Why the Trough Target Over-Doses: A Population Pharmacokinetic Simulation of Trough-Guided against AUC-Guided Vancomycin Dosing

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Abstract

Background: Vancomycin was dosed to a trough of 15–20 mg/L for two decades on the reasoning that this trough corresponds to the exposure associated with efficacy. Consensus guidance now recommends dosing to an area under the concentration–time curve over 24 hours (AUC_{24}) of 400–600 mg·h/L. Many services have not made the change, in part because the magnitude of the difference between the two targets is not widely appreciated at the bedside.

Objective: To quantify, by population pharmacokinetic simulation, the exposure produced by trough-guided and AUC-guided dosing and the discordance between the two targets.

Methods: A one-compartment intermittent-infusion model with literature-typical population parameters was used to simulate 5,000 virtual adults with realistic distributions of weight, age, sex and serum creatinine, giving creatinine clearance from 10 to 160 mL/min. Clearance was scaled to creatinine clearance with 30 % between-subject variability and volume to weight with 20 %. Three strategies were compared: weight-based dosing without therapeutic drug monitoring, dose adjustment to a trough of 15–20 mg/L from a single steady-state level, and dose adjustment to an AUC_{24} of 400–600 mg·h/L estimated from the same single level. A 10 % assay coefficient of variation was applied.

Results: AUC-guided dosing achieved the 400–600 target in 84.3 % of patients against 43.9 % for trough-guided dosing and 28.6 % without monitoring. Exposure above 600 mg·h/L, the threshold associated with nephrotoxicity, occurred in 8.6 % under AUC guidance and 53.9 % under trough guidance. The median total daily dose was 1,500 mg under AUC guidance against 2,250 mg under trough guidance. The discordance between targets was direct: among patients with a steady-state trough of 15–20 mg/L, median AUC_{24} was 624 mg·h/L and 68.5 % exceeded 600, whereas among those with a trough of 10–15 mg/L, 96.1 % were within the AUC target. At an MIC of 2 mg/L neither strategy achieved AUC/MIC ≥ 400 in more than 8.1 % of patients.

Conclusions: The conventional trough target corresponds to an exposure above the recommended range in roughly two patients in three. A trough of 10–15 mg/L is far closer to the AUC target than 15–20, which offers services unable to implement AUC monitoring an interim position with a quantified basis.

Keywords: Vancomycin, Therapeutic Drug Monitoring, Pharmacokinetics, Auc-Guided Dosing, Nephrotoxicity, Monte Carlo Simulation.

1. INTRODUCTION

Vancomycin has been in clinical use for more than sixty years and remains the standard treatment for serious methicillin-resistant staphylococcal infection. Its therapeutic index is narrow, its pharmacokinetics vary substantially between patients, and it is one of the few antibacterials for which routine concentration monitoring is standard practice.

The pharmacodynamic index that predicts efficacy is the ratio of the area under the concentration–time curve over 24 hours to the minimum inhibitory concentration, with a target of at least 400 established from animal models and observational human data. AUC is not directly observable at the bedside, and for two decades the trough concentration served as its surrogate on the reasoning that a trough of 15–20 mg/L

would deliver an AUC_{24}/MIC above 400 for an organism with an MIC of 1 mg/L. Trough monitoring is simple, requires one blood sample at a predictable time, and became the near-universal standard.

Consensus guidance revised in 2020 recommends AUC-guided dosing with a target AUC_{24} of 400–600 mg·h/L, on two grounds. The upper bound reflects accumulating evidence that exposures above 600 are associated with acute kidney injury without additional efficacy. And the trough is a poor surrogate: the relationship between trough and AUC depends on clearance and dosing interval, both of which vary between patients, so a single trough value corresponds to a wide range of exposures.

Implementation has been uneven. AUC estimation requires either two concentrations per interval or Bayesian software with a population prior, both of which impose demands that many services have not met, and the trough remains in wide use. Part of the reason is that the argument for change is usually made qualitatively — the trough is an imperfect surrogate — without conveying how large the discrepancy is. A clinician told that a trough of 17 mg/L is "a bit high" will behave differently from one told that it corresponds to an exposure above the recommended range roughly two times in three.

This study quantifies the discrepancy by simulation. Three questions are asked. What exposure does each dosing strategy actually deliver across a realistic adult population? How do the trough and AUC targets correspond, and where does the trough target sit relative to the AUC range? And what follows for services that cannot implement AUC monitoring immediately?

2. METHODS

2.1 Pharmacokinetic model

A one-compartment model with first-order elimination and intermittent one-hour infusions was used, which is the structural model most commonly applied to vancomycin in adults and is adequate for steady-state exposure prediction. Steady-state concentration during and after the infusion follows the standard superposition solution, and the steady-state AUC over 24 hours reduces to the identity on which all AUC-guided dosing rests:

$AUC_{24,ss}$ = total daily dose / CL (1)

This relationship is exact for a linear system at steady state and is independent of the dosing interval, the infusion duration and the volume of distribution. It is the reason AUC-guided dosing is conceptually simpler than trough-guided dosing: the quantity to be estimated is a single parameter, clearance, whereas the trough depends jointly on clearance, volume and interval.

2.2 Population and parameters

Five thousand virtual adults were generated with weight, age, sex and serum creatinine drawn from distributions chosen to resemble a general inpatient population, and creatinine clearance computed by the Cockcroft–Gault equation and truncated to 10–160 mL/min. Clearance and volume were then assigned from the population model with log-normal between-subject variability.

Table 1. Model parameters and simulated population

Parameter	Specification	Simulated 5th–95th centile
Weight (kg)	Normal, mean 78, SD 18, truncated 45–140	48.5 to 107.7
Age (years)	Normal, mean 62, SD 16, truncated 18–95	36.1 to 87.6
Serum creatinine (mg/dL)	Log-normal, median 0.95, truncated 0.4–6.0	—
Creatinine clearance (mL/min)	Cockcroft–Gault, truncated 10–160	31.3 to 160.0
Clearance (L/h)	0.045 × CrCl, between-subject variability 30 %	1.27 to 8.56
Volume of distribution (L)	0.70 × weight, between-subject variability 20 %	31.7 to 86.5
Infusion duration (h)	1.0	—
Assay error	Coefficient of variation 10 %	—
MIC (mg/L)	1.0 in the base case; 0.5 and 2.0 in sensitivity analysis	—

Note. Parameter values are literature-typical assumptions selected to produce a realistic population, not estimates from any specific dataset. They are stated so that every result can be reproduced or recomputed under different assumptions.

2.3 Dosing strategies

The dosing interval was assigned by renal function in the conventional way: 8-hourly for creatinine clearance of 90 mL/min or above, 12-hourly between 50 and 90, and 24-hourly below 50. The empiric dose was 15 mg/kg per interval, rounded to the nearest 250 mg and capped at 2,000 mg.

Table 2. Strategies compared

Strategy	Adjustment rule	Information used
Weight-based, no TDM	Empiric dose retained; no adjustment	Weight and renal function only
Trough-guided	Dose scaled proportionally to bring the observed trough to 17.5 mg/L	One steady-state trough
AUC-guided	Individual clearance estimated from the same level; dose set to give AUC_{24} = 500 mg·h/L	One steady-state level plus the AUC identity

The AUC strategy is deliberately modelled at its simplest, using a single concentration rather than the two-level or Bayesian approaches recommended in practice. This makes the comparison conservative: a more sophisticated AUC estimate would perform better than what is reported here, so the advantage demonstrated is a lower bound on what AUC guidance can achieve.

2.4 Outcomes

The primary outcome was the proportion of patients with steady-state AUC_{24} within 400–600 mg·h/L. Secondary outcomes were under-exposure below 400, over-exposure above 600 (the threshold associated with nephrotoxicity), the steady-state trough distribution, and the total daily dose required. A separate analysis characterised the correspondence between trough bands and AUC, and a sensitivity analysis examined MIC values of 0.5, 1.0 and 2.0 mg/L. All simulation was performed in Python with a fixed random seed and reproduces exactly.

3. RESULTS

3.1 Exposure achieved by each strategy

Table 3. Exposure and dosing by strategy (5,000 simulated patients)

Outcome	No TDM	Trough-guided	AUC-guided
On target, AUC_{24} 400–600 (%)	28.6	43.9	84.3
Under-exposed, < 400 (%)	10.0	2.2	7.2
Over-exposed, > 600 (%)	61.3	53.9	8.6
Median AUC_{24} (mg·h/L)	670	611	500
5th–95th centile AUC_{24}	345–1,311	433–841	389–619
Median steady-state trough (mg/L)	19.2	17.2	14.0
Trough above 20 mg/L (%)	47.0	12.8	4.6
Median total daily dose (mg)	2,500	2,250	1,500

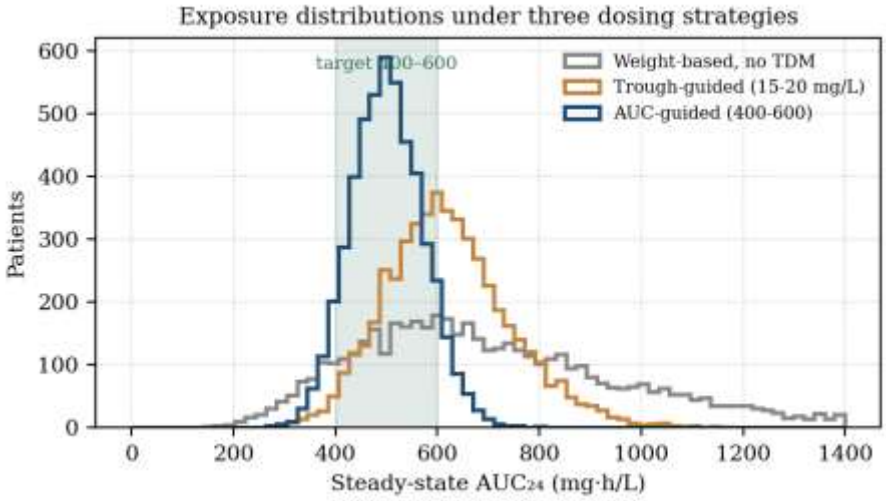

Figure 1. Distribution of steady-state AUC_{24} under each dosing strategy. The shaded band is the recommended target.

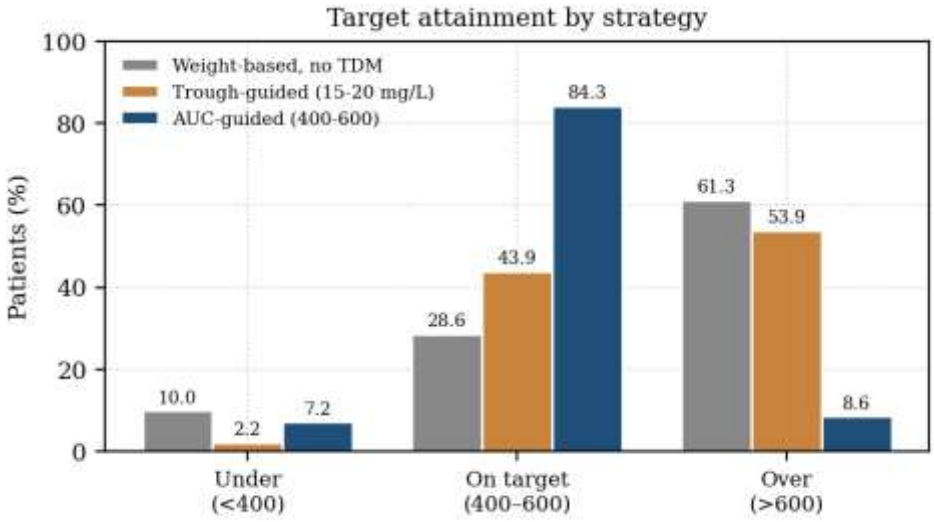

Figure 2. Proportion of patients under-exposed, on target and over-exposed by strategy.

AUC-guided dosing placed 84.3 % of patients within the target range against 43.9 % for trough guidance, and reduced over-exposure from 53.9 % to 8.6 %. The distributions in Figure 1 show why: trough guidance narrows the spread relative to no monitoring but centres it too high, with a median AUC_{24} of 611 mg·h/L, just above the upper bound of the target.

The dose column is the finding most likely to surprise a prescriber. AUC guidance achieved better target attainment on a median total daily dose of 1,500 mg against 2,250 mg for trough guidance — a third less drug, better exposure, and a sixfold reduction in the proportion of patients above the nephrotoxicity threshold. The two goals that dosing strategies are usually assumed to trade against each other do not trade here.

One result runs the other way and should be reported. Under-exposure below 400 mg·h/L was more common with AUC guidance, 7.2 % against 2.2 %, because trough guidance errs systematically high and therefore rarely under-doses. Whether that matters depends on the clinical consequence of brief under-exposure relative to sustained over-exposure, and the guideline's position is that the latter is the greater hazard. It is nonetheless a real trade and not one that should be concealed by reporting only target attainment.

3.2 The discordance between the two targets

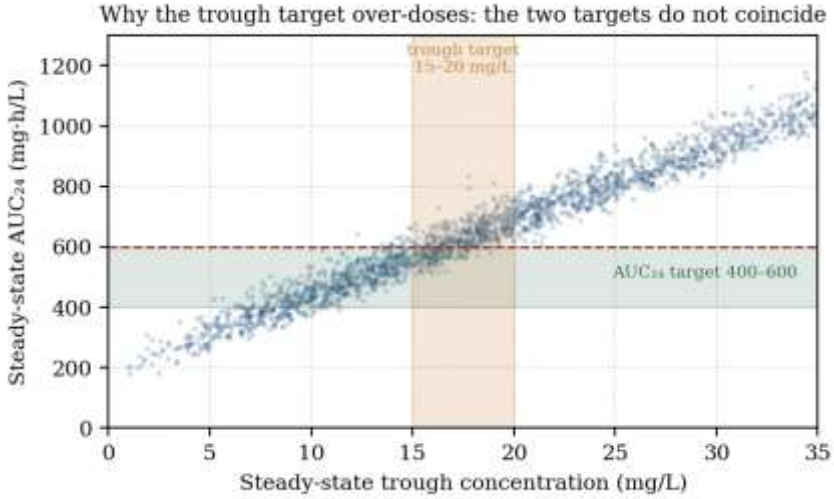

Figure 3. Steady-state AUC_{24} against steady-state trough underweight-based dosing. The horizontal band is the AUC target; the vertical band is the conventional trough target.

Figure 3 is the central result and requires no statistics to read. The two shaded bands overlap only in a corner. A patient whose trough falls in the conventional 15–20 mg/L window sits, in the great majority of cases, above the AUC target rather than within it.

Table 4. AUC_{24} achieved within each steady-state trough band

Trough band (mg/L)	n	Median AUC_{24}	5th–95th centile	AUC > 600 (%)	Within AUC target (%)
5–10	604	387	310–475	0.0	40.1
10–15	907	508	422–592	3.0	96.1
15–20	1,005	624	544–720	68.5	31.5
20–25	733	747	664–842	100.0	0.0

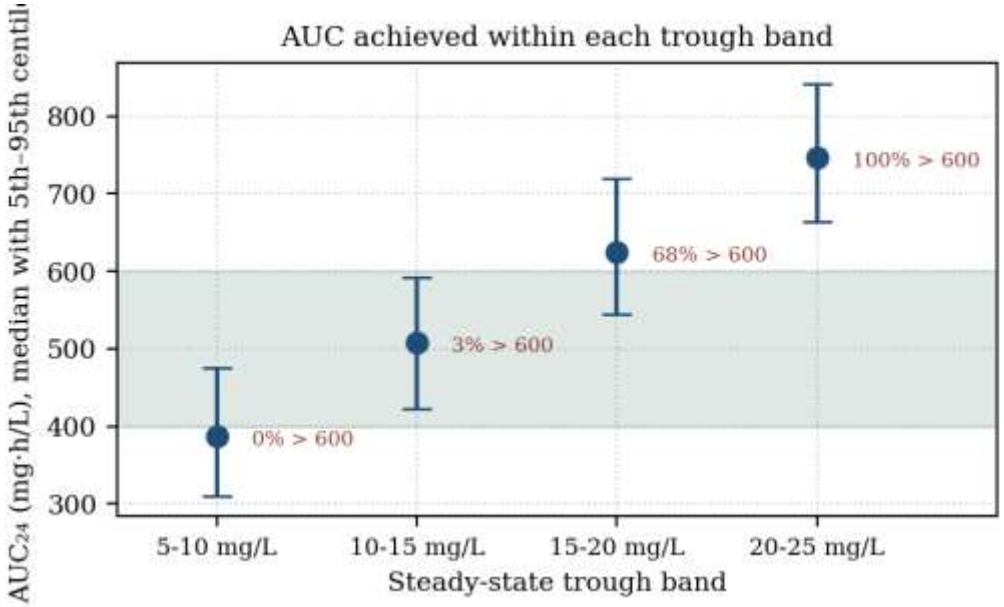

Figure 4. Median and 5th–95th centile AUC_{24} within each trough band, with the proportion exceeding 600 mg·h/L.

The second and third rows of Table 4 carry the practical message. A trough of 10–15 mg/L — the band that two decades of practice treated as sub-therapeutic and to be corrected upward — put 96.1 % of patients within the recommended AUC range, with 3.0 % above 600. The band that practice treated as correct, 15–20 mg/L, put 31.5 % within range and 68.5 % above it. Every patient with a trough of 20–25 mg/L exceeded the exposure threshold associated with nephrotoxicity.

This inverts the conventional interpretation of a vancomycin level. Under the AUC target, a trough of 12 mg/L is not a result requiring a dose increase; it is close to the centre of the desired exposure. A trough of 18 mg/L is not reassuring; it is a signal that the patient is probably over-exposed. Services that continue to monitor troughs while having adopted the AUC target in principle are using a decision rule that points the wrong way at the values they most often encounter.

The width of the intervals is the second point. Within the 15–20 band the 5th to 95th centile range of AUC spans 544 to 720 mg·h/L, so even knowing the trough exactly leaves substantial uncertainty about exposure. This is the irreducible limitation of a single-point surrogate for an integral, and no revision of the trough target removes it — a narrower and better-placed trough target reduces systematic error without addressing the scatter.

3.3 Renal function

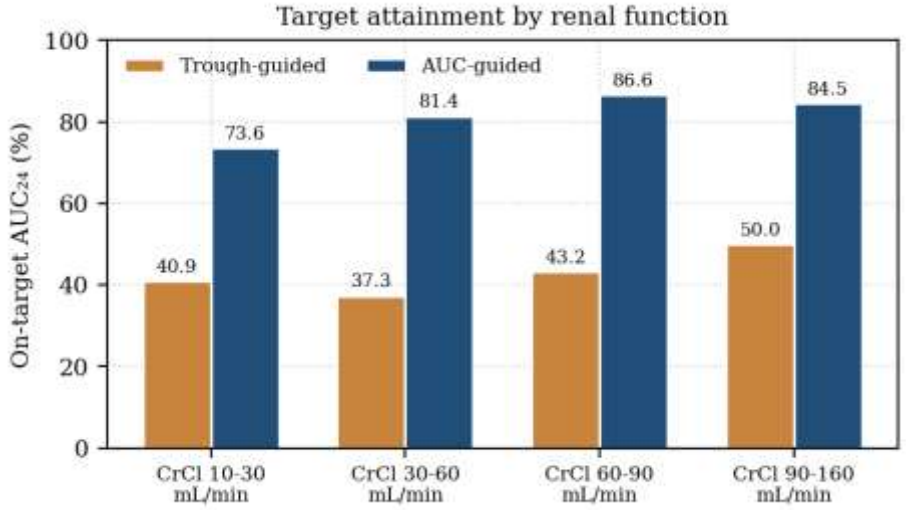

Figure 5. On-target AUC_{24} attainment by creatinine clearance stratum.

Table 5. Target attainment by renal function

Creatinine clearance (mL/min)	n	Trough-guided on target (%)	AUC-guided on target (%)	Difference
10–30	—	40.9	73.6	+32.7
30–60	—	37.3	81.4	+44.1
60–90	—	43.2	86.6	+43.4
90–160	—	50.0	84.5	+34.5

The advantage of AUC guidance holds across the whole range of renal function, from 32.7 to 44.1 percentage points. It is smallest at the extremes, which is worth noting for opposite reasons. In severe renal impairment the interval is long and clearance is low, so the trough is closer to being a valid surrogate for exposure and both strategies struggle with the same underlying variability. At high clearance the 8-hourly interval keeps concentrations from falling far, so the trough again tracks exposure more closely.

The practical implication is that trough guidance is least misleading exactly where vancomycin dosing is already approached with caution, and most misleading in the broad middle range of renal function that describes most inpatients.

3.4 Sensitivity to the MIC

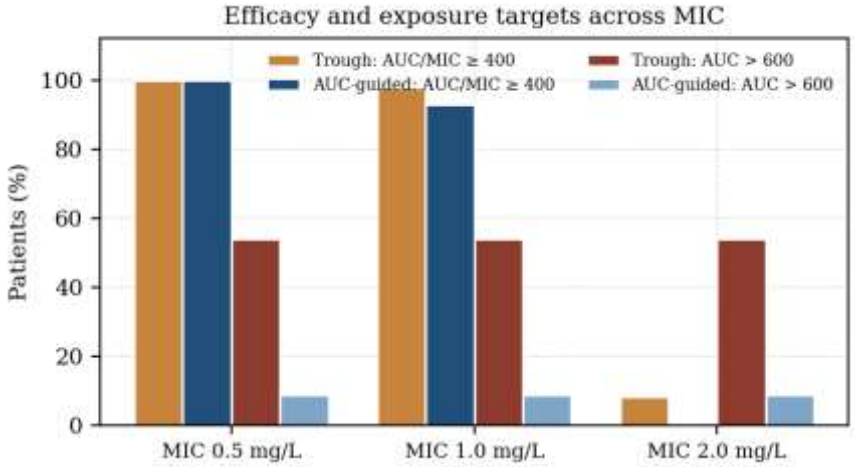

Figure 6. Attainment of AUC/MIC ≥ 400 and of exposure above 600 mg·h/L, across MIC values.

Table 6. Efficacy and exposure targets across MIC

MIC (mg/L)	Trough: AUC/MIC ≥ 400 (%)	AUC-guided: AUC/MIC ≥ 400 (%)	Trough: AUC > 600 (%)	AUC-guided: AUC > 600 (%)
0.5	100.0	100.0	53.9	8.6
1.0	97.8	92.8	53.9	8.6
2.0	8.1	0.0	53.9	8.6

At an MIC of 0.5 mg/L both strategies attain the efficacy target universally, and the entire difference between them is in toxic exposure: 53.9 % against 8.6 % above 600 mg·h/L. Against a fully susceptible organism, trough-guided dosing therefore buys nothing in efficacy and imposes a sixfold higher rate of potentially nephrotoxic exposure.

At an MIC of 2 mg/L the picture reverses and neither strategy works: trough guidance attained AUC/MIC ≥ 400 in 8.1 % of patients and AUC guidance in none, because achieving an AUC of 800 requires exposures far above the toxicity threshold. This is a well-recognised limitation of vancomycin rather than of either monitoring strategy, and the appropriate response is a different agent rather than a higher dose. It is worth stating explicitly because the arithmetic is sometimes obscured by the framing of AUC/MIC as a single target: the numerator cannot be raised indefinitely.

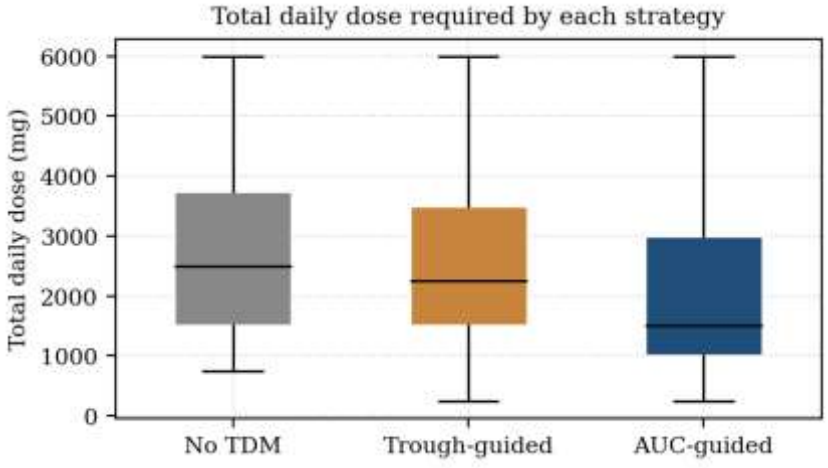

Figure 7. Distribution of total daily dose required under each strategy.

4. DISCUSSION

4.1 Principal findings

Three results follow from these simulations. AUC-guided dosing achieved the recommended exposure in 84.3 % of patients against 43.9 % for trough guidance, and did so on a third less drug. The conventional trough target of 15–20 mg/L corresponds to exposure above the recommended range in 68.5 % of patients, while a trough of 10–15 mg/L falls within the AUC target in 96.1 %. And at an MIC of 0.5 mg/L the two strategies are equally effective and differ only in the rate of potentially toxic exposure.

None of this is a new claim: it is the reasoning behind the 2020 guideline revision. What the simulation adds is magnitude, expressed in terms a prescriber can act on. The difference between the targets is not a technical refinement but a systematic discrepancy affecting most patients in the most common clinical situation.

4.2 Implications for practice

Table 7. Implications

Finding	Implication	Practice
Trough 15–20 exceeded the AUC target in 68.5 %	The conventional target systematically over-doses	Adopt AUC-guided dosing where the capability exists
Trough 10–15 was within the AUC target in 96.1 %	A lower trough band approximates the AUC target well	Where AUC monitoring is unavailable, target 10–15 as an interim measure
AUC guidance used a third less drug	Better targeting is not more drug	Do not present AUC dosing as an intensification
Under-exposure was more common with AUC guidance	The strategies trade differently at the two tails	Retain clinical review of low AUC estimates in deep-seated infection
Advantage smallest at extremes of renal function	Trough is least misleading where caution is already applied	Prioritise AUC implementation for patients with mid-range renal function
Neither strategy worked at MIC 2 mg/L	The problem is the agent, not the monitoring	Escalate to an alternative agent rather than the dose
Even within a trough band, AUC spanned 544–720	A single point cannot determine an integral	Do not expect a revised trough target to solve the problem

The second row is the one with the widest reach. Many services cannot implement two-level sampling or Bayesian software in the near term, and the practical choice is not between AUC monitoring and trough monitoring but between two trough targets. On these simulations, a target of 10–15 mg/L approximates the recommended exposure far better than 15–20, and it costs nothing to adopt: same assay, same sampling time, same workflow, one changed number in a protocol. It is not equivalent to AUC guidance — the scatter within the band remains — but it removes the systematic component of the error, which is the larger part.

4.3 Limitations

This is a simulation, and its conclusions are conditional on the model. A one-compartment structure understates the complexity of vancomycin disposition, particularly the distribution phase, which matters for peak-based estimation though less so for steady-state AUC. Parameters were chosen to be literature-typical rather than estimated from a specific cohort, and services whose population differs — critically ill patients with augmented renal clearance, patients on renal replacement therapy, patients with substantial obesity or fluid shifts — would obtain different absolute figures. The direction of the trough–AUC discordance follows from the structure of the model and would persist, but the specific percentages would not.

Several clinically important groups were excluded entirely. Patients receiving intermittent or continuous renal replacement therapy, patients with rapidly changing renal function, children, and patients on

continuous rather than intermittent infusion are not represented, and vancomycin dosing in each of these raises distinct questions that these simulations do not address.

The exposure–response relationships are treated as fixed thresholds — AUC/MIC ≥ 400 for efficacy, AUC_{24} > 600 for nephrotoxicity — whereas both are continuous, uncertain, and derived largely from observational data with recognised confounding. The nephrotoxicity threshold in particular is an association whose causal interpretation is contested, and concurrent nephrotoxins, baseline renal function and duration of therapy modify it. Simulated exposures are not simulated outcomes, and no claim about clinical outcomes is made here.

Finally, both monitoring strategies were modelled with a single concentration and proportional adjustment. Real AUC-guided practice uses two levels or Bayesian estimation and would perform better than modelled; real trough practice involves clinical judgement, repeated levels and adjustment for the timing of sampling, and might perform better than modelled as well. The comparison is between idealised versions of both, which is the fairest available basis but is not a comparison between what services actually do.

5. CONCLUSION

Across 5,000 simulated adults, dosing vancomycin to a trough of 15–20 mg/L produced exposure above the recommended AUC_{24} range in 68.5 % of patients and placed 53.9 % above the threshold associated with nephrotoxicity, while AUC-guided dosing achieved the target in 84.3 % using a third less drug. A trough of 10–15 mg/L, long treated as inadequate, fell within the recommended exposure range in 96.1 % of patients.

The practical conclusion is therefore in two parts. Services able to implement AUC-guided dosing should, and the case is stronger than the qualitative argument conveys: better exposure, less drug and a sixfold reduction in potentially nephrotoxic exposure. Services not yet able to should recognise that their existing trough target is the systematic problem rather than the monitoring itself, and that lowering it to 10–15 mg/L recovers most of the available benefit at no operational cost. What no trough target can recover is the scatter: a single concentration cannot determine an integral, and the residual uncertainty within any trough band is the argument for eventually measuring what the guideline actually specifies.

Declarations

Ethical approval: Not applicable.

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Conflicts of interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Ayesha Sara	✓		✓	✓			✓	✓			✓	✓		✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

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