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Assessment of an institutional guideline for vancomycin dosing and identification of predictive factors associated with dose and drug trough levels

Qingze Gu[a], Nicola Jones[b], Philip Drennan[b], Tim EA Peto[a,b,d], A Sarah Walker[a,d,1], David W Eyre[b,c,d,1,*]

[a] Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
[b] Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom
[c] Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
[d] NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, University of Oxford, Oxford, United Kingdom

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SUMMARY

Objectives: To evaluate the effectiveness of an antimicrobial guideline for vancomycin prescribing deployed using electronic prescribing aid and web/phone-based app. To define factors associated with guideline compliance and drug levels, and to investigate if antimicrobial dosing recommendations can be refined using routinely collected electronic healthcare record data.

Methods: We used data from Oxford University Hospitals between 01-January-2016 and 01-June-2021 and multivariable regression models to investigate factors associated with dosing compliance, drug levels and acute kidney injury (AKI).

Results: 3767 patients received intravenous vancomycin for ≥24 h. Compliance with recommended loading and initial maintenance doses reached 84% and 70% respectively; 72% of subsequent maintenance doses were correctly adjusted. However, only 26% first and 32% subsequent levels reached the target range, and for patients with ongoing vancomycin treatment, 55–63% achieved target levels at 5 days. Drug levels were independently higher in older patients. Incidence of AKI was low (5.7%). Model estimates were used to propose updated age, weight and eGFR specific guidelines.

Conclusion: Despite good compliance with guidelines for vancomycin dosing, the proportion of drug levels achieving the target range remained suboptimal. Routinely collected electronic data can be used at scale to inform pharmacokinetic studies and could improve vancomycin dosing.

Introduction

Widespread use of electronic patient records provides a major opportunity to improve antimicrobial prescribing. Sophisticated prescribing aids can flag allergies, recommend dosages with adjustment for patient factors such as weight or renal function, as well as automating requesting of therapeutic drug monitoring (TDM). Web and smart phone-based apps can help disseminate guidelines. Electronic patient record data also provide an opportunity to review guideline compliance and (where measured) drug levels achieved, as well as factors associated with both. We describe our experience of deploying a new vancomycin guideline supported by these approaches, and use our findings to provide an example of how real-world pharmacokinetics based on electronic patient record data can be used to suggest improved dosing guidelines.

Vancomycin is widely prescribed to treat infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus facium*. However, vancomycin's narrow therapeutic index (requiring balancing efficacy against the risk of acute kidney injury (AKI)) and inter-personal variability in pharmacokinetics makes dosing difficult and necessitates TDM. International guidelines now recommend that vancomycin is monitored using the ratio of the area under the 24 h unbound drug plasma concentration-time curve to minimum inhibitory concentration (AUC_{24h}/MIC),[1] targeting a ratio of 400–600.[2,3]

* Corresponding author at: Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom.
E-mail address: david.eyre@bdi.ox.ac.uk (D.W. Eyre).
[1] These authors contributed equally to this work.

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However, in practice many hospitals still use vancomycin trough levels as a widely adopted, but imperfect, surrogate target for AUC_{24h}/MIC to simplify clinical management.[2]

The need for individualised vancomycin dosing and TDM, alongside the logistical challenges of coordinating phlebotomy and drug administration in busy hospital settings, hinders implementation. Institutional and national consensus guidelines can facilitate vancomycin dosing and monitoring.[2–5] However, guideline implementation has often been less effective than expected.[6–11] Both incomplete guideline compliance and failure to achieve levels despite following guidance contribute to sub-optimal dosing and may result in antibiotic resistance and increased treatment failure,[12] highlighting the need to further investigate the factors affecting vancomycin dosing and clinical outcomes.

Our hospital group has implemented a new vancomycin dosing guideline since August 2016 using vancomycin trough targets, based on international guidelines from 2009,[2] including increasing the target trough level from 10–15 mg/L to 15–20 mg/L. Our guidelines,[13] delivered via a phone-based app and hospital computers, provide detailed instructions on loading and initial maintenance doses based on the patient's body weight and renal function, and advise clinicians how to adjust subsequent maintenance doses based on TDM. Implementation is supported by a semi-automatic "powerplan" calculator within the hospital's electronic patient record system prompting clinicians to prescribe loading and initial maintenance doses based on the guidelines and automatically generating a request for the first vancomycin drug level. This study aimed to investigate the effectiveness of the new vancomycin dosing guideline, identify factors associated with dose and drug levels, and further optimise the guideline accordingly.

Methods

Data were extracted from the Infections in Oxfordshire Research Database (IORD), containing all admissions to the Oxford University Hospitals (OUH) NHS Foundation Trust in Oxfordshire, United Kingdom. OUH contains 1000 beds in four hospitals, providing secondary care to a population of approximately 600,000 and specialist services to the surrounding region. IORD has approvals from the National Research Ethics Service South Central – Oxford C Research Ethics Committee (19/SC/0403), the Health Research Authority and the national Confidentiality Advisory Group (19/CAG/0144).

Vancomycin is the first-line glycopeptide antibiotic in OUH. The current adult dosing guideline for intravenous vancomycin was implemented on 1 August 2016 (Tables S1–S3). The patient's actual body weight and estimated glomerular filtration rate (eGFR) determine the loading dose and initial maintenance dose. The first drug trough level should be taken after 48 h, i.e., before the fourth maintenance dose for twice-daily dosing and before the second maintenance dose for once-daily dosing. Recommendations are included for adjusting subsequent maintenance doses according to trough levels obtained. The target trough level is 15–20 mg/L.

We included inpatient treatment courses with intravenous vancomycin lasting ≥24 h, defining new treatment courses by >14 days between successive doses. Each treatment course contained at least one prescription plus records of individual drug administrations. Patients under 16 years and those admitted to Paediatrics, Paediatric Surgery and Renal Medicine were not covered by the new guideline and so were excluded. We extracted patient characteristics (age, weight, sex, ethnicity, Charlson and Elixhauser scores) and information related to the prescription, administration and monitoring of vancomycin (date and time of prescription and administration, dose, drug trough levels and serum creatinine measurements). Pre-treatment creatinine was the mean over all measurements within two weeks before each treatment course. eGFR was calculated using the Modified Diet in Renal Disease (MDRD) equation.[14]

Statistical analyses

Regression analyses of different outcomes investigated the new guideline's effectiveness and examined factors associated with doses and drug levels (details in Supplementary Methods; Table S4). Compliance of loading doses with the guideline was examined using logistic regression, and resulting first drug trough levels with linear regression. Multinomial logistic and linear regression was used to investigate dose adjustments during maintenance dosing (higher, lower, unchanged) and their impact on subsequent drug levels. The cumulative incidence of reaching the recommended target drug level was investigated using competing risk analysis, and risk factors for AKI were determined using ordinal logistic regression. AKI was defined using the Kidney Disease Improving Global Outcomes (KDIGO) guideline,[15] with AKI stages 1, 2 and 3 of AKI defined as 1.5–1.9-fold or ≥26.5 μmol/l increase from baseline, 2.0–2.9-fold increase, and ≥3-fold increase or serum creatinine ≥353.6 μmol/l, respectively.

Continuous explanatory variables were truncated at 1% and 99% to reduce the influence of outliers. Potential non-linear associations were investigated using natural cubic splines. The number of knots was determined based on Akaike Information Criteria (AIC) in univariate models, and then the non-linearity was retained in multivariable models only where it improved model fit ($p < 0.05$). Two-way interactions were included in models where the interaction $p < 0.05$.

Regression model findings were used to suggest updated guidelines by predicting the optimal initial maintenance dose across different patient ages, weights and eGFR. We also evaluated the probable impact of these new guidelines using pharmacokinetic models. TDMx which simulates from six population pharmacokinetic models[16] was used to predict trough levels and AUC_{24h}/MIC ratios.

Results

From 1 January 2016 to 1 June 2021, there were 4573 inpatient vancomycin treatment courses lasting ≥24 h in 3767 patients (Fig. S1). The median age, weight and eGFR at the start of each course were 62.5 (IQR 48.9–73.2) years, 80.0 (IQR 67.2–93.7) kg, and 90.8 (IQR 70.1–112.2) mL/min/1.73 m², respectively; 58.1% of courses were in males (Table 1). Patients had relatively few comorbidities, with most admitted to Trauma and Orthopaedics (57.5%), Neurosurgery (10.5%) and Clinical Haematology (8.7%).

Changes in doses following new guideline implementation

Following the implementation of the new vancomycin dosing guideline in August 2016, there were notable shifts in loading doses from predominantly 1000 mg (66%) to 2000 mg (57%), and in initial maintenance doses which were more varied with the new guideline (Fig. 1A/B/D/E). Guideline compliance continued to increase slightly over 2017–2021 for both loading and initial maintenance doses (to 84% and 70%, respectively) (Fig. 1G/H).

There were multiple independent predictors of loading doses complying with the guideline (Tables S5, S6). Guideline compliance independently increased with patient age (odds ratio (OR)=1.14 per 10 years higher, [95%CI 1.09,1.20]) and eGFR (OR=1.05 per 10 mL/min/1.73 m² higher [1.03,1.08]) but decreased with higher Elixhauser scores (OR=0.91 [0.84,0.98]). Compliance was independently lower in those admitted to Trauma and Orthopaedics (OR=0.30 [0.18,0.49]) and Cardiology (OR=0.37 [0.17,0.78]) compared to General Internal Medicine. Compliance increased significantly in the months before the formal implementation of the

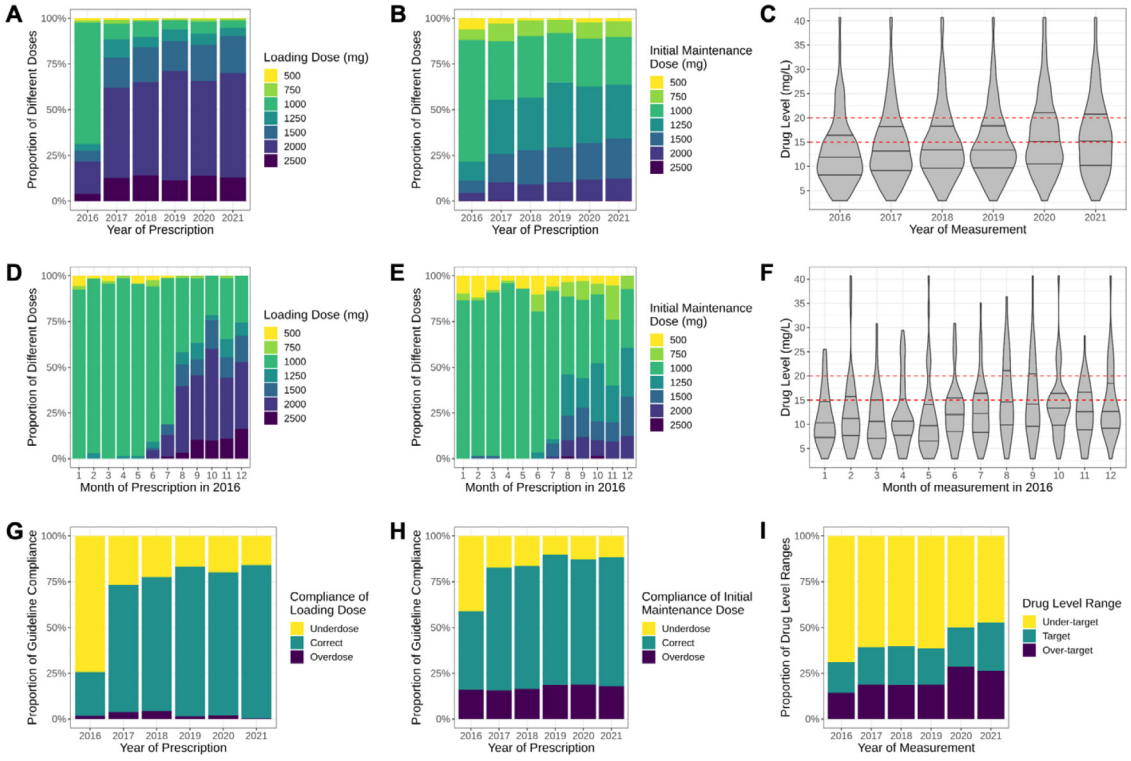

Fig. 1. Vancomycin doses and compliance with guidelines. Loading doses, initial maintenance doses and first drug trough levels are shown in panels A–C, by year for 2016 to 2021, and panels D–F by months in 2016. Panels G and H show the proportion of loading and initial maintenance doses compliant with the guidelines by year, and panel I the proportion of drug levels in range (15–20 mg/L). The dashed red lines in panel C and F indicate the target vancomycin trough level ranges.

Table 1
Patient characteristics. Characteristics are shown per treatment course, at the initial prescription for each vancomycin treatment course between 01 January 2016 and 01 June 2021.

Variable	Overall (N = 4573)
Age at admission (years)	
Median (Q1, Q3)	62.5 (48.9, 73.2)
Sex	
Male	2658 (58.1%)
Female	1915 (41.9%)
Weight (kg)	
Median (Q1, Q3)	80.0 (67.2, 93.7)
eGFR (mL/min/1.73 m²)	
Median (Q1, Q3)	90.8 (70.1, 112.2)
Ethnicity	
White	3567 (78.0%)
Black	70 (1.5%)
Asian	123 (2.7%)
Other	74 (1.6%)
Unknown	739 (16.2%)
Charlson score	
Median (Q1, Q3)	1 (0, 1)
Elixhauser score	
median (Q1, Q3)	2 (1, 3)
Speciality admitted to	
Trauma and Orthopaedics	2630 (57.5%)
Neurosurgery	482 (10.5%)
Clinical Haematology	397 (8.7%)
General Surgery	260 (5.7%)
General Internal Medicine	139 (3.0%)
Geriatric Medicine	104 (2.3%)
Gastroenterology	83 (1.8%)
Infectious Diseases	82 (1.8%)
Cardiology	68 (1.5%)
Emergency Medicine	7 (0.2%)
Other Medical specialties	135 (3.0%)
Other Surgical specialties	166 (3.6%)
Other	20 (0.4%)

guidelines (OR=4.41 per month [1.96,9.91]) and continued to increase after implementation but at a much slower rate (OR=1.02 [1.02,1.03]). Compliance rose slightly from the beginning of August (the annual start time for each new cohort of junior doctors) to the end of the following July (OR=1.04 per month [1.02,1.06]). Additionally, compliance was higher for prescriptions written around midday than at midnight (Fig. S2) and was lower for prescriptions written on Mondays (OR=0.58 vs Wednesday [0.45,0.74]).

3156 (69%) treatment courses had a drug level taken within 72 h of starting intravenous vancomycin (median 43.0 h (IQR 36.9–47.4) [range 19.6,71.9]). The substantial shifts in loading and initial maintenance dose over time (Fig. 1A/B/D/E) had relatively small effects on the first drug trough levels (Fig. 1C/F), with only a modestly increasing trend over 2016–2021 and a limited increase in the proportion of first drug levels reaching the target range (from 17% to 26%, Fig. 1I). Notably, even in those following the guideline-recommended loading and initial maintenance dose, only 20% of first drug levels reached the target range.

First drug trough levels were independently associated with several baseline factors (Tables S7, S8) with the strongest effects from eGFR and age rather than dose per kg or dosing compliance. Drug levels were independently lower in those with higher eGFR (0.74 mg/L lower for every ten mL/min/1.73m² higher [95% CI 0.62,0.86]). Drug levels were higher in older individuals when initial maintenance doses were administered twice daily (1.12 mg/L per 10 years older [0.95,1.28]), with no evidence of the effect of age with once-daily administration (−0.01 mg/L [−0.47,0.45, interaction $p < 0.0001$]). Drug levels were also higher in those with higher Elixhauser scores (0.81 mg/L per unit higher [0.58,1.03]). As expected for levels obtained ~48 h into treatment, the initial maintenance dose had a stronger effect (0.23 mg/L higher per 1 mg/kg/day higher [0.16,0.29]) than the effect of the loading dose (−0.06 mg/L lower per 1 mg/kg/day higher [−0.11,0.01]). Underdosing compared to guideline recommendations in the load-

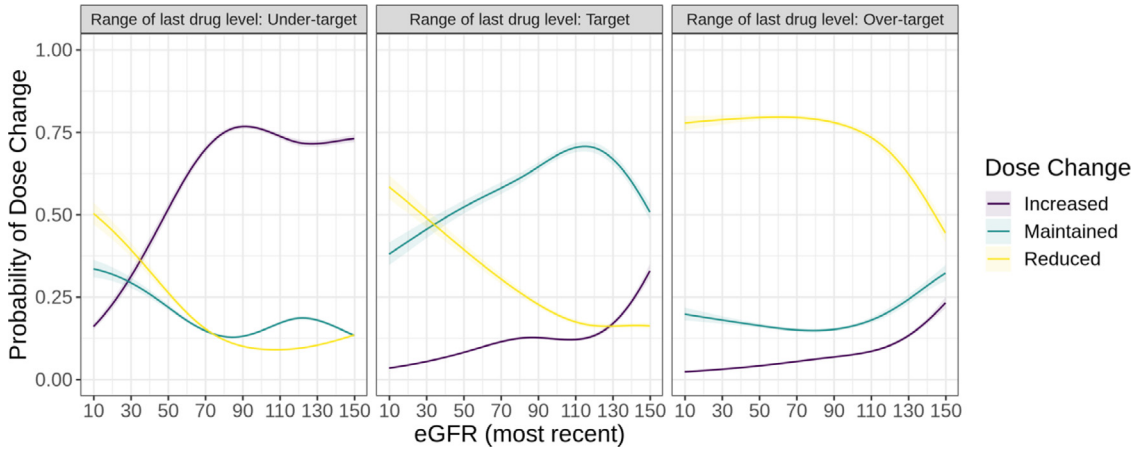

Fig. 2. Changes in vancomycin prescriptions following a drug level by drug level (panels) and renal function (x-axis). Under-target, target and over-target are drug levels <15 mg/L, 15–20 mg/L and >20 mg/L respectively. Effects shown are marginalised over the levels of all other factors.

ing dose and initial maintenance dose resulted in lower drug levels (−0.92 mg/L [−1.47,−0.37] and −0.67 mg/L [−1.45,0.11], respectively) and conversely overdosing in higher drug levels (1.73 mg/L [0.14,3.32] and 1.11 mg/L [0.37,1.84], respectively).

Changes in maintenance doses after initial drug levels

Compared to changes in loading and initial maintenance doses, there were minor changes in the subsequent maintenance doses after guideline implementation (Fig. S3A/B). Subsequent maintenance doses increased slightly from August 2016 and remained high over 2017–2021. Proportionally, doses within 30–40 mg/kg/day rose by about 17%, while doses within 10–20 mg/kg/day fell by about 7% (Fig. S3C).

For maintenance dose prescriptions issued following measured drug levels (N = 4715), 833 (21%) followed a trough level within the target range. Following below target drug levels 2076/2927 (71%) maintenance dose prescriptions increased the dose, and following above target drug levels 706/955 (74%) lowered the dose. The median dose changes (mg/day) following measured drug level at <10 mg/L, 10–15 mg/L, 15–20 mg/L and >20 mg/L were 500 (IQR 200–1000), 500 (IQR 0–500), 0 (IQR −250–0), −500 (IQR −500–0), respectively (Fig. S4, also shows percentage changes). Examining the effects of drug levels on subsequent dose adjustments using multinomial logistic regression (Tables S9, S10), the strongest associations were with most recent eGFR, but these varied according to the previous drug level (Fig. 2). When the previous drug level was below target (<15 mg/L), maintenance doses were generally (72–77% of the time) increased in patients with normal renal function (eGFR≥80 mL/min/1.73 m²), while the likelihood of maintaining or even lowering the current dose increased with lower eGFR. Conversely, high drug levels (>20 mg/L) generally (78–80% of the time) led to lower subsequent maintenance doses, although this decreased at higher eGFR (≥80 mL/min/1.73 m²). Effects of other factors were much smaller (see Supplementary Results).

Subsequent drug levels

Like first drug trough levels, there was also a slightly increasing trend in subsequent drug levels from 2016 to 2021(Fig. S5), with an increasing percentage of subsequent drug levels within the target range (from 28% to 32%).

Subsequent drug levels (N = 5176) were most strongly associated with maintenance doses and dose adjustments as expected (Tables S11, S12). Drug levels increased non-linearly with total daily doses (Fig. S6A), with 20–60 mg/kg/day associated with mean levels in range. Adjustments made to maintenance doses in response to drug levels were typically more successful at reducing levels than increasing them: reducing maintenance doses (by a median 7 mg/kg/day [IQR 6–12]) typically brought the drug levels within the target range, while increasing doses (by a median 9 mg/kg/day [IQR 6–13]) did not (Fig. S6B). Like initial drug levels, drug levels were higher in older adults when maintenance doses were administered twice daily (1.14 mg/L per 10 years older [95%CI 1.03,1.25], with no evidence of an association with age with once-daily dosing (−0.04 mg/L [−0.33,0.24, interaction p < 0.0001], (Fig. S6C). Drug levels were lower in those with higher eGFR (0.46 mg/L lower per 10 mL/min/1.73 m² higher [0.40,0.52]) and were higher in those with higher Elixhauser scores (0.72 mg/L per unit higher [0.57,0.88]). As expected, drug levels were lower the longer the time from the last dose to the drug level measurement (Fig. S6D), with significant variability in the timing of trough levels which did not always follow the recommended timeframe (12 h for twice-daily dosing, 24 h for once-daily dosing).

Time to reach therapeutic levels

There was no evidence that higher loading doses per kg led to a higher cumulative incidence of reaching the target level within 72 h (p = 0.47, Tables S13, S14, Fig. 3A), although they did appear to increase the early probability of reaching target levels (within 40 h). Over the longer term, the probability of reaching the target before stopping vancomycin was higher in the low and medium loading dose groups (p = 0.002). Higher loading doses were also associated with a higher cumulative incidence of vancomycin discontinuation (p = 0.0001).

In those remaining on vancomycin, the conditional probability of achieving target levels at 5 days was 55–63%; it was similar in the medium and high loading dose groups at 10 days (89–90%), slightly higher than the low dose group (85%) (Fig. 3B).

Acute kidney injury

The risk of nephrotoxicity was relatively low, with only 147 (4.5%), 29 (0.9%) and 9 (0.3%) Stage 1, Stage 2 and Stage 3 AKI cases respectively in 3252 courses with post-treatment creatinine measurements (Table S15). Where AKI occurred (n = 185), at the end of treatment 50% (93/185) patients had recovered to within ≤1.5 times their pre-treatment creatinine level; for those cases with data recorded within six months (n = 101), 88% had recovered (89/101). Higher average drug levels were linearly associated

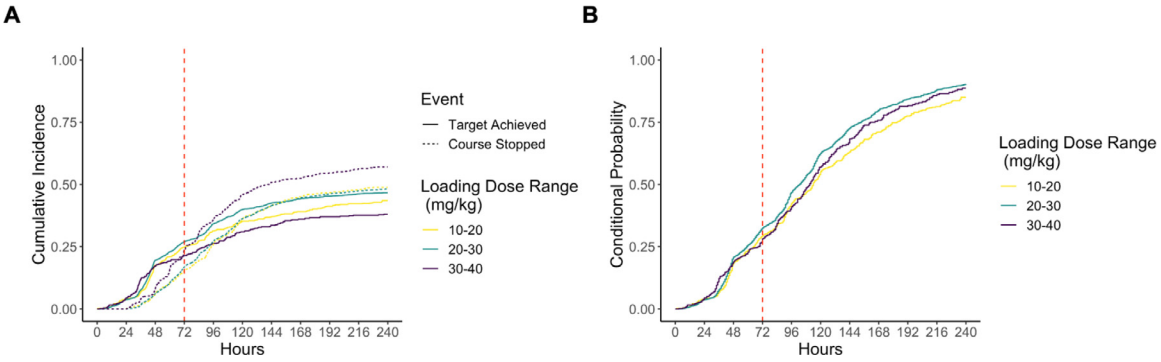

Fig. 3. Cumulative incidence of achieving the target trough level. Panel A shows the cumulative incidence of achieving the target trough level (solid line) versus stopping vancomycin before being observed to reach the target (dashed line). Panel B shows the probability of achieving the target conditional on remaining on vancomycin. Both plots are shown according to loading dose 10–20 mg/kg (yellow), 20–30 mg/kg (green), 30–40 mg/kg (purple). Follow-up time was censored at 240 h.

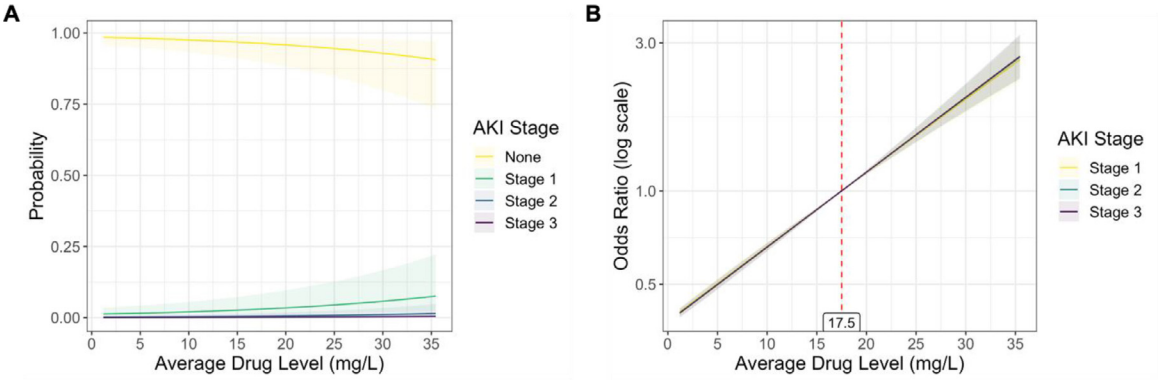

Fig. 4. Associations between the probability of different stages of AKI and average drug levels. Panel A shows the probability of stage 1, 2 and 3 AKI, and panel B the odds ratios for AKI (centred at 17.5 mg/L). Other predictors were held constant at their mean (for continuous variables) or reference levels (for categorical variables). There was no evidence of non-linearity between drug levels and the risk of AKI ($p = 0.34$).

with an increased odds of AKI, such that there was no clear "cut-off" trough value for AKI, however predicted probabilities of AKI with trough levels of 15–20 mg/L were not substantially higher than at 10–15 mg/L (Fig. 4A/B, Table S17). Observed AKI incidence in patients with time-averaged trough levels of 15–20 mg/L was still relatively low (5.5%, 33/596, Table S16). AKI risk was higher in those with lower pre-treatment eGFR and higher Elixhauser scores (Fig. S7, Table S17). There was no evidence of a change in AKI rate over calendar time after guideline implementation after adjusting for baseline characteristics (odds ratio=1.09 per year, 95%CI=0.97–1.22, $p = 0.14$).

Proposed guideline update

Based on a regression model for the relationship between initial maintenance doses and first drug trough levels in patients of different ages groups, eGFR and body weight, the initial maintenance dose required to achieve the target drug levels in the younger patients (40–60 years) was predicted to be 500–1500 mg higher than the daily dose recommended by the current guideline (Fig. 5). The predicted optimal dose for patients aged 60–80 years was similar to the current guideline recommendation in patients with eGFR below 90 mL/min/1.73 m², but was higher than the guideline dose in patients with eGFR above 90 mL/min/1.73 m². For patients 60–80 years and ≥110 kg, the predicted optimal dose was lower than the current guideline-recommended dose. New initial maintenance dosing recommendations, based on the current loading dose, are presented in Table S19. Estimates from pharmacokinetic models[16] supported that our updated guidelines were likely to increase the number of patients achieving trough levels of 15–20 mg/L (Table S20), with all but one age-eGFR-weight group predicted to achieve levels of 14–20 mg/L. Estimated AUC_{24h}/MIC ratios were 400–700 for nearly all groups.

Discussion

Using five years of vancomycin data we show implementing new guidelines increased dosing successfully, but had a more limited impact on achieving therapeutic drug levels. Several previous studies have reported limited vancomycin dosing guideline compliance.[6–10] In contrast and supporting the value of the electronic prescribing aids and web/phone app implemented, loading and initial maintenance dose prescriptions in our hospitals showed rapid and good compliance with the new guidelines (reaching 70–80% compliance). Subsequent maintenance doses also adhered well to the guideline recommendations (with 72% of prescriptions correctly adjusting the dose when the drug level was outside the target range). Some variation in practice remained, e.g., with lower compliance in some specialties or when each new cohort of junior doctors started work. However despite the high levels of compliance achieved and the guidelines being tailored to patients' weight and eGFR, the proportion of drug levels reaching the target range was suboptimal (26% initial trough levels and 32% subsequent trough levels). Similar to previous reports,[17] only 20% of first drug levels achieved the target even when the guideline was followed, with most patients under-dosed, suggesting that current guidelines may need revision or to account for other patient factors, including age. Drug levels were independently lower and more likely to be below target in younger patients, those without morbidities and those with normal renal function.

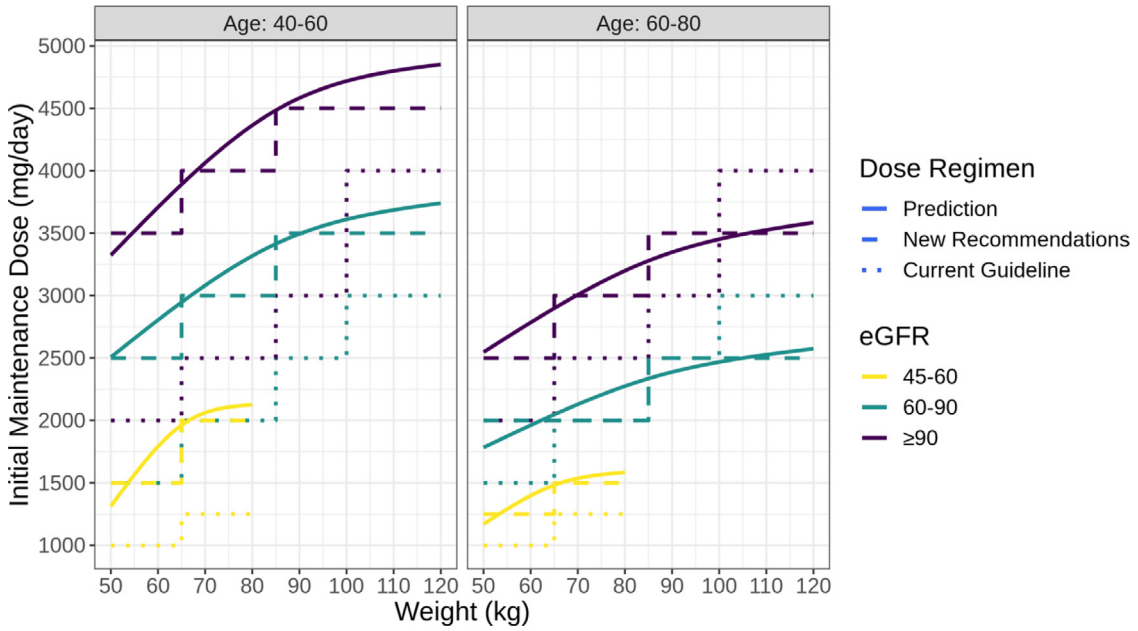

Fig. 5. Proposed updated initial maintenance doses by age group, weight and renal function. Model predictions are shown as a solid line, dosing recommendations rounded to doses that can be reliably administered are shown as a dashed line. The current guideline is shown as a dotted line. Dose predictions were not made for patients aged less than 40 years, with eGFR less than 45 mL/min/1.73 m^2 and in some weight ranges due to a lack of sufficient amounts of data.

The real-world pharmacokinetic data we collected from electronic patient record data allow us to propose updated guidelines. Although current consensus recommendations suggest AUC_{24h}/MIC ratio based dosing, many hospitals still use trough levels to guide dosing for logistical reasons and the existence of current competency in this approach. We therefore propose updates to better achieve trough levels of 15–20 mg/L. Theoretically, higher loading doses may help initial control of infection and more rapidly achieve minimum vancomycin concentrations (e.g., 10 mg/L) needed to prevent the emergence of antibiotic resistance.[18] However, trough drug levels at steady state are more related to initial maintenance doses.[17] We found no evidence that higher loading doses increased the percentage achieving target levels by 72 h, although there was some evidence of increased levels within 40 h. Therefore, while maintaining the current loading dose, we propose updating initial maintenance dosing to optimise drug levels and accounting for patient age, which is not considered at present. Using regression model predictions suggests patients 40–60 years should receive higher maintenance doses than currently recommended (by 500–1500 mg per day) and higher doses than those 60–80 years. Based on our model simulations, the updated guideline achieved trough levels of 15–20 mg/L and AUC_{24h}/MIC of 400–700 in most cases. The latter is within the AUC_{24h}/MIC range recommended by some authors,[19] but higher than the target of 400–600 in US guidelines.[2,3] Despite the higher predicted AUC_{24h}/MIC, the incidence of AKI in our study remained acceptable where trough levels were 15–20 mg/L. Differences between predicted drug levels from our regression models and population pharmacokinetic models in some age-weight-eGFR groups may reflect differences in the calibration of pharmacokinetic models across different population groups. We had insufficient data to produce recommendations for patients <40 or >80 years; careful implementation of recommendations for 40–60 and 60–80 years for these groups could be considered. Further changes such as thrice-daily administration may be required in younger patients, e.g., a retrospective study of 151 patients revealed that 40% of patients under 40 years of age eventually required more frequent dosing (every 8 h) and took longer to achieve target serum levels.[20]

Higher drug levels in older patients reflect vancomycin has a longer half-life, a larger volume of distribution and lower clearance in older patients, such that the same dosing regimen may result in higher drug levels.[21–24] Therefore, solely relying on creatinine-based eGFR calculations may not accurately reflect the true impact of underlying renal function on clearance in older patients.[25] The lack of relationship between age and drug levels in those on once-daily doses in our study likely reflects their poorer renal function, driving a once-daily regime, is the primary determinant of drug levels for these patients rather than age. Although our institutional guideline suggested initial TDM at 48 h in all patients, patients with impaired renal function take longer to reach steady-state concentrations and obtaining trough levels at 72 h in those on once daily dosing with impaired renal function may be more accurate.[26,27]

For subsequent dose adjustments, intriguingly, we found that drug levels were generally reduced to within the target range after reducing the maintenance dose, whilst increasing maintenance doses did not raise drug levels to the target within 72 h. Our current recommendation is to increase dosing by ~25% for those with sub-therapeutic levels (which was broadly followed, Fig. S4C); however, this may be too conservative, particularly with concurrently improving renal function as individuals recover from acute infection or with augmented renal clearance of vancomycin.[28]

Despite the modest and inconsistent effectiveness of AUC_{24h}/MIC in predicting clinical outcomes,[29] the latest consensus guideline suggests transitioning to AUC-guided dosing due to concerns about the increased risk of nephrotoxicity, particularly if trough levels above those actually needed are targetted.[3] However, we found a low overall risk of AKI (5.7%, most of which was mild), which remained low (5.5%) in patients with trough levels of 15–20 mg/L. This is lower than the range reported for vancomycin-induced nephrotoxicity (10–40%),[30–33] and may reflect in part the nature of the condition being treated; many of our cohort were given vancomycin for orthopaedic device or neurosurgical infections rather than blood stream infections. We found no evidence of increased nephrotoxicity after increasing our target trough level from 10–15 mg/L to 15–20 mg/L, suggesting concerns about nephrotoxicity from targeting 15–20 mg/L trough levels may

be smaller than previously reported.[31,34,35] However, the transition to AUC-based monitoring may still be beneficial, allowing for more flexible timing of blood sampling during TDM (e.g., using Bayesian methods, two-point estimates),[6,36,37] which may otherwise lead to misinterpretation of trough levels and consequent failure of dosing adjustments. Many studies have reported inappropriately timed sample collection,[6,36–39] and our observations also show this.

Although the implementation of AUC-guided dosing and/or continuous infusions may further optimise vancomycin dosing, this requires significant training and logistics.[19,40–43] An alternative is to shift to other drugs, e.g. teicoplanin, another glycopeptide antimicrobial with comparable efficacy and better tolerability, which is simpler to dose.[44]

The limitations of this study include that it was performed in a single centre based on electronic health records, so there may have been unmeasured confounding factors and generalisability cannot be assumed. Our guidelines were implemented prior to revised consensus guidelines, with recommendations remaining based on trough levels instead of AUC or AUC_{24h}/MIC. We have not clinically validated our new dosing recommendations, and this should be a focus of future work, however, pharmacokinetic estimates suggest that resulting drug levels are likely to be as intended. We also found that sex affects drug levels, and although we omitted this from our age, weight and renal function specific guideline for simplicity, this could be considered in future guidelines where computer aided prescribing allows for more complex models to be used. We did not update loading dose recommendations, as the effect of loading doses on steady-state levels may be limited. This study did not assess the effect of concomitant use of other nephrotoxic drugs on AKI, e.g., piperacillin-tazobactam.[45,46] Additionally, we focused on meeting an externally specified consensus trough target level. We therefore did not examine the clinical outcomes of patients given the heterogeneity in the indications for treatment ranging from localised orthopaedic device infection to suspected bacteraemia in profoundly immunosuppressed patients, however this clearly a key aspect of setting optimal dosing targets that could be studied further using large-scale electronic patient record data.

Conclusions

Good compliance with vancomycin guidelines was achieved with the assistance of a widely used web and phone app and electronic patient record prompts containing a full suite of antimicrobial guidelines and infection advice. New guidelines successfully achieved higher doses of vancomycin administration, but many patients had sub-therapeutic drug levels. We propose that initial maintenance doses be adjusted for age, as well as weight and renal function. The risk of AKI in our study was relatively low at 5.7%. The narrow therapeutic window of vancomycin poses an ongoing challenge for dosing optimisation, and the impact of existing guidelines needs to be continuously monitored and adjusted to ensure therapeutic drug levels are achieved.

Declaration of Competing Interest

DWE declares lecture fees from Gilead outside the submitted work. No other author has a conflict of interest to declare.

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Data availability

The data analysed are not publicly available as they contain personal data but are available from the Infections in Oxfordshire Research Database (https://oxfordbrc.nihr.ac.uk/research-themes-overview/antimicrobial-resistance-and-modernising-microbiology/infections-in-oxfordshire-research-database-iord/), subject to an application and research proposal meeting on the ethical and governance requirements of the Database.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.06.029.

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