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Augmented Renal Clearance and Its Influence on Vancomycin Pharmacokinetics and Pharmacodynamics in Critically Ill Patients

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Abstract

Augmented renal clearance (ARC), defined as a creatinine clearance (CrCl) greater than 130 mL/min/1.73 m², is increasingly recognized among critically ill patients, affecting roughly one-third to two-thirds of this population. Standard vancomycin dosing regimens are often inadequate for these individuals, as enhanced renal filtration accelerates drug elimination and leads to subtherapeutic serum concentrations, compromising antimicrobial efficacy. The present review examines how ARC influences vancomycin's pharmacokinetic and pharmacodynamic (PK/PD) parameters and explores approaches for optimizing dosing in affected patients. A systematic search of the MEDLINE and EMBASE databases was performed in September 2023 to identify studies evaluating vancomycin use in critically ill adults with ARC. Reports focused on pediatric patients or lacking detailed PK data were excluded. Twenty-one studies met the selection criteria. The collective findings revealed a strong association between elevated CrCl and increased vancomycin clearance, supporting the need for higher or individualized dosing strategies to reach therapeutic exposure. Younger age emerged as a consistent predictor of ARC and altered vancomycin disposition. This review summarizes key PK/PD alterations, assesses available dosing guidelines, and proposes evidence-based adjustments aimed at improving target attainment and reducing the likelihood of treatment failure in patients with ARC.

Keywords: Vancomycin, Augmented renal clearance, Pharmacokinetics, Pharmacodynamics, Creatinine clearance

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Introduction

Hospital-acquired infections remain a major concern in intensive care units (ICUs), where they contribute to prolonged hospitalizations and higher mortality rates. As a result, the use of antimicrobial agents in ICUs is reported to be 5–10 times greater than in general hospital wards [1]. Ensuring prompt administration and achieving optimal serum concentrations of these drugs are essential for effective infection control. However, this objective is often complicated by the profound and variable pathophysiological alterations seen in critically ill patients. These changes arise from the underlying acute or chronic disease processes, as well as from therapeutic interventions administered in the ICU. Such conditions often produce a hyperdynamic circulatory state with increased cardiac output, which enhances drug clearance. Moreover, inflammatory cascades and capillary permeability lead to significant fluid shifts, expanding the

volume of distribution [2,3]. Together, these factors alter the pharmacokinetic and pharmacodynamic (PK/PD) profiles of many antimicrobials, making treatment outcomes unpredictable. Because renal elimination is the main route of clearance for numerous hydrophilic antibiotics—such as β-lactams, aminoglycosides, and vancomycin—any alteration in renal function can markedly affect drug disposition [1,2].

Pharmacokinetics (PK) encompasses the processes that govern the movement of a drug through the body, including absorption, distribution, metabolism, and elimination. Key parameters describing these processes include clearance (CL), volume of distribution (Vd), and elimination half-life ($t_{1/2}$). Pharmacodynamics (PD), in contrast, focuses on the relationship between drug concentration and antimicrobial effect, often expressed as the minimum inhibitory concentration (MIC)—the lowest drug concentration that prevents visible bacterial growth in standardized conditions [4].

Certain pathological states observed in the ICU, such as trauma, burns, and sepsis, are characterized by hyperdynamic circulation and increased renal perfusion, which can enhance glomerular filtration and accelerate the clearance of renally eliminated antimicrobials [4]. This phenomenon, known as augmented renal clearance (ARC), is defined as a creatinine clearance (CrCl) exceeding 130 mL/min/1.73 m² and represents a frequently encountered physiological alteration in critically ill patients [5]. Although its underlying mechanisms are not fully understood, ARC is believed to result primarily from enhanced glomerular filtration associated with increased renal blood flow. The reported prevalence of ARC ranges from 30% to 65% among ICU patients and may reach 50–85% in specific subgroups such as those with sepsis or traumatic injury [6, 7]. Factors such as younger age, male sex, and the absence of chronic comorbidities have been identified as significant predictors of ARC [6,8].

The impact of ARC is particularly important for antimicrobials exhibiting time-dependent activity and short elimination half-lives, as accelerated clearance can lead to subtherapeutic exposure. Vancomycin, a glycopeptide antibiotic primarily eliminated by the kidneys, is especially affected. It serves as the first-line treatment for severe Gram-positive infections, notably those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [9–13]. Vancomycin demonstrates both time- and concentration-dependent killing, with efficacy best described by the ratio of the 24-hour area under the concentration–time curve to the MIC ($AUC_{(24)}$/MIC) [14]. Therapeutic monitoring is typically performed through measurement of both AUC and trough concentration (C_{trou9h}) to ensure adequate exposure while minimizing adverse effects such as nephrotoxicity, ototoxicity, and hypersensitivity reactions [9,15].

Despite the use of therapeutic drug monitoring (TDM), achieving target vancomycin concentrations remains challenging in ICU patients with ARC, as accelerated renal elimination often results in subtherapeutic levels and treatment failure. Accurate dose adjustment is therefore crucial but difficult, as traditional renal function estimation equations such as the Cockcroft–Gault (CG) formula may not reliably predict clearance in patients with ARC [16, 17]. This uncertainty underscores the need for evidence-based dosing strategies and clearer clinical guidelines to ensure effective and safe vancomycin therapy in this population.

The present review aims to systematically evaluate and synthesize existing evidence on vancomycin dosing, efficacy, and safety in critically ill adults with augmented renal clearance. Additionally, it seeks to propose practical dosing recommendations tailored to this patient group to improve therapeutic success and minimize the risk of underexposure.

Materials and Methods

Search strategy

A comprehensive literature search was conducted on 26 September 2023 using the MEDLINE and EMBASE databases. The search aimed to identify all available studies investigating the influence of augmented renal clearance (ARC) on vancomycin pharmacokinetics and pharmacodynamics in critically ill adults. To ensure inclusivity, a broad combination of relevant keywords and Boolean operators was used, including: (“Augmented renal clearance” OR “ARC” OR “increas* renal clearance” OR “enhanc* renal clearance” OR “enhance* renal function” OR “renal hyperfiltration” OR “augmented kidney clearance”) AND (“vancomycin”). All retrieved records from the two databases were combined, and duplicates were removed before initiating the screening process to avoid redundancy.

Study selection

Eligible studies were those that provided quantitative or qualitative data regarding the effect of ARC on vancomycin therapy in critically ill adult patients. Studies were excluded if they were duplicates, non-human research, pediatric studies, abstracts without full publications, review papers, case reports, letters, commentaries, or opinion pieces. Non-English articles were excluded only when they could not be reliably translated using online translation tools.

Following the removal of duplicates in EndNote X9, titles and abstracts were screened for relevance according to the predefined eligibility criteria. The full texts of all potentially eligible studies were then retrieved for detailed

evaluation. Any disagreements or uncertainties regarding study eligibility were resolved by mutual consensus among the reviewing authors.

Data extraction

Two independent reviewers extracted data from each eligible study using a standardized collection form to ensure consistency and accuracy. For every study included, the following information was recorded: author name and publication year, study location and period, research design, study objective, ARC definition, creatinine clearance (CrCl) estimation method, population demographics (age, sex, and clinical setting), details of vancomycin administration (dose, frequency, and regimen), and major outcomes or findings. Any discrepancies between reviewers were resolved by discussion until agreement was reached.

Results

Study selection

The initial database search yielded 267 records, and one additional relevant article was identified through manual searching. After removing duplicates, 191 unique articles remained. Of these, 129 were excluded after screening titles and abstracts because they did not satisfy the inclusion criteria. The remaining 62 articles were retrieved for full-text review. Following comprehensive evaluation, 21 studies fulfilled all eligibility requirements and were included in the final analysis (Table S1). The main reasons for exclusion at this stage were insufficient data related to ARC or vancomycin pharmacokinetics, and a focus on pediatric populations. The overall study selection process is summarized in **Figure 1**.

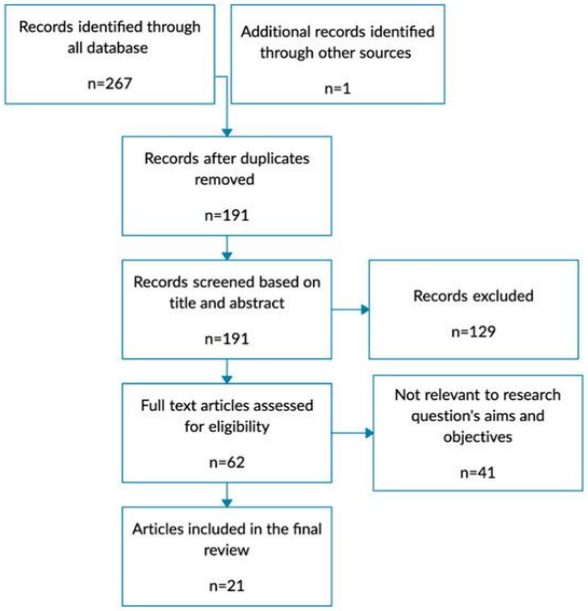

Figure 1. Flowchart of the results of literature search and selection process

Most of the studies included in this review were observational in nature. Fourteen adopted a retrospective design, five were prospective, one combined both prospective and retrospective methods [7], and another was a randomized clinical trial [12]. These investigations encompassed a wide spectrum of intensive care settings, including medical, surgical, neurosurgical, hemorrhagic stroke, traumatic brain injury (TBI), and septic populations, and were conducted across seven different countries. Although some of the reports did not explicitly describe their participants as critically ill or specify their underlying diagnoses, all involved hospitalized adults undergoing vancomycin treatment for severe infections [18]. The average age of the participants ranged between 33 and 76 years, while the proportion of men varied widely, from 28% to 80%, across study populations (Table S1).

Definitions of augmented renal clearance (ARC) varied slightly among the studies, though most adopted the commonly accepted cutoff value of creatinine clearance (CrCl) ≥130 mL/min. Variations in reported units, such as mL/min versus mL/min/1.73 m², were noted. A few exceptions existed—for instance, Campassi *et al.* [19] defined ARC as CrCl ≥120 mL/min, and one study [20] included patients with CrCl ≥120 mL/min without providing a formal definition. Methods for assessing CrCl were inconsistent. The Cockcroft–Gault equation was the most frequently applied, appearing in 57% of studies, followed by measured urinary CrCl in 24% and the CKD-EPI formula in about 4%. A few papers compared more than one estimation method [11,19, 21], while one did not specify its calculation approach [20].

Across nearly all investigations, patients were classified based on the presence or absence of ARC. The reported prevalence of ARC among critically ill patients ranged from 16.4% to 72% [10,18,19, 22–27]. In general, younger individuals, males, those with higher body weight, and patients with trauma or brain injury were more likely to exhibit augmented clearance. Additional factors such as mechanical ventilation, enteral feeding, hemodynamic instability, low serum albumin or platelet levels, reduced serum creatinine, elevated glomerular filtration rate, febrile neutropenia, intracerebral or subarachnoid hemorrhage, and overall lower illness severity were also associated with ARC [20,23,26,28]. Zhao *et al.* [26] further evaluated two predictive tools—the ARCTIC and ARC risk scores—and demonstrated that 58.9% of ICU patients and 88.9% of trauma patients classified as high risk by these scores were found to have ARC.

A substantial number of studies explored how ARC influences vancomycin therapy. Population pharmacokinetic (PopPK) modeling was frequently employed to predict optimal dosing and describe vancomycin kinetics in these patients [8,18,27,29]. Some

investigations focused on developing individualized dosing nomograms or new mathematical models incorporating relevant covariates [7,28,30], while others used data from therapeutic drug monitoring (TDM) to refine dosing recommendations. A few papers validated PopPK software or dosing nomograms across patients with differing renal functions [8,20].

The clinical effects of ARC on vancomycin efficacy were generally assessed through pharmacokinetic and pharmacodynamic parameters, including clearance, volume of distribution, area under the concentration–time curve over 24 hours to minimum inhibitory concentration (AUC24/MIC), and trough concentration (Ctrough). An overall pattern emerged showing that as CrCl increased, vancomycin serum levels declined. When standard dosing regimens were used to achieve a Ctrough target of 10–20 mg/L, a considerable portion of patients with CrCl ≥130 mL/min—ranging from 34% to 100%—failed to reach therapeutic concentrations (Ctrough <10 mg/L) [7,8,10,12,18,20,22–26,31]. In a large prospective study of 363 critically ill patients, Campassi *et al.* [19] reported that even with higher vancomycin doses, no ARC patients achieved target trough levels.

Subtherapeutic vancomycin exposure was also evident in patients with hemorrhagic stroke, traumatic brain injury, and those undergoing neurosurgical procedures [25,29,32]. Studies evaluating AUC24/MIC values confirmed this trend, showing consistently lower drug exposure in ARC patients compared with non-ARC patients. In a retrospective mixed-ICU analysis of 280 vancomycin concentrations, none of the patients reached the target AUC of 400 mg·h/L. Moreover, those with ARC demonstrated a substantially lower mean AUC (232.9 mg·h/L) than non-ARC patients (316 mg·h/L) [24].

Table 1. Overview of vancomycin PK/PD indices in patients with ARC

Population	Age (years)	CrCl	Maintenance Dose	Ctrough (mg/L)	Ctrough <10 mg/L (%)	AUC24 (mg·h/L)	Vd (L)	VCM CL (L/h)	Reference
Mixed ICU	69 (59–75)	160.3 (144.2–199.9) mL/min	14.7 (13.0–18.2) mg/kg	NR	NR	240 (209–300)	NR	NR	Ishigo *et al.* [27]
Mixed ICU	69 (50–73)	171.6 (157.5–203.0) mL/min	34.2 (28.3–42.1) mg/kg	9.4 (5.9–11.9)	NR	NR	NR	NR	Mikami *et al.* [11]
Mixed ICU	**BD:** 44.0 ± 16.6 **TDS:** 42.9 ± 11.8	**BD:** 166.9 ± 41.3 mL/min **TDS:** 171.8 ± 48.6 mL/min	15 mg/kg	**BD:** 5.6 ± 1.9 **TDS:** 14.0 ± 3.0	NR	**BD:** 397.9 ± 76.0 **TDS:** 611.9 ± 148.0	**BD:** 44.4 ± 14.2 **TDS:** 41.9 ± 27.3	**BD:** 6.0 ± 1.5 **TDS:** 5.7 ± 1.9	Sahraei *et al.* [12]
ICU & non-ICU	50.9 ± 15.1	141.2 ± 16.0 mL/min	30.3 ± 6.4 mg/kg	7.1 ± 2.9	80	**JPKD:** 307.4 ± 72.4 **SDose:** 376.6 ± 103.4	**JPKD:** 72.6 ± 10.3 **SDose:** 44.6 ± 6.7	NR	Yu *et al.* [8]
ICU & non-ICU	50 (33–60)	159 (144–193) mL/min	2 g/day	7.1 (3.9–10.6)	71.6	253.8–475.0	NR	NR	Zhao *et al.* [26]
ICU	33 (26–46)	168.4 (148.5–193.2) mL/min	1.28 ± 0.52 g	6.45 (3.72–8.64)	80.8	NR	NR	NR	Chen *et al.* [25]
Hospitalized	45 (33–57.3)	180.5 (152.9–207.4) mL/min	1000 mg q12h	6.8 (3.5–13.3)	>60	NR	NR	NR	Chu *et al.* [18]
Hospitalized	45 (33–57.3)	175.9 (142.2–198.1) mL/min	1000–4000 mg/day q6–12h	NR	NR	NR	155.4	8.5	Chu *et al.* [28]
Mixed ICU	40.0 ± 11.0	180.8 ± 59.3 mL/min	29.0 ± 9.4 mg/kg	6.5 ± 3.8	77.7	232.9 ± 93.6	69.3 ± 9.1	9.7 ± 3.4	He *et al.* [24]

ICH & aSAH	63.3 ± 13.3	161.6 ± 16.7 mL/min	15.1 ± 4.2 mg/kg q8h (8–12h)	12.0 ± 3.6	NR	NR	71.8 ± 11.3	NR	Morbitzer *et al.* [29]
Adult patients	43.8 ± 15.9	187.7 ± 50.0 mL/min	1000 mg q8h	NR	62.9	NR	NR	NR	Chu *et al.* [31]
Mixed ICU	57.5 (39.0–69.3)	157.4 (142.1–173.9) mL/min	35.7 (30.5–40.0) mg/kg	7.4 (5.2–11.6)	NR	447 (400–554)	133 (112–147)	5.3 (4.9–6.0)	Hirai *et al.* [10]
Mixed ICU	48 ± 15	155 ± 33 mL/min	30 mg/kg	NR	100	NR	NR	NR	Campassi *et al.* [19]
ICU & non-ICU	45.5 (21–66)	150.5 (42); 131–324 mL/min	<15, 15–30, >30 mg/kg	NS	31.8	NR	NR	NR	Minkute *et al.* [23]
ICU	41 (32–56)	158.9 (140.9–193.6) mL/min	30 (25.0–32.3) mg/kg	**D1:** 14 **D3:** 20	**D1:** 98.2 **D3:** 48	NR	NR	NR	Baptista *et al.* [22]

Data are presented either as medians with interquartile ranges or as means accompanied by standard deviations (SD). *Creatinine clearance (CrCl) values are expressed in mL/min/1.73 m², and **maintenance doses are listed in mg/kg/day unless otherwise noted. Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; AUC24, area under the plasma concentration–time curve within 24 hours; BD, twice-daily dosing; CL, clearance; CrCl, creatinine clearance; Ctrough, trough concentration; D, day; ICH, intracerebral hemorrhage; ICU, intensive care unit; JPKD, JavaPK for Desktop; NR, not reported; q, dosing interval; SDose, SmartDose; TDS, three times daily; Vd, volume of distribution; VCM, vancomycin.

In a randomized clinical investigation by Sahrai *et al.* [12], two vancomycin dosing strategies—15 mg/kg administered every 8 hours versus every 12 hours—were compared among critically ill patients exhibiting augmented renal clearance. The study demonstrated that a significantly greater proportion of patients in the 8-hour group achieved the target AUC/MIC ratio (82.14%) compared with those receiving the 12-hour regimen (46.42%). Collectively, the body of literature reviewed indicates that conventional vancomycin dosing schemes are frequently inadequate in the presence of augmented renal clearance, as accelerated drug elimination leads to subtherapeutic plasma concentrations. Adjustments involving higher total daily doses or shorter dosing intervals appear necessary to attain therapeutic exposure, though only a limited number of studies have provided concrete dosing guidance for this patient group [12, 24, 30] **(Table 2)**.

Table 2. Proposed vancomycin dosing recommendations in patients with ARC

CrCl (mL/min)	Dosage Regimen	PTA (%)	PD Target	Based on	Reference
120–149	1750 mg q24h	62.33	AUC24 400–650 mg·h/L	PopPK study (Model-based Monte Carlo Simulations)	Zhao *et al.* [30]
150–179	1000 mg q12h	62.56			
≥180	750 mg q8h	61.69			
≥130	46 mg/kg/day	—	Ctrough > 10 mg/L	PopPK study (Bayesian estimation)	He *et al.* [24]
	69 mg/kg/day *	—	Ctrough > 15 mg/L *		
≥130	15 mg/kg q8h	—	AUC/MIC > 400	RCT	Sahraei *et al.* [12]

* In severe cases. CrCl, creatinine clearance; PopPK, population pharmacokinetics; PTA, probability of target attainment; RCT, randomized clinical study; q, dose frequency.

Discussion

The collective evidence from the reviewed studies indicates that patients exhibiting augmented renal clearance (ARC) often require higher doses of vancomycin to attain optimal therapeutic exposure. This is primarily due to accelerated drug elimination, which compromises serum concentrations and, consequently, treatment efficacy.

Importance of creatinine clearance (CrCl) in vancomycin dosing and ARC identification

Achieving effective antimicrobial therapy in critically ill patients hinges on the optimization of dosing regimens—closely linked to accurate assessment of drug clearance. For vancomycin, renal function, typically represented by creatinine clearance (CrCl), is a key determinant of dosing requirements [33]. CrCl represents the rate at which creatinine, an endogenous marker of renal filtration, is

cleared from plasma and is used as a surrogate measure of glomerular filtration rate (GFR). It can be determined directly from timed urine collections or estimated indirectly using serum creatinine (SCr)–based equations, such as Cockcroft–Gault (CG) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, with the latter approach being more common in clinical settings [34].

Although no universally accepted normal range for CrCl exists, values exceeding 130 mL/min/1.73 m² are widely used to define ARC, as such elevations have been consistently linked to reduced antimicrobial exposure [35]. Reports suggest that ARC occurs in roughly 30–65% of intensive care unit (ICU) patients—figures comparable to those found in the studies reviewed. Discrepancies in reported prevalence rates may be attributed to inconsistent definitions, differing CrCl measurement techniques, and variation in study populations [6].

Since CrCl-estimating equations incorporate variables such as age, sex, and body surface area alongside SCr, they offer a more comprehensive assessment than SCr alone. However, in critically ill populations, these formulas often correlate poorly with measured CrCl due to fluctuating SCr levels and rapidly changing physiology [36]. Derived through regression modeling in stable populations, these equations have limited validity when applied to the dynamic context of the ICU, where SCr concentrations may not accurately reflect true renal function [34].

Several recent investigations have compared estimated CrCl values obtained via the CG equation with directly measured urinary CrCl, often collected over 8-hour periods. Across multiple studies, measured CrCl values consistently exceeded those estimated by equations, highlighting substantial underestimation of renal clearance when relying solely on SCr-based methods [11,19,26,29]. Campassi *et al.* reported that estimated CrCl using CG exhibited only 39% sensitivity in detecting ARC [19]. Similarly, Zhao *et al.* conducted a multicenter study showing that CG-based CrCl had limited predictive accuracy for vancomycin pharmacokinetic/pharmacodynamic (PK/PD) indices, correctly estimating target Ctrough and AUC24/MIC values in only 69.1% and 62.6% of cases, respectively [26]. These findings underscore the high interpatient variability in vancomycin exposure among ICU patients and the limitations of formula-based estimations [15].

Taken together, the evidence clearly favors direct measurement of CrCl over estimation methods for assessing renal function in critically ill patients. Among the various urine collection intervals, the 8-hour measurement has shown the highest reliability. Therefore, routine incorporation of measured CrCl into clinical decision-making is recommended, alongside the use of complementary screening tools such as the ARCTIC and ARC risk scores, both of which demonstrate superior sensitivity and specificity for identifying patients at risk of ARC upon ICU admission [26].

Risk factors associated with ARC

Across the reviewed literature, younger age (typically <50 years) consistently emerged as the most influential determinant of augmented renal clearance (ARC) [6,20,26]. Younger individuals often display better baseline organ function and less physiological deterioration, which collectively contribute to higher glomerular filtration rates. Furthermore, the natural decline in renal function with aging reinforces this age-related distinction. As such, individualized dose adjustments should be carefully considered in younger, physiologically robust patients to minimize the likelihood of subtherapeutic antimicrobial exposure.

Increased body weight has also been repeatedly identified as a contributing factor to ARC [8,18,25,26]. Excess weight can influence several hemodynamic parameters—particularly cardiac output and renal perfusion—which, in turn, accelerate drug clearance [37]. Given the growing prevalence of obesity as a global health concern, this factor warrants close attention in designing dosing regimens for vancomycin, especially among critically ill patients with ARC [26].

ARC has additionally been reported with greater frequency among neurocritical populations, including patients suffering from traumatic brain injury (TBI) [10,32,36], recent trauma [6], intracranial infections [36], hemorrhagic stroke, and those undergoing neurosurgical procedures [29,32]. Although the precise mechanisms underlying this association remain uncertain, proposed explanations include activation of the systemic inflammatory response syndrome (SIRS), disruption of cerebral autoregulation, and elevated circulating levels of atrial natriuretic peptide (ANP)—a cardiac hormone commonly observed in TBI patients [6,36]. These physiological responses may lead to hyperdynamic circulation and increased renal filtration. Further investigations are required to clarify the neuro-renal interactions that contribute to the development of ARC in this subset of critically ill patients.

Considerations for vancomycin dosing

Selecting an appropriate vancomycin dosing regimen depends on pharmacokinetic/pharmacodynamic (PK/PD) parameters—most notably, the ratio of the 24-hour area under the concentration-time curve to the minimum inhibitory concentration (AUC_{424}/MIC). Since vancomycin's bactericidal activity is time-dependent, maintaining concentrations above the MIC for a sufficient duration is essential for optimal therapeutic effect [36]. The efficacy threshold is generally defined as an AUC_{424}/MIC ratio of at least 400 mg·h/L [38].

In patients with normal renal function, guidelines recommend an intravenous loading dose of 25–30 mg/kg, followed by maintenance doses of 15–20 mg/kg every 12 hours to reach therapeutic concentrations promptly [15]. However, these conventional regimens often prove inadequate for patients with ARC, where enhanced renal clearance results in subtherapeutic drug levels. Persistently low concentrations not only diminish clinical efficacy but may also foster the development of methicillin-resistant *Staphylococcus aureus* (MRSA) resistance, highlighting the essential role of therapeutic drug monitoring (TDM) to optimize vancomycin therapy while minimizing nephrotoxicity [38].

Earlier recommendations from the Infectious Diseases Society of America (IDSA) advised targeting vancomycin trough concentrations between 15–20 mg/L for severe MRSA infections and 10–15 mg/L for less severe cases to achieve the AUC/MIC goal of ≥400 mg·h/L [15]. However, subsequent evidence has demonstrated that trough-based monitoring correlates poorly with true AUC values because trough levels do not account for the distribution phase, which is influenced by individual variations in volume of distribution (Vd). Consequently, recent IDSA guidelines now endorse AUC-guided monitoring as a more precise approach to dosing. The recommended therapeutic window is an AUC_{24}/MIC ratio of 400–600 mg·h/L, assuming an MIC of 1 mg/L [15].

Two principal methods are currently proposed for estimating AUC-guided dosing. The first relies on first-order pharmacokinetic equations using two plasma concentrations—one obtained 1–2 hours post-infusion and the other immediately before the next dose. The second employs Bayesian-based modeling that integrates one or two measured concentrations (including at least one trough value) within a population pharmacokinetic framework [15]. Several of the reviewed studies—such as those by Zhao *et al.* [30], Chu *et al.* [28], and Yu *et al.* [8]—supported the application of Bayesian or population pharmacokinetic (PopPK) modeling to tailor vancomycin therapy based on patient-specific covariates like age, body weight, and SCr levels. Moreover, early initiation of TDM, ideally within the first 48 hours of therapy, has been advocated to ensure timely optimization of dosing in this time-sensitive phase of MRSA management [27].

Vancomycin kinetics are most accurately represented by a two-compartment model, which accounts for both distribution and elimination phases and provides better prediction of plasma concentrations [39]. This model was adopted in several included studies [24,30]. In contrast, some retrospective investigations used a simplified one-compartment model, primarily due to limited TDM data and mathematical convenience [26,28,32]. Nonetheless, this simplification can introduce substantial bias in AUC estimation because it neglects the distribution phase, potentially leading to inappropriate dosing decisions and suboptimal therapeutic outcomes [40]. Future pharmacokinetic research should therefore assess the validity of one-compartment modeling in predicting vancomycin exposure, particularly in complex clinical populations such as those with ARC.

Implications of ARC for vancomycin pharmacokinetics and pharmacodynamics

AUC_{424}/MIC and trough concentration

Although recent guidelines emphasize AUC-guided vancomycin dosing, many clinical settings still rely on steady-state trough concentrations ($C_{trough,ss}$) due to practical limitations, such as the difficulty of obtaining multiple plasma samples and suboptimal timing of sample collection [41]. Consequently, older studies primarily evaluated the influence of ARC on vancomycin trough concentrations rather than AUC_{424}/MIC ratios. Both approaches, however, demonstrate a consistent inverse relationship between creatinine clearance (CrCl) and vancomycin exposure. In patients with ARC, conventional vancomycin dosing frequently fails to achieve target PK/PD indices, with some studies reporting persistently subtherapeutic trough levels below 10 mg/L, even after increasing doses [10,19,26]. At the same time, clinicians must remain vigilant regarding the risk of nephrotoxicity, particularly acute kidney injury (AKI), when adjusting dosages to counteract ARC [42].

Clearance, Half-Life, and volume of distribution

Low serum creatinine (SCr) levels have been consistently identified as a marker for ARC [7,24,31]. A recent investigation in China demonstrated a strong correlation between SCr and vancomycin clearance, highlighting that dynamic changes in renal function during therapy can significantly affect drug elimination [8]. Patients with ARC often present with reduced SCr due to increased CrCl, resulting in faster vancomycin clearance, shorter half-life, lower AUC, and subtherapeutic serum concentrations relative to patients with normal renal function. Population pharmacokinetic studies further confirm this pattern, showing that vancomycin clearance can be 1.3 to 3.5 times higher in ARC patients compared to those without ARC [8,24,28,30].

Additionally, critically ill patients often exhibit a larger volume of distribution (Vd) for hydrophilic drugs, potentially caused by hyperdynamic circulation and increased organ perfusion. Some studies have reported more than a threefold increase in the central Vd among ICU patients compared with non-ICU populations [28,30]. While the clinical relevance of this increase for vancomycin dosing is less clear—since AUC primarily depends on clearance at steady state—enhanced distribution may facilitate drug penetration into tissues that were previously less accessible. This property can be

strategically exploited to optimize loading doses, improving early drug exposure in ARC patients [30]. Overall, understanding the PK/PD alterations caused by ARC is crucial to achieving effective vancomycin therapy and improving patient outcomes.

Strategies for vancomycin dosing in ARC patients

In critically ill patients with ARC, achieving therapeutic vancomycin concentrations promptly is essential to prevent subtherapeutic exposure and potential treatment failure. A recent retrospective study of 141 ICU patients assessed AUC on days 1 and 2, as well as at steady state, using probability of target attainment (PTA) via Bayesian estimation [27]. The findings demonstrated that initial AUC values were often lower than the AUC observed at TDM, underscoring the importance of early therapeutic drug monitoring to adjust individual dosing and ensure sufficient exposure while avoiding overdosing.

Given the high prevalence of ARC in ICU populations, routine screening is recommended. While existing scoring systems provide initial guidance, additional risk factors—such as traumatic brain injury, subarachnoid hemorrhage, and recent neurosurgical interventions—should be considered when assessing the likelihood of ARC. For high-risk patients, an 8-hour urine collection to directly measure CrCl is advised. Patients with measured CrCl ≥130 mL/min should receive increased vancomycin doses to achieve comparable drug exposure during initial therapy. Current literature supports the use of a loading dose of approximately 30 mg/kg in critically ill ARC patients, although caution is warranted when exceeding 3 grams, as higher doses may elevate the risk of nephrotoxicity [43]. Early dose optimization combined with AUC-guided monitoring is essential for maximizing vancomycin efficacy in this vulnerable patient population. This review further suggests that maintenance vancomycin doses of 15–20 mg/kg every eight hours may be appropriate for patients with ARC. However, caution is advised when total daily doses exceed 4 grams to minimize the risk of adverse effects. Individualized dosing, guided by therapeutic drug monitoring (TDM), is recommended to adjust doses according to measured creatinine clearance (CrCl).

Several limitations should be considered when interpreting the findings of this review. Conducting research in the ICU setting is inherently challenging due to high patient mortality rates and rapidly changing clinical conditions. Consequently, most of the studies included were single-center observational investigations, resulting in limited high-quality evidence. There is a clear need for multicenter prospective studies with larger patient populations to establish more robust dosing strategies for vancomycin in ARC patients. Additionally, the literature search was restricted to only two databases, which may have excluded relevant studies and led to incomplete capture of the available evidence. Despite these limitations, this review provides valuable insights into the characteristics of ARC and its impact on vancomycin therapy, offering a useful resource for clinicians and researchers aiming to optimize treatment strategies and guiding directions for future investigations.

Augmented renal clearance substantially influences vancomycin pharmacokinetics and pharmacodynamics, making a multifaceted approach essential for achieving therapeutic success. In critical infections such as sepsis, even a one-hour delay in antibiotic administration can increase mortality by approximately 9% [44]. Accordingly, understanding ARC and its effects on vancomycin disposition is critical for developing effective dosing regimens in critically ill adult patients. Tailoring therapy based on individual patient characteristics, particularly renal function, is necessary to maximize efficacy while minimizing the risk of toxicity.

Conclusion

This review synthesizes current knowledge on vancomycin therapy in ICU patients with ARC and highlights key areas requiring further investigation. The consistent evidence supporting upward dose adjustments emphasizes the need for standardized dosing guidelines tailored to this population. Given the frequent occurrence of subtherapeutic vancomycin concentrations in ARC patients, early and accurate assessment of renal function is essential for optimal management. As future multicenter interventional studies provide more comprehensive data, coordinated efforts between clinicians and researchers will be crucial for establishing evidence-based, individualized vancomycin dosing protocols for critically ill patients experiencing ARC.

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