Population pharmacokinetics of vancomycin in patients with external ventricular drain-associated ventriculitis

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Background: To determine the distribution of vancomycin into the cerebrospinal fluid (CSF) in patients with external ventricular drain (EVD)-associated ventriculitis, the pharmacokinetics of vancomycin were evaluated and covariate relationships explored.

Methods: For the population pharmacokinetic model patients were recruited in a neurocritical care unit at the University Hospital of Muenster in the period between January 2014 and June 2015. All patients had a clinical evidence of EVD-associated ventriculitis. Population pharmacokinetic analysis of vancomycin was performed using NONMEM.

Results: A total of 184 blood and 133 CSF samples were collected from 29 patients. The final population pharmacokinetic model is a three-compartment model with linear elimination. Creatinine clearance (ClCr) and CSF-lactate were detected as significant covariates, showing that the total vancomycin plasma clearance (Cl) depends on ClCr and furthermore the clearance (Cldif) between the central and CSF compartment correlates with CSF lactate concentration. Based on the final model, the following values were estimated by NONMEM: Cl = 5.15 L/h, Q (intercompartmental clearance) = 3.31 L/h, Cldif = 0.0031 L/h, Vcentral = 42.1 L, VCSF = 0.32 L and the value of Vperipheral was fixed to 86.2 L. With the developed pharmacokinetic model, area under the curve (AUC) values as well as CSF trough levels were simulated.

Conclusion: Based on our analysis, the dosing of vancomycin should be referred to the degree of inflammation (derived from the CSF lactate concentration) and renal function (derived from ClCr).

KEYWORDS
NONMEM, nosocomial ventriculitis, population pharmacokinetics, vancomycin
External ventricular drain (EVD)-associated bacterial ventriculitis is a frequent complication in patients with EVDs. EVDs are used in neurocritical care units for monitoring intracranial pressure, intrathecal drug administration or drainage of cerebrospinal fluid (CSF). Although EVDs are a routine procedure in neurocritical care and EVD-associated bacterial ventriculitis is a common complication, the optimal therapy for EVD-associated ventriculitis has not yet been clearly defined. Current treatment regimens include the (potentially harmful) intraventricular injection of antibiotics and/or their intravenous infusion, the latter of which may not always lead to optimal CSF drug levels.

Infection of the central nervous system, including ventriculitis and meningitis, is predominantly caused by Gram-positive pathogens. Due to the high incidence of penicillin-resistant Gram-positive bacteria, vancomycin is the standard empirical therapy for nosocomial bacterial infections of the central nervous system. Despite widespread use, vancomycin therapy is often suboptimally dosed due to pharmacokinetic variabilities in critically ill patients. For example, augmented renal clearance is common in neurosurgery patients, resulting in subtherapeutic vancomycin levels.

Vancomycin pharmacokinetics can be described using a two-compartment model. In the general population vancomycin has a steady-state volume of distribution of 0.4-1 L/kg and shows an initial half-life of 30 minutes. Protein binding of vancomycin in plasma is 50-55%. After 24 hours 75-80% of the drug is renally excreted unchanged from the body.

Vancomycin was detected in various tissues, with tissue concentration associated with high variability. The drug is distributed into the lung, the bone and muscle tissue, as well as fat and heart tissue. Distribution into the central nervous system, however, has been reported to occur only in pathological conditions or due to inflammatory processes that damage the blood-brain barrier or the blood-CSF barrier.

To date there is a lack of sufficient population pharmacokinetic models describing the distribution of vancomycin into the CSF in neurocritically ill patients with EVD-associated ventriculitis. This study assessed the CSF pharmacokinetics of vancomycin in neurocritically ill patients with EVD-associated ventriculitis to improve dosing recommendations.

2 | METHODS

2.1 | Ethics

The study was approved by the local ethics committee of the Medical Chamber Westphalia-Lippe and the University of Muenster, Germany (approval number 2014-211-f-S).
2.3 | Analytics

Concentration determination of vancomycin was performed using the enzyme-multiplied immunoassay technique (EMIT) method. The minimum quantifiable concentration of vancomycin was 1 mg/L. The precision (coefficient of variation) was between 1.6% and 5.8% and the accuracy (absolute deviation) between 0.032 and 0.414. When modelling in NONMEM, the M2 method was used for handling data below the limit of quantification so that values below the limit of quantification were excluded from the modelling.

2.4 | Pharmacokinetic analysis

Population pharmacokinetic analysis of vancomycin was performed using NONMEM (Version 7.3, Icon Development Solutions, Ellicott City, USA). The graphical evaluation was conducted using R in addition with the Xpose package (version 4.5.3). The program tool Perl-Speaks-NONMEM (Version 4.8.1.) was used to perform simulation-based evaluations, step-wise covariate modelling (SCM) and bootstrap analysis. For parameter estimations in NONMEM the parametric maximum likelihood method was used. The data were analysed using one-, two- and three-compartment models. In the pharmacokinetic analysis initially, a plasma concentration-based model was developed. Subsequently, the CSF compartment was integrated into the plasma concentration model. Finally, the covariate model was developed using SCM. The effect of covariates was assessed based on the influence on objective function value (OFV = −2 × log of likelihood, −2LL). A decrease of 3.84 points between two nested models regarding a change in one degree of freedom (level of significance 5%) in the OFV was considered as significant for forward inclusion into the full model. A difference of 6.63 points (level of significance 1%) in OFV between two nested models was considered significant to keep the covariate in the final model. The following covariates were tested: age, height, weight, sex, creatinine clearance, leukocytes, C-reactive protein, urea, protein (CSF), lactate (CSF), glucose (CSF), granulocytes (CSF), white cell count (CSF), erythrocytes (CSF) and CSF loss.

The final model was graphically evaluated by goodness-of-fit plots (GOFs) of observed and predicted concentrations of vancomycin as well as visual predictive checks (VPCs). The stability and validity of the model was tested by bootstrap analysis, including 1000 resampled estimations.

In this work median with the corresponding interquartile range (IQR) was used. Missing data were supplemented accordingly: the population median was used when data for a patient was completely missing. In the absence of the last value of the time-dependent covariate, the previous value was adopted (last value carried forward method). For data gaps in time-dependent covariates within the individual patient’s record, a median between the two adjacent values was determined.

2.5 | Simulations of new dosing regimen

Based on the developed population pharmacokinetic model, Monte-Carlo simulations were performed with different dosing regimens. In a post hoc estimation step, the area under the curve (AUC) was determined. For the simulations, simulation datasets with different vancomycin doses and a sample population were created. The results of the simulations were interpreted in the form of individual Bayesian forecasts.

3 | RESULTS

3.1 | Patients characteristics

A total of 29 patients suffering from EVD-associated ventriculitis were treated with intravenous vancomycin during the study period (Table 1). Detailed information of the underlying neurological disease (Supporting Information Table S1) of the patients and the detected pathogens (Supporting Information Table S2) are available in the Supporting Information digital content. A total of 184 blood and 133 CSF samples were collected. The median vancomycin concentration (n = 184) in plasma was 17.7 mg/L (IQR 13.00, 23.02). The median vancomycin concentration (n = 103) in CSF was 2.9 mg/L (IQR 1.76, 4.2). The number of samples obtained from each patient and times during the dosing interval is shown in Supporting Information Table S3. Figure 1 shows vancomycin concentrations in plasma and CSF over time for bolus application and continuous infusion. In both groups of patients, CSF-to-plasma ratios which were 0.13 (IQR 0.07; 0.414. When modelling in NONMEM, the M2 method was used for handling data below the limit of quantification so that values below the limit of quantification were excluded from the modelling.

### TABLE 1 | Patients characteristics

| Characteristic          | Median | IQR       |
|-------------------------|--------|-----------|
| Demographic covariates  |        |           |
| Age (years)             | 52     | 44; 61    |
| Height (cm)             | 170    | 168; 180  |
| Weight (kg)             | 80     | 70; 85    |
| Sex (male)              | 14     |           |
| Covariates in plasma    |        |           |
| Leukocytes (10⁹ cells/µL)| 9.96   | 7.53; 13.8|
| ClCr (mL/min/1.73 m²)   | 152    | 109; 174  |
| CRP (mg/dL)             | 2.6    | 1.1; 4.5  |
| Urea (mg/dL)            | 13.5   | 11; 18    |
| Covariates in CSF       |        |           |
| Protein (mg/L)          | 1.100  | 634; 1920 |
| Glucose (mg/dL)         | 64.5   | 54; 73    |
| Lactate (mmol/L)        | 3.3    | 2.8; 4    |
| Granulocytes (cells/µL) | 41     | 6.5; 120  |
| White cell count (cells/µL) | 99  | 54; 238.7 |
| Erythrocytes (cells/µL) | 1920   | 672; 4608 |

**Abbreviations:** ClCr, creatinine clearance; CRP, C-reactive protein; CSF, cerebrospinal fluid; IQR, interquartile range.
0.24) in patients with bolus therapy and 0.08 (0.05; 0.12) under continuous therapy correlated significantly with markers of cerebral inflammation.

3.2 | Population pharmacokinetic analysis

A three-compartment model (two plasma plus a CSF compartment) with first-order elimination best described the vancomycin pharmacokinetics. The model consisted of the central compartment, peripheral compartment and the CSF compartment. The clearance of vancomycin from the central into the CSF compartment is described via the influx clearance (Equation 1). Furthermore, the elimination of vancomycin from CSF is defined by the efflux clearance (Equation 2). Distribution between plasma and CSF was best described using $C_{ldif}$. An additional $C_{bulk}$ parameter was used to define drainage into the venous system. $C_{bulk}$ was fixed on the literature value of 25 mL/h. 

$$C_{lin} = C_{ldif}$$

**Equation 1** $C_{lin}$ = influx clearance: clearance from the central into the CSF compartment, $C_{ldif}$ = passive diffusion (value estimated by NONMEM)

$$C_{out} = C_{ldif} + C_{bulk}$$

**Equation 2** $C_{ldif}$ = efflux clearance: clearance from the CSF to the central compartment, $C_{ldif}$ = passive diffusion (value estimated by NONMEM), $C_{bulk}$ = bulk flow (fixed literature value)

Covariate evaluation detected a significant influence of creatinine clearance on total clearance (Equation 3) and an influence of the CSF lactate concentration on $C_{ldif}$ (Equation 4). The median CSF lactate concentration in the patient population was 3.3 mmol/L (IQR:2.8; 4) equally distributed across 0.5 to 9 mmol/L.

$$TVCl = \theta_{TVCl} = \frac{Cl_{pop}}{C_{152}/C_{18}/C_{19}}$$

**Equation 3** Relationship between the individual Cl (TVCl) and creatinine clearance (ClCr) described with a potency function. $\theta_{TVCl}$ population estimate of clearance; 152 median of ClCr in the population; $\theta_{ClCr}$ estimated value of covariate influence

$$TVC_{ldif} = \theta_{ldif} = e^{\theta_{lakt}}(\text{lactate value}−3.3)$$

**Equation 4** Relationship between the individual $C_{ldif}$ (TVC_{ldif}) and the lactate value described with an exponential function $\theta_{lakt}$ estimated value of lactate impact

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**FIGURE 1** Vancomycin concentrations in plasma and cerebrospinal fluid over time for bolus application and continuous infusion in the patient population. The broken lines show the target concentration of vancomycin.
The median creatinine clearance in the patient population was 152 mL/min (IQR 109; 174) distributed equally between 15 and 200 mL/min. In the final model, the volume of distribution in the peripheral compartment ($V_3$) was fixed to the previously estimated value of 86.2 L. The relative standard errors, reflecting the parameter precision, were less than 30% in the final model for the model parameters and less than 50% for the parameters of the stochastic model (Table 2). The parameter shrinkage was estimated with 6% and 19% for the IIV on Cl and Cl_{dif}, respectively.

The bootstrap analysis, which provides an insight into the stability of the model and the parameter precision of the estimated patient data, shows that the model is stable and the parameters are estimated with sufficient precision (Table 2). Figure 2a,c shows GOF plots for individual predictions. The figures show a uniform distribution of the individual predictions and the measured concentration around the bisecting line. Figure 2b,d shows GOF plots in which the population predictions are plotted against the observed vancomycin concentrations. A VPC was created for the dosing occasions. The observed median and percentiles are complement to the simulated confidence intervals, indicating a good predictive performance of the final model (Supporting Information Figure S1).

| Parameter   | Estimated value | Bootstrap |
|-------------|-----------------|-----------|
| Cl (L/h)    | 5.15            | 5.12      |
| $V_1$ (L)   | 41.13           | 41.13     |
| $V_2$ (L)   | 0.32            | 0.33      |
| $V_3$ (L)$^a$ | 86.2           | 86.25     |
| Q (L/h)     | 3.61            | 3.44      |
| Cl_{dif} (L/h) | 0.0031      | 0.0031    |
| Prop. error (%) (plasma) | 18.5 | 18.5      |
| Add. error (mg/L) (plasma) | 3.16 | 2.58      |
| Add. error (mg/L) (CSF) | 0.79 | 0.78      |
| Cl_{C} on Cl | 0.407         | 0.42      |
| Lactate on Cl_{dif} | 0.11         | 0.12      |
| IIV Cl (%)  | 34.9            | 33.12     |
| IIV Cl_{dif} (%) | 65.4         | 63.66     |

Abbreviations: add. error, additive error; Cl, plasma clearance; Cl_{C}, creatinine clearance; Cl_{dif} clearance between the central and CSF compartment; IIV, interindividual variability; prop. error, proportional error; Q, intercompartmental clearance; $V_1$, volume of distribution in the central compartment; $V_2$, volume of distribution in the CSF compartment; $V_3$, volume of distribution in the peripheral compartment.

$^a$Fixed values
3.3 | Simulations

To depict the influence of the detected covariates creatinine clearance and CSF-lactate concentration, simulations of several dosing regimens were carried out in a sample population. The change of simulated AUC24 across creatinine values with CSF lactate fixed to the population median of 3.3 mmol/L is shown in Supporting Information Figure S2. Elevation of vancomycin CSF trough concentrations at steady state with increasing CSF lactate levels is shown in Supporting Information Figure S3.

The progression of the designated pharmacokinetic-pharmacodynamic (PK/PD) target for vancomycin AUC24:minimum inhibitory concentration (MIC) across common MIC values is shown in Figure 3.

4 | DISCUSSION

In the present study a linear three-compartment model describing pharmacokinetic parameters of vancomycin in plasma and CSF in neurocritically ill patients with EVD-associated ventriculitis was developed. To the best of our knowledge, we are the first to show a correlation between the CSF lactate level as a surrogate to inflammation processes and elevated vancomycin concentrations in the CSF, in addition to the well-known influence of creatinine clearance on vancomycin elimination. Furthermore, we assessed the efficacy of different doses via a PK/PD approach with Monte Carlo simulations.

The pharmacokinetic variability of vancomycin is a well-known issue that has been addressed by TDM of plasma trough concentrations in the past. It has long been known that the AUC:MIC ratio is the far better parameter to relate PK/PD, but measurements of AUC have been cumbersome.26 Vancomycin data for this study mainly consisted of trough levels collected for TDM, but also included information on the drug disposition into the CSF. Nevertheless, regarding vancomycin drug monitoring, Neely et al27 were able to show that by using nonlinear mixed effects modelling (NLME) approaches the AUC can be sufficiently calculated from individual priors or in our case empirical Bayesian estimates. It can further be used to adapt individual dosing or could even be used to calculate optimal sampling time points to derive the most informative individual model. Thus, NLME modelling was used to describe the pharmacokinetics in this neurocritically ill population with EVD and to determine the characteristics that explain interindividual variability throughout the population. Dosing regimens were simulated based on these results to further explore vancomycin exposition in this special population.

The observed data is best described by a linear three-compartment model: a peripheral and central compartment for the distribution in plasma and a further compartment for the CSF. The intercompartmental clearance of vancomycin from the central into the CSF compartment was described via an influx clearance. It is believed that this process occurs via passive transcellular diffusion (Clin). Elimination of vancomycin from CSF is defined by efflux clearance. The model assumes that vancomycin elimination from cerebrospinal fluid consists of passive transcellular diffusion (Cltrans) and excretion via drainage of the cerebrospinal fluid into the venous (bulk flow, Clbulk) system.22–24 In accordance with previous publications, describing the pharmacokinetics of vancomycin in plasma resulted in a two-compartment model.28–33

A correlation between the CSF lactate concentration and the exchange of vancomycin between cerebrospinal fluid and blood has not yet been published. The CSF lactate concentration correlates with the clearance between the central compartment and the CSF compartment. This correlation was described by an exponential model. The complex composition of the blood-cerebrospinal fluid barrier results in a barrier effect, with the blood-cerebrospinal fluid barrier being completely permeable only to water, oxygen and carbon dioxide. The penetration of drugs, for example vancomycin, is impeded,34,35 therefore vancomycin does not penetrate the blood-cerebrospinal fluid barrier in healthy patients easily,36,37 but does so in patients with infections of the central nervous system.38–41 As a

FIGURE 3 Simulated AUC24:MIC vs MIC. With 1000 mg vancomycin q8h, 1,350 mg q8h, 1500 mg vancomycin q8h, 4 g vancomycin continuous infusion (cont.), 3 g vancomycin cont., 2 g vancomycin cont. AUC, area under the curve; MIC, minimal inhibitory concentration
diagnostic parameter, CSF lactate concentration provides information on acute, bacterial or viral inflammation and thus acts as a surrogate parameter for ventriculitis and meningitis. The median CSF lactate concentration in the observed patient population was 3.3 mmol/L and is thus well above the reference range for healthy adults (1.1 mmol/L). The increased lactate concentration indicates inflammation in the patient population and thus the detectability of therapeutic vancomycin concentrations in the CSF.

Vancomycin exposure was simulated for different dosing regimens and is depicted as trough concentration at steady state across a range of CSF lactate levels in Supporting Information Figure S3. With the increase in CSF lactate concentrations, the vancomycin concentration in the CSF increases. Supporting Information Figure S3 also shows that administration of the dosing regimen 1350 mg/L every 8 hours achieved the therapeutic target (above 1 mg/L in the CSF) after 24 hours at a lactate level of 3.3 mmol/L, which was the population median in our observed population. Based on the simulations, the dosing recommendation for continuous infusion is 4 g/24 h of vancomycin.

Creatinine clearance significantly impacts the plasma clearance term and has been implemented via a power function. A correlation between creatinine clearance and total clearance has been previously reported in several publications. The recently suggested updated PK/PD target is in line with findings that targeting AUC:MIC ratios is more reliable than previously used target trough concentrations. It is suggested that an AUC_{24} of 400 mg/L/h should be the aim in empiric treatment. If the pathogen is known, vancomycin can either be de-escalated or adapted to achieve the target AUC_{24}:MIC ratio with regards to the pathogen. The simulations in Figure 3 show that by increasing creatinine clearance, the vancomycin concentration and therefore AUC_{24} decreases. Figure 3 depicts the change of this ratio in our simulated population across commonly detected MIC values. As this population included a broad distribution of creatinine clearance values, between 15 mL/min and 200 mL/min, percentiles of the simulated population are given, where the 50th percentile shows the population mean curve. The 5th and 95th percentiles, respectively, show patients with impaired and augmented renal clearance.

Publications reporting population pharmacokinetics (PopPK) modelling of vancomycin concentrations in the CSF are rare. Recently, Blassmann et al published a population pharmacokinetic model that assessed the disposition of vancomycin in EVD patients. Here, the nonparametric approach was used to fit the data, which does not make the assumption that pharmacokinetic parameter variability is restricted to a normal distribution around the population mean, but rather allows all parameters to be individually estimated across the nonparametric adaptive population grid. Li et al also used a parametric PopPK approach with a three-compartment model including one CSF compartment. The difference is the discovered covariate relationship, especially the link between CSF lactate concentrations and the vancomycin distribution into CSF, that was found in our model. A further difference between the structural model developed in this work and the model of Li et al is the elimination from the CSF compartment. In this work we defined the elimination of vancomycin with the bulk flow mechanism discussed above.

Comparing both previously published models, clearance is well in accordance with our estimate. The models differ in volumes of distribution, especially when it comes to the estimate of the CSF volume of distribution. CSF fluid is thought to be about 150 mL in a healthy adult. We estimated vancomycin to be distributed into the CSF in 320 mL, suggesting further distribution out of the fluid into other brain compartments. Li estimated this parameter to be 26 mL, whereas Blassmann suggests 828 L. A further difference to the published models is the study population. Patients analysed in this study were subarachnoid haemorrhage patients. In contrast, Li et al analysed postoperative patients. It is notable that subarachnoid haemorrhage patients commonly suffer from hydrocephalus and thus increased CSF volumes. On the other hand, up to 300 mL/d of excess CSF may be drained by the EVD.

Our simulations show how variable vancomycin pharmacokinetics are in this specific neurocritically ill population. Depending on the individual's renal function and the permeability of the blood-brain barrier, the disposition of the drug in plasma and CSF can be variable and should thus be monitored via TDM. The use of Bayesian forecasting through a pharmacometric tool can aid the clinician in dose finding and dose adaptation choices.

The results we are reporting were obtained through a retrospective study. Mostly trough samples were available, resulting in a higher uncertainty of the central volume of distribution estimate. Nevertheless, this setup allowed for the quantification of clearance and disposition of vancomycin into the CSF, which were of primary interest in this study. It is possible that not all patients with ventriculitis were identified within the database. In addition, despite a clinical standard operating procedure requiring daily CSF liquor and blood samples to be taken in patients with ventriculitis, daily data were not available in all cases. As a further limitation, vancomycin loss from urine and drained CSF were not measured. In our analysis 30 CSF values were below the quantification limit of 1 mg/L and were therefore excluded from the model. There were no data on vancomycin CSF concentration for three patients. In one of these three patients there was no data on CSF covariates.

5 | CONCLUSION

In this study a population pharmacokinetic model describing vancomycin in intensive care patients with diagnosed ventriculitis was developed and covariate relationships explored. With the developed pharmacokinetic PopPK model, AUC values as well as CSF trough concentrations were simulated across different dosing regimens. The results of this work lead to the conclusion that in order to ensure the optimal vancomycin concentration in the CSF, the dosing of vancomycin should be referred to the degree of inflammation (derived from the CSF lactate concentration) and the renal function (derived from Cl_{Cr}).
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COMPETING INTERESTS
H.M. has received travel fees provided by Amomed Pharma GmbH and Astellas Pharma. K.T.G. received travel reimbursements and honoraria as a consultant from Fresenius Kabi Germany. The remaining authors have disclosed that they do not have any conflicts of interest.

CONTRIBUTORS
K.O.J., G.H., C.E., S.G., and M.H. conceived the study. K.O.J. developed the PK model and wrote the original draft of the manuscript. S.G. designed the figures. K.O.J., G.H., C.E., S.G., and M.H. interpreted data, participated in drafting the article and revised it critically for important intellectual content. P.H.A., C.S., and T.G.K. conducted the database analysis and exported the data. All authors assisted in the review of the manuscript and approved the final version of the manuscript for submission. S.G. and M.H. jointly supervised this work. K.O.J. acts as corresponding author.

DATA AVAILABILITY STATEMENT
Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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