Exploring real-world vancomycin target attainment in neonatal intensive care in the context of Staphylococcal infections: a retrospective observational cohort study

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Timothy Rawson
Abstract

**Background:** Vancomycin is commonly prescribed in late onset sepsis (LOS) in neonatal intensive care (NICU). Despite variation in vancomycin population pharmacokinetics, a paucity of evidence exists to support dose optimisation. This study explored the relationship between trough vancomycin concentrations and estimated area-under-the-concentration-time-curve (AUC) to minimum inhibitory concentration (MIC) ratios in real-world practice.

**Methods:** Patients treated with vancomycin for LOS in two tertiary NICUs between October 2022 and February 2023 were included. Electronic patient record data on demographics, microbiology, dosing, therapeutic drug monitoring (TDM), and outcomes were extracted; these were used to estimate individual patient AUC and AUC:MIC ratios using Bayesian forecasting. Trough and AUC estimates were compared. Target attainment was estimated using an AUC:MIC>400, and toxicity using AUC>600 mg·h/L. Estimates for target attainment were evaluated at different MICs.

**Results:** 32 patients, with 41 discrete treatment episodes, were analysed. Median gestational age at birth was 26.5 (IQR 25-30) weeks. Ten patients (31%) were female and median weight was 0.87 (IQR 0.7-1.4) kg.

Trough concentrations correlated poorly with AUC estimates ($r^2=0.38$). Dose adjustment using troughs did not improve AUC/MIC target attainment. Acute kidney injury (AKI) occurred in 4/41 (10%) treatment episodes; peak median AUC was 1170.4 (IQR 839.1-1493.7) mg·h/L compared to 582.1 (IQR 485.4-699.3) mg·h/L in those without AKI.

For individual episodes, AUC/MIC targets at day 2 would be met for vancomycin in 30/41 (73%) for organisms with an MIC of 1 mg/L, 1/41 (2%) for MIC 2 mg/L, and 0/41 (0%) for MIC 4 mg/L.

**Conclusion:** Using trough based TDM correlated poorly with AUC-based estimates for target attainment. Dose adjustment using trough-based TDM fails to improve drug-exposure, especially with MIC >1mg/L.

Introduction

Optimal dosing of antimicrobial therapy in neonatal sepsis poses a major challenge in clinical practice. During the neonatal period, significant physiological changes occur leading to high and often unpredictable variation in drug pharmacokinetics (PK)\(^1\). Wide PK variation may lead to variation in outcome with sub-therapeutic concentration driving reduced efficacy or supra-therapeutic drug concentrations risking toxicity\(^2\).

In neonatal intensive care units, late onset sepsis (LOS), sepsis occurring greater than 48–72 hours after birth\(^3\), is associated with 10% mortality\(^4\) and significant morbidity in survivors\(^5\). LOS commonly occurs in premature or very-low-birthweight infants\(^6\) who also have the greatest observed variability in antimicrobial PK.
Coagulase negative staphylococci (CoNS) are frequently associated with LOS and are associated with worse outcomes in NICUs\(^3\text{,}7\text{-}10\). LOS CoNS typically carry a methicillin-resistant phenotype\(^11\text{,}12\). Glycopeptides are therefore prescribed as first line treatment for suspected or confirmed CoNS infection\(^3\). Observed glycopeptide resistance and heteroresistance in CoNS is an emerging challenge in NICUs\(^13\).

Heteroresistance describes a phenotype where bacterial isolates contain sub-populations that demonstrate a substantial reduction in antimicrobial susceptibility. The phenotype is often unstable and can appear susceptible when not under antimicrobial selection pressure\(^14\). In a multi-centre study in NICUs in Greece, Italy, Estonia, Spain, and the UK, 101/116 (87\%) of identified CoNS showed vancomycin heteroresistance\(^15\).

Globally, a recognised CoNS of concern in NICUs is the NRCS-A pulsotype of *Staphylococcus capitis* (*S. capitis*\(^13\)). In the UK, NRCS-A *S. capitis* LOS were first documented in 1999\(^16\) and are now recognised as endemic to NICUs worldwide\(^17\). Within the UK, they have been shown to have a distinctive lineage, which has been named NRCS-A\(_{UK}\)\(^16\). In a study of *S. capitis* isolates from UK neonates isolated between 1999 and 2021, the NRCS-A clone was found in neonatal units across all geographic regions in the UK\(^16\). The NRCS-A clone identified within NICUs is of concern given that it can exhibit vancomycin resistance and heteroresistance\(^13\text{,}18\text{-}20\). One study in a French NICU demonstrated vancomycin resistance (defined as minimum inhibitory concentration (MIC) > 2 mg/L) in 15/40 (37.5\%) and heteroresistance in 25/40 (62.5\%) of NRCS-A isolates (see Table 1\(^13\)).

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Vancomycin MIC</th>
<th>Heteroresistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasigade et al (2012)(^13)</td>
<td>2.8mg/L (1.5-12mg/L)</td>
<td>62.5%</td>
</tr>
<tr>
<td>Butin et al (2015)(^39)</td>
<td>1.54mg/L (0.75-3.0mg/L)</td>
<td>75%</td>
</tr>
<tr>
<td>Decalonne et al (2020)(^40)</td>
<td>1.28 mg/L (0.25-4mg/L)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

It has been suggested that vancomycin selective pressure is an important driver for NRCS-A transmission and outbreaks in NICUs\(^20\), highlighting the importance of optimal vancomycin prescribing, including dosing. Although national guidelines in the UK advise flucloxacillin and gentamicin in LOS\(^21\), when there are concerns for methicillin-resistant organisms, intravenous vancomycin is often included in the treatment regimen. In French NICUs, vancomycin is prescribed in up to 30\% of very low birth weight neonates\(^22\).

Vancomycin has wide PK variation and a narrow therapeutic index in neonates, making dosing challenging\(^23\text{,}24\). There has been much debate on optimal dosing strategies, therapeutic targets, and methods of dose optimisation of vancomycin in NICUs\(^25\). Guidelines suggest using Area Under the 24-hour Concentration Time Curve (AUC) to guide therapeutic dosing, but serum trough concentration...
measurement remains a common surrogate measure due to its relative ease of use in real-world practice\textsuperscript{26}. While trough targets are an indicator of toxicity, they might not be effective in guiding dosing to optimise target attainment, which is becoming increasing important in the context of increasing rates of vancomycin heteroresistance within NICUs\textsuperscript{27}. AUC calculations are performed using either PK equations or Bayesian forecasting software\textsuperscript{28}.

This study aimed to evaluate current trough-based vancomycin dosing strategies used in two tertiary NICUs and consider the likelihood of target attainment for the treatment of suspected and confirmed Gram-positive infections, in the context of concerns around NRCS-A \textit{S.capitis}. Specifically, we looked to explore the relationship between trough vancomycin concentrations and AUC:MIC ratios to better understand the extent that real-world practice supports attainment of desired pharmacokinetic – pharmacodynamic (PK-PD) targets.

**Methods**

**Study design and setting**

This retrospective observational cohort study of neonatal patients with LOS treated with intravenous vancomycin for suspected or confirmed Gram-positive infections took place across two tertiary NICU in North West London, UK, between October 2022 and February 2023.

Empirical local guidelines for LOS during the study period were vancomycin and piperacillin-tazobactam. Vancomycin was delivered as an intermittent infusion over one hour with dose calculated using weight based dosing and gestational age (Table 2). Dose adjustment at steady state was made using therapeutic drug monitoring (TDM). TDM targeted a trough concentration for vancomycin of 10-20mg/L at steady-state. Dose adjustment was based on the observed trough concentration, with a percentage change in subsequent dose of 10, 20 or 30%.

<table>
<thead>
<tr>
<th>Gestational Age at birth</th>
<th>Age</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>(&lt; 29) weeks</td>
<td>(&lt; 10) days</td>
<td>20mg/kg 8 hourly</td>
</tr>
<tr>
<td></td>
<td>(\geq 10) days</td>
<td>15mg/kg 8 hourly</td>
</tr>
<tr>
<td></td>
<td>Corrected GA &gt; 37 weeks</td>
<td>15mg/kg 8 hourly</td>
</tr>
<tr>
<td>(\geq 29) weeks</td>
<td>(&lt; 10) days</td>
<td>15mg/kg 12 hourly</td>
</tr>
<tr>
<td></td>
<td>(\geq 10) days</td>
<td>15mg/kg 8 hourly</td>
</tr>
</tbody>
</table>

**Participants**
All NICU patients who received vancomycin for suspected or confirmed LOS between October 2022 and February 2023 with an electronic prescribing record (EPR) were included. Patients were excluded from the analysis if: no drug concentrations were recorded, only one dose of vancomycin was given, or if there was significant heart disease or renal impairment requiring renal replacement therapy. If a patient received multiple treatment courses (for different episodes of LOS) with vancomycin during the study period, these were considered as independent treatment episodes, provided that there was a minimum of 48 hours between vancomycin prescriptions.

Data sources and variables measured

Prospectively documented prescribing data, renal function, gestational age, weight, and health outcome data were extracted from the EPR for all patients receiving vancomycin. Acute kidney injury (AKI) was defined as per Modified, neonatal Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Microbiology data including organism MICs (calculated using vancomycin gradient strip testing, MTS™, Liofilchem®) were extracted from the laboratory management software. Data were anonymised and recorded electronically in csv files, which were stored securely and password protected.

Data analysis and statistical analysis

Vancomycin PK-PD parameters were calculated using the Bayesian NEOVANC model, with the ID-ODS software package (http://www.optimum-dosing-strategies.org). Individual patient parameters and observed vancomycin trough concentrations were inputted into the NEOVANC model to estimated individual patient AUC. Individually determined AUC was compared to observed trough concentrations with coefficient of determination ($r^2$) used to describe agreement. When individual patients had more than one treatment episode during the study period, each episode was analysed using a new model.

AUC/MIC ratios were assessed on day 2, after any dose change, and at end of treatment. An MIC of 1 mg/L was applied as default for AUC/MIC estimates. Vancomycin target AUC/MIC ratio for efficacy were defined as 400–600 based on previously reported PK-PD data. Risk of vancomycin toxicity was defined as AUC > 600 mg·h/L based on previous neonatal literature.

Descriptive analysis was performed using Microsoft Excel and Stata. This observational cohort study was a pilot evaluation designed to explore correlation between trough-based and AUC-based approaches to vancomycin dosing and thus was not powered to demonstrate statistical significance in outcomes. Sample size was pragmatic and reflective of the cohort of patients managed in this real-world setting during the study period.

Data availability

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

Ethics
The project was reviewed and approved as a local service evaluation by the institutional quality improvement department (Reference: 836). Individual patient consent was not required due to the non-interventional, retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulations.

Results

Participant data

Data from 32 patients were included during the study period. Seven patients receiving vancomycin during the study period were excluded as they did not meet inclusion criteria (4/7 (57.1%) had no vancomycin concentration levels recorded, and 3/7 patients (42.9%) had only one dose of vancomycin). Of those included, 24/32 (75%) had one treatment episode with vancomycin (75%), seven (22%) had two episodes, and one (3%) had three episodes. Median gestational age at birth was 26.5 (IQR 25–30) weeks, with most (20/32; 63%) of the patients in this study at a gestational age of less than 28 weeks when treated with vancomycin. Ten patients (31%) were female and median weight was 0.87 (IQR 0.7–1.4) kg.

Baseline characteristics of individual patients are summarised in Table 3. The median duration of vancomycin treatment was 4.22 (IQR 2.0–6.0) days and 5.0 (IQR 4.0–14.0) doses were prescribed per treatment episode. All patients (100%) had concurrent piperacillin-tazobactam co-administered as per hospital protocol. The median number of therapeutic drug monitoring results per treatment episode was 3.0 (IQR 1.0–3.0) per patient.
Table 3
Patient characteristics (n = 32, who had 41 episodes of vancomycin exposure altogether). IQR = interquartile range. This median includes multiple treatment episodes for some people (seven had two episodes, and one had three episodes).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Gestational age at birth (median [IQR]) (weeks)</td>
<td>26.5 [25–30]</td>
</tr>
<tr>
<td>Gestational age (n[%])</td>
<td></td>
</tr>
<tr>
<td>&lt; 28 weeks</td>
<td>20 [62.5%]</td>
</tr>
<tr>
<td>28–36 weeks</td>
<td>9 [28.1%]</td>
</tr>
<tr>
<td>≥ 37 weeks</td>
<td>3 [9.4%]</td>
</tr>
<tr>
<td>Female Sex (n, [%])</td>
<td>10 [31.3%]</td>
</tr>
<tr>
<td>Weight (median [IQR]) (kg)</td>
<td>0.87 [0.7–1.4]</td>
</tr>
<tr>
<td>Postmenstrual age (median [IQR])a (weeks)</td>
<td>29 [27–32]</td>
</tr>
<tr>
<td>Postnatal age (median [IQR]) (days)</td>
<td>15 [8.8–22.3]</td>
</tr>
<tr>
<td>Serum creatinine level (median [IQR]) (umol/L)</td>
<td>50 [43–65]</td>
</tr>
</tbody>
</table>

Microbiological data

Most patients (32/41; 78.0%) had no causative organism identified prior to or during their treatment episode including vancomycin. Causative organisms were identified through blood culture in 9/41 (22%) treatment episodes (Fig. 1). *S. capitis* was isolated in 6/41 (15%) treatment episodes. Methicillin-susceptible *S.aureus* was isolated in 1/41 (2%) treatment episodes (oxacillin MIC 0.5 mg/L). *S.epidermidis* (vancomycin MIC 1.0 mg/L) was isolated in 1/41 (2%) and *Citrobacter freundii* 1/41 (2%) treatment episodes, respectively. The *S. capitis* isolates’ susceptibility results are discussed below.

Treatment episode outcomes

At 30 days post individual treatment episode, 33/41 (81%) patients were still inpatients, 6/41 (15%) had been discharged, and 2 patient (5%) had died. During treatment episodes there were 4/41 (13%) cases of AKI observed. One AKI event was in a neonate who had previously received vancomycin.

Vancomycin target attainment and associated observations

The current vancomycin dosing strategy in the NICU achieved initial trough targets in 32/41 (78.0%) of patients at day 2 of treatment. Median day 2 trough concentration was 16.5mg/L (IQR 10.7-20.8mg/L). Dose adjustment using local policy occurred in 10/41 (24%) of treatment episodes. This led to trough target attainment in 6/10 (60%) of cases (with three having no follow-up trough after dose adjustment).
Correlation between trough and estimated AUC is represented in Fig. 2 and had an r^2 of 0.38. Figure 3 summarises the cohort and their outcomes.

Using Bayesian NEOVANC forecasting, day 2 AUCs were estimated as above 400 mg·h/L in 30/41 (73%) of treatment episodes. At steady state on day 2, 10/41 (24%) patients had an estimated AUC > 600 mg·h/L. Estimated AUC on the final day of treatment demonstrated that 26/41 (63%) achieved an AUC above 400 mg·h/L (8/26 or 31% had a dose adjustment performed). On the final day of treatment, 10/41 (24%) episodes achieved an AUC above 600 mg·h/L.

Of the 10 episodes in which a dose adjustment was made based on trough-based TDM, 4/10 (40%) dose adjustments achieved the target AUC > 400 mg·h/L, 2/10 (20%) still did not achieve the target, and 4/10 (40%) had already achieved the target before the adjustment was made. Dose adjustment achieved an AUC > 600 mg·h/L in 4/10 (40%).

Of the 4/41 (10%) patients who developed an AKI during a treatment episode, the peak median AUC was 1170.4 (IQR 839.1-1493.7) mg·h/L, compared to a peak median AUC for those without an AKI of 582.1 (IQR 485.4-699.3) mg·h/L. The peak median trough level for those four patients was 46.1mg/L (IQR 42.5-49.43mg/L), compared to those without an AKI who had a peak median trough of 18.4mg/L (IQR 12.78-24.05mg/L).

For individual infection episodes, AUC/MIC targets at day 2 would be met for vancomycin in 30/41 (73%) cases for an organism with an MIC of 1 mg/L, 1/41 (2%) for an MIC of 2 mg/L, and 0/41 (0%) for an MIC of 4 mg/L.

**Staphylococcus capitis analysis**

*S.capitis* was isolated in 6/32 (19%) of patients’ blood cultures during the study period. The median gestational age at the time of positive blood culture was 26 weeks (IQR 25–26).

Only 1/6 (17%) treatment episode with *S.capitis* did not achieve an AUC > 400 mg·h/L at day 2 using trough-based TDM dosing. Vancomycin MICs are shown in Table 4.

<table>
<thead>
<tr>
<th>Frequency (%)</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (22.2%)</td>
<td>2 mg/L</td>
</tr>
<tr>
<td>3 (33.3%)</td>
<td>1.5 mg/L</td>
</tr>
<tr>
<td>1 (11.1%)</td>
<td>0.75 mg/L</td>
</tr>
</tbody>
</table>

For the six patients with *S.capitis*, 5/6 (83.3%) achieved an AUC/MIC > 400 at day 2, with a median AUC/MIC of 464.2 (IQR 450.6–474) for this subgroup. Of those undergoing dose adjustment during the
treatment episode (3/6; 50%), all three resulted in an AUC/MIC of > 400. AUC > 600 mg·h/L occurred in 3/6 (50%) and 1/6 (17%) patients developed an AKI during treatment (with a peak AUC of 861.5 mg·h/L).

**Discussion**

This real-world evaluation of trough-based TDM using Bayesian forecasting to estimate vancomycin target attainment using AUC in neonates with LOS suggests that there is a poor correlation between trough concentration and AUC at steady state. For Gram-positive isolates with an MIC of $\leq 1$ mg/L, almost three-quarters of patients achieved a target AUC/MIC of > 400 mg·h/L. For isolates with higher MICs, as is often observed with NRCS-A *S. capitis* cases, current vancomycin dosing appears to be inadequate. Dose adjustment using trough concentrations during treatment did not improve target attainment by the end of therapy. This may be due to the lack of correlation between trough concentration and AUC.

Increased drug exposure, through attainment of higher AUCs, increases the risk of nephrotoxicity and ototoxicity. We observed that those developing AKI had a high AUC, supporting current evidence that an AUC > 600 mg·h/L is associated with increased risk of toxicity in neonates. This association must be cautiously interpreted given that the presence of an AKI may reduce renal clearance, thus raising vancomycin concentration, so the direction of causality is not proven.

There is a paucity of data to support vancomycin dosing in neonates. A previous meta-analysis of vancomycin in neonates used adult study-derived PK-PD targets (AUC of 400 mg·h/L at steady state) and assumed that organism MICs were $\leq 1$ mg/L, which is less frequently observed in NICU populations. Most studies of vancomycin dosing in NICUs are not powered to evaluate efficacy, making correlation of AUC/MIC with clinical outcome challenging. Within our study, despite achieving low observed AUC/MIC ratios, patients with *S. capitis* experienced few treatment failures. Future prospective studies comparing AUC with clinical outcomes and toxicity in NICUs are essential to better understand this relationship.

To support our understanding of exposure-response relationships in NICU patients, better methods of performing drug monitoring and defining antimicrobial PD are required. The development of minimally invasive and low sample volume methods for antimicrobial monitoring may facilitate rich time-point TDM, improving our understanding of antimicrobial PK in this population, and support individualised approaches to dose optimisation. The application of artificial intelligence guided dosing algorithms, such as Model Informed Predictive Control, may support accurate and individualised dosing strategies, utilising a range of individual variables that drive antimicrobial PK variation. Traditional PK-PD indices rely on the use of MIC, an in-vitro measure of organism susceptibility that fails to consider in-vivo host and organism factors. Complimentary measures, such as AUC:EC50 ratios linking drug exposure to biomarker response may provide a more holistic estimate of antimicrobial pharmacodynamics as they develop further. As well as focusing on traditional antimicrobials, such as glycopeptides, the importance of minimising selective pressure and generating data on alternative treatments in the face of increasing MICs, must be a critical focus, particularly in the context of premature neonates in NICUs.
Study limitations

There were several limitations associated with this study. We evaluated drug exposure following initiation of vancomycin using day 2 AUC estimates correlated with trough concentration from the same time period, as used elsewhere\textsuperscript{37}. It remains unclear how well current targets correlate with clinical outcomes in neonates. The impact of TDM guided dose adjustment was evaluated by calculating final day of therapy AUC, although this might not accurately reflect the complete time-period.

The data inputted is only as reliable as the EPR’s information, and so where patients were transferred to other units, or data was incomplete, this may have introduced bias. However, this confers a ‘real-world’ nature to the in-silico predictions, and as such confers applicability to other NICUs. The patients included were representative in terms of being critically unwell, though the present study did not have any patients with significant congenital heart disease or those requiring renal replacement therapy. A potential confounder is the co-prescribing of piperacillin-tazobactam, which was not part of the software predictions; additionally vancomycin and piperacillin-tazobactam in combination may increase the likelihood of AKI\textsuperscript{38}.

Conclusion

Despite widespread use in practice, optimisation of vancomycin dosing in neonates with LOS remains challenging. Appropriate PK-PD targets for this population are unclear with a need to balance effective drug exposure against the risk of toxicity. It is likely that more individualised approaches to dose optimisation and antimicrobial selection within this population are required, especially in isolates with raised MIC, where current approaches to dose adjustment is challenging and often fails to improve target attainment observed. Future work should explore the clinical effectiveness of lower PK-PD target attainment in non-complicated infections, investigate the viability of using minimally invasive and low volume sampling methods for TDM linked to artificial intelligence supported dose optimisation, and consider the role and PK of alternative drugs that may be required in future management of Gram-positive infections in the NICU.

Declarations

Acknowledgements

Contribution statement

TMR and RW conceived and designed the study. JP, FD, LT, & MG supported patient identification. MB, RW, and MG performed data extraction. MB, RW, and YW performed data analysis. AD, CB, and BP provided expert input from UKHSA national response to \textit{S.capitis}. All authors contributed to data interpretation. MB and TMR drafted the initial manuscript. AH and AR contributed to the editing of the manuscript. All authors contributed significantly to its revision and preparation for submission to the journal.
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References


**Figures**

![Bar chart](image-url)

**Figure 1**

Pathogen identified for patients on vancomycin during the period of time studied
Figure 2

Relationship between observed trough and AUC at day 2 ($r^2=0.38$).

Figure 3

Visual representation of area-under-concentration-time-curve for 24-hours (AUC) at day 2 and final day of vancomycin treatment and whether patients remained as inpatients at day 30. AUC=Area Under the Curve, AKI=Acute Kidney Injury