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Prospective Evaluation of Neonatal Vancomycin Dosage Guidelines and Population Parameter Estimates

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This study compared three neonatal population models for vancomycin and two published sets of dosage guidelines. Two hundred and twenty-eight concentration measurements were available from 35 neonates who received 63 courses of therapy. Median (range) clinical data were: postnatal age 13 (2–72) days; weight 1.14 (0.57–3.64) kg; gestational age 27 (24–40) weeks and creatinine concentration 67 (30–130) μmol/L. Clearance estimates arising from the Seay population model (median 0.047 L/h) were lower than those obtained with the Grimsley and de Hoog models (0.062 and 0.065 L/h respectively) but individual estimates obtained by Bayesian analysis were lower with the Grimsley model (median 0.068 L/h) than the de Hoog (0.080 L/h) and Seay (0.078 L/h) models. Individual fits were generally good but there was a slight over prediction of the measured concentrations with all models. When dosage guidelines were compared, the Grimsley guidelines achieved concentrations below the target range of 7–15 mg/L in 85% of courses whereas the de Hoog guidelines achieved satisfactory concentrations in 59% and high concentrations in 38%. A modified version of the Grimsley guidelines should achieve satisfactory concentrations in 78% of courses.

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Introduction

The increase in vancomycin use within neonatal units has prompted the application of population pharmacokinetic analysis techniques to identify factors that influence drug handling and to develop dosage guidelines. However, limited data are available on how these dosage recommendations perform when applied in a routine clinical setting.

The established vancomycin dosing regimen in our unit was changed following the publication of guidelines by Grimsley *et al.*[1], who performed a population analysis of data collected from 59 neonates. These guidelines used the patient's weight and serum creatinine concentration to determine the dosage regimen. However, an audit indicated that many of the trough concentrations were too low, which was of concern because late onset sepsis with an especially virulent coagulase negative Staphylococcus was proving to be a problem.

Vancomycin exhibits time-dependent killing and maintaining trough plasma concentrations of four to five times the minimum inhibitory concentration

(MIC) for the infecting organism is recommended[2]. The targets used in the Grimsley study were troughs of 5–12 mg/L[1]. However, as troughs around 5 mg/L were regarded as too low, it was decided to aim for 7–12 mg/L, with up to 15 mg/L for severe infections. Aiming for a higher trough is supported by the claim that nephrotoxicity is unlikely unless concentrations are maintained above 20 mg/L[3].

To achieve these higher concentrations, an alternative dosage regimen based on a population analysis performed by de Hoog *et al.*[4] in the Netherlands, was introduced in June 2001. This new regimen was 10 mg/kg vancomycin 8 hourly, irrespective of the gestational age or serum creatinine concentration.

The present study was undertaken to determine whether these new guidelines represented an improvement in practice and to guide further dosing regimen development. The audit also offered the opportunity to compare three published sets of population pharmacokinetic parameter estimates in an independent group of patients.

Methods

Protocol

Data from all patients prescribed vancomycin according to the protocol for the treatment of a proven or suspected gram-positive infection were eligible for inclusion in this audit. Ethical approval and parental consent were unnecessary because no changes were made to the patients' routine clinical care and data used in the analysis were anonymised. Where one patient had several courses of vancomycin, each course was treated separately unless the period between doses was less than 72 hours. The following data were collected prospectively: gestational age, postnatal age, weight, serum creatinine concentration, dosage history details, sampling times and measured concentrations. Creatinine concentrations were measured by the O'Leary method (Synermed Europe Ltd®). As both weight and serum creatinine concentrations often changed during therapy or between courses, these factors were recorded each time they were measured. Two patients were excluded from the audit because a regimen other than 10 mg/kg 8 hourly was followed (one intentionally, the other missed a dose accidentally). Patients and courses were excluded from the pharmacokinetic analysis if serum creatinine concentrations were missing and concentration measurements were excluded if dosage or sampling details were missing or uncertain.

Concentrations were typically measured immediately before and one hour after the third dose of vancomycin. However, additional pre and post dose samples were taken on the second, fourth and fifth doses in the first 12 patients who received the new dosage regimen.

Pharmacokinetic analysis

Individual estimates of vancomycin clearance (CL) and volume of distribution (V) for each course were determined by Bayesian analysis within the pharmacokinetic package NONMEM[5]. The analysis was performed three times to allow three population models (Grimsley[1], de Hoog[4], Seay[6]) of CL, V, inter-individual variability and residual error to be used. In each case, a one-compartment model was fitted to the data. Individual estimates of CL and V were obtained using the "POSTHOC" Bayesian option in the programme (with MAXEVALS set to 0). As both the weights and creatinine concentrations changed between courses, each course was analysed assuming it came from a separate individual. If creatinine concentration changed substantially during therapy, the course was split and analysed as two courses.

Population estimates of CL and V arising from the three models were compared by paired *t*-test or the Wilcoxon test if the data were not normally distributed. Statistical significance was set at $P<0.05$ after adjusting for multiple tests. Differences between population and individual estimates within a model and differences in individual estimates between models were compared using the same approach.

The relative performance of each population model was evaluated according to the methodology proposed by Sheiner and Beal[7]. In each case, the individual predicted concentrations (P) obtained from the Bayesian analysis were compared with the observed concentrations (O) by determining prediction error, O – P. Percentage prediction errors (100 x (O-P)/O) were also determined. To account for correlations among data points, the analysis was also performed using the mean prediction error and mean percentage prediction error for each course. Bias was determined by calculating the 95% confidence interval (CI) of the mean (or median where the data were not normally distributed) prediction errors and percentage prediction errors for each model. Precision of the predicted concentrations for each model was assessed by the 95% CI of the unsigned prediction error. Relative bias and precision between models were determined by paired t-test or Wilcoxon test (if the data were not normally distributed).

Table 1. Clinical characteristics of the patients used in previous population analyses and in the present study

Clinical factor	Grimsley *et al.*[1]	de Hoog *et al.*[4]	Seay *et al.*[6]	Present study
Postnatal age (days)	19 (2–76)	14 (3–27)	14 (1–73)	13 (2–72)
Weight (kg)	1.52 (0.57–4.23)	1.05 (0.51–4.41)	1.48 (0.39–4.35)	1.14 (0.57–3.64)
Gestational age (weeks)	29 (25–41)	29 (24–41)	(22–42) 30	27 (24–40)
Creatinine concentration (μmol/L)	49 (18–172)	NR	NR	67 (30–130)

Data expressed as median (range) except for Seay study: mean (range)
NR = not reported

Statistical significance was set at $P<0.05$ corrected for multiple tests.

Evaluation of dosage guidelines

Individual CL and V estimates were used to predict steady state trough concentrations as follows:

$$Css = \frac{IR}{CL}\left(1 - e^{-Cl/V}\right)\left(\frac{1}{1 - e^{-Cl\ \ \tau/V}}\right) e^{-Cl\ \ t/V}$$

where IR is the dose given as an infusion over 1 hour, τ is the dosage interval and t is the dosage interval minus 1 hour. Trough concentrations were predicted for each course using the guidelines proposed by Grimsley *et al.*[1], de Hoog *et al.*[4] and a new set of guidelines that was developed from the original simulations performed by Grimsley *et al.*[1]. Briefly, 21 patients with creatinine concentrations ranging from 20 to 120 μmol/L (with increments of 5 μmol/L) were simulated.

Table 2. Median (range) population and individual estimates of clearance (CL) and volume of distribution (V) obtained using initial estimates from population studies

	Grimsley[1]	De Hoog[4]	Seay[6]
Population CL model (L/h/kg)	3.56/creatinine (μmol/L)	0.057	0.0626 0.656 if GA ≤ 32 weeks
Interindividual variability in CL (% cv)	22%	31%	36.2%
Population V model (L/kg)	0.67	0.43	0.496
Interindividual variability in V (% CV)	18%	25%	19.3%
Residual error (SD)	4.5 mg/L	NR	3.8 mg/L
Population CL estimates (L/h)	0.062 (0.018–0.364)	0.065 (0.032–0.207)	0.047* (0.023–0.228)
Individual CL estimates (L/h)	0.068** (0.022–0.299)	0.080 (0.034–0.257)	0.078 (0.034–0.268)
Population V estimates (L)	0.76## (0.38–2.44)	0.49 (0.25–1.57)	0.56# (0.28–1.81)
Individual V estimates (L)	0.79## (0.40–2.19)	0.53 (0.29–1.67)	0.60# (0.33–1.79)

GA = gestational age, NR = not reported – 20% constant coefficient of variation assumed

* Lower than the Grimsley[1] and de Hoog[4] estimates ($P<0.05$), ** lower than the de Hoog[4] and Seay[6] estimates ($P<0.05$)

\# Higher than the de Hoog[4] estimate ($P<0.05$), ## higher than the de Hoog[4] and Seay[6] estimates ($P<0.05$)

Table 3. Median (95% CI) prediction errors and unsigned prediction errors of all individual predicted versus observed concentrations and after averaging across each course

All concentrations (*n* = 228)	**Grimsley[1]**	**De Hoog[4]**	**Seay[6]**
Median (95% CI) pe	–0.9 (–1.1, –0.6)*#	–0.8 (–1.1, –0.4)*	–1.0 (–1.1, –0.5)*#
Median (95% CI) % pe	–6.0 (–9.1, –4.1)*	–6.6 (–9.2, –3.5)*†	–6.1 (–8.1, –3.4)*
Median (95% CI) unsigned pe	1.5 (1.3, 1.9)	1.4 (1.1, 1.6)	1.6 (1.4, 1.8)
Median (95% CI) unsigned % pe	12.1 (10.1, 14.8)	10.8 (9.4, 11.9)	11.6 (10.3, 13.0)
Averaged across each course (*n* = 63)			
Median (95% CI) pe	–0.7 (–1.5, –0.5)*	–1.3 (–1.7, –1.1)*	–1.1 (–1.9, –0.8)*
Median (95% CI) % pe	–10.4 (–15.3, –3.7)*#	–7.1(–10.3, –4.8)*	–8.2 (–11.1, –4.8)*
Median (95% CI) unsigned pe	1.9 (1.4, 2.7)	1.9 (1.7, 2.4)	1.9 (1.7, 2.3)
Median (95% CI) unsigned % pe	15.1 (12.6, 19.7)#†	11.8 (10.3, 13.2)	12.9 (10.1, 16.1)

pe = prediction error (mg/L), %pe prediction error expressed as a percentage of the measured concentration * significantly biased (P <0.05), # higher than de Hoog[4] model (P <0.05), † higher than Seay[6] model (P <0.05).

Steady state trough concentrations were then calculated for each "patient" using the Grimsley[1] population CL and V model, doses of 10, 12, 15 and 20 mg/kg and intervals of 8, 12, 18 and 24 hours. Dosage regimens that produced troughs of 7–15 mg/L were then identified and used to construct the modified guidelines, which were initially evaluated by using NONMEM to simulate mean (± standard deviation) concentration-time profiles for simulated patients with creatinine concentrations of 25, 35, 45, 55, 70 and 90 μmol/L.

Each set of dosage guidelines was applied to each patient using the individual CL and V estimates and the proportions of predicted steady state trough concentrations that lay between 7 and 15 mg/L were then calculated. These proportions were considered significantly different from each other if the 95% CI of the difference did not include zero.

Results

Patients

Forty patients (approximately one third of those admitted to the unit) received 71 courses of vancomycin therapy during the 10 month audit

Table 4. Modified dosage guidelines based on the approach used by Grimsley *et al.*[1] but aiming for a trough range of 7–15 mg/L

Serum creatinine (μmol/L)	Dose (mg/kg)	Dosage interval (hours)	Number of courses*
20–29	20	8	0
30–39	15	8	2
40–64	10	8	23
65–100	10	12	34
>100	15	Check concentration at 12 hours then dose according to troughs	4

*Number of courses in the present study within each category.

Table 5. Percentage of steady state troughs within various ranges based on individual estimates of clearance and volume of distribution arising from three population models and three sets of dosage guidelines

	Individual Parameters	Grimsley[1] guidelines	De Hoog[4] guidelines	New guidelines
No of courses		59*	63	59*
<7 mg/L	Mean	85	3	22
7-15 mg/L	Mean	15	59	78
>15 mg/L	Mean	0	38	0

* Four were in the category requiring analysis after 12–24 hours to determine future dosing.

period and 292 vancomycin concentrations were measured. All patients also received concurrent treatment with gentamicin but none received dopamine. Five patients, eight courses and 29 samples were excluded from the analysis due to missing creatinine concentrations and 30 concentrations with missing or erroneous sampling details were also excluded. Two patients developed acute renal failure on the last day of therapy and five concentrations associated with this acute decline were removed from the analysis. One course was split into two due to a change in creatinine concentration during therapy. The final data set comprised 35 patients, 63 courses and 228 concentration measurements (median 2, range 1 to 18 per course). A summary of the clinical characteristics of the patients included in the present study and in the previous population analyses is presented in Table 1. Initial doses were 10.0 (SD 1.0) mg/kg 8 hourly, final doses ranged from 8 to 15 mg/kg and intervals were generally 8 or 12 hours. There were 104 peak concentrations ranging from 12.3 to 35.9 mg/L with a mean (SD) of 21.8 (4.4) mg/L. Troughs accounted for 124 measurements ranging from 2.3 to 20.6 mg/L with a mean (SD) of 9.6 (3.8) mg/L.

Comparison of parameter estimates

Table 2 shows the Grimsley[1], de Hoog[4] and Seay[6] population models and the medians and ranges of the population and individual estimates of CL and V. Non-parametric analysis was required for all comparisons. The population CL estimates based on the Seay[6] model were significantly lower than those obtained with the other models (median difference (95% CI) –0.014 (–0.007 to -0.023) L/h versus the Grimsley[1] model and –0.018 (–0.016 to -0.020) L/h versus the de Hoog[4] model). Individual CL estimates were higher than the population estimates for all models with median increases ranging from 0.005 L/h (Grimsley[1]) to 0.025 L/h (Seay[6]). Individual estimates of V were also higher than the population values (median increases were 0.01 L (Grimsley[1] model) and 0.04 L (De Hoog[4] and Seay[6] models). When the individual CL estimates were compared, those derived from the Grimsley[1] population model were lower than those from the de Hoog[4] and Seay[6] models; differences (95% CI) were –0.006 (–0.010 to –0.002) L/h and -0.004 (–0.008 to –0.001) L/h respectively. Both the population and individual estimates of V varied significantly among the models, with the Grimsley[1] model consistently producing the highest and the de Hoog[4] model the lowest estimates.

Figure 1 a–c shows the individual predicted versus measured concentrations and Table 3 shows the median prediction errors and percentage prediction errors using all data and after averaging across each course. All models overestimated the measured concentrations by around 6–10% and the overall performances of the models were similar. However, the median prediction errors (all data) were lower with the de Hoog[4] model and the percentage prediction errors (course averaged data) tended to be higher with the Grimsley[1] model (Table 3).

Table 4 shows the modified Grimsley[1] guidelines that were developed in the course of this analysis and the number of patients in the present study in each category. Predicted steady state trough concentrations arising from the new, the original Grimsley[1] and the de Hoog[4] dosage guidelines were determined for each course by using the individual CL and V estimates obtained from an analysis where the mean of the three population estimates of CL and V were used as starting values.

The percentages of troughs within 7–15 mg/L are presented in Table 5. Eighty five percent were too low with the Grimsley[1] guidelines and 38% were too high with the de Hoog[4] guidelines. The modified guidelines achieved 78% of predicted concentrations within the target range and were significantly better than the other two sets of guidelines.

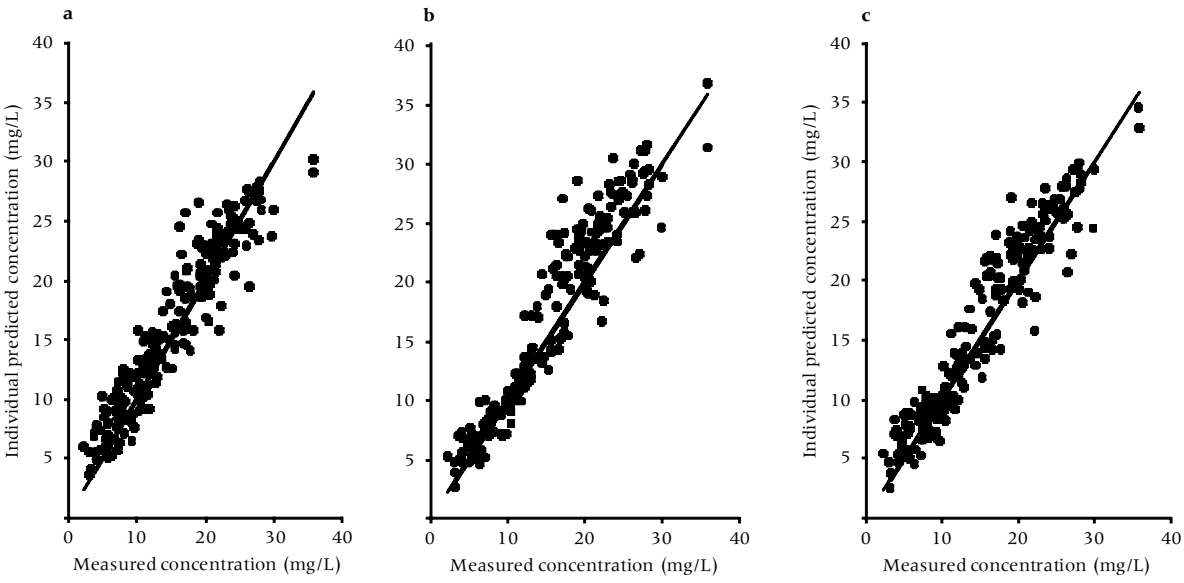

Figure 1. Individual predicted vancomycin concentrations obtained from POSTHOC Bayesian analyses versus measured concentrations. Panel (a) Grimsley[1] population model; (b) de Hoog[4] population model, panel; (c) Seay[6] population model. The solid line is the line of identity.

Discussion

This audit arose from anecdotal observations that published vancomycin dosage guidelines did not consistently achieve trough concentrations within the desired target range. It allowed three population models and three sets of dosage guidelines to be compared.

Clinical characteristics were similar to those observed in the previous population studies but postnatal ages and weights were slightly higher and creatinine concentrations lower in the Grimsley[1] study (Table 1). Trough concentrations were generally within the target range but were measured after only 16 hours of therapy (*i.e.* before the third dose). Since the median elimination half-life was 6.2 hours (range 3 to 18 hours) further accumulation was likely and in 18 courses of therapy (29%) predicted steady state concentrations were excessive. This suggests that samples should be taken after about 31 hours (5 times 6.2 hours, *i.e.* before the 5th dose) and is consistent with the recommendations of de Hoog *et al.*[4]. Samples taken earlier can be interpreted if a pharmacokinetic approach is used[8].

Individual estimates of CL and V were slightly higher than population values. However, estimates arising from the Seay[6] model increased by 54% from the population values compared to 8% and 17% with the Grimsley[1] and de Hoog[4] models. The biggest differences occurred in infants less than 32 weeks gestational age, where the Seay[6] model reduced CL to 66% of the initial estimate. Since the other models did not identify gestational age as an important factor, this finding may have been spurious. Alternatively, another clinical factor, such as renal impairment, may have confounded the Seay *et al.*[6] population model.

Figure 2 shows the average CL estimates in L/h/kg plotted against serum creatinine concentration. The shape of this relationship is consistent with that observed by others[1,9] and indicates that renal function has an important role in the handling of vancomycin in neonates. However, the use of serum creatinine has limitations and these were highlighted in the present study. Many neonates had variable creatinine concentrations and the clearances of some neonates were underestimated by the Grimsley[1] model. Creatinine concentrations in these neonates typically fell rapidly, indicating an improvement in renal function or that early measurements reflected the mother's creatinine. However, clearances in infants with persistently high or increasing creatinine were overestimated by the de Hoog[4] model. As creatinine measurements were not reported in the de Hoog[4] or Seay[6] studies, it is difficult to compare this factor between populations.

Following Bayesian analysis, individual concentrations were overestimated by around 6% with a typical difference of around 10%. These increased to 7–10% for median prediction error and 12–15% for unsigned prediction error when data within a course were averaged (Table 3). Most of the bias occurred with the troughs using the Grimsley[1] model, whereas peaks were overestimated by the de Hoog[4] and Seay[6] models (Figure 1). The proportional residual error model

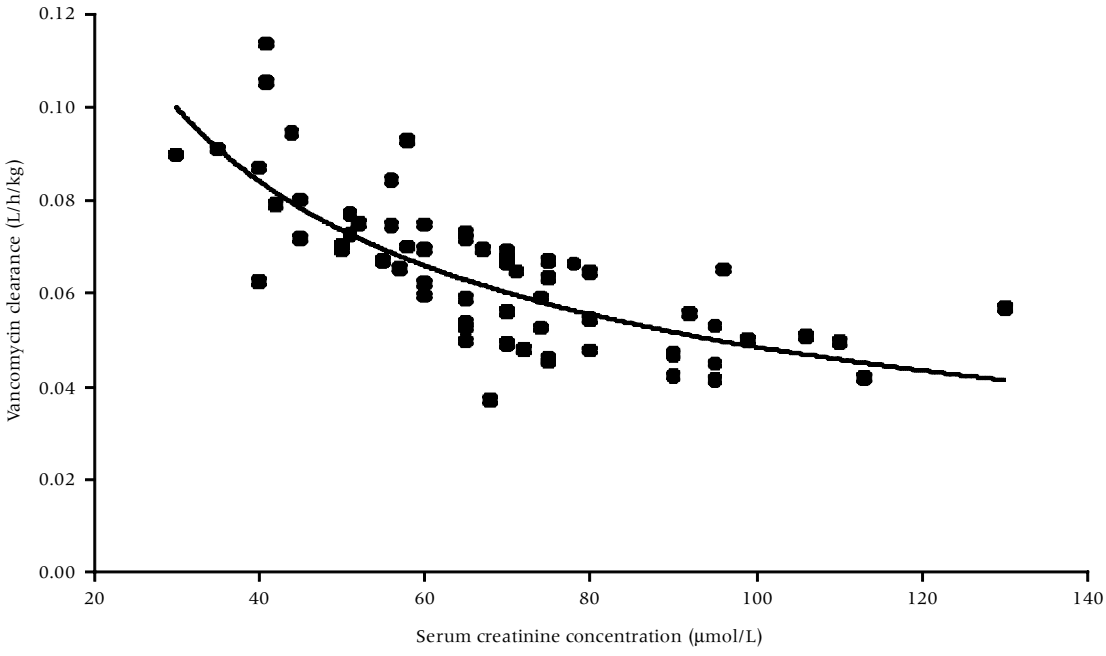

Figure 2. Mean clearance estimates for each individual plotted against creatinine concentration.

and higher variability in CL (31%) and V (25%) may have contributed to the better fit of troughs seen with the de Hoog[4] model (Figure 1) compared to the Grimsley[1] model where variability in CL was 22%, in V was 18% and the residual error was additive. Re-analysis with 50% variability on CL and V and a proportional error of 20% reduced the median prediction error to 1.8% (mean error 0.2 mg/L), produced similar CL estimates to the other models (median 0.075 L/h) but had no effect on V (median 0.76 L). This suggests interpatient variability in pharmacokinetics is higher than estimated and that wider ranges may be appropriate if the population model is implemented in a Bayesian forecasting programme[8]. Alternatively, the results may simply reflect bias due to the relatively small numbers of patients used in the population analyses and the current audit.

Differences in target ranges, patient populations and modelling approaches contributed to the problems observed when published dosage guidelines were implemented in a different clinical setting. The guidelines reported by Grimsley *et al.*[1] aimed to avoid high troughs and, due to the local microbiology policy, to maintain high peaks. However, the present study confirmed anecdotal observations that these guidelines produced too many low troughs. In contrast, the 8 hourly dose of 10 mg/kg suggested by de Hoog *et al.*[4] put some neonates with poor renal function at risk of excessive accumulation. Although the modified guidelines performed best in the present population, a prospective study is required to confirm dose requirements, especially in neonates with low creatinine concentrations. (In the present audit, no creatinine concentrations were below 30 μmol/L and only two courses were associated with measurements less than 40 μmol/L). If there is concern about low troughs in the first 24 hours of therapy for neonates who require 12 hourly dosing, one option is to "load" with three doses of 10 mg/kg 8 hourly then return to the guideline dose. This allows an additional day to assess renal function before the maintenance dose is determined. Finally, it is important to recognise that guidelines only offer advice on initial doses and that measured concentrations and changes in clinical condition (especially renal function) are more important indicators of vancomycin dosage requirements.

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