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THERAPEUTIC DRUG MONITORING OF VANCOMYCIN IN CRITICALLY ILL PATIENTS

KATRIN OBERDORFER[1]*, IRENE BERMEJO[2], ELLEN JANSSENS[3]

Affiliation

[1]Department of Clinical Pharmacy, Neckar Valley Institute of Pharmaceutical Sciences, Heilbronn, Germany
[2]Department of Internal Medicine, Navarre Plain Institute of Pharmacy, Pamplona, Spain
[3]Department of Internal Medicine, Kempen Centre for Pharmaceutical Analysis, Geel, Belgium

*Corresponding author: Katrin Oberdorfer, k.oberdorfer@nvips.de
ORCID iD: Katrin Oberdorfer 0000-0001-0651-4502; Irene Bermejo 0000-0001-4962-316X; Ellen Janssens 0000-0001-1966-3494

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Abstract

Vancomycin remains a first-line agent for serious infections caused by methicillin-resistant Staphylococcus aureus, but its dosing in critically ill patients is unusually difficult because pharmacokinetics change rapidly and unpredictably. This narrative review summarises published evidence on therapeutic drug monitoring of vancomycin in intensive care: altered distribution and clearance, the move from trough targets towards area-under-the-curve guidance, Bayesian software, renal replacement and extracorporeal support, infusion strategies and nephrotoxicity. It also considers how monitoring services can be organised in practice. The review reports no new patient data. Randomised evidence for improved outcomes is limited, and many recommendations rest on observational studies and modelling.

1. INTRODUCTION

Vancomycin has been in clinical use since the late 1950s, and for much of that time it was given with little concern for blood concentrations. Levine's history of the drug noted how often it had been abandoned and then rescued, most recently by the rise of methicillin-resistant Staphylococcus aureus (MRSA) in hospitals [1]. Today it is a mainstay for MRSA bacteraemia, pneumonia and endocarditis, and for empirical cover in septic shock until cultures return [2, 3]. In the intensive care unit (ICU), it is prescribed often and to patients whose physiology makes any fixed dose a gamble. That uncertainty is the case for measuring drug concentrations and adjusting doses.

Therapeutic drug monitoring (TDM) rests on a simple premise: if the relationship between exposure, effect and toxicity is reasonably

well defined, and if exposure varies a great deal between patients, then measured concentrations can guide dosing better than weight or renal function alone. For vancomycin, both conditions are plausible. Exposure varies widely, particularly in the critically ill [4, 5], and there are links between exposure and both bacterial killing and kidney injury [6, 7]. Yet the evidence that monitoring improves hard outcomes is weaker than many clinicians assume. A meta-analysis found that TDM raised the proportion of patients reaching target concentrations and may have reduced nephrotoxicity, but the studies were mostly observational [8].

This review addresses a practical question: what does the published literature tell a clinical pharmacist or intensivist about how to monitor vancomycin in critically ill adults? The scope includes the pharmacokinetic changes that complicate dosing, the exposure targets and how they were derived, the choice between trough-based and area-under-the-curve (AUC) approaches, special situations such as augmented renal clearance and extracorporeal therapies, and the safety signal around acute kidney injury. It is a narrative synthesis drawing on guidelines, pharmacokinetic studies and clinical cohorts, and it reports no data from individual patients and no new analysis [9, 10].

The article is organised from physiology towards practice. Early sections describe why critical illness disturbs pharmacokinetics, followed by evidence on targets and monitoring methods. Later sections turn to patients on renal replacement or extracorporeal support, to infusion strategies, and to nephrotoxicity. A final section considers service organisation and limitations of the evidence. Representative findings are gathered in table 1, with their distribution by theme shown in fig. 1. Throughout, an effort is made to separate what randomised or well-controlled work shows from what is inferred from simulation or retrospective cohorts, since the distinction affects how firmly any recommendation can be held [11, 12].

2. PHARMACOKINETICS IN CRITICAL ILLNESS

Vancomycin is a large, hydrophilic glycopeptide eliminated mainly by glomerular filtration, so its clearance tracks renal function closely. Early pharmacokinetic work described a two- or three-compartment model with a volume of distribution near 0.7 L/kg in healthy adults [13]. Critical illness upsets both parameters. Sepsis, capillary leak and large-volume resuscitation enlarge the extracellular space and thus the volume of distribution of hydrophilic drugs, which tends to lower the peak concentration for a given dose. At the same time, renal function can move in either direction within hours. Blot and colleagues reviewed how such pathophysiological changes alter antimicrobial pharmacokinetics in the ICU and concluded that standard doses derived from other populations are often inappropriate [5].

Augmented renal clearance (ARC) is the best-known example of clearance moving upwards. Udy and colleagues described it as enhanced renal elimination of circulating solutes, seen in younger patients with trauma, burns, sepsis or neurological injury, often with a normal serum creatinine [14]. Their work on beta-lactams showed that patients with ARC were more likely to have subtherapeutic concentrations [15]. For vancomycin, Baptista and colleagues found that septic patients with high creatinine clearance often failed to reach the target trough on conventional doses, and they proposed adjusted regimens [16]. A systematic reason lies behind the pattern: the serum creatinine is a lagging, insensitive guide to glomerular filtration in a patient whose muscle mass and creatinine production are changing [14, 17].

The opposite problem is just as common. Acute kidney injury (AKI) appears in a large proportion of ICU patients, and when filtration falls, vancomycin accumulates. Consensus criteria define AKI by changes in serum creatinine and urine output, but these criteria again lag behind the actual loss of function [18]. A patient who has lost kidney function in the last day may still have a near-normal creatinine, leading to an

overestimate of clearance and a dose that is too high. Estimation equations such as Cockcroft-Gault, derived in stable outpatients, perform poorly when creatinine is not at steady state [17]. In practice, clinicians use repeated measured concentrations to correct course instead of trusting any estimate of renal function [4, 19].

Population studies in ICU patients have confirmed substantial variability. Del Mar Fernández de Gatta Garcia and colleagues analysed pharmacokinetic and pharmacodynamic data from critically ill patients and found that routine regimens produced a wide spread of concentrations, with many patients outside the target range [20]. Roberts and colleagues approached the problem from the angle of dosing method, showing that continuous infusion regimens with a loading dose, adjusted for creatinine clearance, could achieve target concentrations more reliably than standard intermittent dosing in a simulation and clinical dataset [21]. The two studies reached similar conclusions through different routes, namely that dose requirements in the ICU cannot be predicted from body weight alone [4, 20].

Table 1: Published findings relevant to vancomycin therapeutic drug monitoring in critically ill adults

Topic or study	Reported finding	Ref.
ICU pathophysiology	Altered distribution and clearance make standard doses unreliable	[4, 5]
Augmented renal clearance	High clearance in septic patients led to low troughs on conventional doses	[14, 16]
Continuous infusion with loading dose	Improved target attainment in ICU patients in modelling and clinical data	[21, 22]
Continuous versus intermittent infusion	Similar efficacy; nephrotoxicity benefit uncertain across studies	[22, 23]
AUC/MIC in S. aureus pneumonia	AUC/MIC of 400 or more linked to better response	[6, 24]
Trough-based dosing	Trough of 15 to 20 mg/L advised for serious MRSA infection	[19]
2020 consensus guideline	AUC24 of 400 to 600 mg·h/L advised; trough-only monitoring not recommended	[9]
AUC-guided dosing programmes	Lower nephrotoxicity and lower dose reported after adoption	[25, 26]
Vancomycin with piperacillin-tazobactam	Higher reported rates of acute kidney injury than with other combinations	[27, 28]
TDM meta-analysis	More patients at target; possible nephrotoxicity reduction in observational data	[8]

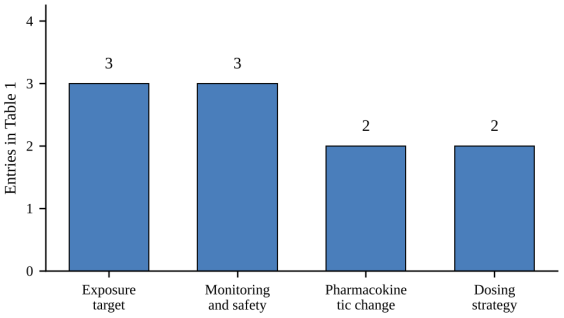


Fig. 1: Number of entries in table 1 by theme

Other covariates matter too. Obesity changes volume of distribution in a way that does not scale linearly with weight, hypoalbuminaemia may alter the free fraction (though vancomycin is only moderately protein bound), and concomitant vasopressors, diuretics and nephrotoxic drugs alter renal perfusion and function. Reviews of antibiotic dosing in the critically ill emphasise that no single covariate captures this variation and that population models built on ward patients fit ICU patients poorly [4, 5]. The DALI study, although concerned with beta-lactams, showed how widely drug exposure varied among ICU patients receiving standard doses [29]. The consequence for TDM is that the first concentration is usually the start of a correction process, not a confirmation of a plan. Early sampling, within the first one or two days, is more valuable than a single measurement at steady state [9, 10].

3. EXPOSURE TARGETS AND CLINICAL OUTCOMES

The pharmacodynamic index most closely linked to vancomycin efficacy is the ratio of AUC to MIC. Craig's classic review of antibacterial pharmacodynamics placed glycopeptides among the time-dependent agents with prolonged persistent effects, for which total exposure over 24 hours is the sensible index, and a later terminology paper

formalised ratios such as AUC/MIC [30, 31]. Moise-Broder and colleagues examined patients with S. aureus lower respiratory tract infection and found that an AUC/MIC ratio of 400 or more was associated with better clinical and microbiological response [6]. Later cohort studies of S. aureus bacteraemia reported lower mortality at AUC/MIC values near this threshold, though the exact cut-off varied between studies [24, 32].

The practical difficulty is that AUC cannot be measured directly in routine care. For years, the trough concentration stood in as a surrogate, and troughs of 15 to 20 mg/L were advocated for serious MRSA infection, partly because that range was thought to give an AUC/MIC above 400 for organisms with an MIC of 1 mg/L [19]. The recommendation was largely based on pharmacokinetic simulation and expert opinion. Jeffres and colleagues had earlier reported, for MRSA pneumonia, that vancomycin pharmacokinetic indices were not independent predictors of mortality, whereas inappropriate initial therapy was, which shows how mixed the early evidence was [33]. The trough target nevertheless became standard practice, even in settings where evidence for it was thin.

Problems with the trough target emerged as data accumulated. Trough and AUC correlate only moderately, and a given trough can correspond to a wide range of AUC values depending on clearance and dosing interval. Targeting the higher trough led many patients to AUC values well above 600 mg·h/L, a level associated in several cohorts with a higher incidence of kidney injury [7, 34]. Neely and colleagues, in a prospective study, compared trough-based and AUC-based dosing, and reported that the AUC-guided approach achieved target exposure with a lower dose and lower vancomycin trough values [25]. Meanwhile, observational work in MRSA bacteraemia found little survival difference among patients with troughs above and below 15 mg/L, which weakened the case for high trough targets [12, 24].

The 2020 revised consensus guideline reflected this evidence. It recommended AUC-guided dosing with a target AUC24 of 400 to 600 mg·h/L, assuming an MIC of 1 mg/L, for serious MRSA infection, and advised against trough-only monitoring in this setting [9]. For loading, a dose of 20 to 35 mg/kg of actual body weight was suggested in critically ill patients, with a cap on the single dose. The guideline accepted that evidence for patient-level benefit of AUC monitoring came largely from non-randomised work, but it considered the reduction in nephrotoxicity to be sufficiently consistent to support the change [9, 26]. Some intensive care groups have questioned how far these recommendations apply to patients with unstable kidney function, where steady-state assumptions break down [10, 12].

Target selection also depends on the organism and site. An MIC of 1 mg/L at the upper end of the susceptible range changes the achievable AUC/MIC substantially, and different testing methods give MIC values that differ by one doubling dilution. Sakoulas and colleagues linked bacteraemia outcomes to vancomycin MIC and bactericidal activity, reporting worse efficacy as MIC rose within the susceptible range [35]. For this reason, some clinicians consider an alternative agent such as linezolid or daptomycin when the MIC is high or the infection is difficult to reach [9, 36]. Wunderink and colleagues compared linezolid and vancomycin in MRSA nosocomial pneumonia and found higher clinical cure with linezolid, though the study design drew criticism [36].

4. MONITORING METHODS AND DOSING SOFTWARE

Two ways of estimating AUC are available at the bedside. The first uses two measured concentrations, one soon after the end of infusion and one before the next dose, and applies the log-linear trapezoidal method or an analytical solution of the one-compartment model to compute AUC24. This approach is simple and needs no specialised software, but it assumes steady state and accurate timing of both the dose and the samples. The second approach uses Bayesian estimation, in which a population pharmacokinetic model supplies prior information that is updated by one or two measured concentrations to produce individual parameters [9, 37]. Pai and colleagues compared the approaches and discussed their strengths and limits.

Bayesian methods suit the ICU for several reasons. They can work from a single concentration, they permit estimation before steady state, and they handle irregular dosing intervals and changing renal function better than closed-form equations. Wicha and colleagues described how model-informed precision dosing extends TDM beyond reading a number against a range, towards forecasting the exposure that would result from a new regimen [11]. The quality of the answer depends on the prior model, however. A model built on non-critically ill patients can bias estimates in a septic patient, and software that allows the user to select ICU-specific models is therefore preferable [11, 37]. Validation of the model against local data is a reasonable precaution.

The 2020 guideline supports either approach, with a preference for Bayesian estimation when the software is available [9]. Evidence on the clinical superiority of one method over the other is limited. Finch and colleagues, using a quasi-experimental design, compared nephrotoxicity before and after a hospital switched to AUC-guided dosing and found a reduction after the change, but the design does not exclude other temporal influences [26]. Neely's prospective study found similar effects on dose and trough, but was not powered for clinical outcomes [25]. For ICU patients with unstable renal function, repeating levels every one to three days, or after any major change in kidney function, is a common pragmatic approach [9, 10].

Timing and handling of samples cause avoidable errors. A level drawn from the same line through which the drug was infused, or drawn before distribution is complete, can mislead. The position-in-cycle recorded on the laboratory request matters as much as the result, and errors in documented timing have been identified as a frequent cause of apparently implausible levels. Hospital pharmacists often check the infusion record before accepting a result for dosing decisions [9]. Assay methods also differ slightly, with immunoassays and chromatographic techniques showing small but occasionally relevant systematic differences, which is worth remembering when results from different laboratories are compared or a patient is transferred between hospitals [8, 10].

Beyond the single measurement, there is the question of how often to monitor. Position papers on TDM of antimicrobials in critically ill patients recommend sampling early, ideally after the first or second dose, and then repeating at intervals that reflect the stability of the patient's renal function [10]. A patient with stable function and a level in range may need only occasional checks, whereas one with fluctuating creatinine or on renal replacement therapy may need daily samples. The costs of repeated assays are small compared with the costs of AKI or treatment failure, although the evidence base for a specific schedule is thin, and local protocols vary [8, 9]. Documented review dates in the chart help to avoid drift.

Alternative drugs bring their own monitoring needs. Daptomycin and linezolid are sometimes chosen when vancomycin exposure cannot be achieved safely, and linezolid in particular has exposure-related haematological toxicity that has led some centres to monitor its concentrations as well. The principle that exposure should be individualised, and that fixed doses fail some patients, extends beyond vancomycin to several other anti-infectives used in the ICU, which makes a shared TDM service attractive [10, 36]. A single laboratory and pharmacy workflow can then support several drugs, spreading the fixed costs and keeping staff skills current.

5. RENAL REPLACEMENT, EXTRACORPOREAL SUPPORT AND INFUSION STRATEGIES

Renal replacement therapy complicates dosing because clearance now has two components: the patient's residual function and the extracorporeal circuit. Vancomycin is removed by high-flux haemodialysis and by continuous modes, with the extent depending on membrane, effluent flow and the dialysis dose. Covajes and colleagues examined continuous infusion of vancomycin in septic patients on continuous renal replacement therapy and reported that a fixed regimen achieved target concentrations in many patients, although some needed adjustment

[38]. The wide variation in practice reflects the diversity of circuits, and published recommendations generally advise measuring concentrations early and repeating them whenever the modality or the intensity changes [9, 10].

Extracorporeal membrane oxygenation (ECMO) adds a different set of changes. The circuit increases the volume of distribution, and the drug may adsorb to tubing and oxygenators, though vancomycin, being hydrophilic, appears less affected by sequestration than lipophilic agents. Mulla and Pooboni, in a population pharmacokinetic analysis of patients on ECMO, reported altered clearance and volume compared with non-ECMO patients [39]. Such studies tend to be small, and conclusions from them are cautious. Consensus papers recommend that TDM be used in ECMO because published pharmacokinetic data do not support a standard adjustment, and variation between circuits and patients is considerable [4, 10].

Continuous infusion is one strategy proposed to simplify exposure targeting. Wysocki and colleagues randomised patients with severe staphylococcal infections to continuous or intermittent vancomycin and found similar clinical efficacy, with the continuous arm reaching target concentrations more consistently [22]. A later meta-analysis found a possible reduction in nephrotoxicity with continuous infusion in observational studies but not clearly in randomised ones, and it called for larger trials [23]. Roberts and colleagues argued that a loading dose followed by a continuous infusion dose based on creatinine clearance could improve target attainment in the ICU [21]. The attraction is practical, since steady-state concentration can be sampled at any time, removing the dependence on timing [22, 23].

Continuous infusion also has drawbacks. It requires a dedicated line or a compatible one, because vancomycin is physically incompatible with several drugs given routinely in intensive care, such as some beta-lactams and heparin at certain concentrations. Stability of the infused solution over 24 hours is acceptable at the concentrations normally used, but rates and concentrations must be controlled. A total daily dose given continuously produces an average concentration that equals AUC24 divided by 24, so a target AUC24 of 400 to 600 mg·h/L corresponds to a steady-state concentration of roughly 17 to 25 mg/L [9, 21]. Some clinicians find this reassuring because it links trough-style thinking to AUC targets, while others worry about missing the benefit of peaks that kill bacteria quickly.

6. NEPHROTOXICITY AND SAFETY

Vancomycin-associated kidney injury is the main safety concern. Bamgbola reviewed the evidence on vancomycin-induced renal toxicity and discussed likely mechanisms, including proximal tubular injury, oxidative stress and tubular obstruction by casts [40]. Incidence reported in the literature varies widely depending on definition and population. Lodise and colleagues found that higher daily doses, higher troughs and longer treatment were associated with nephrotoxicity in hospitalised patients, though the observational design makes confounding possible, since sicker patients receive higher doses [7, 34]. Hall and colleagues reported that empirical weight-based dosing within guideline recommendations was still associated with substantial nephrotoxicity in MRSA bacteraemia [41].

A second concern is the combination of vancomycin with piperacillin-tazobactam, which became prominent as stewardship programmes promoted this pair for empirical cover. Burgess and Drew found a higher incidence of nephrotoxicity with the combination than with vancomycin alone or with other beta-lactams [27]. A systematic review and meta-analysis later reported an increased risk of AKI with the combination, although the authors acknowledged heterogeneity and that the clinical significance of creatinine rises is uncertain [28]. Whether the rise reflects true tubular injury or inhibition of creatinine secretion is debated. Until that question is settled, many units monitor creatinine and vancomycin levels closely when the pair is prescribed, and avoid it in patients at high risk of AKI [27, 28].

The link between monitoring and fewer kidney injuries is plausible but not established

beyond doubt. Finch and colleagues found lower nephrotoxicity after introduction of AUC-guided dosing [26], and Neely and colleagues reported lower exposure with the AUC method [25]. The meta-analysis of TDM studies suggested a lower risk of nephrotoxicity in monitored patients [8]. Against this, all of these are non-randomised or short studies, and some compare against a backdrop of changing practice, such as lower doses and fewer combination regimens. A cautious reading is that AUC-guided dosing probably reduces unnecessary overexposure, and the 2020 guideline took the view that the trade-off favours it, while recognising uncertainty [8, 9, 26].

7. ORGANISING A MONITORING SERVICE

A guideline is only useful if it can be implemented. Pharmacist-led vancomycin services have been described in many hospitals, in which pharmacists order levels, interpret results and recommend doses under protocol. The 2020 ASHP consensus update gives practical advice on training, documentation and communication, and specifically addresses the resources needed to move to AUC-based monitoring [9]. In the ICU, bedside pharmacists attend ward rounds, which allows dose changes to follow changes in clinical state without delay. This integration is, in many centres, the real strength of the service, more than any particular formula or software package [8, 10].

Moving from trough to AUC monitoring demands preparation. The software must be chosen, validated and integrated with the electronic record where possible, and staff must be trained to use it. Laboratory turnaround times need to be short enough for results to affect the next dose, which may require sample collection at set times and rapid processing. Sampling protocols should specify the timing in relation to the dose, the line to use and the way the time is recorded. Some units have introduced automated alerts for rising creatinine in patients on vancomycin, which supports early review [9, 26, 37]. Few of these steps have been formally evaluated, but their logic is straightforward and they were part of the programmes reported by Finch and colleagues [26].

Cost and workload are real constraints. Bayesian software often requires a licence, and the extra samples and time may strain a small pharmacy team. Yet the downstream costs of AKI, including longer ICU stay and the possible need for renal replacement, are high, and even modest reductions can offset the investment. No robust randomised economic evaluation is available to confirm this, so the argument remains inferential [8, 26]. A tiered approach is sometimes adopted: full Bayesian AUC monitoring for ICU patients, patients with unstable renal function and those with serious infections, and simpler checks for stable ward patients on short courses [9, 10]. Local audit of target attainment and AKI rates helps to show whether the service is working.

8. LIMITATIONS AND FUTURE DIRECTIONS

The evidence base has clear weaknesses. Most studies of vancomycin exposure and outcome are retrospective, with confounding by indication, since patients with severe infection receive higher doses and also have worse outcomes. Definitions of nephrotoxicity differ, which makes pooling difficult, and many studies exclude the most unstable ICU patients, who are exactly those for whom monitoring is hardest [7, 12]. Randomised trials of AUC-guided versus trough-guided dosing with clinical outcomes as the endpoint are scarce. For this reason, table 1 should be read as a map of reported findings and not as a set of effect sizes that could be combined statistically [8, 25].

Several questions remain open. The optimal AUC range for different sites of infection is poorly defined, and the assumption of MIC 1 mg/L for all isolates is a simplification. The right approach for patients with rapidly changing kidney function, for whom steady-state methods do not apply, has not been settled, and Bayesian methods have not been shown to be superior in this group by trial evidence [11, 37]. The role of real-time monitoring devices and of dried blood spot or other microsampling is unproven. There are also gaps in dosing for patients on novel

extracorporeal therapies, and for the extremes of body weight [4, 39].

Future work would benefit from pragmatic randomised trials comparing monitoring strategies in the ICU, with kidney injury, clinical cure and mortality as outcomes, and from open ICU-specific population models that can be validated across centres. Wider adoption of model-informed precision dosing may improve consistency, provided that clinicians understand the assumptions inside the software [10, 11]. Alternatives to vancomycin, including newer anti-MRSA agents, may reduce reliance on the drug, although vancomycin is likely to remain widely used because of cost and experience [9, 36]. Whatever the direction, the principle that critically ill patients need individualised dosing is well supported and is unlikely to change [4, 5].

9. CONCLUSION

Vancomycin dosing in critically ill adults is a problem of moving targets. Volume of distribution, clearance and renal function can change within hours, and the published evidence consistently shows that fixed or weight-based regimens leave many patients under- or over-exposed [4, 5, 16, 20]. Monitoring is the logical response. The recent consensus favours an AUC-guided approach with a target of roughly 400 to 600 mg·h/L, using either two-sample calculations or Bayesian software, and moves away from troughs alone, mainly because the higher troughs once advised were linked with more kidney injury and little proven gain [7, 9, 25, 26].

The strength of evidence should be stated plainly. Much of it is observational, many studies exclude the sickest patients, and trials with clinical outcomes are lacking [8, 12]. Even so, the physiological argument and the consistent safety signal provide a sound reason to monitor early, repeat often when renal function is unstable, and combine concentrations with clinical judgement and a well-run pharmacy service [9, 10]. Pragmatic trials, shared ICU models and better handling of renal replacement and extracorporeal support are the most useful next steps [11, 38, 39]. Until then, careful application of existing guidance is the best course.

10. ABBREVIATIONS

AKI-Acute kidney injury, ARC-Augmented renal clearance, ASHP-American Society of Health-System Pharmacists, AUC-Area under the concentration-time curve, ECMO-Extracorporeal membrane oxygenation, ICU-Intensive care unit, KDIGO-Kidney Disease: Improving Global Outcomes, MIC-Minimum inhibitory concentration, MRSA-Methicillin-resistant Staphylococcus aureus, TDM-Therapeutic drug monitoring

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Nil

12. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

13. CONFLICT OF INTERESTS

Declared none

14. REFERENCES

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