Population Pharmacokinetics and Dosing Optimization of Vancomycin in Children with Malignant Hematological Disease

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An increase in vancomycin dose has been proposed in adults with malignant hematological disease. As pediatric data are limited, our aim was to evaluate the population pharmacokinetics of vancomycin in order to define the appropriate dosing regimen in children with malignant hematological disease. Vancomycin concentrations were collected prospectively during therapeutic monitoring. Population pharmacokinetic analysis was performed using NONMEM software. Seventy children (age range, 0.3 to 17.7 years) were included. With the current recommended dosing regimen of 40 to 60 mg/kg/day, 53 children (76%) had subtherapeutic steady-state trough concentrations ($C_{\text{SS/min}}$ of <10 mg/liter). A one-compartment model with first-order elimination was developed. Systematic covariate analysis identified that weight significantly influenced clearance (CL) and volume of distribution (V) with power functions of 0.677 for CL and 0.838 for V. Vancomycin CL also significantly increased with increases in creatinine clearance and seemed to be higher in children with malignant hematological disease than in the general pediatric population. The model was validated internally. Its predictive performance was further confirmed in an external validation by Bayesian estimation. A patient-tailored dosing regimen was developed based on the final pharmacokinetic model and showed that a higher proportion of patients reached the target $C_{\text{SS/min}}$ than with the traditional mg/kg-basis dose (60% versus 49%) and that the risks associated with underdosing or overdosing were reduced. This is the first population pharmacokinetic study of vancomycin in children with malignant hematological disease. An optimized dosing regimen, taking into account patient weight, creatinine clearance, and susceptibility of the pathogens involved, could routinely be used to individualize vancomycin therapy in this vulnerable population.

Vancomycin is primarily effective against Gram-positive cocci. *Staphylococcus aureus* and *Staphylococcus epidermidis*, including both methicillin-susceptible (MSSA and MSSE, respectively, for *S. aureus* and *S. epidermidis*) or methicillin-resistant (MRSA and MRSE, respectively, *S. aureus* and *S. epidermidis*) species, are usually sensitive to vancomycin. It is often included in the initial empirical antibiotic therapy in patients with malignant hematological disease (1).

Vancomycin is administered intravenously. It is 25 to 50% protein bound, mainly to albumin and IgA, and is almost exclusively eliminated by the renal route. The pharmacokinetic-pharmacodynamic breakpoint of vancomycin was defined as the ratio of the area under the concentration-time curve from 0 to 24 h ($AUC_{0-24}$) to the MIC and is at least 400 h in adults with *Staphylococcus aureus* pneumonia (2).

The pharmacokinetics of vancomycin has shown large interindividuality variability, primarily linked to a patient’s age, clinical condition, and disease (3, 4). Patients in oncology represent a critical population in whom inadequate empirical antibacterial therapy may result in infection-related morbidity and increased mortality. In addition, the pharmacokinetic parameters often present different characteristics than in nononcology patients (5–7), making optimization of the dosing regimen essential. Vancomycin was reported to have an increased clearance in adults with malignant hematological disease compared with adults without cancer (8, 9). In children with cancer, pharmacokinetic data are limited (10, 11), and the optimal dosing regimen remains undefined. Innovative strategies, such as modeling and simulation approaches, were initiated to individualize dosing of vancomycin in neonates and adults based on identified covariates (12). Thus, the objectives of the present work were to evaluate the population pharmacokinetics of vancomycin in children with malignant hematological disease and to optimize vancomycin therapy based on a defined pharmacokinetic-pharmacodynamic breakpoint.

**MATERIALS AND METHODS**

**Study population.** Children with malignant hematological disease receiving vancomycin as an intravenous infusion were included in the Department of Pediatric Hematolo-Oncology at Robert Debré Hospital between 2010 and 2011 if at least one vancomycin serum concentration was assayed for therapeutic drug monitoring (TDM). The following data were collected prospectively by a trained research assistant: age, weight, serum creatinine concentration, and details of vancomycin administration (dose and infusion start and stop times), type of hematological disease, and bone marrow transplantation. Patients with incomplete dosing information were excluded. This study was designed in accordance with legal requirements and the Declaration of Helsinki, registered at the Commission Nationale Informatique et Liberté (CNIL), and approved by the local...
Dosing regimen and sampling. Vancomycin (Sandoz, Levallois-Perret, France) was administered as an intravenous infusion over 60 min. The empirically initial dosing regimen is 40 to 60 mg/kg/day in four divided doses. Monitoring of vancomycin concentrations was performed in order to maintain a steady-state trough concentration per minute (C_{ss/min}) of between 10 and 20 mg/liter.

Assay of serum vancomycin and creatinine. The serum vancomycin concentrations were determined by a fluorescence polarization immunoassay method (FPIA) using the Cobas Integra 400 plus system (Roche Diagnostics, Meylan, France). The calibration curve ranged from 0.74 to 21.4 mg/liter (CV of 3.9%, respectively. The lower limit of quantification (associated CV) of 0.74 mg/liter (CV of 3.9%). Laboratory controls (7.2, 21.4, and 35.6 mg/liter) were 90% to 110% and 99% (CV of 12%), respectively. The serum creatinine was measured by an enzymatic method using an Advia 1800 chemistry system (Siemens Medical Solutions Diagnostics, Puteaux, France).

Pharmacokinetic modeling. Pharmacokinetic analysis was carried out using the nonlinear mixed-effects modeling program NONMEM, version 7.2.0 (Icon Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation (FOCE) method with the interaction model (effect model), which is the interaction model in the population pharmacokinetic parameters and their variability.

Structure model. One- or two-compartment open models with first-order elimination were compared. The basic model was evaluated through visual inspection of routine diagnostic plots. Interindividual variability of the pharmacokinetic parameters was estimated using an exponential model and was expressed as follows:

$$\theta_i = \theta_{\text{TV}} \times e^{\eta_i}$$  \hspace{1cm} (1)

where \( \theta_i \) represents the parameter value of the \( i \)th subject, \( \theta_{\text{TV}} \) is the typical value of the parameter in the population, and \( \eta_i \) is the variability between subjects, which is assumed to follow a normal distribution with a mean of zero and variance of one.

A residual-variability (additive, proportional, exponential, or mixed) model was selected according to improvement of the objective function value (OFV) and visual inspection of routine diagnostic plots.

Covariate analysis. The effects of age, weight, serum creatinine concentration, creatinine clearance, and type of hematological disease (leukemia or lymphoma) were investigated as potential variables on pharmacokinetic parameters. The stepwise covariate modeling and likelihood ratio test were used to test the effect of each variable.

The selection of covariates was based on a forward-backward process and biological plausibility. During forward selection, a covariate was selected if a significant (P < 0.05, \( \chi^2 \) distribution with 1 degree of freedom) decrease (reduction of > 3.84) in the OFV from the basic model was obtained. At the end, all the significant covariates were added simultaneously into a “full” model. The importance of each covariate was reassessed by backward selection, and a covariate was independently removed from the full model if the increase in the OFV was less than 7.88 (P < 0.005, \( \chi^2 \) distribution). The resulting model was considered the “final” population pharmacokinetic model.

Model validation. Model validation was based on graphical and statistical criteria. Goodness-of-fit plots, including observed (DV) versus predicted (PRED) and individual prediction (IPRED), DV versus population prediction (PRED), and conditional weighted residuals (CWRES versus time), were used initially for diagnostic purposes (13). The stability and performance of the final model were also assessed by means of a nonparametric bootstrap with resampling and replacement. Resampling was repeated 500 times, and the values of estimated parameters from the bootstrap procedure were compared with those estimated from the original data set. The entire procedure was performed in an automated fashion, using the PsN module (14). The final model was also evaluated graphically and statistically by visual predictive checks (VPCs) and normalized prediction distribution errors (NPDE) (15). One thousand data sets were simulated using the final population model parameters. For the VPCs, the 5th, 50th, and 95th percentiles of the simulated concentrations were processed using the R platform, plotted against elapsed time, and compared to observed concentrations. For a model in which random effects are well estimated, approximately 90% of the observed data are expected to be within the 5th to 95th prediction interval. NPDE results were summarized graphically by default as provided by the research ethics committee (Comité de l’Evaluation de l’Ethique des Projets de Recherche Biomédicale [CEERB], Robert Debré Hospital, Paris, France).
NPDE R package (version 1.2) (16) using (i) a Q-Q plot (where Q is quantile) of the NPDE and (ii) a histogram of the NPDE.

Given that the objective of the analysis was to use the final model for prediction purposes, the predictive performance of the developed model was further evaluated in an independent group of children with malignant hematological disease. The individual concentrations were predicted by Bayesian estimation (MAXEVAL = 0 in the estimation step, where MAXEVAL is the maximum number of model evaluations that can be used) with NONMEM using the population pharmacokinetic parameters. The predictive performance was evaluated by calculating the prediction error (PE) and absolute prediction error (APE) using the following equations (ABS is the absolute function):

\[
\text{PE} \% = \left( \frac{\text{Bayesian estimated concentration} - \text{measured concentration}}{\text{measured concentration}} \right) \times 100
\]

\[
\text{APE} \% = \left( \frac{\text{ABS (Bayesian estimated concentration) - measured concentration}}{\text{measured concentration}} \right) \times 100
\]

Dosing optimization based on a pharmacokinetic model. Monte Carlo simulations were performed using the parameter estimates obtained from the final model in order to define the optimal dosing regimen able to attain the target AUC/MIC of 400 h in about 50% of patients, under the assumption of a comparable safety profile.

Traditional pediatric dose (mg/kg basis) simulation approach. In the traditional approach, the pediatric dose of vancomycin was simulated on a mg/kg basis according to different age groups. Thus, various mg/kg dosing regimens (40, 50, 60, 70, 80, 90, and 100 mg/kg) were simulated in each pediatric group: infants (28 days to 23 months), children (2 to 11 years), and adolescents (12 to 18 years). One thousand simulations were performed using the original data set, and AUC\(0-24\) and \(C_{\text{Cmin}}\) values were calculated for each patient simulation. The target attainment rate was then calculated for each dosing regimen to define the optimal dose regimen in each pediatric group.

Patient-tailored dose. A patient-tailored dose was assessed to evaluate the advantage of personalized therapy. In this simulation scenario, the individual dose was calculated based on population pharmacokinetic parameters and covariates in each patient as follows:

Optimized daily dosing \(i \) (mg/day) = target \(\text{AUC}_{0-24} \times \text{CL}_i \) (4)

where \(\text{CL}_i\) is calculated using the equation developed from the model, and \(i\) stands for individual. The target \(\text{AUC}_{0-24}\) was defined according to the pharmacokinetic-pharmacodynamic breakpoint of vancomycin: \(\text{AUC}_{0-24}/\text{MIC} \geq 400\) h. For example, if the MIC was 1 mg/liter, the target \(\text{AUC}_{0-24}\) should be at least 400 mg h/liter.

The simulation process was similar to that described above for dose simulation on a mg/kg basis. At the end, we compared the variability of \(\text{AUC}_{0-24}\) and \(C_{\text{Cmin}}\) values between the mg/kg basis and patient-tailored dose.

RESULTS

Serum concentrations of intravenous vancomycin infusion over 60 min were monitored in 70 children (41 boys) with a mean age of 6.8 years (standard deviation [SD], 4.8 years; range, 0.3 to 17.7 years) and a mean weight of 25.7 kg (SD, 15.5 kg; range, 3.6 to 71.0 kg). A total of 98 vancomycin concentrations were analyzed. A summary of patient demographic and clinical characteristics is presented in Table 1.

Blood samples were drawn at the median of 54 h after initiation of treatment. The concentrations ranged from 1.8 to 27.3 mg/liter. The number of patients in the concentration ranges (<5, 5 to 10, 10 to 15, and >15 mg/liter) were 12 (17%), 41 (59%), 11 (16%), and 6 (9%), respectively.

Population pharmacokinetic modeling. A total of 98 vancomycin concentrations were available for population modeling. Data fitted a one-compartment model with first-order elimination. Interindividual variability was best described by an exponential model and was then estimated for \(V\) and \(\text{CL}\). Residual variability was best described by a combined proportional and additive model.

The systematic covariate analysis identified body weight as the most important covariate implemented on \(V\), which caused a significant drop in the OFV of 35.5 points. For clearance, body...
weight was also identified as a significant covariate, causing a significant drop in the OFV of 46.3 points. The model was further significantly improved by introducing creatinine clearance (ΔOFV of 26.3 points) on CL (Table 2). Therefore, the influence of covariates on CL and V was retained in the model as follows:

\[
CL_i = CL_{ref} \times \left( \frac{WT_i}{WT_{ref}} \right)^{0.61} \times \left( \frac{CLCR_i}{CLCR_{ref}} \right)^{0.2}
\]

\[
V_i = V_{ref} \times \left( \frac{WT_i}{WT_{ref}} \right)^{0.53}
\]

where \(CL_i\) and \(V_i\) are, respectively, the CL and V of the \(i\)th individual, \(WT_i\) and \(CLCR_i\) are the weight and creatinine clearance of the \(i\)th individual, and \(WT_{ref}\) and \(CLCR_{ref}\) are the reference weight and creatinine clearance values, respectively. In our study, the reference weight and creatinine clearance were the median values of our population, 20.2 kg and 191 ml/min. The exponents were estimated by the model.

After incorporation of all significant covariates, interindividual variability decreased from 61.6 to 34.8% for CL and from 117.9 to 77.0% for \(V\). The shrinkage was 21% for CL and 23% for \(V\). The final population pharmacokinetic parameters are given in Table 3.

Model diagnostics showed acceptable goodness-of-fit criteria for the final model. As shown in Fig. 1A to D, population and individual predictions are acceptable. In addition, the mean parameter estimates resulting from the bootstrap procedure very closely agreed with the respective values from the final population model, indicating that the final model is stable and can redetermine the estimates of population pharmacokinetic parameters. The results of 500 bootstrap replicates are summarized in Table 3. The NPDE distribution and histogram indicate that the assumption of normal distribution of the differences between individual predictions and observed data is acceptable \((P = 0.45,\) Shapiro-Wilk test of normality) (Fig. 1E and F). No trends were observed on the diagnostic plots of NPDE versus time or predicted concentrations. The VPC (Fig. 1G) shows that observed concentrations were well predicted by the model (exact binomial test, 11.2% out of limits observed; 95% confidence interval, 5.7% to 19.2%). Box plots of the distributions of observed and predicted \(C_{ss/min}\) from 1,000 simulations derived from the final model are presented in Fig. 1H. The median values of \(C_{ss/min}\) from the observed data and the simulation as well as the interquartile range were similar, indicating acceptable predictive capability of the final model. Figure 2 shows the relationship between individual vancomycin clearance and covariates (body weight and creatinine clearance). The typical CLs of patients weighting 20, 40, and 60 kg were 4.3, 6.9, and 9.1 liters/h, respectively.

The performance of the developed model was further evaluated in an independent group of 20 children with malignant hematological disease with a mean age of 8.1 years (SD, 4.1 years; range, 2.4 to 17.2 years), a mean weight of 28.8 kg (SD, 11.6 kg; range, 13.9 to 62.0 kg), and a mean creatinine clearance of 191.3 ml/min (SD, 61.2 ml/min; range, 84.0 to 350.7 ml/min; Schwartz formula). Twenty-five concentrations consisting of peak, trough, and scavenged samples were available and ranged from 4.1 to 67.2 mg/liter. The Bayesian estimated concentrations were highly correlated with measured concentrations \((r^2 = 0.99)\). The mean PE and APE were 1.0% (5th to 95th percentile, −4.7% to 8.7%) and 4.7%, respectively, indicating a good predictive performance of the developed model on new patients. The estimates of population pharmacokinetic parameters did not change obviously after inclusion of the validation data set into the model.

**Dosing optimization based on pharmacokinetic model.** (i) **Traditional pediatric dose (mg/kg basis).** The target attainment rates as a function of dose and age groups for a standard MIC susceptibility breakpoint of 1 mg/liter are shown in Fig. 3. The current recommended dose of 60 mg/kg/day results in only 15% of infants and 24% of children and adolescents achieving the target.
get AUC/MIC. These simulated values were in agreement with the observed values in the present study. In fact, 76% of our patients had a risk of underdosing ($C_{\text{ss/min}}$ of <10 mg/liter). To reach the target AUC/MIC of 400 h in about 50% of patients, 90 mg/kg/day was required for infants, and 80 mg/kg/day was required for children and adolescents (Fig. 3). The proportion of patients with risks of overdosing ($C_{\text{ss/min}}$ of >20 mg/liter) was 26% for the new proposed dosing regimen (Fig. 3).

(ii) **Patient-tailored dose.** A patient-tailored dose was calculated for each patient based on equations 4 and 7:

$$\text{CL} = 4.37 \times \left(\frac{\text{body weight}}{20.2}\right)^{0.677} \times \left(\frac{\text{creatinine clearance}}{191}\right)^{1.03}$$

where body weight is in kg and creatinine clearance is in ml/min (Schwartz formula).

The expected $AUC_{0-24}$ and $C_{\text{ss/min}}$ values in simulated trials for infants receiving 90 mg/kg/day and in children and adolescents receiving 80 mg/kg/day in comparison to a patient-tailored dose are shown in Fig. 4. The proportion of patients achieving the target $C_{\text{ss/min}}$ (10 to 20 mg/liter) is 60% using the patient-tailored dose, which is higher than the percentage for the traditional mg/kg-basis dose (49%). The proportions of patients with risks of underdosing ($C_{\text{ss/min}}$ of <10 mg/liter) or overdosing ($C_{\text{ss/min}}$ of >20 mg/liter) are 20% and 20%, respectively, using the patient-tailored dose, which is lower than values for the traditional mg/kg-basis dose (24% for underdosing and 26% for overdosing).

**DISCUSSION**

In the present study, the population pharmacokinetics of vancomycin was evaluated for the first time in children with malignant hematological disease. The high variability of vancomycin concentrations emphasizes the need for dosing optimization and TDM-based dosage adaptation in this high-risk population.

The population pharmacokinetic model offered a practical tool to optimize vancomycin dosing in children with malignant hematological disease. The rational dosing of antimicrobials...
should take into account pharmacokinetics in the target population, the relationship between drug exposure and outcome, and the susceptibility of the pathogens involved. In children, the standard dose evaluation studies of antimicrobials are usually based on a “nonselected” pediatric population and do not take into account the potential impact of the disease and disease state, which are the main factors that ultimately influence drug exposure in the clinical setting (17). For the purposes of comparison, the demographics and pharmacokinetic parameters of vancomycin obtained from different pediatric studies (10, 18, 19) are summarized in Table 4. The magnitude of the differences provides strong argument for studying pharmacokinetics in selected subgroups of patients. Indeed, the estimated vancomycin CL in children with malignant hematological disease was higher than that reported in general nonselected pediatric populations. Such an impact of hematological malignancies was previously reported with vancomycin (8, 9) and additional antimicrobials in adult patients (5–7).

According to regulatory guidelines (20, 21), vancomycin is a good example of a drug for which the modeling and simulation approach can be used to establish optimal dosage recommendations in children. The pharmacokinetic-pharmacodynamic breakpoint of vancomycin was defined as an AUC₀–₂₄/MIC ratio of at least 400 h in adults with *Staphylococcus aureus* pneumonia (2), in which the MIC for of methicillin-resistant *Staphylococcus*

### Table 4: Pharmacokinetics of vancomycin in children

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for the group (reference or source)³⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pediatric patients with vancomycin TDM according to:</td>
</tr>
<tr>
<td></td>
<td>Reference 18</td>
</tr>
<tr>
<td>No. of patients</td>
<td>78</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7⁵</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>25⁶</td>
</tr>
<tr>
<td>CL (liters/h/kg)</td>
<td>0.103</td>
</tr>
</tbody>
</table>

³ Values are expressed as mean (range) except where indicated.

⁴ Median value.

![AUC and Cₓₘₙₐᵢₙ distribution. Simulated vancomycin AUC and Cₓₘₙₐᵢₙ distribution in infants and in children and adolescents receiving the mg/kg-basis dose and patient-tailored dose.](image-url)
Vancomycin was 0.5 mg/liter in 76% (n = 28) of infected patients and 1 mg/liter in 24% (n = 9). The pharmacokinetic-pharmacodynamic breakpoint is postulated to be similar in children and is therefore used for dosing optimization in children.

The current recommended pediatric dose of vancomycin is 40 to 60 mg/kg/day (i.e., on a classical mg/kg-basis dose) and resulted in a high risk of underdosing in our target population, as 76% patients had $C_{\text{area}}$ of <10 mg/liter. The dose simulation was in agreement with this observation and showed that the dose of 60 mg/kg/day resulted in 15% of infants and 24% of children and adolescents achieving the target AUC/MIC. Therefore, in order to increase the likelihood of treatment, the vancomycin dose needs to be increased in children with malignant hematological disease. In the present study, the simulation approach demonstrated that the doses of 90 mg/kg/day for infants and of 80 mg/kg for children and adolescents allow nearly 50% of patients to achieve the AUC/MIC target, with the standard MIC susceptibility breakpoint of 1 mg/liter which was clinically validated primarily in adult pneumonia studies in MRSA. However, according to recent data, there is a trend to a decrease in vancomycin efficacy, linked to the increase in the vancomycin MIC during MRSA infection (22, 23). Indeed, to obtain similar efficacy, treatment of MRSA with a higher MIC would require a higher AUC. An increase in vancomycin CL together with mic in MIC values will require an increase in the vancomycin daily dosage to overcome the risk of therapeutic failure. However, until now, the pharmacokinetic parameters and safety of increased vancomycin dosing have not been available. The dosing simulation was based on the assumption of linear pharmacokinetics. Extrapolation of the dosing regimen outside the observed range cannot preclude the possibility of nonlinear pharmacokinetics and should be evaluated in further study. In addition, when increased vancomycin doses are administered, the infusion-related adverse events (i.e., “red man syndrome”) need to be evaluated, and slowing the rate of infusion so that it exceeds 2 h should be recommended.

One of the main advantages of modeling and simulation approaches is to optimize personalized therapy. Therefore, in the second simulation scenario, we evaluated the patient-tailored dose. Traditionally, the pediatric dose is defined on a mg/kg basis according to the different age groups, as we did in the first simulation scenario. This approach assumes an “average child” with an “average weight” in each age group (neonates, infants, children, and adolescents) and a standard mg/kg dose is calculated accordingly. However, both developmental factors and clinical conditions have a profound impact on pharmacokinetics. Many demographic, biological, and clinical covariates are known to influence vancomycin pharmacokinetics. In our data, vancomycin clearance increased with body weight and creatinine clearance, showing that in children the standard weight-based dosing (mg/kg) is not adapted to the whole range of pediatric ages. This could be explained by the nonlinear correlation between body weight and developmental changes in vancomycin clearance (24). Furthermore, the individual dose needs optimization according to abnormal renal function. Therefore, weight and renal function have the most important impact on vancomycin pharmacokinetics in children (3), providing the scientific basis for rational patient-tailored dosing schemes. The simulation clearly supports the use of a patient-tailored dose, which showed a narrow spread between AUC and $C_{\text{area}}$ values compared with the traditional mg/kg-basis dose. The patient-tailored dose resulted in a higher proportion of patients within the target trough concentrations, associated with lower risk of underdosing or overdosing. Individual dosage prescription and adjustment based on these covariates will require a computer-based tool. This practice has been set up in our neonatal intensive care unit (NICU) to individualize vancomycin dosing in neonates (25) and undoubtedly will be implemented for the treatment of pediatric patients with selected diseases.

A limitation of our study was that the population pharmacokinetic model was developed based on vancomycin TDM data; the prediction of maximum concentration at steady state will likely shrink toward population mean values, reducing the ability to identify a “special” patient. Taking scavenged pharmacokinetic samples should improve individual parameter estimation without increasing the burden of pediatric clinical practice.

Conclusion. In the present study, we developed a population pharmacokinetic model of vancomycin in children with malignant hematological disease. Vancomycin clearance was markedly higher than that in children without cancer, with weight and creatinine clearance being significant covariates. We have shown that the patient-tailored dose reduced variability in vancomycin AUC and $C_{\text{area}}$ values compared to the mg/kg-basis dose, making the modeling approach an important tool for dosing individualization. Explaining residual variability requires the identification of additional covariates. A prospective study is warranted to evaluate the potential clinical benefits and safety of this optimized dosing regimen.

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We declare that we have no conflicts of interest related to this work.

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