy (C_{mean}) was reported (n = 9 studies representing 1479 patients; R^2 = 0.1174). (c) Studies in which mean vancomycin area under the serum concentration–time curve for 24 h for continuously administered vancomycin (AUC_{24}) was reported (n = 5 studies representing 613 patients; R^2 = 0.0411). Filled black diamond = AKIN; filled black square = KDIGO; squared triangle = other definition of AKI; star = RIFLE; non-filled triangle = RRT; non-filled diamond = Rybak2009. AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease: Improving Global Outcomes; LOT, length of therapy with continuously administered vancomycin; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; RRT, renal replacement therapy; Rybak2009, consensus recommendation from ASHP/IDSA/SIDP on therapeutic monitoring of vancomycin (2009) [113]; ASHP, American Society of Health-System Pharmacists; IDSA, Infectious Diseases Society of America; SIDP, Society of Infectious Diseases Pharmacists).

[34]. Similarly, Lin et al. and Spadaro et al. noticed higher mortality with higher AUC_{24} and AUC_{24}/MIC values [42,43]. An increase in SCr followed by an increase in C_{mean} or AUC_{24} could be a marker of treatment failure. Consequently, the usefulness of C_{mean} or AUC_{24} for monitoring treatment efficacy is questionable and can only be assessed if renal function prior to initiation of therapy and pre-existing nephrological conditions, as well as duration of therapy, are known. With II, higher trough levels or AUC_{24}/MIC values resulted in better clinical and microbiological cure [95–97].

4.3. Safety

The nephrotoxicity of vancomycin is known [98], with CI being significantly associated with a lower risk compared with II [22–25]. However, definitions of reported AKI varied. As Hutschala et al. and Koeze et al. showed, this has implications for the reported incidence, timing and outcome of AKI [33,99]. Newer definitions such as AKIN (Acute Kidney Injury Network) [100] or KDIGO (Kidney Disease: Improving Global Outcomes) [101] are more sensitive, resulting in higher reported rates of AKI. In our comparison, we related only similar AKI definitions. Due to poor tissue penetration [81], therapy with vancomycin is limited as the dose cannot be increased arbitrarily. The upper limit of C_{ss} that keeps the impairment of renal function within acceptable limits, weighing the benefits and harms, is much debated. In dataset plots of C_{ss} against AKI rate, we found that higher C_{ss} and longer duration of therapy increased the rate of AKI (Fig. 5), as also calculated by Cianferoni et al. and Hanrahan et al. with multiple regression (Table 2) [56,76]. For II, an upper trough level limit of 20 mg/L was established and AUC_{24}/MIC ≤ 600 (if MIC ≤ 1 mg/L, determined by BMD) was set as the PK/PD target for safety [83,84]. For CI, this target corresponds to a C_{ss} of 25 mg/L [84] and coincides with the preferred concentration we calculated. However, due to a lack of data, we could not compare 25 mg/L with other thresholds such as the previously described upper limits of 28 mg/L or 30 mg/L [46,102]. Elevated AUC_{24} levels have also been reported to increase the risk of AKI in CI [37,83]. AKI per se (vancomycin-independent) has been associated with worse treatment outcome (e.g. mortality, long-term impaired renal function) [20] and longer ICU and hospital stays as well as higher costs for the healthcare system [103–105]. Cianferoni et al. and Spapen et al. also noted prolonged deterioration in renal function after AKI, and they and Omuro et al. described increased mortality in patients who developed AKI with CI [46,56,61]. AKI with CI has negative consequences and should consequently be avoided.

4.4. Limitations

Several limitation should be considered when interpreting the results. First, of the 21 included studies, only 2 were RCTs; most were retrospective or observational studies. Because of their observational design, allocation bias, selection bias and various types of other confounding factors may influence the results of this report. Publication bias is to be expected since publications that demonstrate an effect are more likely to be published. Second, no raw data were available. Instead, the plotting of datasets was performed with means and medians. Thus, the compilation of a meta-analysis or the calculation of cut-off values for efficacy was not possible. Third, the forest plot included data only from the studies that provided the number of patients with concentration-dependent AKI. Fourth, to distinguish vancomycin-induced nephrotoxicity from the naturally high rate of AKI in ICU patients, a comparison group would have been necessary in all studies. However, only Omuro et al. used a control group, but the included patients were randomly selected and no matching was done [61]. Fifth, in accordance with clinical therapeutic drug monitoring routine, only the total amount of vancomycin in serum (bound + free) was measured in the studies, although it is rather the drug not bound to plasma proteins that is active [106,107]. Variations in protein binding of vancomycin (<10–82%) [107–110] and albumin concentration of critically ill patients [15] have been described. Thus, the active vancomycin concentration varies greatly. Berthoin et al. reported poor correlation between total and free vancomycin concentration (R^2 = 0.55) [111] and concluded that to reduce the treatment failure rate in infections by less-susceptible organisms, the free concentration should rather be determined. The procedure for susceptible micro-organisms remains unclear. Since the free concentration cannot be determined in most laboratories, it should be investigated whether the individual protein concentration is a useful surrogate parameter for free vancomycin. Finally, only a few AUC_{24} and only one AUC_{24}/MIC value were available. Rybak et al. argue for sufficiency of AUC_{24} determination because the MIC distribu-

tion is narrow at ≤1 mg/L, measurement is not very accurate or values are not readily available, and test methods vary widely [84]. Nevertheless, knowledge of MIC values and inclusion of these in therapy assessment is important, since higher therapy failure has been described for MIC > 1 mg/L and higher necessary dosage would increase nephrotoxicity [86,112].

5. Conclusions

Despite currently sparse data availability, it appeared that for CI of vancomycin mortality was reduced and clinical cure was increased with C_{24} > 15 mg/L, and AKI may be reduced with C_{ss} < 25 mg/L. The range of 15–25 mg/L to aim for in CI needs to be validated by direct comparison with other concentration ranges, just as the definition of specific AUC(/MIC) or indication-dependent target C_{ss} needs to be further investigated to achieve a safe (i.e. least damaging to the kidneys) and simultaneously most effective (i.e. therapeutically successful) therapy. To this end, future research should always sort patients by vancomycin serum concentration groups. Large prospective controlled studies are needed for this purpose.

Acknowledgments: The authors acknowledge Viola Fuchs for support in supervising the research project. They also thank Daniel Mai for providing the R Statistical Software, Alexander and Renate Viertel for assistance with data analysis, and Andreas Ismair for basic help in the writing process of the manuscript.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

Sequence information: Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.107005.

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