Vancomycin prescription in neonates and young infants: toward a simplified dosage

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ABSTRACT

Background There is no consensus on vancomycin dosing in newborns and young infants.

Objective The first objective was to assess the efficiency of a simplified dosing regimen with a cohort study. The secondary objective was to examine pharmacokinetic data to determine how this simplified dosing could be improved.

Methods All neonates admitted to our intensive care unit and treated with vancomycin were included in the pharmacokinetic study (PK group, 83 treatments, 156 measurements). The vancomycin dosing regimen consisted of a loading dose of 7 mg/kg, followed by a constant continuous dose of 30 mg/kg/day. The target serum vancomycin concentration ranged from 10 mg/l to 30 mg/l. Data from patients whose medications followed the scheduled dosing without modifications or prescription errors (actual dosing group: 62 treatments, 108 measurements) were analysed separately. A population pharmacokinetic analysis was performed (PK group) to simulate several vancomycin dosings.

Results Prescription errors were found in 10 of 83 treatments (12%). In the actual dosing group, 89.2% of vancomycin measurements were within the target range. Serum creatinine remained stable throughout treatment. Vancomycin concentrations varied widely. The modified regimen for a target vancomycin concentration of 25 mg/l consisted of a bolus of 20 mg/kg followed by continuous infusion of 30 mg/kg.

Conclusion Our pharmacokinetic data and bedside results suggest that a simplified schedule of vancomycin can achieve the targeted drug concentrations in most patients while avoiding secondary renal toxicity. The proposed new dosing scheme should be validated in a drug survey, but due to pharmacokinetic variability, still requires therapeutic drug monitoring.

What is already known on this topic

- There is considerable inter-individual variation in the pharmacokinetics of vancomycin in neonates and infants.
- Current therapeutic protocols for vancomycin in newborns and young infants are complex.
- Vancomycin prescription errors are frequent in neonates.

What this study adds

- Despite simplified dosing, the rate of prescription errors was high.
- A loading dose (7 mg/kg) followed by constant infusion of 30 mg/kg/day resulted in therapeutic serum vancomycin concentrations in most patients.
- Pharmacokinetic simulations indicated that a loading dose of 20 mg/kg will result in more rapid achievement of therapeutic levels.

INTRODUCTION

When clinicians initiate empiric vancomycin treatment in critically ill newborns and young infants, their aim is to achieve serum drug levels in the target range within a short time, and then to maintain levels within the target range throughout treatment so that the concentration of vancomycin is sufficient but not potentially toxic.

The optimal dosing regimen required to reach these goals has not been completely established. Most pharmacokinetic studies[1–9] have used intermittent vancomycin dosing, whereas the current regimen of neonatal dosing consists of a loading dose followed by continuous infusion. Moreover, factors influencing the pharmacokinetics of vancomycin (eg, weight, gestational age, age, small-for-gestational-age status, postmenstrual age (PMA), mechanical ventilation, creatinine concentration, non-steroidal anti-inflammatory drugs, vasoactive drugs) and hence the serum concentration of the drug, vary from study to study. Such differences are not surprising, as some of these factors (eg, gestational age and PMA) are interdependent. Moreover, all of these properties, with the exception of gestational age, vary significantly from day to day (particularly creatinine concentration, which is highly variable in patients with sepsis).

There is no consensus in the literature regarding vancomycin dosing in newborns and young infants. Following the study of Pawlotsky *et al*,[10] a loading dose followed by continuous administration is increasingly used in newborns. Consistent with previous reports,[11] our experience has been that these complicated dosing recommendations (involving 11 different dosing regimens, depending on gestational age and creatinine concentration) often result in insufficient vancomycin serum concentrations and prescription errors. Therefore, we decided on a simplified dosing schedule derived from that proposed by Pawlotsky *et al*[10] (same loading dose, but daily dose irrespective of gestational and postnatal factors), wherein repeated serum vancomycin measurements were used to conduct a population pharmacokinetic analysis without requiring supplementary blood puncture. This joint endeavour by clinicians and pharmacologists attempts to address the pitfalls of vancomycin administration in neonates.

The first objective was to assess with a cohort study the efficiency of a simplified vancomycin dosing regimen in neonates (ie, as determined by prescription accuracy, observed vancomycin measurements and renal tolerance). The secondary objective was to use the pharmacokinetic data generated by our population to determine how best to improve this simplified dosage regimen.

PATIENTS AND METHODS

Dosing schedule

The vancomycin dosing schedule for all non-anuric patients with creatinine levels less than or equal to 120 µmol/l consisted of a loading dose of 7 mg/kg administered over 2 h, followed by a constant continuous dose of 30 mg/kg/day, irrespective of age, gestational age or creatinine level. In the absence of bacteriological documentation, the targeted serum vancomycin concentration ranged from 10 mg/l to 30 mg/l.

Inclusion criteria

We screened all neonates who were admitted in our intensive care unit (ICU) and treated with vancomycin between 2006 and 2008. Patients with no vancomycin measurement, and patients for whom vancomycin treatment was initiated elsewhere, were not included in the cohort. A prospective database was built from medical charts and therapeutic drug monitoring results and designed to allow pharmacokinetic analysis.

All the patients in the cohort were included in the pharmacokinetic study (PK group). Our dosing schedule was analysed using only data from patients who received the accurately prescribed dosing regimen with neither modification nor prescription errors (ie, the actual dosing group). In accordance with French law (as confirmed by the local ethics committee), parents were informed that laboratory and medical chart data can be used for research work.

Vancomycin therapeutic monitoring and tolerance

Treatment was monitored by measuring vancomycin concentration once 24–48 h after initiating treatment, and at least once again after 48 h. The decision to measure serum creatinine and vancomycin concentrations was made by the attending clinician. Dosage was adjusted when serum concentrations were outside the target range, or if the attending physician judged that an adjustment was needed because of the minimal inhibitory concentration (MIC) of the isolated bacteria.

Renal tolerance of the simplified dosing regimen was determined according to variations in creatinine concentration (measured by an enzymatic method) during treatment (ie, creatinine concentration at the end compared with the beginning of treatment).

Plasma concentrations of vancomycin were determined using a Dimension RxL autoanalyser (Dade Behring, Liederbach, Germany) within 12 h of sample collection. The lower limit of detection was 1 mg/l. Calibration curves were linear between 1 mg/l and 100 mg/l. The intra-day and inter-day coefficients of variation ranged from 2.5% to 14% and from 2.8% to 13%, respectively.

Population pharmacokinetic analysis

Population pharmacokinetic analysis was performed using a non-linear mixed-effects model, with NONMEM v VI 2 software.[12] Data were analysed using a first-order conditional estimation method. Population predictions from the NONMEM analysis subroutines ADVAN1 and ADVAN3 were employed for the one- and two-compartment models. An exponential error model was used to assess inter-subject variability for each pharmacokinetic parameter. Several error models (ie, additive, exponential or both), using both statistical and graphical methods,[13 14] were assessed for their abilities to describe residual variability. The minimal value of the objective function, as calculated by NONMEM, was also used to assess the goodness-of-fit. An increase in goodness-of-fit was accompanied by a decrease in objective function, and this decrease was asymptotically distributed as a χ^2 distribution. Standard errors were calculated. The following graphs were compared for the purposes of graphic model diagnostics: observed concentrations versus predictions (PRED), weighted residuals (WRES) versus time, weighted residuals versus PRED, individual predictions (IPRED) versus observed concentrations, normalised prediction distribution errors (npde) versus time, and npde versus PRED.[15]

An initial analysis was performed to identify the base model that best described the data. The influences of each covariate on the pharmacokinetic parameters were then tested. These covariates were chronological age in days, PMA in weeks, serum creatinine (µmol/l), vasoactive drugs and positive pressure ventilation. The parameters were standardised for a body weight of 70 kg using an allometric model, using powers of 0.75 and 1 for clearance and volume of distribution, respectively.[16] The diagnostic plots described above, the change in objective function, and the change in parameter variability were noted to select factors that improved the model's prediction. A decrease of at least 6.61 in the objective function value (ie, χ^2 distribution with one degree of freedom for $p<0.01$) relative to the base pharmacokinetic model was required for the addition of a single parameter to the model.

Bootstrap procedures were performed using Wings for NONMEM (www.wfn.sourceforge.net) to non-parametrically evaluate the 95% CI. One thousand bootstrapped data sets were generated by re-sampling subjects from the original data set with replacements. These data sets were analysed using the final model described previously. Finally, the 2.5th and 97.5th percentiles of the parameter estimates were obtained to construct the confidence intervals.

A visual predictive check was performed by asking the final model and the corresponding parameter values to simulate 1000 replicates.

Simulation using the Monte-Carlo method was also performed using different dosing (ie, dose per administration and time of administration) to determine the most appropriate scheme to satisfy the therapeutic criteria. For this purpose, the vancomycin concentration target was set at 25 mg/l, and 1000 replicates were simulated.

RESULTS

The PK group consisted of 68 preterm or full-term neonates (table 1) who were included in the study over a 20-month

Table 1 Epidemiological data

	Mean (SD)	Min–Max	25-50-75 Percentile
Gestational age (weeks)	29.5 (27)	23–41	26–27–30
Chronological age at inclusion (days)	21.6 (23.0)	4–169	10–14–27
Post-menstrual age (weeks)	32.7 (5.3)	27–47	29–31–35
Weight (kg)	1.50 (0.97)	0.58–4.60	0.90–1.10–1.62

period (ie, 83 treatments and 151 vancomycin measurements). A total of 47 patients (ie, 62 treatments and 108 vancomycin measurements) were eligible for inclusion in the actual dosing group.

Accuracy of medical prescriptions

Thirteen prescription errors were found, with three patients experienced two prescription errors, giving a rate of at least one prescription error in 10 of 83 treatments (12%). There were seven errors in the loading dose, including five instances where the loading dose was not prescribed, one instance of a prescription delay, and one instance of higher than intended dosing. Errors in continuous infusion prescriptions included five instances of inadequate dosing regimens and one instance of a higher than intended dose. In three cases (33% of the treatments with at least one error), errors corresponded to a significant underdosing, with serum vancomycin concentrations below the lower limit of the target (10 mg/l).

Simplified dosing regimen

In the actual dosing group (62 treatments, 108 measurements) (figure 1), seven measurements (5.8%) were less than 10 mg/l and six (5.0%) were more than 30 mg/l, with the remaining 89.2% of the vancomycin concentrations within the target range.

Serum creatinine remained stable throughout treatment, with variations of –7±20 µmol/l and –10±12 µmol/l from the beginning to the end of treatment among patients with 7 or more days of treatment. Only two patients experienced an increase in creatinine concentration at the end of the treatment; however, these patients had developed septic shock during their first days of treatment. Creatinine concentration rose from 80 µmol/l to 124 µmol/l in one patient, while the vancomycin serum concentration was 38 mg/l. Despite sustained diuresis, the second patient experienced creatinine concentration of 238 µmol/l and a concomitant vancomycin measurement of 46.3 mg/l, followed by rapid improvement in haemodynamic status. For these two patients, creatinine concentration 3 weeks after treatment was normal (<50 µmol/l).

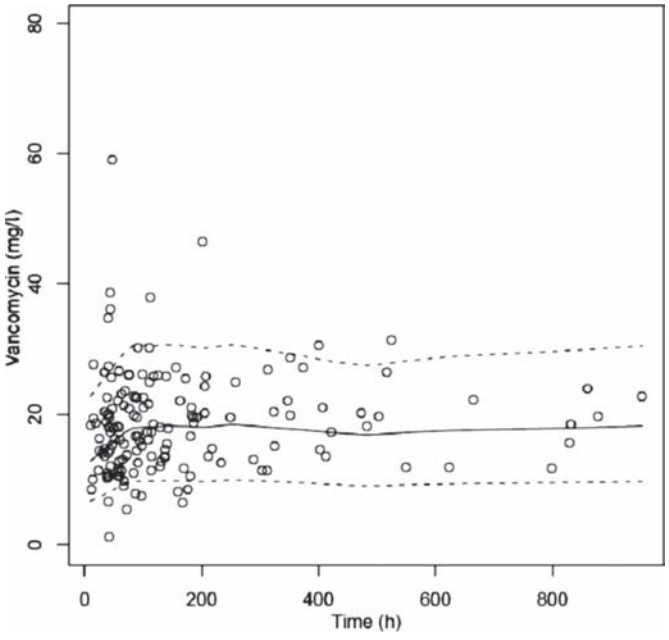

Figure 1 Observed (open circle) and simulated (solid line) vancomycin concentrations over time. Median and dotted lines indicate the 90% population-predicted interval.

Population pharmacokinetic analysis

Data were collected from 151 samples obtained from 83 treatments. Plasma concentrations of vancomycin ranged from 5.3 mg/l to 58.9 mg/l. The one-compartment model provided a better description of data than the two-compartment model and thus was used as the base model. Inter-subject variability on central clearance (CL) and volume of distribution (V) and the residual variability were exponentially modelled. None of the following covariates tested (ie, chronological age in days, PMA, dopamine combination and positive pressure ventilation) showed a decrease in objective function; therefore, none was retained in the final model. Body weight and serum creatinine significantly improved the fit when incorporated in the clearance estimation. Body weight also decreased the inter-subject variability of the volume of distribution. The final equations describe the clearance and the volume of distribution, as follows:

$$CL = \Theta 1 \times (WT/70)^{0.75} / \text{serum creatinine} \quad (1)$$

$$V = \Theta 2 \times (WT/70). \quad (2)$$

In the above equations, CL refers to clearance (l/h), V refers to the volume of distribution (l), Θ1 and Θ2 are two constants, WT refers to body weight (kg) and the serum creatinine is presented in µmol/l.

The final pharmacokinetic estimate parameters and 95% CIs obtained from the bootstrap procedures are summarised in table 2. Determination of the pharmacokinetic model and estimation of the parameters permitted the relationship between the creatinine concentration and the dose to be described (figure 2).

Simulations of vancomycin concentrations versus time with two dosing regimens are displayed in figure 3.

Figure 1 describes the observed vancomycin concentrations versus time, with the median prediction and the 95% CI prediction obtained from the simulation. No formal bias was observed in the goodness-of-fit plots.

DISCUSSION

This clinician- and pharmacologist-led study addresses the various pitfalls of vancomycin administration in neonates. The patient population was relatively large and included newborns and young infants. The studied population may be representative of actual practice in the neonatal ICU.

Table 2 Population pharmacokinetic parameters of vancomycin

	Estimation			
Parameters	**Finalestimate**	**SE (%)**	**Bootstrap 95% CI**	
Pharmacokinetic				
Θ (1) (l/h/70 kg/µmol/l)	82.1	3.06	71.1	85.4
Θ (2) (l/70 kg)	60.5	26.3	28.1	99.5
Inter-subject variability				
η_{CL}	0.23	33.4	0.18	0.32
η_{V}	0.47	33.3	0.38	0.90
Residual variability				
σ Exponential	0.24	18.1	0.17	0.30

CL = Θ1× (WT/70)0.75 / creatinine concentration.
V=Θ2×(WT/70).
CL, clearance; V, volume of distribution.

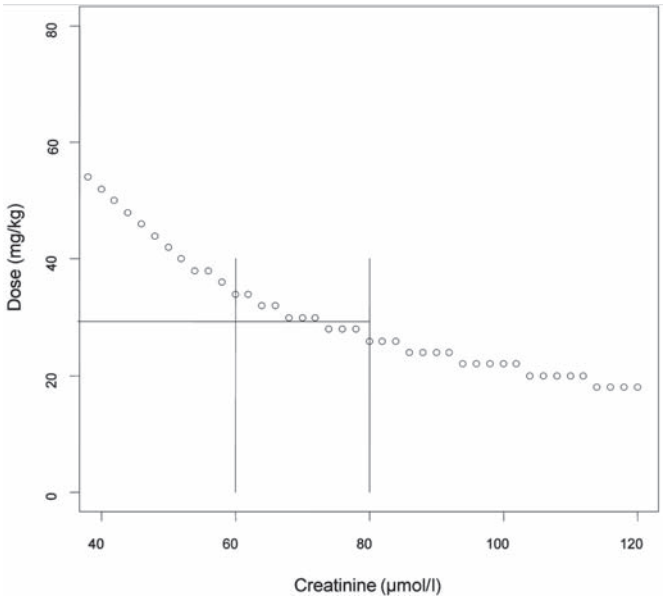

Figure 2 For patients with normal creatinine concentration (ie, 60–80 µmol/l), the model calculates that a daily dose of 30 mg/kg/day is needed to obtain a serum concentration of 25 mg/l vancomycin. Creatinine concentration at the onset of sepsis and before any treatment may not reflect actual glomerular filtration during the following hours.

To accurately describe the results of the simplified dosing (actual dosing group), we excluded treatments with prescription errors. Vancomycin measurements after any dosing modification were also excluded, but data before the modification were used in the analysis (ie, none of the vancomycin measurements outside the target range due to the simplified dosing were excluded). In this group, we observed agreement between the expected and observed values of vancomycin measurement. Among patients who received scheduled doses without any modifications, nearly 90% of measurements were within the target range and no renal secondary effects were observed. This very simplified dosing regimen achieved the desired vancomycin serum concentrations throughout the entire course of treatment, even for non-anuric patients with an initial creatinine concentration as high as 120 µmol/l.

The review of our medical prescriptions revealed that despite simplified dosing regimens, the prescription error rate remained high. The rate of prescription errors observed in this study was twofold higher than that reported by Kaushal *et al*[17] and Ghaleb *et al*,[18] but smaller than a report of acyclovir prescription in children (40%).[19] Our findings are consistent with a study of vancomycin prescriptions in 145 newborns, where a relatively complex dosing scheme was followed for only 46% of prescriptions.[20] These errors have important consequences. Nearly one case out of three resulted in insufficient levels of vancomycin, which limits the antibacterial activity of this drug. One case experienced an excessive loading dose that may have exceeded the target range; however, this remains speculation as vancomycin concentrations were measured 2 days later. Prescription mistakes are a well-known class of medication errors in children, and a complex dosing scheme is at greater risk of error.[20 21] Therefore, simplified dosing is very much needed.

Blood punctures (ie, for vancomycin therapeutic monitoring) were scheduled in accordance with clinical rather than pharmacological needs; therefore, few measurements were taken just after the loading dose. Even including patients with

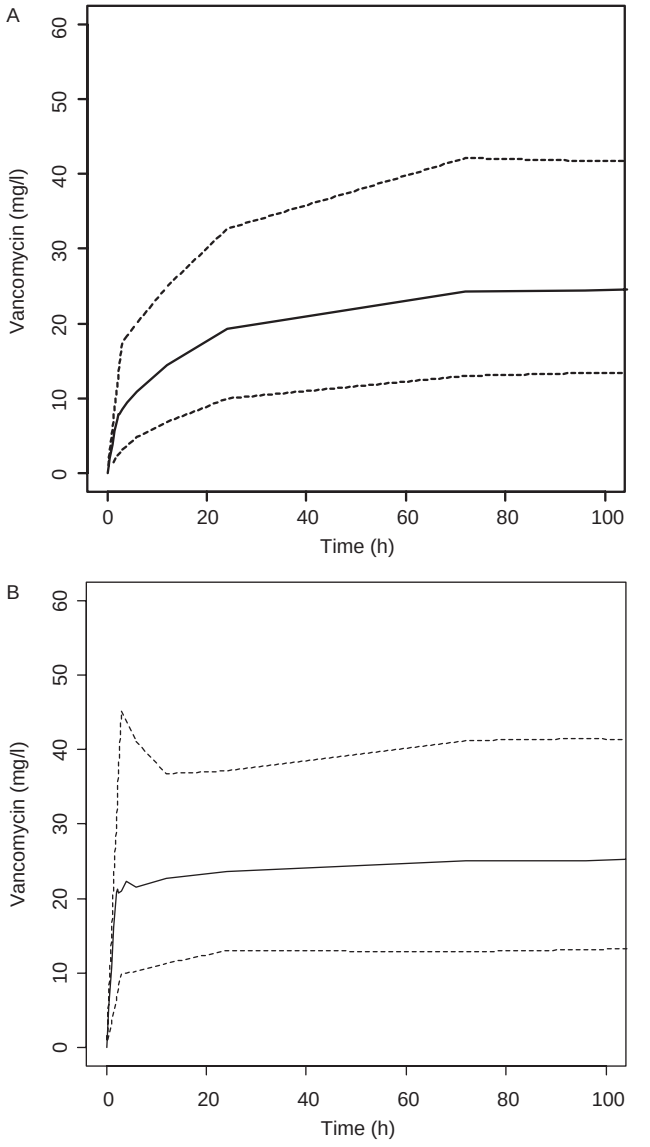

Figure 3 Vancomycin concentrations simulated over time for two regimens: (A) bolus of 7 mg/kg, daily dose 30 mg/kg/day and (B) bolus of 20 mg/kg, daily dose 30 mg/kg/day. Continuous line: median; dotted lines: 95% CI.

creatinine concentration up to 110 µmol/L, vancomycin measurements were comparable with those reported by Pawlotsky *et al*[10] and Plan *et al*.[11] While these two studies focused on the first days of treatment, our results suggest that a daily dose of 30 mg/kg yields satisfactory vancomycin concentrations throughout a 10–15-day treatment period.

The renal tolerance of our dosing regimen appeared satisfactory, as creatinine concentration remained constant throughout treatment. Two patients with increased creatinine concentration developed septic shock after the initiation of vancomycin treatment, which probably reduced glomerular filtration. We chose to use a higher maximum creatinine concentration level than that used by Plan *et al*[11] (ie, 120 µmol/l vs 90 µmol/l). The glomerular filtration rate is difficult to estimate accurately in newborns. Despite a rapid decrease after birth in normal newborns, serum creatinine is frequently higher than 90 µmol/l during the first days of life.[22 23] Moreover, an initial worsening of glomerular filtration at the onset of sepsis will frequently resolve after antibiotic therapy and haemodynamic support.

For these reasons, and based on our current results, systematic modification of the dosing regimen for non-oliguric patients with serum creatinine below 120 µmol/l is unnecessary; however, close monitoring of vancomycin measurements remains prudent because glomerular filtration may be diminished.

Our study used a population approach, using as few as one observation per patient. This allows description of the concentration versus time profile in real conditions and investigation of the most accurate dosing regimen.

Of particular note was the high inter-individual variability, estimated as 23% and 47% for clearance and volume of distribution, respectively (table 2). It should be noted that these values were obtained after considering body weight and creatinine concentration, which significantly decreased the variability. Other sources of variability remain unknown. However, as observed (figure 1 and table 2), the model obtained is sufficiently robust to allow for the simulation of different doses.

From a clinical perspective, the two goals are to reach a steady state concentration within the therapeutic target and to obtain this value as soon as possible. The target concentration was arbitrary and was chosen as follows. In our unit, as commonly reported elsewhere,[24] the most frequently isolated bacteria is coagulase-negative *Staphylococcus*, with most bacteria having an MIC of between 2 mg/l and 4 mg/l (table 3). Depending on the site of infection, vancomycin levels ranged from fourfold to 10-fold greater than required according to the MIC.[20 25] Recent guidelines for vancomycin concentration recommend trough serum vancomycin concentrations of 15–20 mg/l if the MIC is <1 mg/l.[26] For continuous administration, the target for the steady state concentration should then be higher. There is no recommendation for target value for continuous administration. A target of 25 mg/l for the model seems to strike the best balance between the risks of under- and over-dosing, considering the high prevalence of *Staphylococcus* with an MIC >1 mg/l in our population.

Our simulations reveal that the most accurate dosing regimen consisted of a 2 h infusion of 20 mg/kg, followed by continuous infusion of 30 mg/kg per day (figure 2). The concentration versus time profile that corresponds to this dosing regimen is depicted in figure 3. The increase in the loading dose suggested by the simulation needs further validation by early measurements after the start of administration. The main benefit of the proposed regimen is to dramatically simplify daily dosing. This regimen, suggested by the simulation, is supported by our therapeutic monitoring data. Due to the variability in serum drug levels, this regimen should be combined with therapeutic drug monitoring.

Table 3 Bacteriological data

Site of infection	
No bacteriological data	14
Infection not confirmed within 72 h of treatment	11
Catheter related infection suspected or confirmed	33
Pulmonary infection suspected or confirmed	13
Others	12
Isolated bacteria	
Staphylococcus aureus oxacillin resistant	3
Oxacillin-resistant coagulase-negativ *Staphylococcus*	39
MIC (*Staphylococcus*)	
<1 mg/l	8 (19%)
2 mg/l	23 (55%)
4 mg/l	11 (26%)

MIC, minimal inhibitory concentration.

CONCLUSION

Here, we describe a simplified dosage schedule for the administration of vancomycin to newborns and young infants. Using this method, the desired serum vancomycin concentration was achieved in most patients, regardless of gestational age, PMA and weight, and no renal secondary effects were observed.

Despite the simplicity of the proposed dosing scheme, we observed some minor and major dosage deviations due to prescription errors. However, it is likely that such deviations would occur more often with more complicated dosage schemes.

Our pharmacokinetic data and clinical observations suggest that a safe and efficient dosage schedule for newborns and young infants consists of a loading dose of 20 mg/kg, followed by the continuous administration of 30 mg/kg/day for the first day of vancomycin treatment. This new dosing scheme should be validated in a prospective study. Due to the variability in serum drug levels, this regimen should be combined with therapeutic drug monitoring.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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