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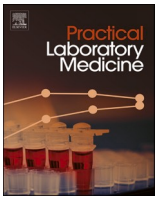

Characteristics and calculations of paired vancomycin measurements for determination of 24-h area-under-curve (AUC)

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ABSTRACT

Background: Current pharmacy practice guidelines recommend 24-h area-under-curve (AUC_{24}) targets for use of vancomycin against methicillin-resistant Staphylococcus aureus (MRSA). AUC protocol-specific vancomycin orders were begun recently (2022) at our institution. We reviewed initial AUC protocol-associated data and calculations.

Methods: AUC_{24} calculations are derived from timed, paired measurements of vancomycin (V1, V2). We retrieved paired (V1,V2) measurements for a 90-day interval. Calculations to obtain AUC_{24} were performed according to two accepted methods (A, B) that assume first-order kinetics for vancomycin elimination between V1 and V2.

Results: 44 (V1,V2) measurement pairs were from among 27 patients. Dosing intervals were 8, 12, or 24 h. The first-order rate constant k was normally distributed ($k = 0.096 \pm 0.046$ 1/h); $t_{1/2}$ ranged from 3 to 30 h. For target $AUC_{24} = 400–600$ h × μg/mL, 55% of calculated AUC_{24} results were within target. Imprecision for calculated k was predicted to be least when V2 is a trough level. Method B results were greater than Method A results by a factor of 1.07.

Conclusions: 45% of AUC_{24} results indicated need for change in dosage. Recommendations are that average results from A and B methods of calculation should be used, and that V1 and V2 should be as widely separated as possible.

1. Introduction

Current pharmacy practice guidelines recommend a target 24-h area-under-curve (AUC_{24}) for vancomycin in treatment for infection by methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. The clinical objective of controlled AUC is to maximize efficacy without induction of renal toxicity [2]. At the request of pharmacy, new lab order codes for vancomycin measurements specifically associated with AUC determinations were recently created to make such measurements readily identifiable in the medical record. A first measurement (order code V1) is intended to be a post-infusion measurement; a second measurement (order code V2) is intended to be a following measurement made prior to administration of the next dose of vancomycin (ostensibly, but not necessarily, a trough measurement). AUC for the dosing interval is determined assuming a first order rate of decrease between V1 and V2 [3]. The calculated AUC_{24} is compared to the target value for AUC_{24}, and is used to adjust subsequent vancomycin dosing in order to attempt to achieve the target AUC_{24}.

Data for designated V1, V2 measurements associated with the AUC protocol are relatively new at our institution (beginning in 2022). The laboratory is not involved in the conversion of results of paired vancomycin measurements to AUC_{24}. For purposes of

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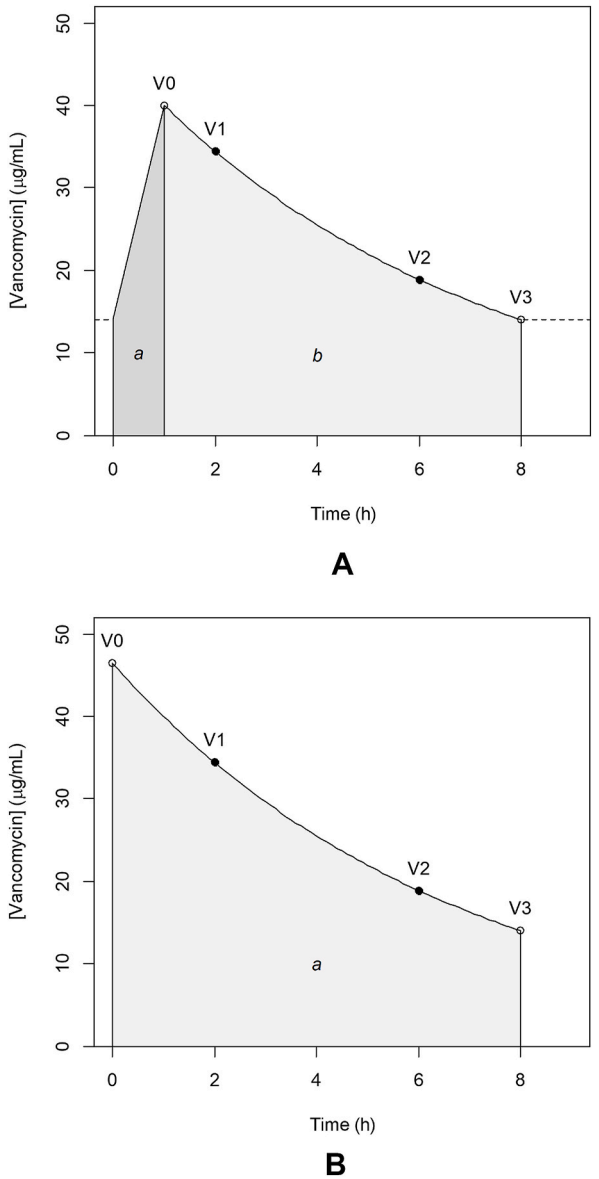


Fig. 1. Schematic diagrams for calculation of AUC for an example (V1,V2) pair. A. Method A. B. Method B. Methods differ in integration between start of infusion and V1. Both methods are considered to be estimates of the AUC for interval *q*: Method A is considered to be an underestimate of the actual AUC; method B is considered to be an overestimate [3]. In this example, k = 0.15/h; AUC_{24} (A, B) = (601, 650) h × μg/mL, respectively (ratio A/B = 1.08).

education of our staff and students, we conducted a review of data and calculations associated with this protocol. There are two available methods of determination of AUC_{24} based on vancomycin measurement pairs. We compare results obtained by both methods.

2. Methods

2.1. Primary data and data reduction

Primary data were obtained from reports generated by the Hospital Information System (Epic) over a 90-day interval containing V1 or V2 measurements indicating an AUC protocol. Results were obtained for all V1 and V2 and their associated times. There was no restriction or distinction made as to whether AUC protocol patients were being given vancomycin for the first time in their hospital stay, or who were already having repeated vancomycin infusions. There were no AUC-protocol patients receiving continuous vancomycin infusions.

Vancomycin measurements were performed by Roche Cobas VANC3 immunoassay (Roche Diagnostics, Indianapolis, IN).

Creatinine measurements used for calculation of the estimated glomerular filtration rate (eGFR) were by the Roche Cobas CREJ2 Jaffe method assay (Roche Diagnostics, Indianapolis, IN). eGFR calculations used the EPI-CK creatinine 2021 equation having inputs of creatinine, age, and sex [4].

Dosing interval (e.g., q8h), time of the start of the infusion, and infusion length were those given in medical records. We examined characteristics of the primary data (V1, V2, ΔV (= V1-V2), time between start or end of infusion and V1, and time between V1 and V2) and of the calculated data (V1/V2, the first-order rate constant for elimination, k, and values for 24-h AUC (AUC_{24})). Calculation of AUC_{24} was by two guidelines-sanctioned methods from Pai et al. [3] (see details below). Data analyses were performed by programming in R.

2.2. Calculation of first-order rate constant for vancomycin clearance, k, using V1 and V2

Vancomycin clearance is assumed to be a first order process ($d[V]/dt = -kt$) [3]. Using V1 and V2 to represent first and second measured vancomycin concentrations (μg/mL), the relationship between V1 and V2 is given by:

$$V2 = V1\ exp(-k\ \Delta t) \tag{1}$$

where Δt is the time difference (≡ h) between V1 and V2 measurements (t2-t1). From Eqn. (1), the first order rate constant k (≡ 1/h) is calculated from V1 and V2 according to:

$$k = -ln(V2 / V1)/\Delta t \tag{2}$$

The associated $t_{1/2}$ for clearance is given by:

$$t_{1/2} = -ln(0.5)/k \tag{3}$$

2.3. Calculation of area-under-curve (AUC)

AUC_{24} guidelines [1] reference the methods given by Pai et al. [3] for calculation of AUC_{24} using paired vancomycin measurements. There are two methods given, which we will refer to as methods A and B. A schematic diagram for each method is shown in Fig. 1. The methods differ in how they calculate the early segment of the AUC between the start of infusion and measurement of V1.

2.3.1. Calculation of area-under-curve (AUC): Method A

In Method A (Fig. 1A), there are seven data elements used as inputs: time of start of infusion, duration of infusion (viz., length of time of infusion), times and results for V1 and V2, and the infusion frequency (e.g., q8h, here designated as $q = 8$). First, a post-infusion vancomycin concentration V0 is projected backwards in time using k and V1:

$$V0 = V1/exp(-k\ \Delta t) \tag{4}$$

where Δt is the time difference between the end of infusion and measurement of V1. Second, a vancomycin concentration V3 is projected forward for an interval of duration q post start of infusion:

$$V3 = V1\ exp(-k\ \Delta t) \tag{5}$$

where Δt is the time difference between V1 and the time of q hours past the time of the start of infusion. An estimate for total AUC for interval q (AUC_q) is calculated in two segments. The early segment (a) is the trapezoidal area between start of infusion and end of infusion, using V3 as one of the vertices:

$$\text{area } a = (V3 + V0)/2 \times (\text{length of time of infusion}) \tag{6}$$

The later segment (b) is given by the integral between V0 and V3:

$$\text{Area } b = (V0 - V3)/k \tag{7}$$

The total area AUC_q (≡ h × μg/mL) is obtained by summation of areas a and b:

$$AUC_q = a + b \tag{8}$$

2.3.2. Calculation of area-under-curve (AUC): Method B

Calculation of AUC_q by Method B (Fig. 1B) s as follows. First, a vancomycin concentration V0 is projected backwards to the time of start of infusion using k and V1:

$$V0 = V1/exp(-k\ \Delta t) \tag{9}$$

where Δt is the time difference between the start of infusion and measurement of V1. Second, a vancomycin concentration V3 is projected forward for an interval of duration q post start of infusion:

$$V3 = V0\ exp(-k\ q) \tag{10}$$

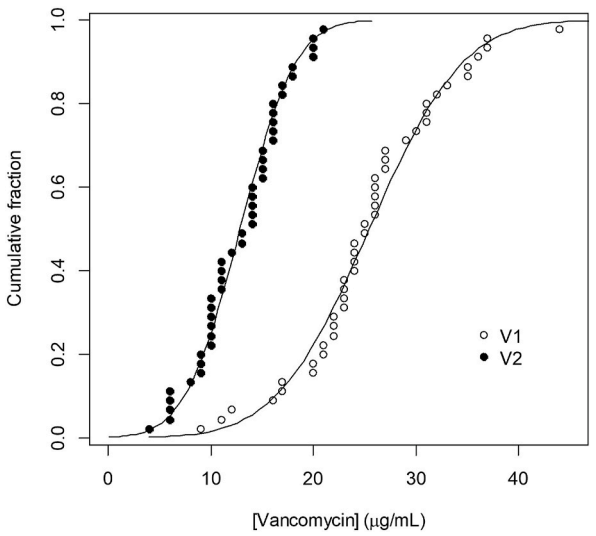


Fig. 2. Primary data distributions for V1 and V2 (n = 44). When characterized as normal distributions (mean ± SD): V1 = 25.3 ± 7.1 μg/mL; V2 = 12.7 ± 4.3 μg/mL (lines). In comparison to V2, the distribution for at-large results for inpatient trough vancomycin during the same 90-day interval was V = 16.4 ± 6.5 μg/mL (n = 1,251) (not shown).

AUC_q is then given by:

$$AUC_q = (V0 - V3)/k \tag{11}$$

2.3.3. Calculation of 24-h area-under-curve (AUC_{24}): Methods A and B

For both methods A and B, AUC_{24} is calculated as multiples of AUC_q relative to 24 h:

$$AUC_{24} = (24 / q) \times AUC_q \tag{12}$$

AUC_{24} is then used to compare results for each patient to recommended AUC_{24}. Results for AUC_{24} from both Methods A and B are regarded as estimates of the actual AUC_{24}. It is anticipated that Method A is likely to produce an underestimate of the actual AUC_{24}, and that Method B produces an overestimate [3].

2.4. Ethics

This study was classified as "Exempt" by review of the Institutional Review Board of Jefferson University, pursuant to federal regulations governing exempted protocol declarations. Specifically, patient consent for retrospective collection and use of de-identified data for this study was not required.

3. Results

3.1. Characteristics of primary data

During the first 90 days after institution of order sets for V1 and V2, there were 101 orders designated as V1 or V2. Among these measurements, 88 were identifiable as being part of a "successful" (V1, V2) measurement pair (n = 44), viz., those entries for which records included all data elements needed for calculation of AUC_{24} by both methods A and B. These 44 pairs were from among 27 individual patients (10 female (37%), 17 male (63%); age range 22–77 y; median age = 55 y), hereinafter referred to as "AUC protocol patients". For comparison, there were 2,062 non-(V1, V2) vancomycin measurements made for 772 inpatients at-large during this interval (trough: 63%; random: 37%). This number included 94 non-(V1, V2) vancomycin measurements (4.6%) from among the 27 AUC protocol patients (32 random (34%), 62 trough (66%)). Designated (V1, V2) measurements comprised 4.7% of all vancomycin results produced during the 90-day interval.

Vancomycin dosing frequencies (VDF) among the 44 AUC protocol (V1, V2) pairs were according to q8h (16/44, 36%; $q = 8$), q12 h (25/45, 57%; $q = 12$), or q24 h (3/44, 7%; $q = 24$). Infusion times were 60 min (n = 24; 55%), 90 min (n = 19, 43%), or 120 min (n = 1, 2%).

3.2. Distributions for V1, V2, and measurement intervals (Δt)

Distributions for V1 and V2 were essentially normal distributions (Fig. 2). These distributions were not significantly segregated

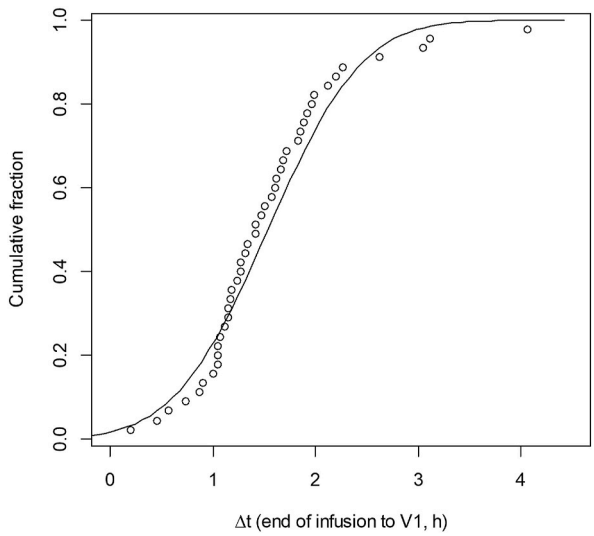


Fig. 3. Time between end of infusion and V1 (Δt). Line: normal distribution for Δt = 1.54 ± 0.72 h (mean ± SD).

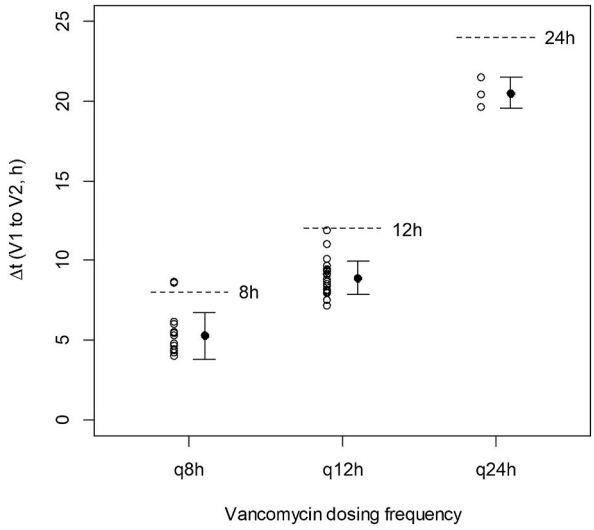


Fig. 4. Time between V1 and V2 (Δt) segregated by VDF (open points). Solid points plus lines = mean ± SD. With one exception, measurement of V2 was expectedly in the latter half of the time interval *q*.

according to patients' VDF. The distribution of time intervals Δt between the end of infusion and time of collection of V1 are shown in Fig. 3. For this graph, we manually altered the designated infusion length from 90 min to 60 min for one instance in the dataset, because the time of collection for V1 was otherwise apparently within the infusion interval. This alteration was maintained for all subsequent analyses. Values for Δt were generally a minimum of 1–2 h after the end of infusion, and were not segregated by VDF. Intervals between V1 and V2 were expectedly a function of VDF, showing a majority in each case being within the latter half of each dosing interval (Fig. 4).

3.3. Distributions for ΔV, (V2/V1)

The distribution for ΔV (= V1 - V2) for all (V1, V2) pairs is shown in Fig. 5. These values were roughly normally distributed (ΔV = 12.6 ± 5.5 (1SD) μg/mL). As was true for the V1 and V2 distributions, the distributions for ΔV were likewise not significantly segregated according to patients' VDF.

The ratio (V2/V1) is a factor in determination of AUC (Eqn. (2)). The distribution for the ratio V2/V1 is shown in Fig. 6 (V2/V1 = 0.51 ± 0.14 (1SD)). This ratio is a factor in evaluation of the effects of imprecision in vancomycin on imprecision in calculated *k*, as discussed below in section *3.6*.

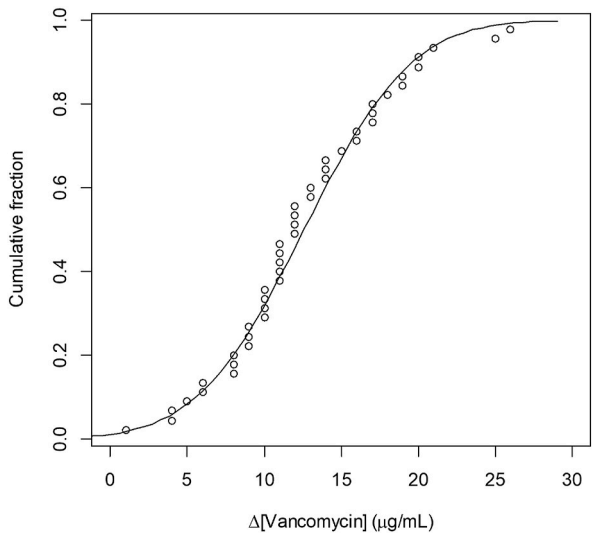


Fig. 5. Vancomycin concentration difference between V1 and V2 (ΔV = V1-V2). When characterized as a normal distribution (mean ± SD), ΔV = 12.6 ± 5.5 μg/mL (n = 44) (line).

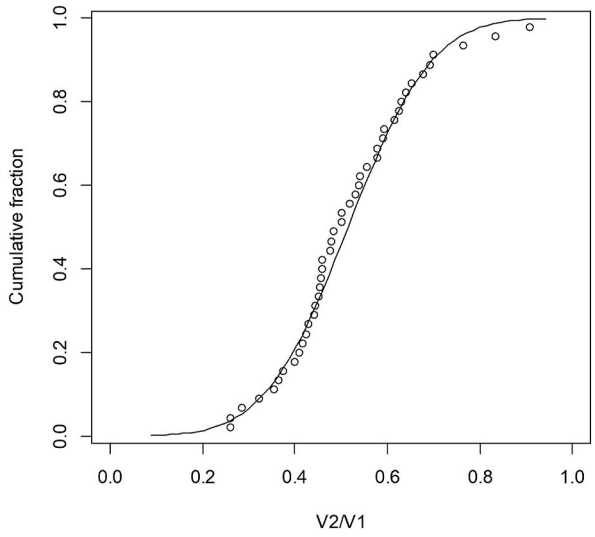
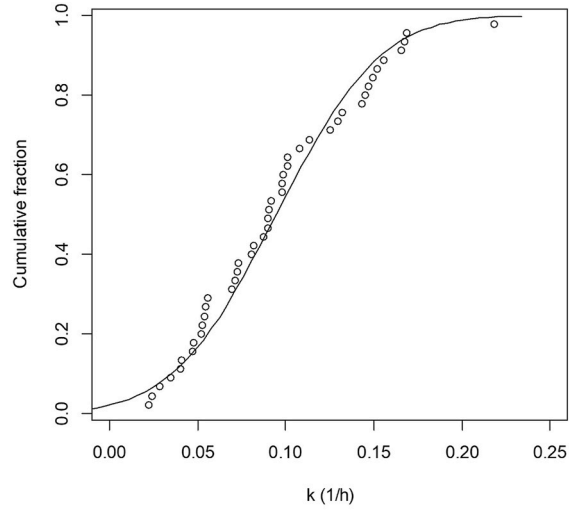


Fig. 6. Distribution of the ratio V2/V1. When characterized as a normal distribution (mean ± SD), V2/V1 = 0.51 ± 0.14 (line).

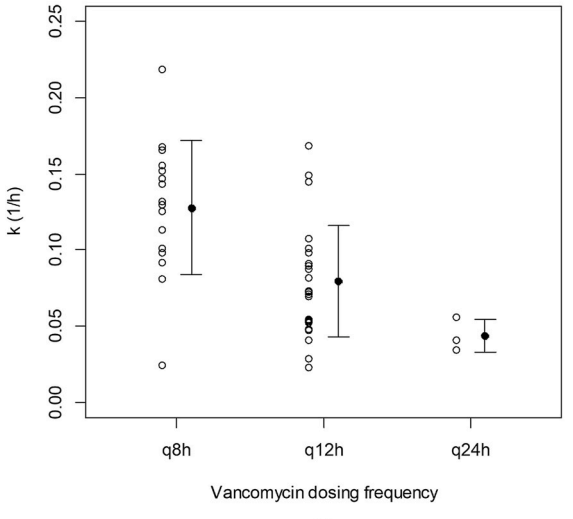
3.4. Distribution for calculated k

Using paired V1 and V2 measurements and the time difference (Δt) between the paired measurements, the first-order rate constants *k* were calculated according to Eqn. (2). These values were essentially normally distributed ($k = 0.096 \pm 0.046$ (1SD) (1/h)) (Fig. 7A). The range of values for *k* were progressively segregated according to VDF as shown in Fig. 7B. The segregated means were significantly different across VDF (by *t*-test, $p < 0.05$ for all comparisons), wherein higher *k* values were more prevalent among higher frequency VDF patients. Values for *k* corresponded to a range for $t_{1/2}$ of 3–30 h, with a median value of 7.7 h (Fig. 7C). A normal value for $t_{1/2}$ is 6.5 h ($k = 0.017$/h) [5].

Distributions for *k* in Fig. 7B are comparable in their progression according to VDF as were distributions of estimated glomerular filtration rates (eGFR) among the 27 AUC-protocol patients when segregated according to VDF (Fig. 8). This comparability is an anticipated result, in that assignment of VDF by Pharmacy involves use of creatinine measurements and estimation of creatinine clearance using the Cockroft-Gault equation [6], which are likely to be correlated with eGFR. Overall, however, for eGFR restricted to measurements made within 24 h of determination of AUC_{24}, values for *k* were only weakly correlated eGFR ($r = 0.57$) (data not shown).



A



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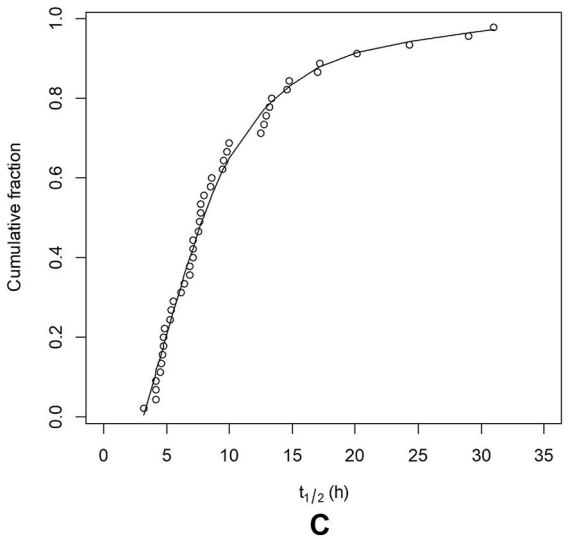

C

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Fig. 7. Properties of calculated *k*. A. Distribution of calculated *k* (n = 44). When characterized as a normal distribution (mean ± SD): $k = 0.096 \pm 0.046$ (1/h) (line). B. Ranges for *k* segregated by VDF. Solid points plus lines = mean ± SD. C. Distribution of $t_{1/2}$ associated with *k* ($t_{1/2}$ = -ln (0.5)/k).

3.5. Results for AUC_{24}

AUC_q (≡ h × μg/mL) was calculated for both methods A and B as described in Methods. The corresponding AUC_{24} was then calculated from AUC_q for each method using Eqn. (12). Results for AUC_{24} for methods A and B are shown in Fig. 9. For both methods, distributions of AUC_{24} across patients were roughly normally distributed (AUC_{24} (A) = 471 ± 121 (1SD) h × μg/mL; AUC_{24} (B) = 501 ± 130 (1SD) h × μg/mL) (Fig. 9A). By *t*-test, the difference between means was not statistically significant (p = 0.26). Practice guideline recommendations specify target AUC_{24} = 400–600 μg/mL × h [1]. The correlation between results of calculations for AUC_{24} by Methods A and B for each patient is shown in Fig. 9B. In aggregate, results from Method B show a proportional bias by a factor of 1.07 compared to results from Method A. Only 3 results (6.8%) among 44 produced a discordance in interpretation between Method A and Method B calculations with respect to inclusion within the AUC_{24} target interval.

A comparison of results for Methods A and B relative to target is given in Table 1. Using an average AUC_{24} value from results of calculations by Method A and Method B, 55% of AUC_{24} were within target, 27% were below target, and 18% were above target. A total of 45% of AUC_{24} results would indicate recommendation either to increase or decrease vancomycin dose for the given VDF. The distributions of average AUC_{24} results were not strongly dependent on VDF (data not shown).

3.6. Evaluation of uncertainty in k determinations due to vancomycin assay imprecision

As for all laboratory measurements, there is imprecision in the measurement of vancomycin. CVs for the vancomycin assay at our institution are shown in Table 2. This imprecision affects the precision for the determination of *k*. We demonstrate this effect by simulation for a particular hypothetical time course for post-infusion vancomycin concentration as an example (Fig. 10).

Fig. 10A shows a theoretical time course for V2 relative to V1 assuming $k = 0.106$/h. Per Eqn. (2), calculation of *k* depends on the ratio V1/V2. The distribution of the ratio V2/V1 is shown in Fig. 10B when accounting for assay imprecision. Results were from simulation for 1,000 replicates of the ratio for random independent sampling of V1 and V2 from normal distributions having fixed CVs of 4.3% (average value from Table 2). Simulation to obtain the distributions of the ratio V2/V1 was performed because there is no direct (analytical) equation to calculate imprecision for a ratio of variables having normal distributions. The distributions of ratios for each point were themselves normally distributed, with a fixed %CV of 6.1% (Fig. 10B). Calculation of *k* depends on *ln*(V2/V1), however (Eqn. (2)); thus, despite the fixed %CV for (V2/V1), the imprecision in calculated *k* is nonetheless a function of (V2/V1). Fig. 10C shows examples of simulated distributions for *k* for different values of V2/V1. Each of these distributions is a normal distribution, and they all have the same mean that is the correct value for *k* (0.106/h); their imprecision varies, however, according to the V2/V1 ratio (Fig. 10D; Fig. 10E). Overall, there is less uncertainty in the measured *k* as the ratio V2/V1 decreases. Correspondingly, it is advantageous for V2 to be as near to a trough value as possible to minimize uncertainty in the determination of *k*.

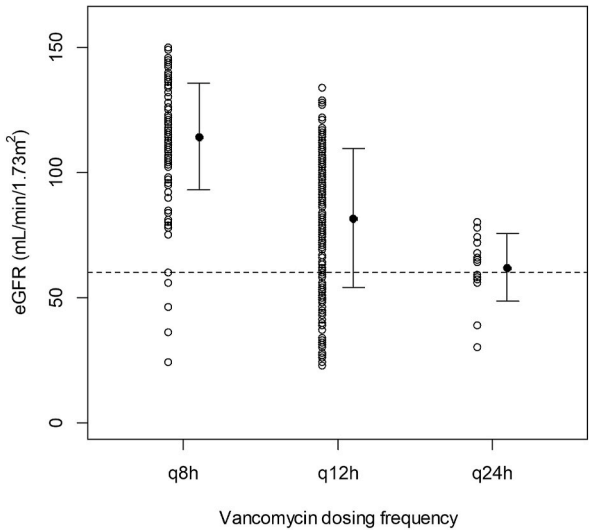

Fig. 8. Patient eGFRs segregated by VDF. For comparison to Fig. 7B. eGFR units = mL/min/1.73 m^2. Line segments show mean ± SD for eGFR by VDF: q8H, 114 ± 21 units (n = 147); q12 h, 82 ± 28 units (n = 263); q24 h, 63 ± 13 units (n = 15). Data were all eGFR reported for AUC-protocol patients during the 90-day interval. eGFR reference interval = >60 units (dashed line).

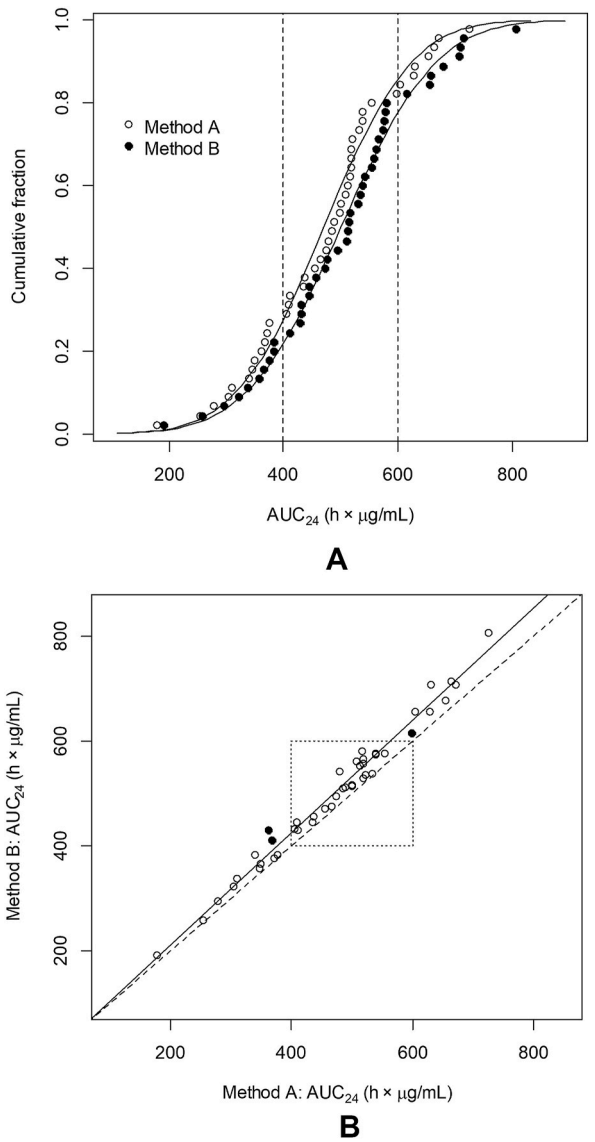

Fig. 9. Calculated AUC_{24}. A. Distributions for AUC_{24}. Distributions were approximately normally distributed (lines): AUC_{24} (A) = 471 ± 121 h × μg/mL; AUC_{24} (B) = 501 ± 130 h × μg/mL. Dashed line: $y = x$. Vertical dotted lines: boundaries of recommended target range for AUC_{24} (400–600 h × μg/mL). B. Correlation of results for Method B vs. Method A. By linear regression: B = 1.072 A - 3.7 (r = 0.990); by linear regression with intercept = 0: B = 1.065 A (r = 0.990). Dotted lines: boundaries of target range for AUC_{24}. Closed points: points for which there is discordance between Method A and Method B results with respect to position within/without AUC_{24} target range.

Table 1
AUC_{24} results interpretations relative to target for Method A, Method B, and average.

AUC_{24} result relative to target	Method A	Method B	Average[a]
Below target	12 (27.3%)	10 (22.7%)	12 (27.3%)
Within target	25 (56.8%)	26 (59.1%)	24 (54.5%)
Above target	7 (15.9%)	8 (18.2%)	8 (18.2%)

[a] (Method A result + Method B result)/2.

4. Discussion

Availability of vancomycin orders that were specifically identifiable in the medical record as being associated with use for AUC determination began at our institution in mid-2022. Our study was undertaken to familiarize ourselves with properties of these data

Table 2
1-month interassay precision data for the Roche vancomycin immunoassay using commercial control materials (Liquichek Immunoassay Plus, Bio-Rad Laboratories, Irvine, CA).

Control level	Mean (μg/mL)	Standard deviation (μg/mL)	CV (%)[a]
A	7.2	0.45	6.2
B	19.9	0.60	3.0
C	32.0	1.20	3.8

[a] Average = 4.3%.

and their analysis. We analysed the first 90 days of data derived from these orders. Use of the AUC protocol was relatively infrequent (approximately 1 instance per every 2 days). There was a relatively high rate of miscollections among V1 and V2 samples (viz., duplicate collections, missed second collections, or collections with missing associated time of infusion data), which collections could not be matched to a (V1,V2) pair (13/101 collections, or 12.9%). AUC protocol-associated vancomycin measurements comprised <5% of all vancomycin measurements made during the data interval.

Overall, average AUC_{24} for the majority of cases (55%) were within the boundaries of the recommended range (400–600 μg/mL × h) [1]; 27% were below the target range (indicating an apparent need for an increase in dose), and 18% were above the target range (indicating an apparent need for an decrease in dose).

Data for the rate constant k used to determine AUC were normally distributed, not far from being centered on normal values for k. Variation in k was such that there was a 10-fold variation in associated $t_{1/2}$. Values for k and $t_{1/2}$ in our dataset appear to be segregated by q, which in turn likely reflects segregation of q by glomerular filtration rate or creatinine clearance.

Vancomycin disposal in the normal case is via renal excretion [5]. There was, however, only poor correlation of k with eGFR. It is important to note that eGFR is highly imprecise with respect to GFR for individual patients (95% confidence interval greater than ± 30%) [4], and is therefore probably more generally useful in assessment of longitudinal changes in GFR rather than in estimation of GFR [7]. Correspondingly, eGFR would not be useful in predicting AUC from a single sample measurement of vancomycin.

Our analysis compared two prescribed methods of determination of AUC_{24} based on (V1, V2) measurement pairs [3]. Method B results showed a proportional positive bias relative to Method A results (B = 1.07 A). Whereas A and B methods results are likely to represent underestimate and overestimates for AUC_{24}, respectively, a positive bias of B relative to A was the expected result, although the scale of the bias was unknown. Given the simplicity of the calculations for either method, it is reasonable to suggest that results for both methods should be calculated, with use of the average for results reporting and interpretation. Beside use of Method A or Method B, alternative procedures for determination of AUC_{24} include use of "Bayesian" model calculations, for which only a single vancomycin measurement is needed [1].

It is important to note that temporal vancomycin profiles are in detail best described by two-compartment pharmacokinetics [8]. Calculations as obtained from the two-point models may thus in fact have bias relative to a true AUC curve as could be determined by more points and more sophisticated modeling. The use of the simple two-point models is a practical compromise. Shingde et al. note that use of 1-compartment models for assessment of need for vancomycin dose adjustments is likely to be adequate with respect to intent [8].

Practice guidelines for AUC_{24} refer to target ranges in terms of AUC_{24}/MIC, where MIC is the minimum inhibitory vancomycin concentration for MRSA. Formally, units of AUC_{24}/MIC are hours (h); this can be thought of as time multiples of MIC. Guidelines, however, refer to AUC/MIC as having units of (h × μg/mL) [1]. This is in error; what they mean is simply that AUC_{24} is not different numerically from AUC_{24}/MIC when MIC has a numeric value of 1 μg/mL. In practice, MIC is assumed to be 1 μg/mL (= 1 mg/L) [1]. This value for MIC is the most common value reported for MRSA isolates, constituting 74.3% of all measurements among 77,145 isolates in one large North American study, with no significant variation over a 20 year study period [9]. A difficulty associated with use of a different MIC to determine AUC_{24}/MIC is that reporting of MIC varies only according to factors of 2, meaning that use of anything other than a standardized MIC will result in quantum changes in AUC_{24}/MIC by factors of 2. From our AUC_{24} results distribution shown in Fig. 6, quantization of result by factors of 2 in the denominator would be highly problematic with respect to interpretation of results in comparison to guidelines that assume MIC = 1 μg/mL. In the study cited above by Diekema et al. [9], 74.3% of results were MIC 1 μg/mL, 20.5% were MIC 0.5 μg/mL, 4.9% were MIC 2 μg/mL, and only 0.4% of results were more than one 2-fold dilution separated from MIC 1 μg/mL. From these data, use of MIC other than 1 μg/mL would generate quantized over- or underestimates of the AUC_{24}/MIC ratio in more than 25% of cases. In principle, however, site-specific MIC would be used in initial vancomycin dosing calculations. MIC is reviewed with MRSA bacteremia since MIC ≥ 2 μg/mL makes it difficult to reach therapeutic AUC/MIC of 400–600 h without increasing risk of nephrotoxicity. In such cases, pharmacy would likely opt for an alternative anti-MRSA agent (e.g. daptomycin) [10].

For determination of k, it is important to recognize that the time interval between V1 and V2 should in principle make no difference in the determination of k, other than that V2 must be before the next dose of vancomycin. However, due to imprecision in measurement of vancomycin concentrations V1 and V2, our example calculations indicated that uncertainty for k is predicted to be improved as the ratio V2/V1 decreases, that is, V1 and V2 should be as widely separated in time as possible. From this finding, our recommendation is that V2 measurements should be as close to trough measurements as possible, so as to utilize the lowest V2/V1 ratio obtainable within the interval q.

Laboratories generally may not be involved in determination of AUC_{24}, beyond production of the protocol-associated vancomycin measurements. Our study was undertaken therefore to inform our general understanding of utilization and properties of the AUC

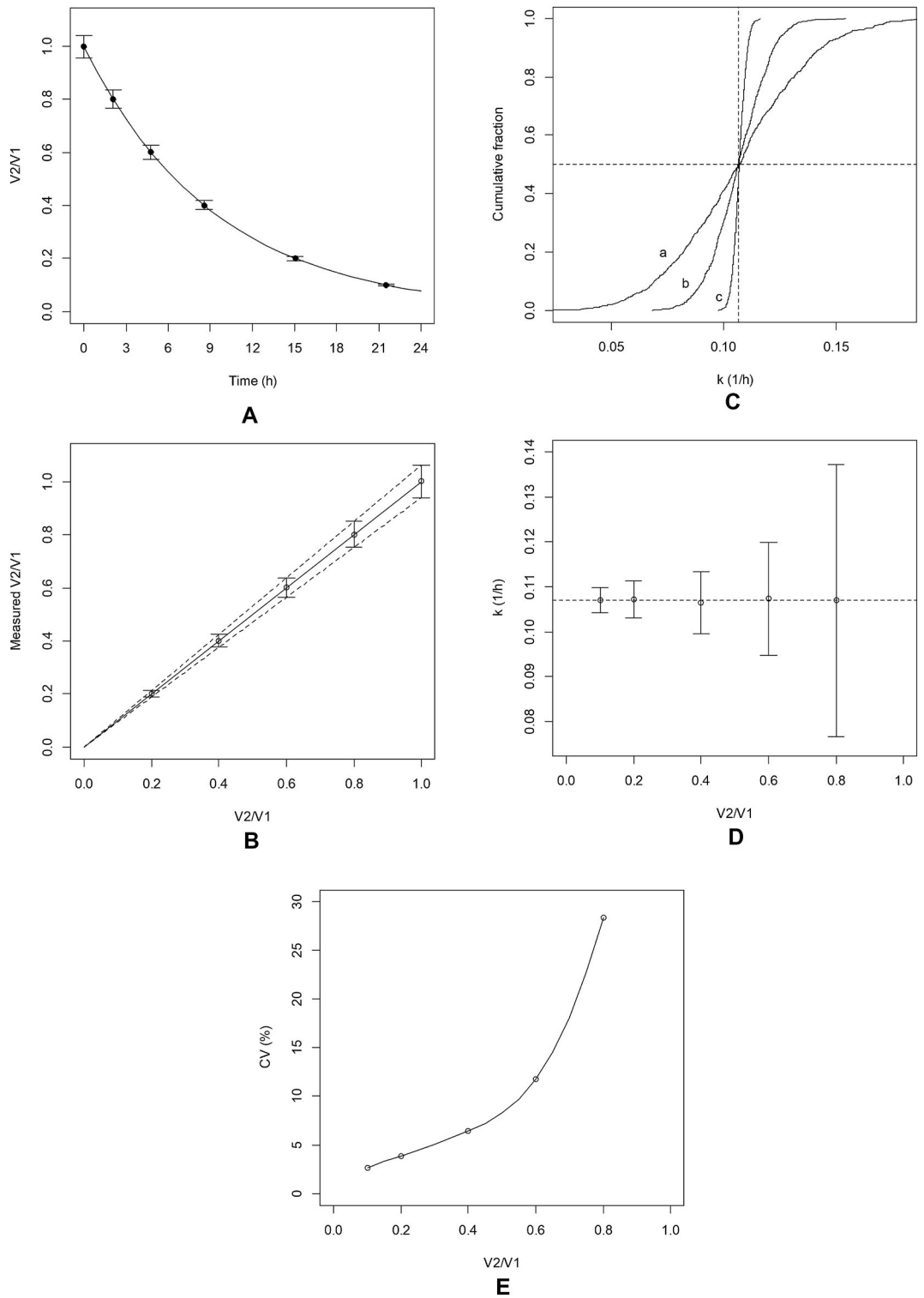

Fig. 10. Theoretical uncertainty for k based on vancomycin assay imprecision: example. A. Relative V2/V1 vs. time for $t_{1/2} = 6.5$ h. Line: theoretical time course assuming perfect measurement (CV = 0%). Points: simulation for vancomycin (mean ± SD) assuming measurement CV = 4.3% (average value from Table 2). B. Measured ratio (V2/V1) (mean ± SD) vs. theoretical ratio (V2/V1). Results were obtained by simulation (n = 1,000). Dashed lines: bounds of +1SD, -1SD, which were linear with V2/V1. This indicates that SD for the measured (V2/V1) ratio was in constant proportion to V2/V1 across all V2/V1 (%CV = 6.1 ± 0.1%). C. Distributions for *k* by simulation assuming CV = 4.3% for measurement of vancomycin. Parameter = V2/V1: a = 0.8; b = 0.6; c = 0.1. D. *k* (mean ± SD) vs. (V2/V1) by simulation, from (C). E. CV for *k* as a function of (V2/V1), from (D).

protocol and its results. Overall, we anticipate that results of the study will be valuable in education of students, technologists, and residents in laboratory medicine regarding this important practice.

CRediT authorship contribution statement

Yutao Deng: Conceptualization, Project administration, Investigation, Data curation, Writing – review & editing. **Zachary W. Rebollido:** Conceptualization, Investigation, Data curation, Writing – review & editing. **Matthew A. Pettengill:** Conceptualization, Investigation, Data curation, Formal analysis, Writing – review & editing. **Douglas F. Stickle:** Conceptualization, Investigation, Data curation, Formal analysis, Software, Writing, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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