

1 **Cerebrospinal fluid penetration of vancomycin in critical care patients with proven or**
2 **suspected ventriculitis: a prospective observational study**

3 **Running Titel: Cerbrospinal fluid penetration of vancomycin**

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23 1. Synopsis

24 **Background:** Vancomycin is recommended for ventriculitis. However, penetration into the
25 CNS is relatively poor.

26 **Objectives:** To investigate the population pharmacokinetics of vancomycin serum and CSF in
27 critical care patients with proven or suspected CNS infections from neurosurgical procedures.

28 **Patients and methods:** This was an observational pharmacokinetic study in critical care
29 patients with proven or suspected CNS infections receiving intravenous vancomycin. Multiple
30 blood and intraventricular CSF samples were collected. Population pharmacokinetic analysis
31 and simulation were undertaken with ADAPT5 and Pmetrics.

32 **Results:** 187 blood and CSF samples were collected from 21 patients. The median (range)
33 C_{max} and C_{min} concentrations in serum were 25.67 (10.60-50.78) and 9.60 (4.46-23.56) mg/L,
34 respectively, with a median daily dose of 2500 (500-4000) mg. The corresponding median
35 concentrations in CSF was 0.65 (<0.24-3.83) mg/L and 0.58 (<0.24-3.95) mg/L, respectively.
36 The median AUC_{0-24} in serum and CSF was 455.09 mg*h/L and 14.10 mg*h/L, respectively. A
37 three-compartment linear population pharmacokinetic model best fitted the observed data.
38 Vancomycin demonstrated poor penetration into CSF, with a median CSF/serum ratio of 3%
39 and high inter-subject pharmacokinetic variability of its penetration.

40 **Conclusion:** Therapeutic drug monitoring (TDM) in both serum and CSF and higher daily
41 doses may be an option to ensure adequate trough levels and to optimize patient therapy.
42 Novel dosing strategies designed to reduce renal toxicity, such as administration by continuous
43 infusion, should be investigated in further clinical studies to avoid antibiotic underexposure in
44 CSF.

45

46 2. Introduction

47 Gram-positive cocci, especially *Staphylococcus* spp., are the leading cause of surgical site
48 infections resulting from neurosurgical procedures.¹ Despite the development of novel
49 antibiotics active against Gram-positive pathogens, vancomycin generally remains the
50 standard of care, particularly of methicillin resistant MRSA and methicillin resistant
51 *Staphylococcus epidermidis* (MRSE).² Furthermore, vancomycin is used in combination with
52 meropenem as empiric antibiotic therapy in critical care patients with infections of the CNS
53 such as meningitis or ventriculitis.¹ However, in the absence of meningeal inflammation the
54 penetration into CSF of vancomycin is hampered by its large molecular weight and
55 hydrophilicity.^{3, 4} Recent data suggest there is highly variable penetration of vancomycin into
56 the CSF.⁵ Relatively little is known about the pharmacokinetics (PK) of vancomycin in the CSF
57 of patients with ventriculitis.^{5, 6}

58 A serum AUC/MIC value of 400 in serum is often used as a pharmacodynamic target.² There
59 is less clarity about the relevant drug exposure at the target site of infection (e.g. the CSF for
60 critical care patients with proven or suspected CNS infections) and the regimens required to
61 achieve these targets. Conventionally used regimens of 500 mg every 6 h (q6h) or 1 g every
62 12 h (q12h) have little evidence supporting their efficacy in specific populations particularly
63 critically ill patients.⁷ Guidelines recommend 30-60 mg/kg/day vancomycin for meningitis and
64 ventriculitis to ensure sufficient CSF concentrations.^{1, 2} Due to very few studies in meningitis
65 patients an alternative agent should be considered, if vancomycin MIC is ≥ 1 mg/L.¹ However,
66 drug as well as disease factors, such as the presence of meningeal inflammation and the
67 integrity of the blood-liquor barrier, are important to consider when devising dosing strategies.^{3,}
68 ^{4, 6} The meninges in ventriculitis are typically normal or only minimally inflamed.^{3, 4, 6} Therefore,
69 penetration into the CNS in patients with ventriculitis should not be extrapolated from other
70 patient populations.^{3, 4, 6}

71 The purpose of this study was to investigate the population pharmacokinetics of vancomycin
72 in serum and CSF in critical care patients with external ventricular drains (EVD) and proven or

73 suspected ventriculitis. Such an analysis is fundamental to characterize the inter-individual
74 variability of vancomycin concentrations in CSF and to further investigate optimal vancomycin
75 regimens for patients with ventriculitis.

76

77 **3. Patients and methods**

78 **3.1. Study design and population**

79 This prospective observational PK study was conducted at the intensive care unit of Munich
80 Ludwig-Maximilians-University (LMU) Hospital, Germany between April 2014 and January
81 2016. Patients older than 18 years of age who required an EVD and in whom a proven or
82 suspected EVD-associated ventriculitis developed were enrolled in the study. The diagnosis
83 of ventriculitis was defined as a positive CSF culture combined with clinical signs of infection.⁸
84 Suspected ventriculitis was defined by abnormal CSF parameters, such as low CSF glucose
85 levels (<50% of serum glucose), high CSF protein (>50 mg/dL) or CSF pleocytosis, combined
86 with clinical signs of infection in the absence of a positive CSF culture.⁸ Patients were excluded
87 if they were under 18 years of age or death within 72 h was expected.

88 **3.2. Ethics**

89 The trial was conducted in accordance with the Declaration of Helsinki. Ethical approval was
90 obtained from the university ethics committee (registration number 111-14). Written informed
91 consent was obtained from all patients or a legally authorized representative before enrolment.

92 **3.3. Study procedures**

93 All included patients received vancomycin (Vancomycin CP®, Hikma Pharma, Germany) as a
94 prolonged infusion over 4 h, targeting trough concentrations of 10-15 mg/L in serum. Serial
95 blood and CSF sampling occurred for initial dose and steady state. Blood samples (4 mL) were
96 collected using the indwelling arterial catheter just before the start of the infusion (trough
97 concentration; C_{min}) and after the end of the infusion (peak concentration; C_{max}). CSF samples

98 (1 mL) were collected using the indwelling EVD nearest to the site of insertion (3 mL volume
99 to sampling location) simultaneously with each blood sample just before the start of the infusion
100 (cerebrospinal fluid concentration at serum trough concentration [C_{trough}]) and after the end of
101 the infusion (cerebrospinal fluid concentration 4 h after serum trough concentration [$C_{\text{after 4h}}$]).
102 Samples were centrifuged for 5 minutes at 4000 rpm and stored at -80°C within 45 minutes
103 after sample collection for a maximum of 4 weeks until the measurement of drug. Serum and
104 CSF concentrations of vancomycin were analysed using an *in vitro* chemiluminescent micro
105 particle immunoassay (ARCHITECT Vancomycin assay, Abbott; measuring range: 0.24 mg/L-
106 100.00 mg/L). For CSF concentrations of vancomycin, spiked CSF samples were carried out
107 on a regular basis in addition to the routine validation process. Only vancomycin total
108 concentration (bound plus unbound) was measured.

109 Additional data were obtained from the medical record including weight, height, serum
110 creatinine, bilirubin, serum C-reactive protein (CRP), serum interleukin-6 (IL-6), serum
111 procalcitonin (PCT), serum leucocytes, CSF cells, CSF erythrocytes, CSF IL-6, CSF glucose,
112 CSF protein, CSF drain in 24 h, Simplified Acute Physiology II Score (SAPS II), SOFA Score,
113 Glasgow Coma Score (GCS), and dexamethasone therapy.

114 **3.4. Population pharmacokinetic analysis**

115 A three-compartment model with zero order infusion for vancomycin was fitted to the study
116 data.⁹ The structural model took the form:

$$117 \quad (1) \quad dX_C/dt = R(t) - (SCL/V_c + k_{cp} + k_{cb}) \times X_C + k_{pc} \times X_P + k_{bc} \times X_{\text{CSF}}$$

$$118 \quad (2) \quad dX_P/dt = k_{cp} \times X_C - k_{pc} \times X_P$$

$$119 \quad (3) \quad dX_{\text{CSF}}/dt = k_{cb} \times X_C - k_{bc} \times X_{\text{CSF}}$$

120 The three equations above describe the rate of change of vancomycin (mg) in the central (1),
121 peripheral (2) and CSF (3) compartments, respectively. The equation elements are defined in
122 figure 1 legend. Equation (1) describes the rate of change of the amount of vancomycin (in
123 milligrams) in the central compartment (X_C). Equation (2) describes the rate of change of the

124 amount of vancomycin (in milligrams) in the peripheral compartment (X_P). Equation (3)
125 describes the rate of change of the amount of vancomycin (in milligrams) in the CSF (X_{CSF}). A
126 schematic representation of the structural model is shown in Figure 1.

127 We used the Pmetrics package v. 1.5.0.¹⁰ to model the concentration-time data for
128 vancomycin, simulate from the model, generate plots and perform standard data summaries
129 and statistical tests. The observed data were weighted by the inverse of individual error
130 coefficients that were obtained using the maximum likelihood estimator in ADAPT 5. Additional
131 process noise such as errors in sampling time or dosing was modelled using gamma as a
132 multiplicative error term in Pmetrics.

133 **3.5. Population pharmacokinetic model diagnostics**

134 Acceptance of the final model was evaluated by the log-likelihood, the coefficient of
135 determination (r^2) of the linear regression and visual inspection of diagnostic scatterplots,
136 where model predictions were generated either by the median population parameter values or
137 by the medians of each subject's individual Bayesian posterior parameter value distributions.

138 **3.6. Population pharmacokinetic covariate screening**

139 The impact of weight, height, CrCL, bilirubin, serum CRP, serum IL-6, serum PCT, serum
140 leucocytes, CSF cells, CSF erythrocytes, CSF IL-6, CSF glucose, CSF protein, CSF drain in
141 24 h, SAPS II, SOFA Score, GCS and dexamethasone therapy as covariates were initially
142 assessed by visual inspection. For that reason, graphical representation in Pmetrics of each
143 covariate versus population parameter was performed to evaluate for inclusion in the final
144 model.

145

146 **3.7. Other pharmacokinetic calculations**

147 C_{max} , C_{min} , $C_{after\ 4h}$, and C_{trough} are the observed values. AUC in serum and CSF was calculated
148 using the Bayesian estimates from each patient using the trapezoidal rule that is implemented

149 within Pmetrics. We divided each subject's cumulative AUC by the total time in hours and
150 multiplied the result by 24 to estimate the daily average AUC (AUC_{0-24}). The correlation
151 between these values was assessed using Pearson's test. Penetration of vancomycin into
152 CSF was described using the CSF/serum ratio, which was calculated by dividing the
153 cumulative AUC in CSF by the cumulative AUC in serum. Half-life was calculated using
154 transfer rate constants. Creatinine clearance (CrCL) was calculated using the Cockcroft-Gault
155 equation.¹¹ All calculations were performed using IBM SPSS Statistics version 23.0 software
156 (IBM, Armonk, NY, USA).

157 **3.8. Assessment of vancomycin concentration in CSF**

158 We performed simulation of 3000 patients using Pmetrics to compare different dosing
159 regimens in this study population (1000 mg every 12 h, 2000 mg every 12 h with each
160 administered as a 4 h infusion. Additionally, the outcome of 4000 mg, and 6000 mg
161 administered as a continuous infusion was examined). A PTA in CSF was analysed using
162 Pmetrics targeting vancomycin concentrations of 0.25 mg/L, 0.5 mg/L, 1 mg/L, and 2 mg/L.

163 **4. Results**

164 The study included 196 blood samples and 186 CSF samples from 21 patients. Detailed
165 demographic characteristics are presented in Table 1. One CSF sample was excluded from
166 the study because of concentration 3 times the standard deviation (n=1). Serum samples were
167 excluded because of uncertain sample collection time (n=2).

168 The study population was relatively young (median age 52 years, range 46–80 years) and had
169 well-preserved renal function on the day of inclusion (median CrCL 120.1 ml/min, range 52.3-
170 217.6 ml/min). The median (range) SAPS II score was 47 (13–62). All patients received
171 meropenem therapy in addition to vancomycin. Seven patients (33.3%) received concomitant
172 fosfomycin for 7 days, although one (4.8%) of them also received rifampicin, which then was
173 replaced by fosfomycin. Patient 1 additionally received dexamethasone during the first 2 days,
174 and patient 14 additionally received dexamethasone during the first 5 days.

175 The most frequent neurological disease was subarachnoid haemorrhage, which was
176 diagnosed in 17 (81.0%) patients. In the remaining four patients, an EVD was placed for
177 intracranial bleeding (4.8%), tumour (9.5%) or traumatic brain injury (4.8%). A total of 20
178 patients (95.2%) were CSF culture-negative, and one patient (4.8%) had a positive culture for
179 *Pseudomonas aeruginosa*. In serum, median C_{max} (range) was 25.67 (10.60-50.78) mg/L and
180 median (range) C_{min} was 9.60 (4.46-23.56) mg/L. In CSF, median C_{max} (range) was 0.65
181 (<0.24-3.83) mg/L and median C_{min} 0.59 (<0.24-3.95) mg/L. In total, 64 CSF samples were
182 below the detection limit. Median daily dose of vancomycin was 2500 (500-4000) mg
183 administered in two divided doses. Individual observed vancomycin concentrations and doses
184 are shown in Table S1, available as supplementary data at JAC Online. CrCL on sample days
185 ranged from 52.3 to 122.5 mL/min (median CrCL 122.5 mL/min). The median AUC_{0-24} in CSF
186 was 14.10 mg*h/L and in serum 455.09 mg*h/L. The median values for the AUC_{0-24} in CSF and
187 serum ranged from 2.64 to 81.30 mg*h/L and 277.35 to 521.02 mg*h/L, respectively. The
188 median CSF/serum ratio (range) was 0.03 (0.01-0.18). There was no statistically significant
189 correlation between the AUC in serum and CSF ($r=-0.112$, $p=0.629$). Individual AUC_{0-24} and
190 penetration results are shown in Table S2, available as supplementary data at JAC Online.

191 **4.1. Pharmacokinetic model building**

192 The fit of the mathematical model to the observed data was acceptable according to visual
193 inspection of the observed-versus-predicted plots and r^2 of the observed-versus-predicted
194 values ($r^2 = 0.930$ in serum, $r^2 = 0.579$ in CSF) (Figure S1, available as supplementary data at
195 JAC Online). Individual PK results in serum and CSF obtained by Pmetrics for the PK model
196 are shown in Table S2. The mean, median, and SD for the population parameters identified
197 by Pmetrics for the PK model are shown in Table 2. Population parameter value covariance
198 matrix are shown in Table S3, available as supplementary data at JAC Online. Values of these
199 pharmacokinetic parameters in the population were estimated by using all data, replacing data
200 below the quantification limit with the value $QL/2$, where QL is the quantification limit.¹² No
201 covariate relationships could be supported for any of the model parameters.

202 4.2. Assessment of vancomycin concentration in CSF

203 Simulated vancomycin concentration–time profiles in serum and CSF of each regimen are
204 shown in Figure 2. The simulated AUC in steady-state of vancomycin 1000 mg every 12 h is
205 shown in Figure 3. Vancomycin concentrations in CSF greater than or equal to 0.25 mg/L, 0.5
206 mg/L, 1 mg/L, and 2 mg/L were exceeded in 99.8%, 96.0%, 61.4%, and 0.1 % of simulated
207 patients, respectively for a regimen of 2000 mg every 12 h. Similarly, these thresholds were
208 exceeded in 87.2%, 57.8%, 5.6%, and 0% of simulated patients receiving 1000 mg every 12
209 h. With continuous infusion vancomycin concentrations in CSF greater than or equal to 0.25
210 mg/L, 0.5 mg/L, 1 mg/L, and 2 mg/L were exceeded in 100.0%, 100.0%, 96.8%, and 25.6% of
211 patients receiving a daily dose of 6000 mg, and in 100.0%, 97.4%, 67.4%, and 0.3% receiving
212 a daily dose of 4000 mg.

213 5. Discussion

214 To our knowledge, this is the first population PK study of vancomycin concentrations in serum
215 and CSF in critical care patients with proven or suspected ventriculitis. We found that
216 penetration of vancomycin into CSF is poor, with a median penetration ratio of only 3% and a
217 large intersubject variability in CSF vancomycin concentration as well as resultant CSF/serum
218 ratios. However, PK variability in CSF was not explained by any covariates. Our study suggests
219 the additional need for therapeutic drug monitoring of vancomycin in CSF if vancomycin MIC
220 is ≥ 1 mg/L to avoid treatment failures due to underexposure in CSF and to identify patients for
221 a change of therapy.

222 It is generally accepted, that the drug penetration into CSF is indicative of the transport across
223 the choroid plexus at the blood–CSF barrier.¹³ Therefore, a separate CSF compartment was
224 considered in our model and linked to the central compartment by a first-order process. Our
225 PK model suggest that vancomycin penetration (median $t_{1/2cb}$ 9 h) into CSF is slower than CSF
226 clearance (median $t_{1/2bc}$ 8 h) (Table S2). This is consistent with other studies in ventriculitis
227 patients¹⁴ as well as in non-inflamed meninges.¹⁵ CSF drain volume from the EVD can be high
228 in patients with hydrocephalus after placing the EVD. Therefore, loss through an EVD could

229 be an additional route of drug elimination from CSF.¹⁶ However, a CSF drain over the course
230 of treatment was not found to influence the pharmacokinetics of vancomycin. The high
231 apparent volume of CSF reflects the relatively low CSF concentrations compared with serum.
232 V_{CSF} is not a physiological CSF volume; it is merely a scalar that explains the concentration
233 observed in the CSF. Previous studies identified CSF albumin level as a determinant of CSF
234 vancomycin concentration.¹⁶⁻¹⁸ However, albumin level as a predictor of the blood brain barrier
235 is not validated in patients with external drain.¹⁹ This is because an increased CSF albumin is
236 influenced by blood in the CSF through subarachnoid bleeding or intracerebral bleeding.
237 Furthermore, CSF albumin may vary with time and patients in previous studies were included
238 after neurosurgery for only 72 h.¹⁶⁻¹⁸ Since the majority of EVD-related infections occurs within
239 the first 5 to 14 days after insertion, CSF albumin level as a surrogate guide to CSF vancomycin
240 concentration should not be extrapolated to ventriculitis patients.^{20, 21} In our study, all patients
241 were at least five days post neurosurgery.

242 Vancomycin does not show universally low penetration into CSF. While penetration in inflamed
243 meninges is reportedly as high as 81%, penetration into CSF in normal or mildly infected
244 meninges are conflicting varying from 0 – 36%.⁵ Other studies suggest that neurosurgical
245 procedures may damage the blood-brain-barrier and facilitate penetration of vancomycin into
246 CSF.^{16, 18} Although, many studies have estimated CSF penetration using a single point
247 estimates of serum and CSF vancomycin concentrations. Vancomycin CSF-to-serum ratios in
248 six patients with ventriculitis ranged from 5 to 17%, with patients achieving CSF concentrations
249 of 1.1–6 mg/L.⁵ This variability is consistent with the PK variability in our study population with
250 penetration ranging from 1 to 18%. No covariate predicted vancomycin CSF penetration, as
251 reported by Beach and colleagues.⁵ Furthermore, there was no statistically significant
252 correlation between plasma AUC and CSF AUC, which poses challenges for the use of serum
253 TDM to ensure therapeutic concentrations in CSF. However, 34% of our CSF samples showed
254 very low vancomycin concentrations. Patients with ventriculitis may benefit from continuous
255 infusion to ensure higher CSF concentrations of vancomycin.^{15, 22} Continuous infusion may
256 also simplify therapeutic drug monitoring (TDM) in daily routine because concentration

257 measurement is time-independent and facilitates calculation of the AUC. As reported by Neely
258 and colleagues, more than approximately 50% of the interindividual variability in the AUC are
259 not explained by trough concentration.²³ Further clinical studies are warranted to investigate
260 the pharmacokinetics, safety and efficacy of vancomycin infusions for the treatment of
261 ventriculitis.

262 From a PD point of view, MRSA and MRSE are the most challenging pathogens in nosocomial
263 CNS infection.¹ It is unclear which PK-PD target should be used to optimise the outcome for
264 infections within the CNS.^{6, 24} Data from an experimental pneumococcal meningitis model
265 suggest peak concentration of vancomycin 4 times the MBC for a maximal bacterial killing rate
266 in CSF.²⁵ An AUC/MIC value of 400 has been established as the PK - PD target in serum
267 based on in-vitro and animal data.² In CSF of our patients, an AUC/MIC target of 400 is hardly
268 exceeded. More work is required to better understand PD targets at the site of infection for
269 patients with ventriculitis. In our study, 61.4% of the simulated patients with 2000 mg every 12
270 h as a prolonged infusion exceeded CSF trough concentrations of 1 mg/L assuming all drug
271 in the CSF is unbound, whereas 96.0% exceeded 0.5 mg/L.

272 Patients in our study were generally young without any measured renal dysfunction on day of
273 inclusion (median CrCL 122 mL/min, Table 1) in contrast to the renal function in other studies
274 (mean CrCL 90 mL/min²⁶, 56 mL/min and 78 mL/min²³). In concordance vancomycin
275 clearance in serum (6 L/h) was higher comparing to other PK studies in critically ill patients
276 (4.6 L/h²⁶, 3.0 L/h²³). In severe infections and/or deep infections trough concentrations in
277 serum of 15-20 mg/L (AUC of 600-800 mg/L*h) are recommended.^{1, 2} Young patients with
278 augmented renal clearance presented in this study (8 of 21 patients with CLCr \geq 130 mL/min,
279 Table S1) are at high risk of insufficient concentrations of vancomycin with conventional dosing
280 regimens. Therefore, in critical care patients with CNS infections caused by MRSA or MRSE
281 with an MIC \geq 1 mg/L, the standard dosing regimen of vancomycin 2000 every 12 h as a
282 prolonged infusion is unlikely to ensure adequate CSF concentrations. However, TDM in CSF
283 may identify patients with sufficient vancomycin concentrations in CSF. In those displaying

284 ARC, increased frequency of dosing or continuous infusion with serum AUC of 600-720 mg/L*h
285 may be more appropriate.²⁷ In addition, continuous infusion may reduce renal toxicity
286 especially with high doses.²⁸ Alternatives like linezolid, daptomycin or sulfmethoxazol-
287 trimethoprim should be considered in patients with high serum concentrations (AUC up to 800
288 mg/L*h) and low CSF concentrations (<1 mg/L).¹

289 There are several limitations of our study. First, the study was relatively small, which may have
290 hampered robust estimates of the extent of PK variability and the identification of covariates
291 that may have explained some of the observed variance. CrCL was estimated, because the
292 measurement is not routinely performed in routine clinical care. Secondly, pharmacokinetic
293 data were not adjusted for protein binding, because we measured the total concentration in
294 serum and CSF. Due to negligible protein levels in CSF compared to serum and that protein
295 binding of vancomycin is not high, CSF concentrations might be free concentrations for
296 vancomycin. However, protein binding of vancomycin in the CSF is currently unknown. Third,
297 the ethical approval allowed two samples per day and of the 186 samples, 64 (34%) were
298 reported below the limit of quantification which might have an impact on the final parameter
299 estimates from the population PK model.

300 In conclusion, this is the largest PK study of critical care patients with proven or suspected
301 ventriculitis. Population pharmacokinetic modeling approach is a useful tool to predict drug
302 exposure under different dosage regimens. We found, that vancomycin showed low
303 penetration into CSF. However, because of inter-subject variability of vancomycin TDM in both
304 serum and CSF and higher daily doses may be an option to ensure adequate trough levels at
305 the target site of infection and to identify patients for a change of therapy. Novel dosing
306 strategies of vancomycin should be investigated in further clinical studies in ventriculitis
307 therapy such as administration by continuous infusion in order to reduce renal toxicity and to
308 avoid antibiotic underexposure in the context of augmented elimination or impaired target site
309 penetration.

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317 The authors declare that they have no competing interests.

318 Authors' contributions:

319 UB participated in the design of the study, measured vancomycin concentrations by
320 immunoassay, was responsible for acquisition of data, performed the pharmacokinetic
321 analysis and drafted the manuscript. VH conceived of the study, participated in its design and
322 coordination, and was responsible for acquisition of data. ORF participated in the design of the
323 study, including interpretation of results, and measured vancomycin concentrations by
324 immunoassay. CVK participated in the design of the study, including interpretation of results,
325 and was responsible for acquisition of data. ACR measured vancomycin concentrations by
326 immunoassay. WH performed the pharmacokinetic analysis and helped to draft the
327 manuscript. NT made substantial contributions to the conception and design of the study and
328 also interpreted the results. JB made substantial contributions to the conception and design of
329 the study and also interpreted the results. All authors critically revised the manuscript for
330 important intellectual content, and all authors read and approved the final manuscript.

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332 **7. References**

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395

Age (years), median (range)	52 (46-80)
Weight (kg), median (range)	76 (55-105)
Body mass index, median (range)	25.95 (20-33)
Sex, %male/%female	52,4%/47,6%
CrCL on day of inclusion (mL/min), median (range)	120.1 (52.3-217.6)
CRP in serum on day of inclusion (mg/dL), median (range)	3.1 (0.4-36.7)
Interleukin 6 in serum on day of inclusion (pg/mL), median (range)	13.7 (2.4-274.0)
CSF drain in 24 h on day of inclusion (mL), median (range)	183 (21-360)
Interleukin 6 in CSF on day of inclusion (pg/mL), median (range)	3398 (140-24522)
Cells in CSF on day of inclusion (/uL), median (range)	503 (4-2894)
Protein in CSF on day of inclusion (mg/dL), median (range)	10.7 (1.3-30.3)
Glucose in CSF on day of inclusion (mg/dL), median (range)	72 (47-126)
Glucose CSF/serum ratio on day of inclusion, median (range)	0.55 (0.38-0.99)
SAPS II on day of inclusion, median (range)	47 (13-62)
SAPS II on day of exclusion, median (range)	32 (13-61)

SOFA Score on day of inclusion, median (range)	6 (1-12)
SOFA Score on day of exclusion, median (range)	2.5 (0-8)
30-day mortality	0

396

397 **Table 1** Patient characteristics

398 CrCL: Estimated creatinine clearance (calculated using the Cockcroft–Gault equation ¹¹); CRP:

399 C-reactive protein; SAPS II: Simplified Acute Physiology II Score

400

	mean	± SD	median	95% CI
SCL (L/h)	6.11	±2.16	5.89	5.19-7.23
V _c (L)	24.33	±11.47	25.40	16.42-28.59
k _{cp} (h ⁻¹)	1.44	±1.22	1.18	0.61-1.86
k _{pc} (h ⁻¹)	2.38	±1.47	2.47	1.56-3.08
k _{cb} (h ⁻¹)	0.18	±0.23	0.07	0.03-0.18
k _{bc} (h ⁻¹)	0.12	±0.10	0.09	0.06-0.12
V _{CSF} (L)	828.51	±203.78	819.43	731.77- 999.97

401

402 **Table 2** Population pharmacokinetic mean and median parameters of vancomycin obtained

403 by Pmetrics

404 SCL: clearance in L/h; V_c: apparent volume of distribution of the central compartment in L;

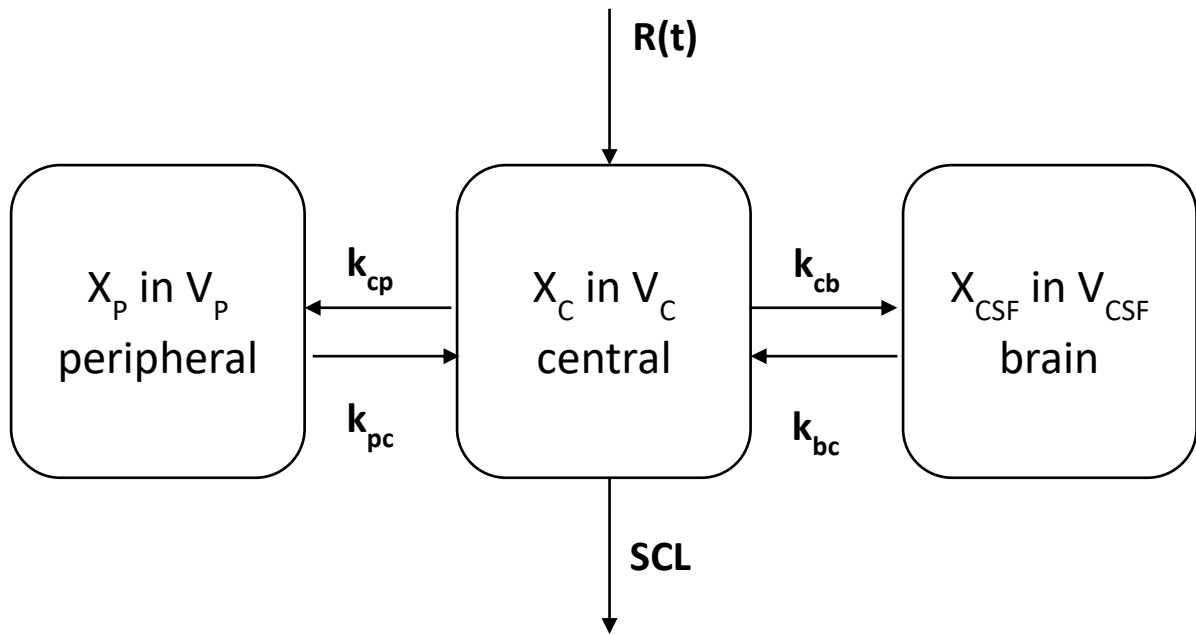
405 V_{CSF}: apparent volume of distribution of the cerebrospinal fluid compartment in L; k_{cp}, k_{pc}, k_{bc},

406 k_{cb}: linear transfer rate constants in h⁻¹

407

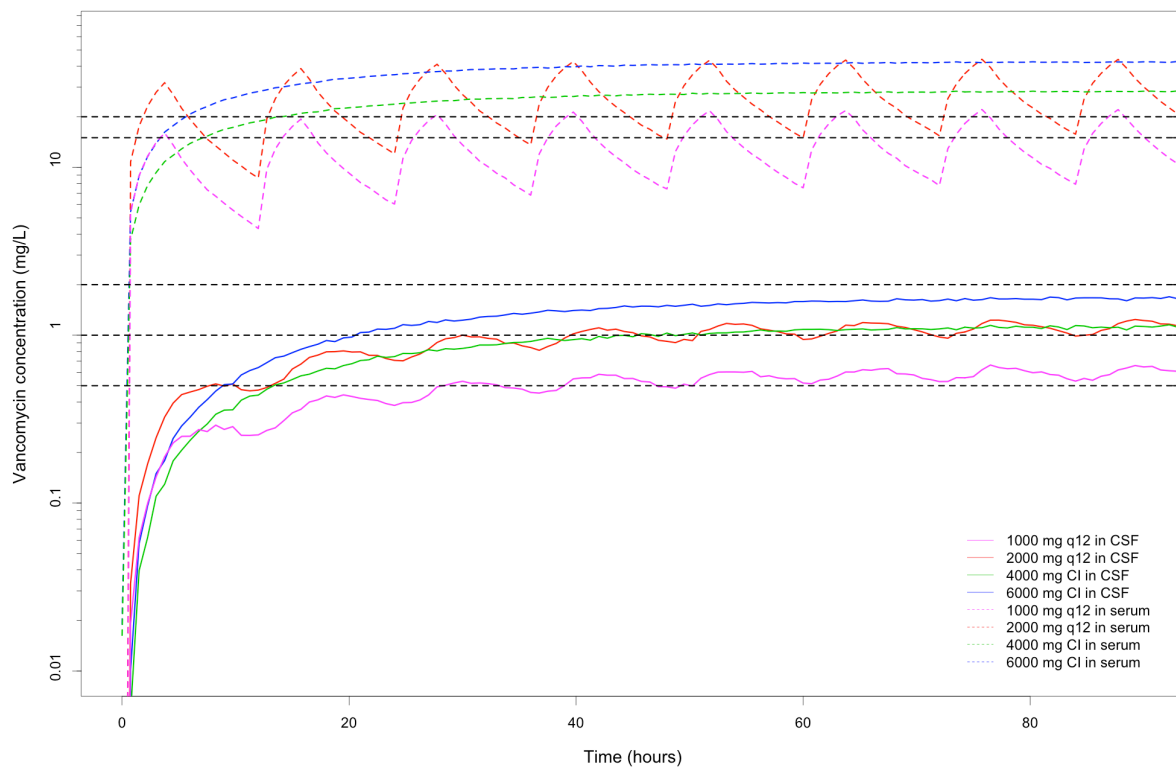
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418 **Figure 1** Structural model

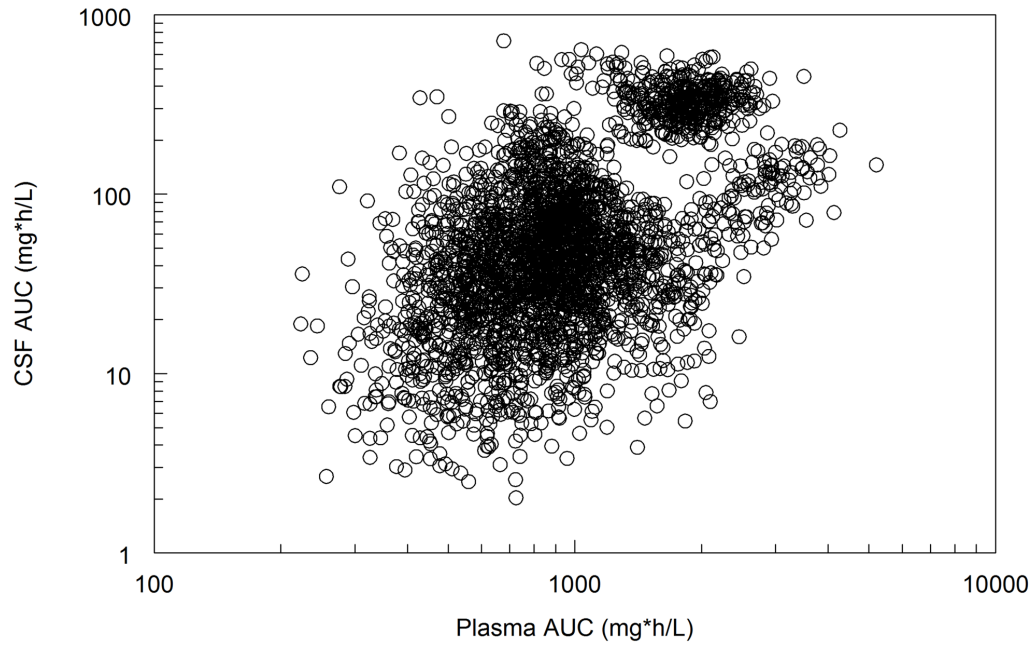
419 X_c is the total amount of vancomycin (mg) in the central compartment. $R(t)$ is the zero-order-
420 infusion of vancomycin into the central compartment (mg/h). SCL is the clearance of
421 vancomycin from the central compartment (L/h) with a volume V_c (L). X_p is the total amount of
422 vancomycin (mg) in the peripheral compartment with a volume V_p (L). k_{cp} , k_{pc} , k_{bc} and k_{cb} in h^{-1}
423 represent first-order transfer constants connecting the various compartments. The CSF
424 compartment (X_{CSF}) has an apparent CSF volume (V_{CSF} ; given in litres).



425

426 **Figure 2** Comparison of different dosing regimens as prolonged infusions over 4 h or
 427 continuous infusion (CI) using the pharmacokinetic model

428 Median time course of vancomycin concentrations simulated in serum and CSF over four days
 429 without loading dose. Targeted vancomycin trough concentrations in CSF were 0.25 mg/L, 0.5
 430 mg/L, 1 mg/L, and 2 mg/L. Targeted vancomycin trough concentration in serum were 15-20
 431 mg/L for intermittent administration. This figure appears in color in the online version of *JAC*
 432 and in black and white in the print version of *JAC*.



433

434

435 **Figure 3** Simulated AUC in steady-state (AUC_{0-24}) of vancomycin

436 Simulation of 3000 patients with vancomycin 1000 mg every 12 h as prolonged infusion using

437 the pharmacokinetic model.