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Population pharmacokinetics and dosing simulations of total and unbound temocillin in the plasma and CSF of neurocritically ill patients with external ventricular drain-related cerebral ventriculitis

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Background: Cerebral ventriculitis might be caused by Gram-negative bacteria, including ESBL producers. Temocillin may be a useful treatment option in this scenario; however, no consistent data are available regarding its penetration into the CSF.

Objectives: To describe the population pharmacokinetics of temocillin in plasma and CSF and to determine the probability for different simulated dosing regimens to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets in the CSF.

Methods: Ten post-neurosurgical critically ill adult patients requiring continuous drainage of CSF were included in this monocentric, prospective, open-label, non-randomized study. They received 2 g loading dose temocillin over 30 min IV infusion, followed by a 6 g continuous infusion over 24 h. Total and unbound concentrations were measured in plasma ($n=88$ and 86) and CSF ($n=88$ and 88) samples and used to build a population PK model. Monte Carlo simulations were performed to estimate the PTA at 100% C_{ss}>MIC (steady state concentration above the MIC) in CSF.

Results: All patients were infected with Enterobacterales with temocillin MICs ≤8 mg/L. The median (min-max) temocillin penetration in CSF was 12.1% (4.3-25.5) at steady state. Temocillin unbound plasma pharmacokinetics were best described by a one-compartment model. PTA for the applied dosing regimen was >90% for bacteria with MIC ≤ 4 mg/L.

Conclusions: The currently approved dose of 6 g by continuous infusion may be adequate for the treatment of ventriculitis by Enterobacterales with MIC ≤ 4 mg/L if considering 100% C_{ss}>MIC as the PK/PD target to reach. Higher maintenance doses could help covering higher MICs, but their safety would need to be assessed.

Introduction

Temporary CSF drainage via an internalized shunt system or an external drainage in cases of acute increases of intracranial pressure is commonly used to treat patients with acute or chronic hydrocephalus.[1,2] Infection is the most common serious complication of these procedures.[3,4] More specifically, ventriculitis incidence can reach 22% in patients with external ventricular drainage (EVD).[3,5] These infections are associated with increased morbidity and mortality, drain revision, pain, neurological

deterioration, prolonged hospital stay and higher costs.[6] Gram-negative bacteria represent 10%–20% of the incriminated germs.[7,8] Meropenem is commonly used as empirical treatment in this clinical context, due to its adequate penetration into the CSF and broad spectrum of activity, including against ESBL-producing Gram-negative bacteria.[6,9,10] Antibiotics with a more narrow spectrum would, however, be desirable to prevent resistance development.

Considered as a carbapenem-sparing drug, temocillin (6-methoxy-ticarcillin) is characterized by a spectrum covering Enterobacterales, including most ESBL producers.[11,12] It is reported to minimally impact human intestinal microbiota.[13,14] It is currently licensed for use in septicaemia as well as in urinary tract, wound and lower respiratory tract infections caused by susceptible Enterobacterales.[15] The role of temocillin as a therapeutic option for CNS infections is uncertain with a very few data available on its penetration into CSF, including those that are neurocritically ill. The only old available data report low concentrations (1–8 mg/L), close to the MIC of offending organisms after the administration of 2 g three times a day.[16] The currently recommended dose for critically ill patients is 6 g/day divided in three administrations, with a susceptibility breakpoint set by EUCAST at 16 mg/L (restricted to complicated urinary tract infections).[17] However, no pharmacokinetic/pharmacodynamic (PK/PD) evaluation has been performed to provide reassurance of the appropriate dosage.

For β-lactams, the time that unbound drug concentrations exceeds the MIC ($fT>MIC$) is the PK-PD index driving efficacy,[18] even if the precise exposure target (from 1 to 4×MIC during 40% to 100% of the dosing interval) remains debated.[19] For critically ill patients with high β-lactam PK variability, continuous infusion can help to improve PD target attainment and has been successfully applied for temocillin.[20] Of note, temocillin is one of the rare β-lactams to show a high protein binding (85% in healthy volunteers), which is saturable and dependent on the plasma albumin concentrations.[21] In critically ill patients with cerebral ventriculitis, we previously showed that unbound fractions ranged from 32% to 52% for total plasma concentrations between 20 and 200 mg/L, possibly ensuring increased exposure compared with what would have been estimated based on unbound fractions determined for healthy volunteers.[21] The effect of critical illness on temocillin protein binding is not well characterized.

The aims of this study were (i) to investigate and characterize the PK of total and unbound temocillin in plasma and CSF after administration of 6 g of temocillin by continuous infusion in neurocritically ill patients suspected of cerebral ventriculitis after EVD, and (ii) to build a population PK model and use it to perform Monte Carlo simulations to define optimized dosing regimens for these patients.

Materials and methods

Ethical approval

Ethical approval was obtained from the Comité d'Ethique Hospitalo-Facultaire of the Cliniques uiniversitaires St-Luc; unique Belgian registration number B403201629439. Studies have been registered at EudraCT (number 2015-003457-18). A written consent was obtained from the patients or nearest relatives before inclusion.

Study design, patients and data collection

This prospective, monocentric, open-label and non-randomized PK study enrolled patients hospitalized in the ICU of the Cliniques universitaires St-Luc (Brussels, Belgium) and requiring EVD. Patients were included if ≥18 years old, diagnosed with or showing clinical signs of cerebral ventriculitis, and with CSF cultures positive for Enterobacterales with a temocillin MIC ≤ 8 mg/L. Patients were excluded if aged <18 years, were potentially infected with a pathogen resistant to temocillin, allergic to any penicillin, or had participated in another experimental study with temocillin within 4 weeks, as well as pregnant or lactating women.

The following parameters were collected: demographics (age, sex, weight, BMI), treatment duration, daily CSF culture, with Gram strain and corresponding MIC, WBC count, severity scores (APACHE II and SOFA), C-reactive protein, medical history, biological and physiological parameters—plasma/CSF protein and albumin concentrations, CSF glucose and lactate concentrations, creatinine clearance [calculated as (urine creatinine × 24 h urine volume/blood creatinine)/1440 min]—and hepatic enzymes (GGT, ALT and AST).

Antibiotic treatment

Temocillin was given as monotherapy for documented infections caused by susceptible pathogens or in combination in case of polymicrobial infection with bacteria resistant to temocillin (comedication selected based on their susceptibility profile). All patients received a temocillin loading dose (2 g) administered over 30 min in 50 mL of saline for injection, followed by continuous infusion over 24 h (6 g/day in 48 mL of water for injection infused at a rate of 2 mL/h) for up to 12 days.

Blood and CSF sample collection

Blood and CSF samples were taken at the end of the loading dose, and one or two samples were taken during each 24 h continuous dosing interval. Blood samples were drawn with an arterial catheter, collected in EDTA tubes and centrifuged for 15 min at 2000 **g** and 4°C. CSF samples were obtained via the EVD, and collected in dry tubes simultaneously with each blood sample whenever possible. All samples were stored at −80°C until analysis.

Analytical method

Chemicals and reagents

Temocillin was obtained from EUMEDICA S.A. (Manage, Belgium) as the branded product (NEGABAN) approved for parenteral human use in Belgium, the UK and France. Ticarcillin disodium (internal standard) was acquired from Sigma-Aldrich Corp. (St Louis, MO, USA); HPLC-grade methanol and acetonitrile were from J.T. Baker (Deventer, The Netherlands); formic acid and ammonium acetate were from Merck KgaA (Darmstadt, Germany).

Total and unbound temocillin determination

Total and unbound temocillin plasma and CSF concentrations were measured by an HPLC-MS/MS assay using ticarcillin as internal standard. Ultrafiltration was used to collect the unbound drug. The method was previously fully validated in plasma[22] for both total and unbound concentrations and partially validated here in CSF (see Supplementary method 1 for methodological details and Figure S1 and Tables S1 and S2 for validation data; available as Supplementary data at *JAC* Online), according to the FDA recommendations.[23]

Plasma and CSF total protein and albumin content

Total proteins were measured by the biuret method,[24] and albumin by the bromocresol green dye method[25] using a Cobaz® analyser (Cobaz® 8000

Table 1. Characteristics of the study population

	Demographics				Biological and physiological parameters							Severity scores	
ID	Sex	Age (years)	Weight (kg)	BMI (kg/m^2)	CRP (mg/L) <5[a]	CrCl (mL/min) >78[a]	Plasma proteins (g/L) 64–83[a]	Plasma albumin (g/L) 35–52[a]	GGT (IU/L) <40[a]	ALT (IU/L) 7–35[a]	AST (IU/L) 13–35[a]	SOFA score	APACHE II score
1	Female	56	75	25.9	131.0	129.0	63.0	38.0	315.0	150.0	94	2	21
2	Male	55	70	24.2	74.0	126.5	69.0	32.9	224.0	59.0	25	3	22
3	Male	58	80	26.2	24.9	110.0	70.8	32.6	41.0	19.0	9	1	15
4	Male	60	80	25.8	29.2	97.5	69.2	26.6	32.0	48.0	33	4	11
5	Female	54	65	23.8	98.9	132.5	68.3	24.8	244.0	235.0	221	3	17
6	Female	60	75	33.3	14.7	110.5	65.0	36.0	38.0	19.0	22	3	21
7	Female	59	90	31.1	123.7	66.0	60.0	40.2	52.0	17.0	32	3	14
8	Female	50	120	45.2	31.3	109.0	65.0	36.8	63.0	44.0	48	3	18
9	Male	20	80	26.1	53.2	153.0	60.8	34.8	72.0	48.0	18	0	5
10	Female	55	59	21.9	45.9	221.0	69.4	40.5	15.0	29.0	28	1	10
Median		55.5	77.5	26.0	49.6	118.5	66.7	35.4	57.5	46.0	30	3	16
Mean		52.7	79.4	28.4	62.7	125.5	66.1	34.3	109.6	66.8	53	2.3	15.4

CrCl, creatinine clearance based on a 24 h urine collection test; CRP, C-reactive protein; ID, patient identification.
[a]Reference value or range for this parameter.

series; Roche/Hitachi Cobaz Systems Diagnostics, F. Hoffmann-La Roche Ltd, Basel, Switzerland).

Microorganisms and MIC determinations

Identification and antimicrobial drug susceptibility of the isolates were determined using automated systems of the clinical microbiology laboratory of the Cliniques Universitaires St-Luc (MALDI-TOF MS; Phoenix®, Becton-Dickinson, Franklin Lakes, NJ, USA; and Etest®, bioMérieux, Marcy-l'Etoile, France).

PK analysis

Plasma and CSF total and unbound temocillin concentrations were plotted against time, and the AUC at steady state was determined every day between the first and the last day of treatment using Equation 1:[26]

$$\text{AUC} = C_{ss} \times \tau, \quad (1)$$

where C_{ss} is the temocillin concentration measured at steady state and τ is the dosing interval (24 h).

The other calculated parameters included the unbound fraction (UF) of temocillin (Equation 2), the penetration (PE) ratio[27] (Equation 3) and the proportion (PR) of total temocillin in CSF (Equation 4). The PR is a better estimate for the diffusibility of temocillin through the blood–brain barrier.

$$\text{UF}(\%) = 100 \times (C_{\text{unbound}}/C_{\text{total}}) \quad (2)$$

$$\text{PE}(\%) = 100 \times (\text{AUC}_{\text{total in CSF}}/\text{AUC}_{\text{total in plasma}}) \quad (3)$$

$$\text{PR}(\%) = 100 \times (\text{AUC}_{\text{total CSF}}/AUC_{\text{unbound in plasma}}) \quad (4)$$

Population PK modelling

Population PK analysis was performed using the non-linear mixed-effect modelling program Monolix version 2021R1 (LIXOFT, Antony, France) implementing the stochastic approximation expectation maximization algorithm. The PK model was built to fit three types of data simultaneously: temocillin unbound and total plasma concentration and temocillin unbound concentration in CSF. The details about model development, covariate screening and model validation are presented in the Supplementary material 1 and Supplementary method 2.

Monte Carlo simulation assessment for different dosing regimens

Monte Carlo simulations were performed by Simulx 2021R1 based on the final PK model to generate 1000 profiles of total temocillin in plasma and temocillin in CSF for each candidate dosing regimen (see details in Results). The target was set as 100% C_{ss}>MIC for temocillin concentration in CSF between 24 and 150 h after treatment. Peak concentrations for a loading dose of 6 g were also simulated. For each dosing regimen, the PTA was evaluated for MIC of 2, 4, 8 and 16 mg/L.

Statistical analysis

Statistical analyses of correlations between plasma and CSF concentrations were performed using version 4 of GraphPad software (GraphPad Prism Software, San Diego, CA, USA). Data were described as the mean ± SD or the median (range). Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Ten patients were included in the study. In total, 88 measured total plasma concentrations and 86 measured unbound plasma concentrations (two outliers discarded) together with 88 measured total/unbound CSF concentrations were used for model development. The demographics and baseline clinical characteristics of the patients are summarized in Table 1. All patients showed low

Table 2. Microbiological data, treatment characteristics and CSF analysis for individual patients

	Microbiological data		CSF analysis						
ID	Isolates	MIC (mg/L)	Proteins (mg/dL) 15–45[a]	Albumin (mg/dL) <28[a]	CSF/blood albumin ratio	Lactate (mmol/L) 1.1–2.4[a]	WBC<5/μL[a]	Glucose (mg/dL) 40–80[a]	Duration of temocillin treatment (days)[b,c]
1	*Klebsiella pneumoniae*[d,f]	4	4.30	2.60	0.068	2.30	143	70	7
	Klebsiella oxytoca[e]	2							
2	*K. pneumoniae*[d]	4	1.70	0.90	0.027	3.90	485	50	5
	K. pneumoniae[e]	4							
3	*Enterobacter cloacae*[d,g]	4	0.56	0.23	0.007	10.00	1945	18	7
4	*Escherichia coli*[d]	4	2.40	1.20	0.045	16.70	3620	3	7
5	*E. aerogenes*[d,f]	8	1.60	0.70	0.028	24.20	8504	3	4
6	*E. cloacae*[d,f]	8	8.60	4.50	0.125	20.20	2931	3	5
	K. pneumoniae[e]	4							
7	*K. pneumoniae*[d,f]	4	0.69	0.32	0.007	4.30	499	57	4
8	*E. cloacae*[d,g]	6	1.30	0.70	0.019	4.70	496	24	6
9	*E. cloacae*[d,g]	4	0.80	0.19	0.005	1.30	6	67	7
	E. coli[e]	8							
10	*E. cloacae*[d]	8	2.60	1.02	0.025	22.40	5894	3	13
Median			1.65	0.80	0.026	7.35	1222	21	7
Mean			2.46	1.24	0.036	11.00	2452	30	7

ID, patient identification.
[a]Reference value or range for this parameter.
[b]All patients received a 2 g loading dose followed by a daily dose of 6 g given by continuous infusion.
[c]See Table S3 for the whole antibiotic treatment received by the patients and the microbiological and clinical outcomes.
[d]Isolate from CSF.
[e]Isolate from blood.
[f]ESBL producer.
[g]Cephalosporinase producer.

SOFA and APACHE II severity scores. Median (range) plasma protein and albumin concentrations were 66.7 (60.0–70.8) and 35.4 (24.8–40.5) mg/L, respectively. Nine patients showed high (>78 mL/min) creatinine clearance, and a majority of them elevated hepatic enzymes in plasma. Microbiological data, treatment characteristics and CSF analysis for individual patients are presented in Table 2. Bacteria isolated in CSF had temocillin MICs of 4, 6 or 8 mg/L. The median (range) duration of temocillin treatment was 7 (4–13) days (see Table S3 for the global treatment of these patients). All patients had fever and CSF WBC count >5/μL before treatment. CSF protein and albumin concentrations ranged from 0.56 to 8.60 g/L and 0.23 to 4.50 g/L, respectively. CSF lactate was elevated (>2.4 mmol/L) in seven patients, and CSF glucose was low (<40 mg/dL) in six patients.

PK analysis

Individual data of plasma and CSF concentration profiles of temocillin are presented in Figure 1. Differences were observed among patients with respect to both the concentrations achieved in the plasma and in the CSF, and to the time needed to reach the steady state in CSF. In plasma, the median (min–max) total and unbound concentrations after the loading dose (2 g) administered over 30 min (C_{30min}) were 145.80 (126.80–166.30) mg/L and 51.11 (46.40–79.96) mg/L, respectively. During the continuous infusion (6 g/24 h), steady-state total and unbound median concentrations ($C_{24–168h}$) were 91.04 (60.08–129.80) mg/L and 29.05 (13.67–54.00) mg/L, respectively. The unbound median fraction was 29.05 (19.96–52.52)%.

In CSF, more than 6 h was needed to reach concentrations >8 mg/L (MIC of most infecting bacteria), with total and unbound CSF steady-state median concentrations ($C_{24-168h}$) of 11.18 (2.77–22.55) mg/L and 9.37 (2.60–20.50) mg/L.

The concentration of temocillin was measured after the end of the treatment by continuous infusion in five patients. After 12 h, the median (min–max) total and unbound concentrations in CSF were 6.08 (2.98–10.40) mg/L and 5.60 (2.01–8.10) mg/L, respectively.

The median (min–max) percentage of penetration of temocillin in the CSF was 0.99 (0.43–2.30)% 30 min after the loading dose and 12.07 (4.26–25.47)% at steady state, both with high inter- and intra-individual variability (Figure 2a). The proportion of temocillin in the CSF was also highly variable but much higher [median (min–max) = 36.7 (18.1–69.9)%]. A positive correlation was observed between the unbound concentration in plasma and in CSF (Figure 2b), as well as between total and unbound concentrations in CSF (Figure 2c). In this case, a linear regression with a slope close to 1 (0.907) was observed, indicating that the drug is

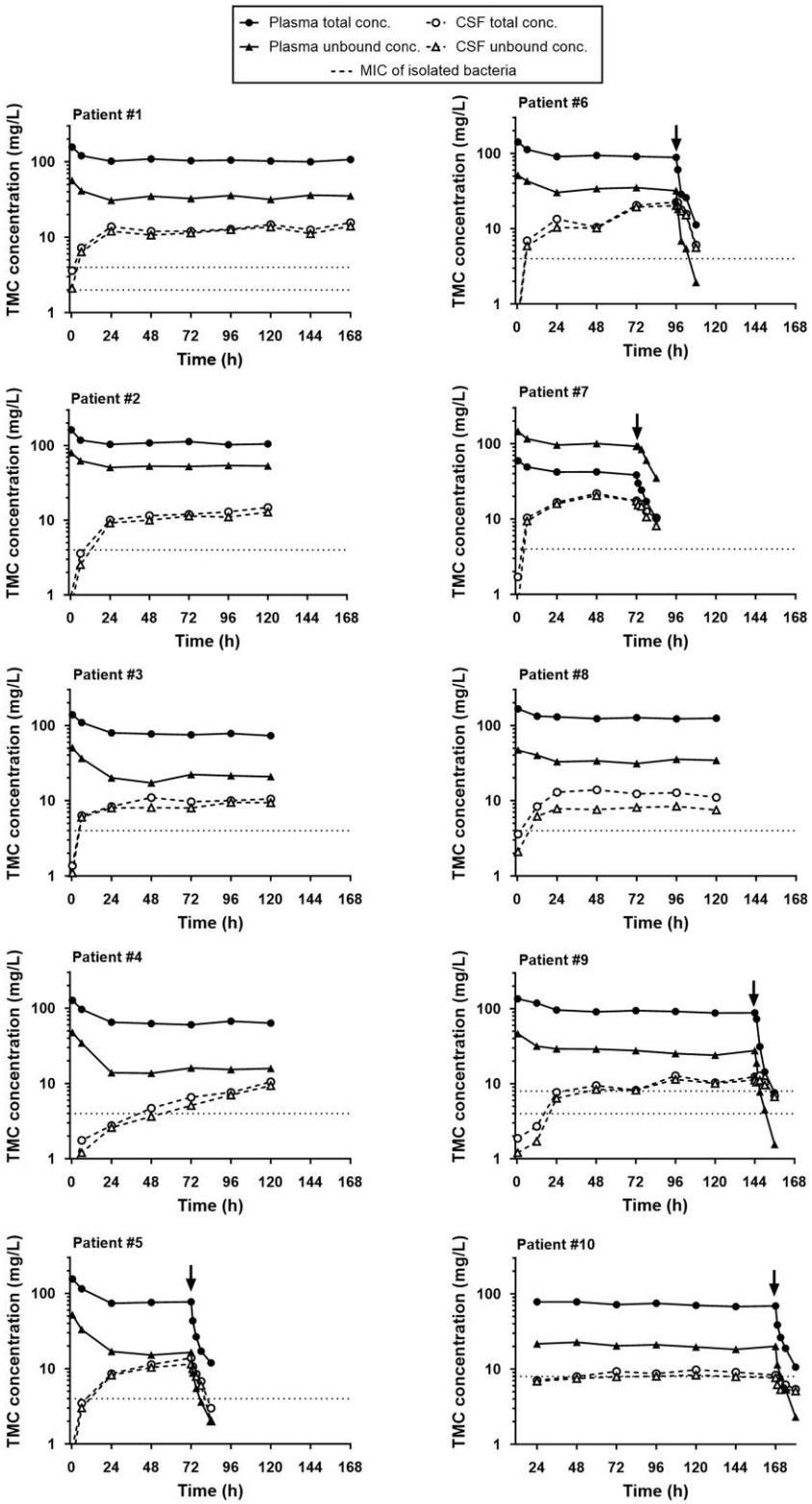

Figure 1. Individual profiles of temocillin total and unbound concentrations in the plasma and the CSF of patients. All patients received a loading dose (2 g) administered over 30 min followed by continuous infusion (6 g/day). The vertical arrow points to the time point at which the infusion was stopped in patients for whom the clearance of temocillin was followed. The dotted lines correspond to the MIC for the bacteria isolated in each patient. TMC, temocillin.

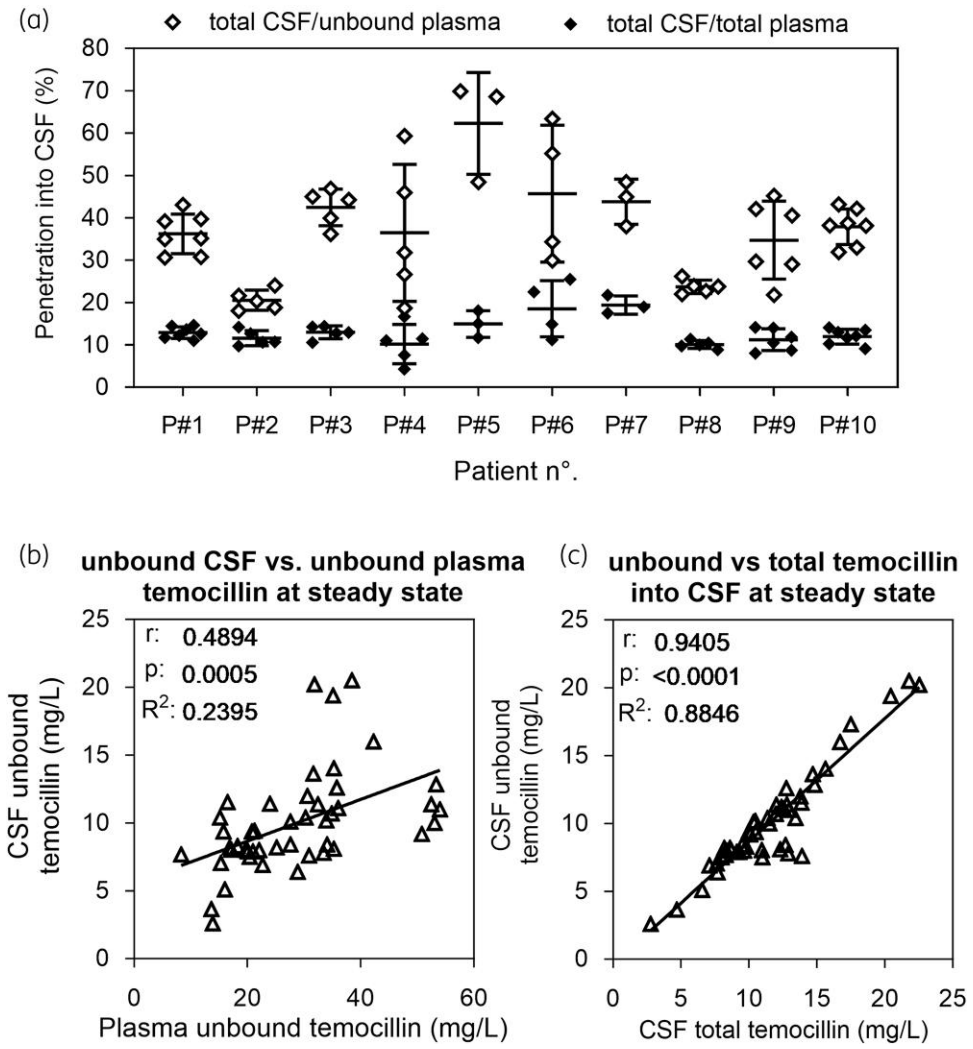

Figure 2. Temocillin penetration in CSF. (a) Individual data of penetration (total CSF/total plasma 24 h-AUC) and proportion (total CSF/unbound plasma 24 h-AUC) ratios at steady state. Each symbol corresponds to the AUC calculated for a 24 h interval, with the horizontal lines linked by a vertical line corresponding to the mean +/- SD. (b) Correlation between plasma unbound concentrations and CSF unbound concentrations. (c) Correlation between CSF total and unbound concentrations at steady state. Each symbol corresponds to a set of data at a specific time for a single patient. In (b) and (c) Pearson correlation coefficient (r) and *P* values of the correlation as well as R^2 of the linear regression are shown.

essentially unbound in this fluid [median unbound fraction of 89.64 (73.42–100.00)%] owing to the low protein concentration in CSF.

PK modelling

Temocillin unbound plasma concentration versus time profiles were best described by a one-compartment model with first-order elimination and first-order transferring to the CSF compartment. Building a two-compartment model and considering a back-transfer of temocillin from CSF to the central compartment did not improve the model fitting (no decrease in corrected Bayesian information criteria BICc; Table S4). The final structural model describing temocillin PK and its binding in plasma and CSF is illustrated in Figure 3. Inter-individual variability was estimated for all parameters. Variability on association and dissociation constants *k*_on and *k*_off was included to take into consideration potential variability in availability of binding sites between individuals. Additive error model was selected to describe residual variability for unbound and total plasma concentrations, whereas combined error model (additive plus proportional error) was used to describe residual variability for CSF concentration.

Initial screening of the correlation between PK parameter estimates and covariates indicated that WBC count in CSF (CSF_WBC), APACHE II score, AST, and lactate in CSF (CSF_ACLAC) could be potential covariates. Based on the criteria (Table S4), only the effect of CSF_ACLAC (calculated weighted mean[28] in the population: 7.15 mmol/L) on transferring rate constant from the central compartment to the CSF compartment (k_{13}) was retained in the final model as

expressed as below:

$$k_{13i} = k_{13pop} \times \left(\frac{CSF\_ACLAC_i}{7.15}\right)^{0.074} \times e^{\eta_{Cl,\,i}}$$

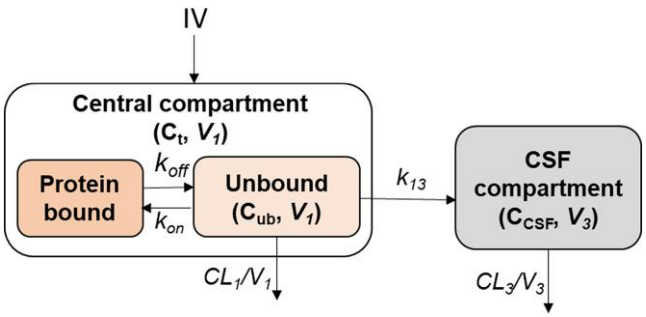

Figure 3. Schematic diagram of the final PK model for temocillin in the central compartment and in the CSF after IV infusion. $C_{CSF,}$ CSF unbound concentration; C_t, concentration at instant t; C_{ub}, plasma unbound concentration; CL_1, plasma clearance; CL_3, CSF clearance; k_{off}, first-order dissociation rate constant; k_{on}, second-order association rate constant; k_{13}, transferring rate constant from central to CSF compartment; V_1, volume of distribution in the central compartment; V_3, volume of distribution in CSF compartment. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

PK parameters of the final Model l together with bootstrap results from 1000 successful runs are reported in Table 3. The goodness-of-fit (GOF) plots of the final models are presented in Figures S2 and S3, and the Visual Predictive Checks (VPC) plots, in Figure S4.

CSF penetration/uptake was estimated using individual values for AUC_{24h} predicted from the model. The median (min–max) percentage of penetration was 0.62 (0.31–0.82)% 30 min after the loading dose and 11.3 (10.5–17.4)% at steady-state, and the median (min–max) percentage of proportion was estimated to be 37.3 (27.6–49.0)%. These values are close to those calculated in the non-compartimental analysis.

Monte Carlo simulations

Nine temocillin dosing regimens were simulated (Table 4). Regimen #1 is the original dosing regimen used in the study. To evaluate the effects of lactate concentration in CSF, unbound CSF and total plasma concentrations of temocillin time profiles of patients with lactate concentration of 2, 10 and 20 mmol/L were simulated and are presented in Figures 4 and 5, respectively. Increased CSF lactate concentration led to higher unbound CSF concentrations of temocillin (Figure 6a), but had little effect on total plasma concentrations (Figure 6b). Increasing the loading dose to 6 g resulted in the median of the peak total plasma concentration exceeding 350 mg/L from 1000 simulations and

Table 3. Estimates of the population pharmacokinetic parameters

Parameter	Estimate (%RSE) [shrinkage %]	Bootstrap median (95% CI)
Fixed effects		
CL_1 (L/h)	8.43 (11.1)	8.52 (6.76–10.70)
V_1 (L)	13.3 (3.93)	13.3 (12.6–14.2)
k_{13} (h^{-1})	3.38×10^{-4} (4.77)	2.71×10^{-4} (2.10×10^{-4} to 3.63×10^{-4})
V_3 (L)	0.17 (23.5)	0.130 (0.089–0.200)
CL_3 (L/h)	0.012 (5.76)	0.0097 (0.0070–0.0130)
k_{on} (L/mg/h)	0.076 (14.5)	0.065 (0.040–0.102)
k_{off} (h^{-1})	9.02 (14.9)	7.58 (4.74–12.10)
Effect of CSF_ALAC on k_{13}	0.074 (41.1)	0.100 (0.001–0.264)
Random effects		
BSV_CL_1 (%)	34.6 (22.9) [0.40]	33.2 (21.7–43.1)
BSV_V_1 (%)	6.90 (48.0) [13.5]	6.50 (1.46–10.30)
BSV_k_{13} (%)	4.69 (89.0) [29.0]	4.10 (1.19–15.10)
BSV_V_3 (%)	70.3 (25.0) [19.0]	64.2 (28.3–102.0)
BSV_CL_3 (%)	6.67 (93.3) [–32.3]	5.20 (1.33–13.00)
BSV_k_{on} (%)	18.9 (63.5) [–6.05]	13.90 (1.98–33.40)
BSV_k_{off} (%)	22.2 (49.6) [6.89]	16.50 (2.32–37.60)
Residual variability		
a_C_{ub} (mg/L)	4.88 (8.45)	4.88 (3.74–5.84)
a_C_{total} (mg/L)	12.4 (8.27)	12.40 (8.24–16.10)
a_C_{CSF} (mg/L)	0.73 (23.3)	0.73 (0.16–1.41)
b_C_{CSF} (mg/L)	0.10 (24.0)	0.0970 (0.0013–0.2100)

a, additive error; b, proportional error; BSV, between subject variability; C_{ub}, plasma unbound concentration; C_{total}, plasma total concentration; $C_{CSF,}$ CSF unbound concentration; CL_1, plasma clearance; CL_3, CSF clearance; CSF_ALAC, lactic acid concentration in CSF; k_{off}, first-order dissociation rate constant; k_{on}, second-order association rate constant; k_{13}, transferring rate constant from central to CSF compartment; RSE, Relative Standard Errors; V_1, volume of distribution in the central compartment; V_3, volume of distribution in CSF compartment.

Table 4. Summary of PTA estimation based on a target of 100% $C_{ss>MIC}$ in the CSF for proposed dosing regimens maintaining temocillin total plasma concentrations <350 mg/L

CSF lactate concentration (mmol/L)	MIC (mg/L)	#1 LD: 2 g/0.5 h MD: 6 g/24 h	#2 LD:4 g/0.5 h MD: 6 g/24 h	#3 LD: 2 g/0.5 h MD: 12 g/24 h	#4 LD:4 g/0.5 h MD: 12 g/24 h	#5 LD: 2 g/0.5 h MD: 18 g/24 h	#6 LD: 4 g/0.5 h MD: 18 g/24 h	#7 LD: 4 g/0.5 h; ID: 2 g/1 h MD: 6 g/24 h	#8 LD: 4 g/0.5 h; ID: 2 g/1 h MD:12 g/24 h	#9 LD: 4 g/0.5 h; ID: 2 g/1 h MD: 18 g/24 h
2	2	**99.9**[a]	**100**	**99.6**	**99.6**	**96**	**96**	**98.3**	**97.4**	**95.2**
	4	**93.4**	**97**	**99.5**	**99.5**	**96**	**96**	**96.8**	**97.4**	**95.2**
	8	49.2	60.5	**90.7**	**93.2**	**94.6**	**95**	65.1	**91.9**	**94.4**
	16	3.7	6.1	43	49.7	71.4	76	6.2	51.2	76.4
10	2	**100**	**100**	**99.6**	**99.6**	**96**	**96**	**98.3**	**97.4**	**95.2**
	4	**96.2**	**98.8**	**99.5**	**99.6**	**96**	**96**	**97.8**	**97.4**	**95.2**
	8	60.5	72.3	**93.4**	**95.9**	**95.2**	**95.6**	75.6	**94.7**	**95**
	16	6.5	10.2	53.8	60.9	79.5	82	11.4	61.8	82.3
20	2	**100**	**100**	**99.6**	**99.6**	**96**	**96**	**98.3**	**97.4**	**95.2**
	4	**97.1**	**99.2**	**99.6**	**99.6**	**96**	**96**	**98**	**97.4**	**95.2**
	8	64.8	76.9	**94.7**	**96.9**	**95.4**	**95.8**	80.6	**95.3**	**95**
	16	8.2	13.5	58.6	65.2	81.2	84.6	15.2	66	84.4

ID, intermediate dose; LD, loading dose; MD, maintenance dose.
[a]Values in bold highlight dosing regimens for which the PTA is >90%.

was not considered in further simulations, as this was the highest concentration reached in a single patient in a previous study, for which no adverse reaction was observed[21] (Figure 6b). Increasing the maintenance dose led to higher steady state concentrations in plasma and in CSF. Adding a 1 h infusion dose of 2 g after the loading dose slightly reduced the time needed to reach the steady state in CSF without marked influence on plasma concentrations.

Because the drug was administered by continuous infusion, PTA was assessed for 100% C_{ss}>MIC with MIC set for 2, 4, 8 or 16 mg/L (Table 4). PTA (100% C_{ss}>MIC) for the original dosing regimen (#1) was >90% for bacteria with MICs ≤ 4 mg/L whatever the CSF lactate concentration. Increasing the loading dose to 4 g (regimen #2) would not improve PTA significantly whereas doubling the maintenance dose to 12 g (regimen #3) could reach PTA (100% C_{ss}>MIC) of 90% for MIC ≤ 8 mg/L whatever the CSF lactate concentration while maintaining total plasma concentration below 350 mg/L. Our simulation suggests that a PTA (100% C_{ss}>MIC) of 90% for MICs of 16 mg/L could not be reached even when combining increasing loading doses and maintenance doses (regimens #4–6), or when adding after the loading dose a 2 g infusion over 2 h in order to reach faster the steady-state concentration (regimens #7–9). Considering the time needed to reach the steady state, lower targets (40%–70% *f*T>MIC) could be reached for 90% of isolates with MICs of 16 mg/L with the highest dosing regimen proposed (#9), whatever the CSF lactate concentration (not shown).

Discussion

This study is to our knowledge the first to describe the plasma and CSF pharmacokinetics of temocillin administered by continuous infusion in neurocritically ill patients with cerebral ventriculitis and external ventricular drainage with the aim to optimize dosing strategies in this specific population.

As for other β-lactams, the penetration of temocillin into CSF is weak, which was anticipated based on its physicochemical properties (hydrophilic molecule doubly negatively charged at physiological pH, with high plasma protein binding).[9] Lipophilicity is indeed a major characteristic of drugs that cross the blood–brain barrier by passive diffusion.[29] At steady state, the proportion of temocillin in the CSF is highly variable, due to differences in its binding to plasma proteins among patients,[21] whereas its penetration rate (12%) is comparable to that previously reported for this drug (8%–15%),[16] and in the range of those reported for other penicillins (6%–26%),[30,31] cephalosporins (0.7%–26%)[29,32–34] or carbapenems (1%–25%)[35–37] in infected patients. As for other β-lactams,[38,39] the penetration of temocillin in CSF is modest compared with that reported in other body fluids (peritoneal, vesicular, epithelial lining, ascitic fluids),[40–43] where temocillin concentrations reach 40%–70% of those measured in the plasma. This can be easily explained by the structure and function of the blood–brain barrier, protecting the brain from invasion by potentially toxic molecules, like drugs.[29] Lower penetration values in CSF are also reported for β-lactams in non-infected patients[33,44] as inflammation is well known to increase β-lactam diffusion in the CSF by opening tight junctions.[45]

Population PK modelling of temocillin has been reported previously in intensive care patients[20,40,43,46] and in

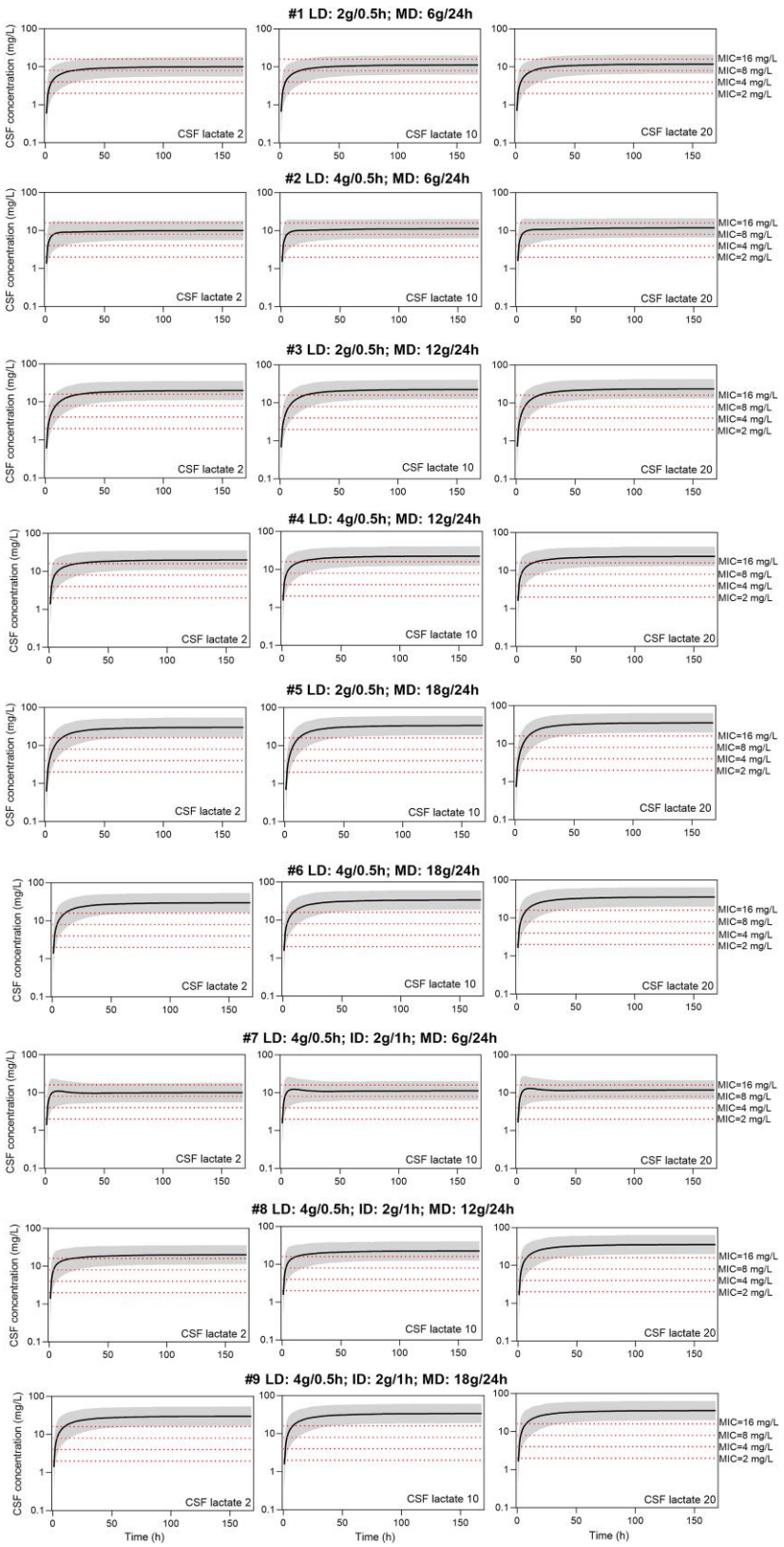

Figure 4. Simulated unbound CSF concentration-time profiles for temocillin when administered with different dosing regimens. The solid line represents the median of 1000 simulations,- and the limits of the grey area represent the 5th and 95th percentiles of simulations, and the dotted lines represent various MICs. Simulations were performed for CSF lactate concentrations of 2 (left), 10 (middle) and 20 (right) mmol/L. ID, infusion dose; LD, loading dose; MD: maintenance dose. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

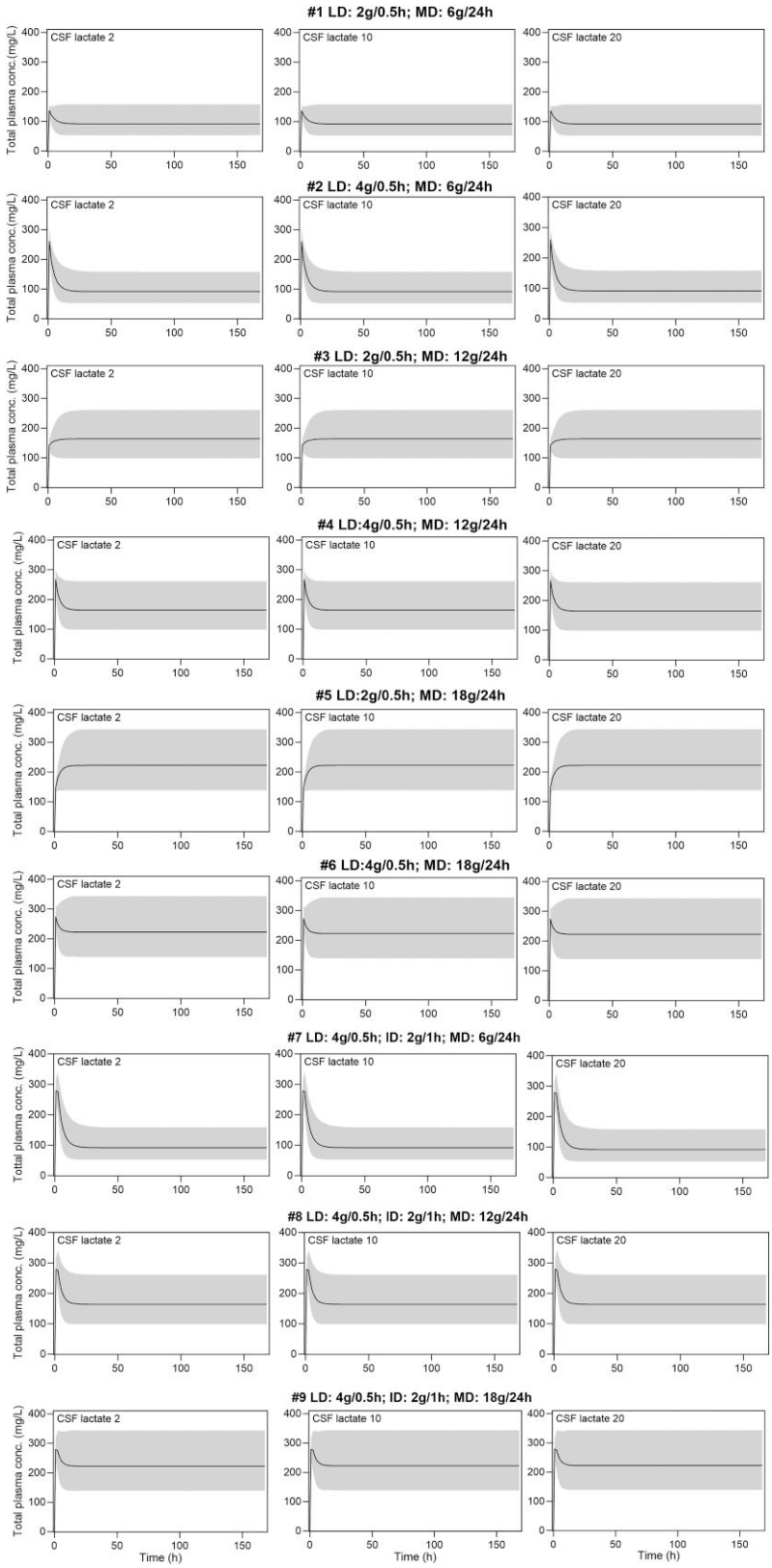

Figure 5. The simulated total plasma concentration-time profiles for temocillin when administered with different dosing regimens. The solid line represents the median of 1000 simulations and the limits of the grey area represent the 5th and 95th percentiles of simulations. Simulations were performed for CSF lactate concentrations of 2 (left), 10 (middle) and 20 (right) mmol/L. ID, infusion dose; LD, loading dose; MD, maintenance dose.

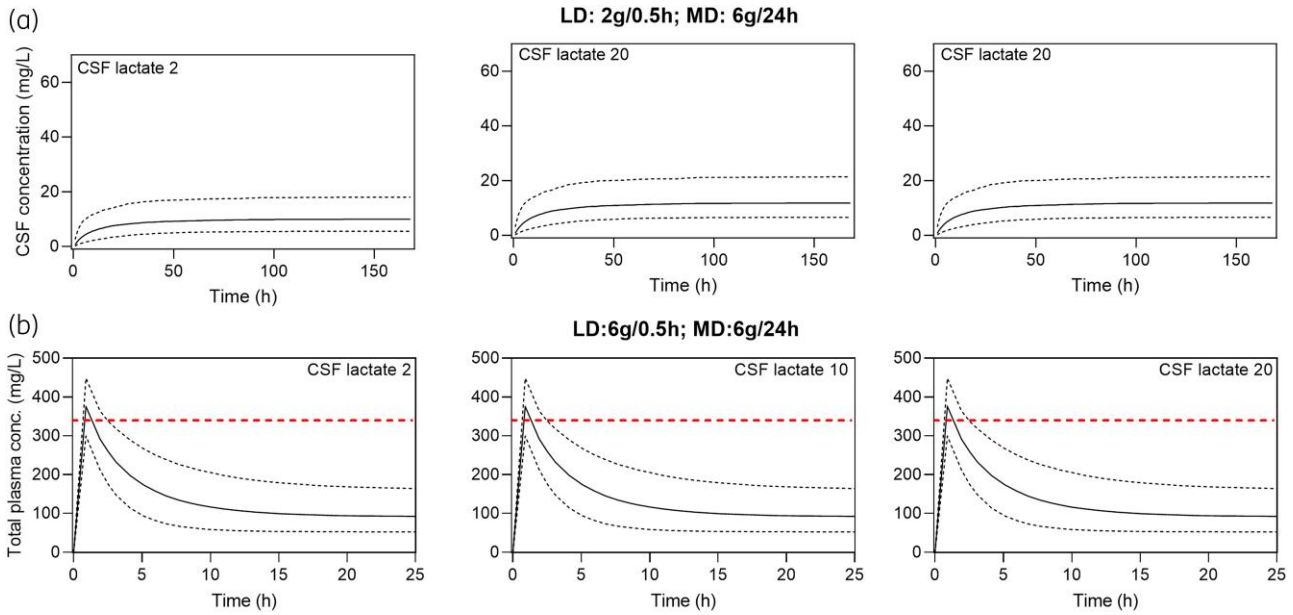

Figure 6. Effects of CSF lactate concentration on unbound CSF and total plasma concentration of temocillin. (a) Simulated CSF concentration-time profiles of temocillin for dosing regimen used in the study with CSF lactate concentrations of 2, 10 and 20 mmol/L; (b) simulated total plasma concentration-time profiles of temocillin for high loading dose of 6 g with CSF lactate concentrations of 2, 10 and 20 mmol/L. The solid black line represents the median of 1000 simulations, and the dashed lines represent the 5th and 95th percentiles of simulations. The red dashed lines indicate total plasma concentration of 350 mg/L. LD, loading dose; MD, maintenance dose. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

haemodialysis patients[47] using either one-compartment[46] or two-compartment[20,40,43,47] models. In the present study, a one-compartment model was found to be the best-performing model, which could be due to limited sampling (1–2 samples) among each dosing 24 h interval, because at least five samples were collected in studies using two-compartment models. Nevertheless, the volume of distribution found in the present study (13.3 L) is comparable to that of the central compartment in most of the studies using one- or two-compartment models in ICU patients (~14.0 L[20,43,46]). The clearance of unbound temocillin estimated here (8.43 L/h) was higher compared with previous studies in ICU patients (2.45–3.69 L/h),[20,43] probably related to the fact that creatinine clearance was higher in the patients from this study (125.5 mL/min) than in previous ICU cohorts (40–94 mL/min).[20,43] Of note, a single study in ICU patients by Layios *et al.*[40] reported much higher clearance of unbound temocillin (15.2 L/h) and volume of distribution in the central compartment (31 L). These patients had a mean creatinine clearance of 115 mL/min, but values were widely dispersed. This could explain discrepancies in estimated clearance, as renal clearance was used as a covariable. The reason for a higher volume of distribution is less clear, but is possibly related to the fact that patients were treated by intermittent (3×/day) or continuous infusion or that they had higher APACHE II scores.[40] Lastly, protein and albumin concentrations were not reported in Layios' article.

In our work, no relationship was found between the creatinine clearance and total clearance of temocillin. This is probably due to the narrow range of creatinine clearance in the current patient population (only 1/10 patients below 90 mL/min). No efflux clearance from the CSF to the blood compartment was considered as patients were undergoing external ventricular drainage, with an estimated clearance from CSF of 0.012 L/h, close to the reported daily CSF drainage volume of 200–300 mL (0.008–0.0125 L/h). Including this process was also not justified mathematically during the model development, in line with previous PK models for other drugs in patients with EVD that considered this clearance as negligible or low compared with the elimination via the drain.[33,48] The estimated volume of the CSF compartment was 0.17 L, which is close to the 0.15 L of CSF volume in adults.

During covariate analysis, lactate concentration in CSF was the only covariate retained in the final model, which showed a significant effect on temocillin transferring rate constant from the central compartment to CSF. Of note, this covariate, suggested as a surrogate parameter for ventriculitis and meningitis, has already been used in a population pharmacokinetics (popPK) model of vancomycin in a similar patient population, and also found to correlate with the inter-compartment clearance between the central and the CSF compartment.[49] However, how to justify this covariate clinically needs to be considered.

Monte Carlo simulations showed that exposure to temocillin in the CSF was insufficient to cover bacteria with MICs ≥8 mg/L when administered as a continuous infusion of 6 g/24 h after a loading dose of 2 g (i.e. the maximal registered dose) and that much higher maintenance doses should be used for higher MICs if aiming at maintaining the unbound concentration above the MIC during the whole treatment duration. Although limited to dosing regimens that do not expose the patients to peak concentrations >350 mg/L, our simulations propose therapeutic schemes leading to prolonged exposure to high unbound

concentrations in the plasma and the CSF, the safety of which would need to be assessed. Moreover, we do not know at this stage what is the PK/PD target needed to obtain optimal efficacy in CSF. In this context, the few population PK/PD analyses and Monte Carlo simulations performed with other β-lactams suggest suboptimal PTAs when using the highest registered doses, as shown for cefepime, ceftriaxone, ceftazidime or meropenem, if targeting 100% *f*T>EUCAST susceptibility breakpoints.[32,33,50,51] There is thus still room for research in order to define the most clinically relevant CSF PK/PD targets and protocols for dose adjustment before optimizing dosing based on therapeutic drug monitoring for these infections.[52]

The present data are also subject to some limitations. First, there is a huge inter- and intra-individual variability of the PK parameters estimated in CSF due to the presence of an EVD. Indeed, in shunt CSF, flow rates are variable between and within patients and may affect the amount of CSF produced.[53] Second, the number of included patients is small. Moreover, the study was not powered enough to evaluate the treatment's clinical efficacy and to correlate it with PK/PD markers. Our data should also be interpreted cautiously when considering temocillin for other CNS infections.

In conclusion, temocillin shows a CSF penetration comparable to that of other β-lactams. Our simulations suggest that, with the currently approved dosing, temocillin monotherapy may be adequate for the treatment of ventriculitis infections by Enterobacterales with low MICs (≤4 mg/L). The dose adjustments proposed based on our simulations would need to be clinically evaluated, particularly with respect to their safety, as only few studies reported the administration of 8–12 g/day in adults patients and healthy volunteers, but encouragingly, they do not mention adverse effects.[54–56]

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Transparency declarations

P.N.P. was an employee of the Université catholique de Louvain. X.W., A.V., C.C., P.F. and P.-F.L. are or were employees of the Cliniques universitaires Saint-Luc. F.V.B. is Research Director of the Fonds de la Recherche Scientifique (F.R.S.-FNRS). G.-J.W. is a postdoc and Eumedica, the commercial producer of temocillin, serves as an industrial partner on his BEWARE 2-funded postdoctoral project. The laboratories and/or clinical units of F.V.B. and P.-F.L. have received research supporting grants and/or honoraria from various industries for research work and/or presentations unrelated to the topic of the present paper. All other authors have no potential conflicts of interest to declare.

Supplementary data

Figures S1 to S4, Tables S1 to S4, Supplementary methods 1 and 2, and Supplementary material 1 are available as Supplementary data at *JAC* Online.

References

1 Changa AR, Czeisler BM, Lord AS. Management of elevated intracranial pressure: a review. *Curr Neurol Neurosci Rep* 2019; **19**: 99. https://doi.org/10.1007/s11910-019-1010-3

2 Schizodimos T, Soulountsi V, Iasonidou C *et al.* An overview of management of intracranial hypertension in the intensive care unit. *J Anesth* 2020; **34**: 741–57. https://doi.org/10.1007/s00540-020-02795-7

3 Martin RM, Zimmermann LL, Huynh M *et al.* Diagnostic approach to health care- and device-associated central nervous system infections. *J Clin Microbiol* 2018; **56**: e00861-18. https://doi.org/10.1128/JCM.00861-18

4 Ramasy Razafindratovo RM, Migliavaca CB, Chevret S *et al.* Internal ventricular cerebrospinal fluid shunt for adult hydrocephalus: a systematic review and meta-analysis of the infection rate. *Neurosurgery* 2022; **92**: 894–904. https://doi.org/10.1227/neu.0000000000002301

5 Ramanan M, Lipman J, Shorr A *et al.* A meta-analysis of ventriculostomy-associated cerebrospinal fluid infections. *BMC Infect Dis* 2015; **15**: 3. https://doi.org/10.1186/s12879-014-0712-z

6 Karvouniaris M, Brotis A, Tsiakos K *et al.* Current perspectives on the diagnosis and management of healthcare-associated ventriculitis and meningitis. *Infect Drug Resist* 2022; **15**: 697–721. https://doi.org/10.2147/IDR.S326456

7 Srihawan C, Castelblanco RL, Salazar L *et al.* Clinical characteristics and predictors of adverse outcome in adult and pediatric patients with healthcare-associated ventriculitis and meningitis. *Open Forum Infect Dis* 2016; **3**: ofw077. https://doi.org/10.1093/ofid/ofw077

8 Pelegrin I, Lora-Tamayo J, Gomez-Junyent J *et al.* Management of ventriculoperitoneal shunt infections in adults: analysis of risk factors associated with treatment failure. *Clin Infect Dis* 2017; **64**: 989–97. https://doi.org/10.1093/cid/cix005

9 Lutsar I, McCracken GHJ, Friedland IR. Antibiotic pharmacodynamics in cerebrospinal fluid. *Clin Infect Dis* 1998; **27**: 1117–27. https://doi.org/10.1086/515003

10 Tunkel AR, Hasbun R, Bhimraj A *et al.* 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis* 2017; **64**: e34–65. https://doi.org/10.1093/cid/ciw861

11 Livermore DM, Tulkens PM. Temocillin revived. *J Antimicrob Chemother* 2009; **63**: 243–5. https://doi.org/10.1093/jac/dkn511

12 Livermore DM, Hope R, Fagan EJ *et al.* Activity of temocillin against prevalent ESBL- and AmpC-producing Enterobacteriaceae from south-east England. *J Antimicrob Chemother* 2006; **57**: 1012–4. https://doi.org/10.1093/jac/dkl043

13 Balakrishnan I, Awad-El-Kariem FM, Aali A *et al.* Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC beta-lactamase-producing Enterobacteriaceae. *J Antimicrob Chemother* 2011; **66**: 2628–31. https://doi.org/10.1093/jac/dkr317

14 Mittermayer HW. Influence of temocillin on human bowel flora. *Drugs* 1985; **29** Suppl 5: 43–8. https://doi.org/10.2165/00003495-198500295-00010

15 Alexandre K, Fantin B. Pharmacokinetics and pharmacodynamics of temocillin. *Clin Pharmacokinet* 2018; **57**: 287–96. https://doi.org/10.1007/s40262-017-0584-7

16 Bruckner O, Trautmann M, Borner K. A study of the penetration of temocillin in the cerebrospinal fluid. *Drugs* 1985; **29** Suppl 5: 162–6. https://doi.org/10.2165/00003495-198500295-00033

17 EUCAST. Breakpoints for temocillin. 2020. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Addenda/Addendum_Temocillin_breakpoints_and_AST_2020.pdf

18 Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am* 2003; **17**: 479–501. https://doi.org/10.1016/S0891-5520(03)00065-5

19 Wong G, Briscoe S, McWhinney B *et al*. Therapeutic drug monitoring of beta-lactam antibiotics in the critically ill: direct measurement of unbound drug concentrations to achieve appropriate drug exposures. *J Antimicrob Chemother* 2018; **73**: 3087–94. https://doi.org/10.1093/jac/dky314

20 Laterre PF, Wittebole X, Van de Velde S *et al*. Temocillin (6g daily) in critically ill patients: continuous infusion versus three times daily administration. *J Antimicrob Chemother* 2015; **70**: 891–8. https://doi.org/10.1093/jac/dku465

21 Ngougni Pokem P, Matzneller P, Vervaeke S *et al*. Binding of temocillin to plasma proteins in vitro and in vivo: the importance of plasma protein levels in different populations and of co-medications. *J Antimicrob Chemother* 2022; **77**: 2742–53. https://doi.org/10.1093/jac/dkac286

22 Matzneller P, Ngougni Pokem P, Capron A *et al*. Single-dose pharmacokinetics of temocillin in plasma and soft tissues of healthy volunteers after intravenous and subcutaneous administration: a randomized crossover microdialysis trial. *J Antimicrob Chemother* 2020; **75**: 2650–6. https://doi.org/10.1093/jac/dkaa176

23 U.S. Department of Health and Human Services. Guidance for industry: bioanalytical method validation. 2018. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf

24 Weichselbaum TE. An accurate and rapid method for the determination of proteins in small amounts of blood serum and plasma. *Am J Clin Pathol* 1946; **10**: 40–9. https://doi.org/10.1093/ajcp/16.3_ts.40

25 Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromcresol green. *Clin Chim Acta* 1971; **31**: 87–96. https://doi.org/10.1016/0009-8981(71)90365-2

26 Pai MP, Russo A, Novelli A *et al*. Simplified equations using two concentrations to calculate area under the curve for antimicrobials with concentration-dependent pharmacodynamics: daptomycin as a motivating example. *Antimicrob Agents Chemother* 2014; **58**: 3162–7. https://doi.org/10.1128/AAC.02355-14

27 Nau R, Zysk G, Thiel A *et al*. Pharmacokinetic quantification of the exchange of drugs between blood and cerebrospinal fluid in man. *Eur J Clin Pharmacol* 1993; **45**: 469–75. https://doi.org/10.1007/BF00315520

28 Model for individual covariates. Monolix; 2023. https://monolix.lixoft.com/statistical-model/individual-model/covariate/

29 Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev* 2010; **23**: 858–83. https://doi.org/10.1128/CMR.00007-10

30 Richards ML, Prince RA, Kenaley KA *et al*. Antimicrobial penetration into cerebrospinal fluid. *Drug Intell Clin Pharm* 1981; **15**: 341–68. https://doi.org/10.1177/106002808101500505

31 Bakken JS, Bruun JN, Gaustad P *et al*. Penetration of amoxicillin and potassium clavulanate into the cerebrospinal fluid of patients with inflamed meninges. *Antimicrob Agents Chemother* 1986; **30**: 481–4. https://doi.org/10.1128/AAC.30.3.481

32 Lodise TPJ, Rhoney DH, Tam VH *et al*. Pharmacodynamic profiling of cefepime in plasma and cerebrospinal fluid of hospitalized patients with external ventriculostomies. *Diagn Microbiol Infect Dis* 2006; **54**: 223–30. https://doi.org/10.1016/j.diagmicrobio.2005.09.007

33 Sime FB, Lassig-Smith M, Starr T *et al*. Cerebrospinal fluid penetration of ceftolozane-tazobactam in critically ill patients with an indwelling external ventricular drain. *Antimicrob Agents Chemother* 2020; **65**: e01698-20. https://doi.org/10.1128/AAC.01698-20

34 Dahyot-Fizelier C, Frasca D, Gregoire N *et al*. Microdialysis study of cefotaxime cerebral distribution in patients with acute brain injury. *Antimicrob Agents Chemother* 2013; **57**: 2738–42. https://doi.org/10.1128/AAC.02570-12

35 Poeppl W, Zeitlinger M, Donath O *et al*. Penetration of doripenem in human brain: an observational microdialysis study in patients with acute brain injury. *Int J Antimicrob Agents* 2012; **39**: 343–5. https://doi.org/10.1016/j.ijantimicag.2011.11.019

36 Blassmann U, Roehr AC, Frey OR *et al*. Cerebrospinal fluid penetration of meropenem in neurocritical care patients with proven or suspected ventriculitis: a prospective observational study. *Crit Care* 2016; **20**: 343. https://doi.org/10.1186/s13054-016-1523-y

37 Nau R, Lassek C, Kinzig-Schippers M *et al*. Disposition and elimination of meropenem in cerebrospinal fluid of hydrocephalic patients with external ventriculostomy. *Antimicrob Agents Chemother* 1998; **42**: 2012–6. https://doi.org/10.1128/AAC.42.8.2012

38 Drwiega EN, Rodvold KA. Penetration of antibacterial agents into pulmonary epithelial lining fluid: an update. *Clin Pharmacokinet* 2022; **61**: 17–46. https://doi.org/10.1007/s40262-021-01061-7

39 Wise R. Methods for evaluating the penetration of beta-lactam antibiotics into tissues. *Rev Infect Dis* 1986; **8** Suppl 3: S325–32. https://doi.org/10.1093/clinids/8.Supplement_3.S325

40 Layios N, Visee C, Mistretta V *et al*. Modelled target attainment after temocillin treatment in severe pneumonia: systemic and epithelial lining fluid pharmacokinetics of continuous versus intermittent infusions. *Antimicrob Agents Chemother* 2022; **66**: e0205221. https://doi.org/10.1128/aac.02052-21

41 Brown RM, Wise R, Andrews JM. Temocillin, in-vitro activity and the pharmacokinetics and tissue penetration in healthy volunteers. *J Antimicrob Chemother* 1982; **10**: 295–302. https://doi.org/10.1093/jac/10.4.295

42 Wise R, Donovan IA, Drumm J *et al*. The intraperitoneal penetration of temocillin. *J Antimicrob Chemother* 1983; **12**: 93–6. https://doi.org/10.1093/jac/12.1.93

43 Ngougni Pokem P, Wittebole X, Collienne C *et al*. Population pharmacokinetics of temocillin administered by continuous infusion in patients with septic shock associated with intra-abdominal infection and ascitic fluid effusion. *Antibiotics (Basel)* 2022; **11**: 898. https://doi.org/10.3390/antibiotics11070898

44 Nau R, Kinzig-Schippers M, Sorgel F *et al*. Kinetics of piperacillin and tazobactam in ventricular cerebrospinal fluid of hydrocephalic patients. *Antimicrob Agents Chemother* 1997; **41**: 987–91. https://doi.org/10.1128/AAC.41.5.987

45 Quagliarello VJ, Long WJ, Scheld WM. Morphologic alterations of the blood-brain barrier with experimental meningitis in the rat. Temporal sequence and role of encapsulation. *J Clin Invest* 1986; **77**: 1084–95. https://doi.org/10.1172/JCI112407

46 De Jongh R, Hens R, Basma V *et al*. Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care

patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection. *J Antimicrob Chemother* 2008; **61**: 382–8. https://doi.org/10.1093/jac/dkm467

47 Miranda Bastos AC, Vandecasteele SJ, Spinewine A *et al*. Temocillin dosing in haemodialysis patients based on population pharmacokinetics of total and unbound concentrations and Monte Carlo simulations. *J Antimicrob Chemother* 2018; **73**: 1630–8. https://doi.org/10.1093/jac/dky078

48 Chauzy A, Nadji A, Combes JC *et al*. Cerebrospinal fluid pharmacokinetics of ceftaroline in neurosurgical patients with an external ventricular drain. *J Antimicrob Chemother* 2019; **74**: 675–81. https://doi.org/10.1093/jac/dky489

49 Jalusic KO, Hempel G, Arnemann PH *et al*. Population pharmacokinetics of vancomycin in patients with external ventricular drain-associated ventriculitis. *Br J Clin Pharmacol* 2021; **87**: 2502–10. https://doi.org/10.1111/bcp.14657

50 Lodise TP, Nau R, Kinzig M *et al*. Pharmacodynamics of ceftazidime and meropenem in cerebrospinal fluid: results of population pharmacokinetic modelling and Monte Carlo simulation. *J Antimicrob Chemother* 2007; **60**: 1038–44. https://doi.org/10.1093/jac/dkm325

51 Lodise TPJ, Nau R, Kinzig M *et al*. Comparison of the probability of target attainment between ceftriaxone and cefepime in the cerebrospinal fluid and serum against *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis* 2007; **58**: 445–52. https://doi.org/10.1016/j.diagmicrobio.2007.03.015

52 Arkell P, Wilson R, Watkins K *et al*. Application of therapeutic drug monitoring to the treatment of bacterial central nervous system infection: a scoping review. *J Antimicrob Chemother* 2022; **77**: 3408–13. https://doi.org/10.1093/jac/dkac332

53 Kadowaki C, Hara M, Numoto M *et al*. CSF shunt physics: factors influencing inshunt CSF flow. *Childs Nerv Syst* 1995; **11**: 203–6. https://doi.org/10.1007/BF00277654

54 Michelon H, Bouabdallah-Perrin L, Singh S *et al*. Utilisation de la témocilline: étude de cohorte. *Méd Mal Infect* 2020; **50**: S50–1. https://doi.org/10.1016/j.medmal.2020.06.094

55 Nunn B, Baird A, Chamberlain PD. Effect of temocillin and moxalactam on platelet responsiveness and bleeding time in normal volunteers. *Antimicrob Agents Chemother* 1985; **27**: 858–62. https://doi.org/10.1128/AAC.27.5.858

56 Amaddeo A, Poli F, Barbi E *et al*. Temocillin: time to rediscover it? *J Cyst Fibros* 2010; **9**: S121. https://doi.org/10.1016/S1569-1993(10)60462-6

Title:

Population pharmacokinetics and dosing simulations of total and unbound temocillin in the plasma and cerebrospinal fluid of neurocritically-ill patients suspected of cerebral ventriculitis after external ventricular drainage.

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Supplementary material

Supplementary method 1: Temocillin assay in CSF: methodology and validation

The method is based on that previously developed and validated in plasma.[1] Briefly, separation was made using a XBridge® phenyl, 2.1 × 50mm, 3.5 µm column (Waters, Milford, MA, USA) maintained at 40°C. The auto sampler used a rinsing solution of formic acid/water/acetonitrile (0.1:50:50 v/v/v). The mobile phase consisted of a linear gradient formed between solvent A (0.1% formic acid in 0.2 mM ammonium acetate) and solvent B (0.1% formic acid in acetonitrile), which varied 90 to 10 % and from 10 to 90%, respectively. The flow rate was 0.3 mL/min and the total run time 6 min. Multiple Reaction Monitoring (MRM) data were collected by the mass spectrometer using a micromass Quatro Micro™ source with electrospray ionization (ESI) in positive mode. The source temperature was set at 140°C and the ion spray voltage at 3500V. The transitions m/z 415.34 → 339.10 and m/z 385.31→160.30 were used for quantification of temocillin and of the internal standard, respectively. The cone voltages (CoV) and collision energies (CE), which were optimized for the assay, were 20 V and 25 V, and 12 and 14 eV, respectively for temocillin and the internal standard, respectively. Ion transitions m/z 415.34 → 172.20 (CoV = 20 V, CE = 35 eV) and m/z 385.31→243.30 (CoV = 20 V CE = 23 eV) were used for temocillin and internal standard qualification, respectively.

The method was validated according to the recommendations for best practices and harmonization from the global bioanalysis consortium harmonization team,[2] and the new advances in method validation,[3] with determination of linearity, trueness, precision, accuracy, matrix effect, and recovery.

Linearity

Linearity was evaluated by the goodness-of-fit of a regression line between back-calculated concentrations of the validation standards and exact concentrations. Measured concentrations were plotted as a function of the introduced concentrations and the built regression line was compared with the identity line y = x. For both total and unbound temocillin concentrations in CSF, the slope value was close to 1 (0.997 and 0.998 respectively), demonstrating the linearity of the method. Furthermore, the absolute 80% β-expectation tolerance limits were within the absolute acceptance limits set at ± 20%, confirming the linearity of the method between 1-100mg/L and 1-50mg/L for total and unbound temocillin, respectively [Figure S1A/1B].

Trueness, precision and accuracy

Trueness was calculated at each concentration level of the validation standards and expressed in relative bias (RB). Relative bias was <2.920 and 3.542% for total and unbound temocillin concentrations in CSF samples respectively, showing the excellent trueness of the method. Precision was evaluated intra-day (repeatability) and inter-day (intermediate precision) and expressed as relative standard deviations (RSD). The repeatability was <4.132 and 3.164% and the intermediate precision 5.537 and 3.752% for total and unbound temocillin concentrations in CSF samples, respectively. Accuracy profiles, evaluating the sum of systematic and random errors of the test values (total error) showed that the relative upper and lower 80% β-expectation tolerance limits were inside the acceptance limits, set at ± 20% for total and unbound temocillin concentrations in CSF samples [Figure S1C/1D]. The method can thus be considered as accurate in the 1-100 mg/L and 1-50mg/L range for total and unbound temocillin concentrations in CSF samples respectively. All the trueness, precision and accuracy results are in accordance with FDA guidelines criteria (≤15%),[4] and illustrated in [Table S1 for total temocillin and Table S2 for unbound temocillin].

Matrix effects and recovery

The influence of the matrix was evaluated by comparing the slope and the intercept of the linear regression obtained with CSF matrix vs. water. No significant difference was observed for the intercepts ($p = 1$) or for the slopes ($p = 0.7$) (Mann Whitney test, Two-tailed, $p > 0.05$). Temocillin extraction recovery from CSF sample ranged from 99.3 to 103.5% with a coefficient of variation <5.537 for both total and unbound temocillin.

Figure S1 Validation of the assay of temocillin in CSF. A-B. Linearity of the assay of total (A) and unbound temocillin (B) concentration in CSF. The black dotted lines are the upper and lower EMA acceptance limits, the blue broken lines are the upper and lower 80% β-expectation tolerance limits, both expressed in mg/L, and the red continuous line is the mean calibration curve. The symbols represent the data points for the different samples across the concentration range. **C-D.** Accuracy profile of the assay of total (C) and unbound (D) temocillin concentration in human CSF using a linear regression model. The lack dotted lines are the upper and lower EMA acceptance limits, the broken lines are the upper and lower 80% β-expectation tolerance limits, both expressed in mg/L, and the red continuous line is the relative bias. The symbols represent the relative error of the measured concentrations for each QC sample and are plotted with respect to their target concentration.

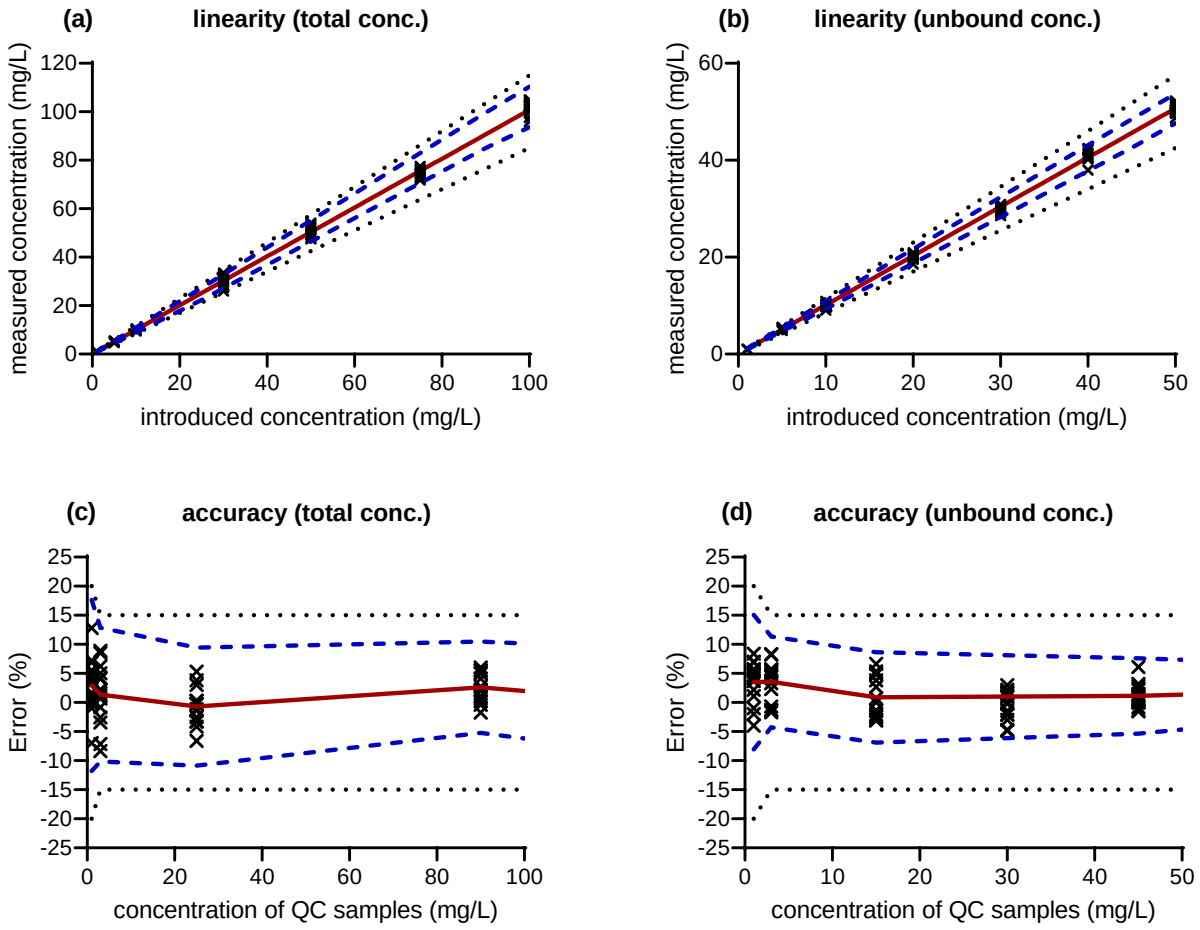


Table S1. Results of the validation of the assay used for quantification of total temocillin in human CSF.

Sample	concentration (mg/L)	Trueness		Precision		Accuracy		Recovery (%)
		Absolute bias (mg/L)	Relative biais (%)	Reproducibility (RSD %)	Intermediate Precision (RSD %)	β-Expectation tolerance intervals (mg/L)	β-Expectation tolerance limits (%)	
LOQ	1	0.029	2.920	4.132	4.532	[0.877; 1.180]	[-11.78; 17.62]	102.9
QC1	3	0.040	1.351	3.730	5.537	[2.690; 3.390]	[-10.14; 12.84]	101.3
QC2	25	0.174	0.696	3.090	3.172	[22.30; 27.34]	[-10.84; 9.45]	99.3
QC3	90	2.350	2.612	2.298	2.437	[85.09; 99.60]	[-5.243; 10.460]	102.9
LOQ, Limit of quantification; RSD, relative standard deviation; QC, quality control.								

Table S2. Results of the validation of the assay used for quantification of unbound temocillin in human CSF.

Sample	concentration (mg/L)	Trueness		Precision		Accuracy		Recovery (%)
		Absolute bias (mg/L)	Relative biais (%)	Reproducibility (RSD %)	Intermediate Precision (RSD %)	β-Expectation tolerance intervals (mg/L)	β-Expectation tolerance limits (%)	
LOQ	1	0.035	3.500	3.164	3.552	[0.915; 1.154]	[-8.08; 15.08]	103.5
QC1	3	0.106	3.542	1.734	3.679	[2.862; 3.349]	[-4.29; 11.37]	103.5
QC2	15	0.132	0.883	2.608	3.752	[13.95; 16.30]	[-6.882; 8.648]	100.8
QC3	45	0.507	1.028	1.884	2.006	[42.56; 48.45]	[-5.341; 7.598]	101.1
LOQ, Limit of quantification; RSD, relative standard deviation; QC, quality control.								

Table S3: Characteristics of antibiotic treatments for each patient (limited to anti-Gram-negative agents). Each table shows the main reason for admission in the ICU, the main indication for which temocillin was used, the microbiological and clinical outcomes, and the antibiotic treatment per day, with their respective daily doses.

Acronyms: CI: continuous infusion; CAZ : ceftazidime ; CIP : ciprofloxacin ; CRO : ceftriaxone ; GEN: gentamicin; MEM : meropenem ; TMO : temocillin ; TZP : piperacillin-tazobactam

Patient #1									
Medical diagnosis at admission	Aneurysmal subarachnoid haemorrhage								
Indication of antibiotic treatment	Ventriculitis caused by *Klebsiella pneumoniae* (+ *Klebsiella oxytoca* in blood)								
Outcome (microbiological / clinical)	eradication / success								
Day	1	2	3	4	5	6	7	8	9
Antibiotic	CRO	CRO	TMO	TMO	TMO	TMO	TMO	TMO	TMO
dosing	CRO : 2g q12h ; TMO : 2g loading dose then 6g q24h (CI)								

Patient #2														
Medical diagnosis at admission	Aneurysmal subarachnoid haemorrhage													
Indication of antibiotic treatment	Ventriculitis caused by *Klebsiella pneumoniae*													
Outcome (microbiological / clinical)	eradication / success													
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Antibiotic	CIP	CIP TMO	CIP TMO	CIP TMO	CIP TMO	CIP TMO	CIP	CIP	CIP	CIP	CIP	CIP	CIP	CIP
dosing	CIP : 400 mg q12h ; TMO : 2g loading dose then 6g q24h (CI)													

Patient #3									
Medical diagnosis at admission	Meningitis in a context of CSF fistula (necrosis of craniotomy wound)								
Indication of antibiotic treatment	Meningitis caused by *Enterobacter cloacae*								
Outcome (microbiological / clinical)	eradication / success								
Day	1	2	3	4	5	6	7	8	9
Antibiotic	MEM	MEM	TMO	TMO	TMO	TMO	TMO	TMO	TMO
dosing	MEM : 6g q24h (prolonged infusion) ; TMO : 2g loading dose 6g q24h (CI)								

Patient #4							
Medical diagnosis at admission	Postoperative monitoring after ventriculostomy and drainage of right parieto-occipital abscess.						
Indication of antibiotic treatment	Ventriculitis caused by *Escherichia coli*						
Outcome (microbiological / clinical)	eradication / success						
Day	1	2	3	4	5	6	7
Antibiotic	TZP CRO TMO	TZP CRO TMO	TZP CRO TMO	TZP CRO TMO	CRO TMO	CRO TMO	CRO TMO
dosing	TZP 4g q6h ; CRO : 2g q12h ; TMO : 2g loading dose then 6g q24h (CI)						

Patient #5									
Medical diagnosis at admission	Aneurysmal subarachnoid haemorrhage								
Indication of antibiotic treatment	Ventriculitis caused by *Enterobacter aerogenes*								
Outcome (microbiological / clinical)	eradication / success								
Day	1	2	3	4	5	6	7	8	9
Antibiotic	CAZ	CAZ	CAZ TMO	CIP CAZ TMO	CIP CAZ TMO	CIP CAZ TMO	CIP CAZ	CIP CAZ	CIP CAZ
dosing	CAZ : 2g loading dose then 6g q24h (CI) ; CIP 400 mg q12h; TMO : 2g loading dose then 6g q24h (CI)								

Patient #6										
Medical diagnosis at admission	Subarachnoid haemorrhage									
Indication of antibiotic treatment	Ventriculitis caused by *Enterobacter cloacae* (+ *Klebsiella pneumoniae* in blood)									
Outcome (microbiological / clinical)	eradication / failure									
Day	1	2	3	4	5	6	7	8	9	10
Antibiotic	CRO	CRO TMO MEM	TMO MEM	TMO MEM	TMO MEM	TMO MEM	MEM	MEM	MEM	MEM
dosing	MEM : 6g q24h (prolonged infusion) ; CRO : 2g q12h ; TMO : 2g loading dose then 6g q24h (CI)									

Patient #7											
Medical diagnosis at admission	Aneurysmal subarachnoid haemorrhage										
Indication of antibiotic treatment	Ventriculitis caused by *Klebsiella pneumoniae* (ESBL producer)										
Outcome (microbiological / clinical)	eradication / success										
Day	1	2	3	4	5	6	7	8	9	10	11
Antibiotic	MEM	MEM	MEM TMO	MEM TMO	MEM TMO	MEM TMO	MEM	MEM	MEM	MEM	MEM
dosing	MEM: 4g q24 for 2 days then 6g q24h (prolonged infusion) ; TMO : 2g loading dose then 6g q24h (CI)										

Patient #8							
Medical diagnosis at admission	Aneurysmal subarachnoid haemorrhage						
Indication of antibiotic treatment	Ventriculitis caused by *Enterobacter cloacae*						
Outcome (microbiological / clinical)	eradication / success						
Day	1	2	3	4	5	6	7 → 17
Antibiotic	TZP CAZ TMO	TZP TMO	TZP TMO CIP	TMO CIP	TMO CIP	TMO CIP	CIP
dosing	TZP: 4g q6 h; CAZ: 2g loading dose then 6g q24h (CI) ; CIP 400 mg q12h; TMO : 2g loading dose then 6g q24h (CI)						

Patient #9							
Medical diagnosis at admission	Post-operative monitoring after removal of a tumour from the 4th ventricle						
Indication of antibiotic treatment	Tracheobronchial infection under ventilation						
Outcome (microbiological / clinical)	eradication / success						
Day	1	2	3	4	5	6	7
Antibiotic	TMO	TMO	TMO	TMO	TMO	TMO	TMO
dosing	TMO : 2g loading dose then 6g q24h (CI)						

Patient #10				
Medical diagnosis at admission	Aneurysmal subarachnoid haemorrhage			
Indication of antibiotic treatment	Ventriculitis caused by *Enterobacter cloacae*			
Outcome (microbiological / clinical)	eradication / success			
Day	1 → 7	8 → 13	14 → 17	18 → 23
Antibiotic	TMO CIP	TMO MEM	MEM GEN	MEM
dosing	CIP: 400 mg q12h; MEM : 6g q24h (prolonged infusion); GEN: intraventricular injection; TMO : 2g loading dose then 6g q24h (CI)			

Supplementary method 2: Pharmacokinetic model

Model Development

One- and two-compartment models with first order elimination (for plasma concentration) integrated with the CSF compartment with first order elimination were initially compared. Protein binding of temocillin in plasma was considered as a kinetic process and described by the maximum binding concentration of temocillin (B_{max}) in mg/L, the first order dissociation rate constant (k_{off}) in h^{-1} and the second-order association rate constant (k_{on}) in L/mg/h. B_{max} was calculated as $plasma\ protein\ x\ \frac{414.5}{87400}\ x\ 1000$ where 414.5 is the molecular weight of temocillin, and 87400, the mean molecular weight for total plasma proteins (both in grams).

One binding site per molecule of plasma protein was assumed.

All individual parameters were assumed to be log-normally distributed. The between-subject variability (BSV) was described using an exponential model. To describe the residual variability, several error models (constant, proportional or combined error model) were tested. The most appropriate model was selected based on the following criteria: corrected Bayesian information criterion (BICc), usual goodness-of-fit (GOF) plots, and relative standard error (RSE) of parameter estimates.

Population pharmacokinetic analysis was performed using the non-linear mixed-effect modelling program Monolix version 2021R1 (LIXOFT, Antony, France) implementing the stochastic approximation expectation maximization (SAEM) algorithm. The model code is included at the end of this section. All of 1000 runs were successful in the bootstrap.

Model Diagnostics

Evaluation of the model was based on GOF plots, including observations versus individual and population predictions, weighted individual residuals (IWRES) versus individual predictions and time, plots of normalized prediction distribution error (NPDE) versus population predictions and time. The visual predictive check (VPC) was performed using 500 simulations with the final model. This plot shows the time course of the 5th, 50th, and 95th percentiles of the simulated profiles and compared with observed data.

A 1000-run bootstrap resampling procedure was performed in Monolix using the Rsmlx (R Speaks 'Monolix', version 4.0.2) package in R software (version 4.1.3). The median, 2.5% and 97.5% values obtained from the 1000 bootstrap runs for each parameter was calculated. All of 1000 runs were successful in the bootstrap.

Covariate screening

From the base model, the correlation of the following covariates with temocillin PK parameters was evaluated: age, body weight, Body Mass Index (BMI), measured GFR, plasma concentration of total protein, albumin and C-reactive protein, Sepsis-related Organ Failure Assessment (SOFA) score, Acute Physiology And Chronic Health Evaluation II (APACHE II) score, serum level of gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), levels of total protein, albumin, glucose, lactic acid, white

blood cell in CSF and volume of CSF. Both linear and exponential parameters-covariate relationship were evaluated:

$$P_i = \theta_p \times e^{\beta_{COV} \times COV_i} \times e^{\eta_{Cl,i}}$$

$$P_i = \theta_p \times \left(\frac{COV_i}{COV_{weightedmean}}\right)^{\beta_{COVi}} \times e^{\eta_{Cl,i}}$$

Where θ_p is the population estimate of the parameter P, β is the covariate effect to be estimated, COV_i is the covariate value for the subject *i*, and $COV_{weightedmean}$ *i*s the weighted mean value of the covariate in the study population. The weighted mean of the covariate is defined as

$$\text{weighted mean (cov)} = \exp\left(\sum_{\text{i}} \frac{\text{nbObs}_\text{i}}{\text{nbObs}} \log(\text{cov}_\text{i})\right)$$

where nbObs_i is the number of observations for the i^{th} individual and nbObs is the total number of observations.

The covariate model was built using a stepwise procedure with forward inclusion and backward deletion. The covariate was added to the structure model if the addition caused a decrease of 3.84 ($p<0.05$) on -2log likelihood ratio (-2LL). The addition of covariates was stopped when no more decrease of --2LL was obtained. The statistical significance of covariate was individually evaluated during the stepwise deletion. The covariate was kept in the model if the elimination could result in an increase of at least 6.63 ($p<0.01$) of -2LL.

Supplementary material 1: **Description of the model code**

```
[LONGITUDINAL]
input = {CL1, CL3, kon, koff, k13, V1, V3,PLPROT}
PLPROT= {use=regressor}

PK:
depot(target= Aub)

EQUATION:
; Initial conditions
t0    = 0
Aub_0 = 0
Ab_0  = 0
Acsf_0= 0

;Secondary parameter
Bmax=PLPROT*4.74
ke1= CL1/V1
ke3= CL3/V3

;Differential equations
ddt_Aub = -(k13+ke1)*Aub+koff*Ab-(kon/V1)*(Bmax*V1-Ab)*Aub
ddt_Ab  = (kon/V1)*(Bmax*V1-Ab)*Aub-koff*Ab
ddt_Acsf= k13*Aub-ke3*Acsf

At  = Aub+Ab

;Output equations
Cub = Aub/V1
Ct  = At/V1
Ccsf= Acsf/V3

OUTPUT:
output = {Cub, Ct, Ccsf}
```

Table S4. Summary of model selection process.

No.	Model	-2LL	BICc
1	One-compartment for unbound plasma	1654	1731
2	As model 1, considering drug return from CSF to plasma compartment	1668	1737
3	Two-compartment for unbound plasma	1639	1732
4	As model 1, adding CSF lactate level effect on k_{13}	1641	1721

Figure S2. Observed versus population predictions (left) and observed versus individual predictions (right) plots for unbound plasma concentration (A), total plasma concentration (B), and CSF concentration (C) of temocillin.

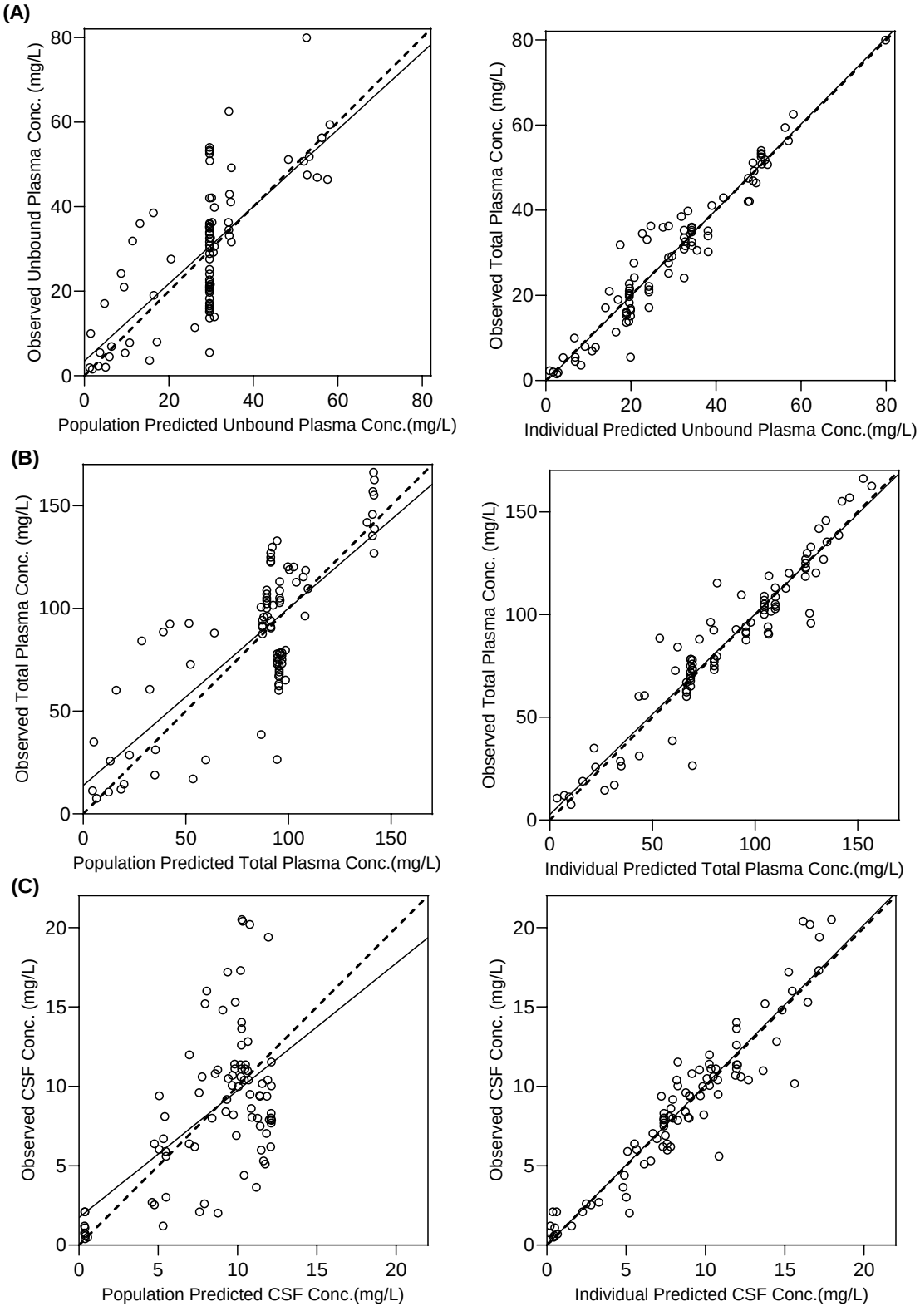
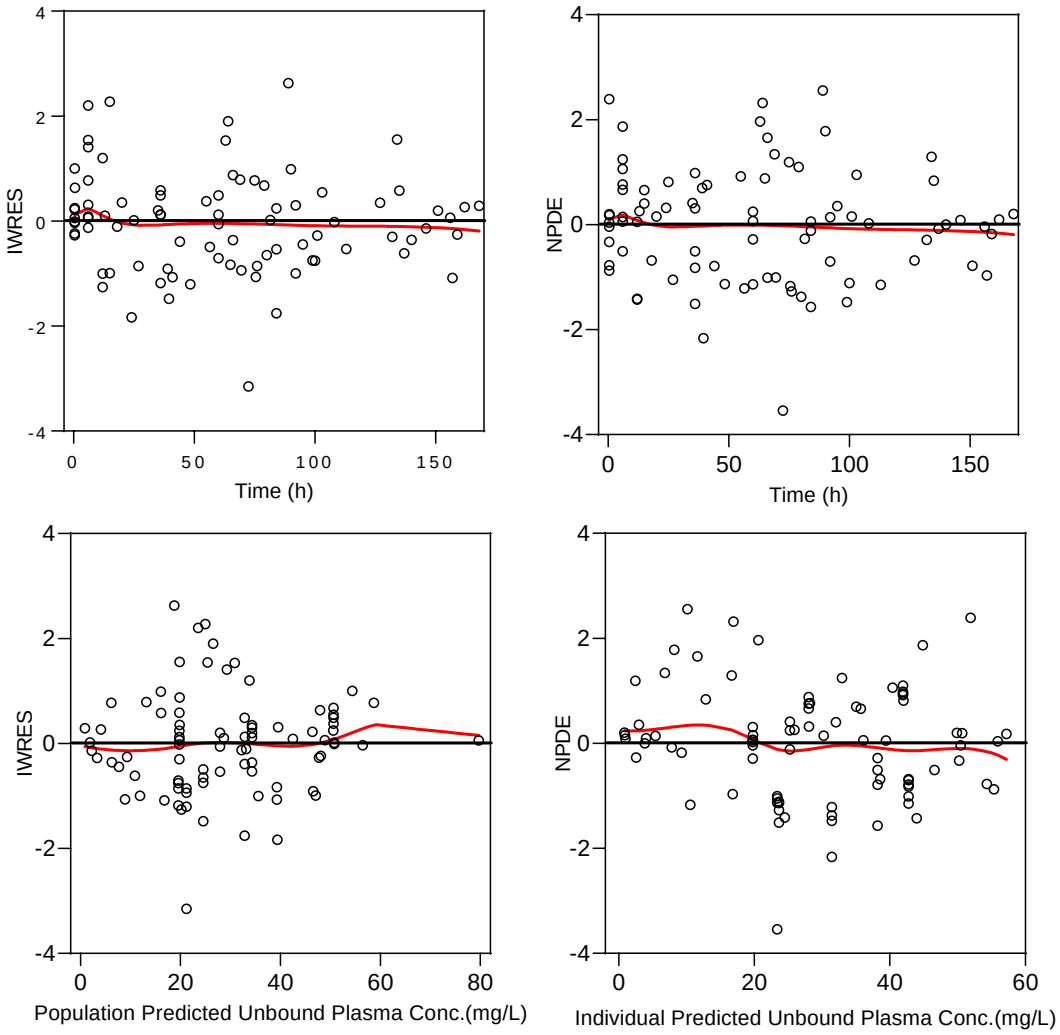
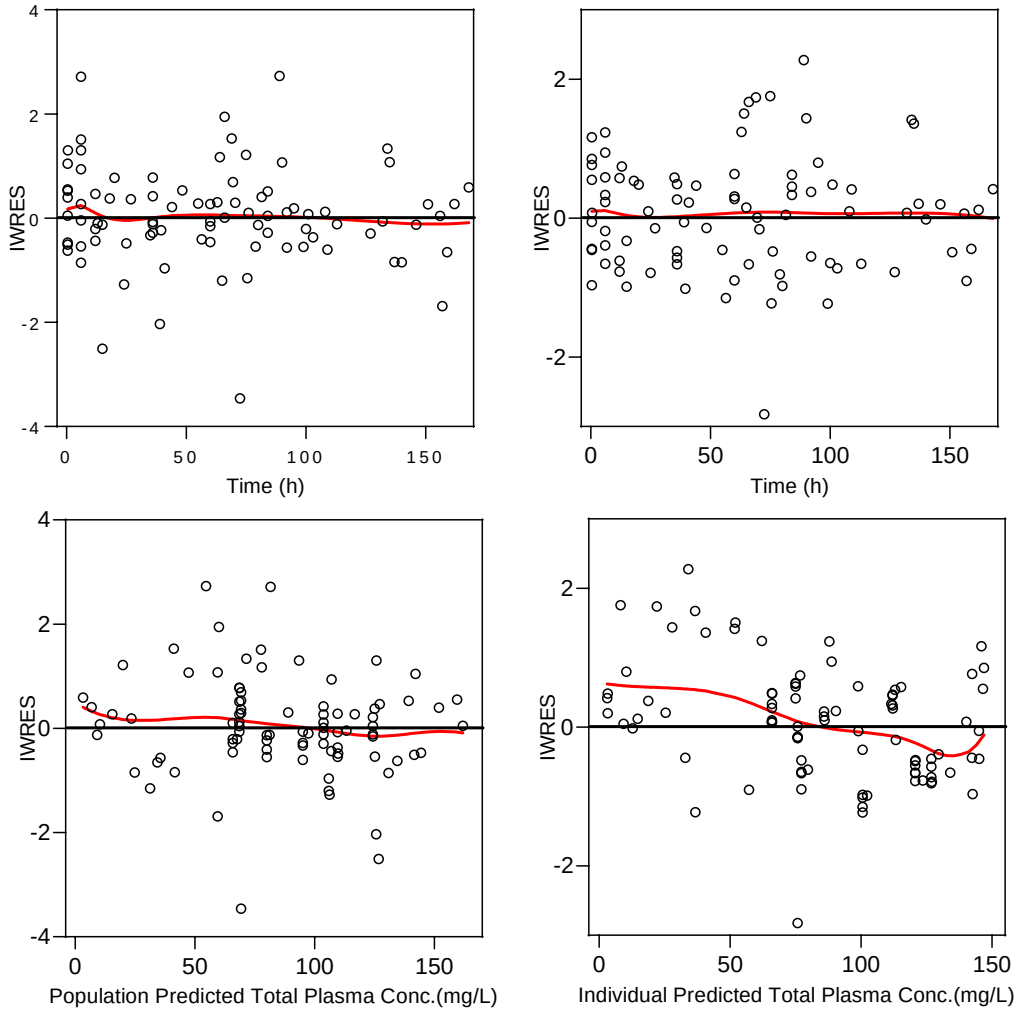

(A)
Observed Unbound Plasma Conc. (mg/L)
Population Predicted Unbound Plasma Conc.(mg/L)
Observed Total Plasma Conc. (mg/L)
Individual Predicted Unbound Plasma Conc.(mg/L)
(B)
Observed Total Plasma Conc. (mg/L)
Population Predicted Total Plasma Conc.(mg/L)
Observed Total Plasma Conc. (mg/L)
Individual Predicted Total Plasma Conc.(mg/L)
(C)
Observed CSF Conc. (mg/L)
Population Predicted CSF Conc.(mg/L)
Observed CSF Conc. (mg/L)
Individual Predicted CSF Conc.(mg/L)

Figure S3. Individual weighted residual (IWRES) versus time after dose (top-left) and individual predictions (bottom-left) and Normalized prediction errors (NPDE) versus time after dose (top-right) and population predictions (bottom-right) plots for unbound plasma concentrations (A), total plasma concentrations (B) and CSF concentrations (C) of temocillin.

(A)


IWRES
Time (h)
NPDE
Time (h)
IWRES
Population Predicted Unbound Plasma Conc.(mg/L)
NPDE
Individual Predicted Unbound Plasma Conc.(mg/L)

(B)


IWRES
Time (h)
IWRES
Time (h)
IWRES
Population Predicted Total Plasma Conc.(mg/L)
IWRES
Individual Predicted Total Plasma Conc.(mg/L)

(C)

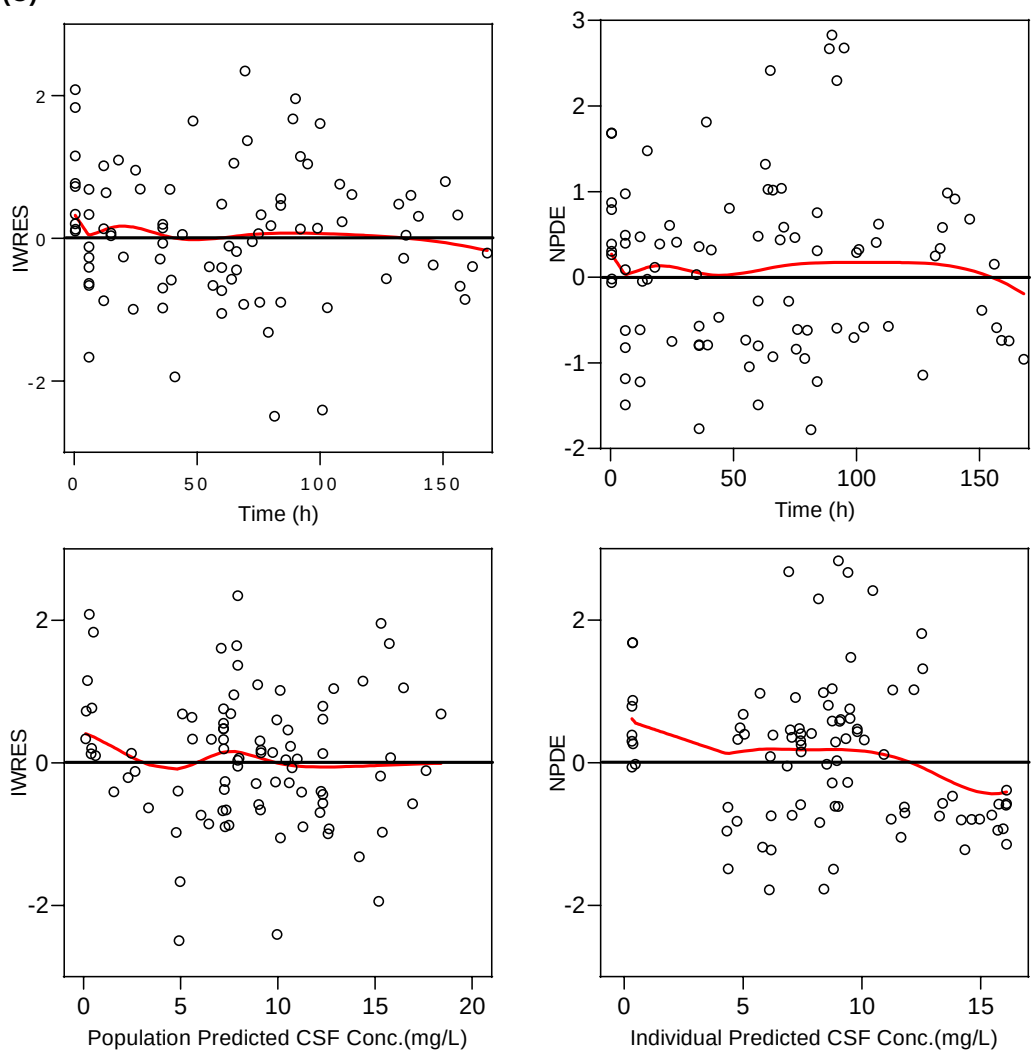
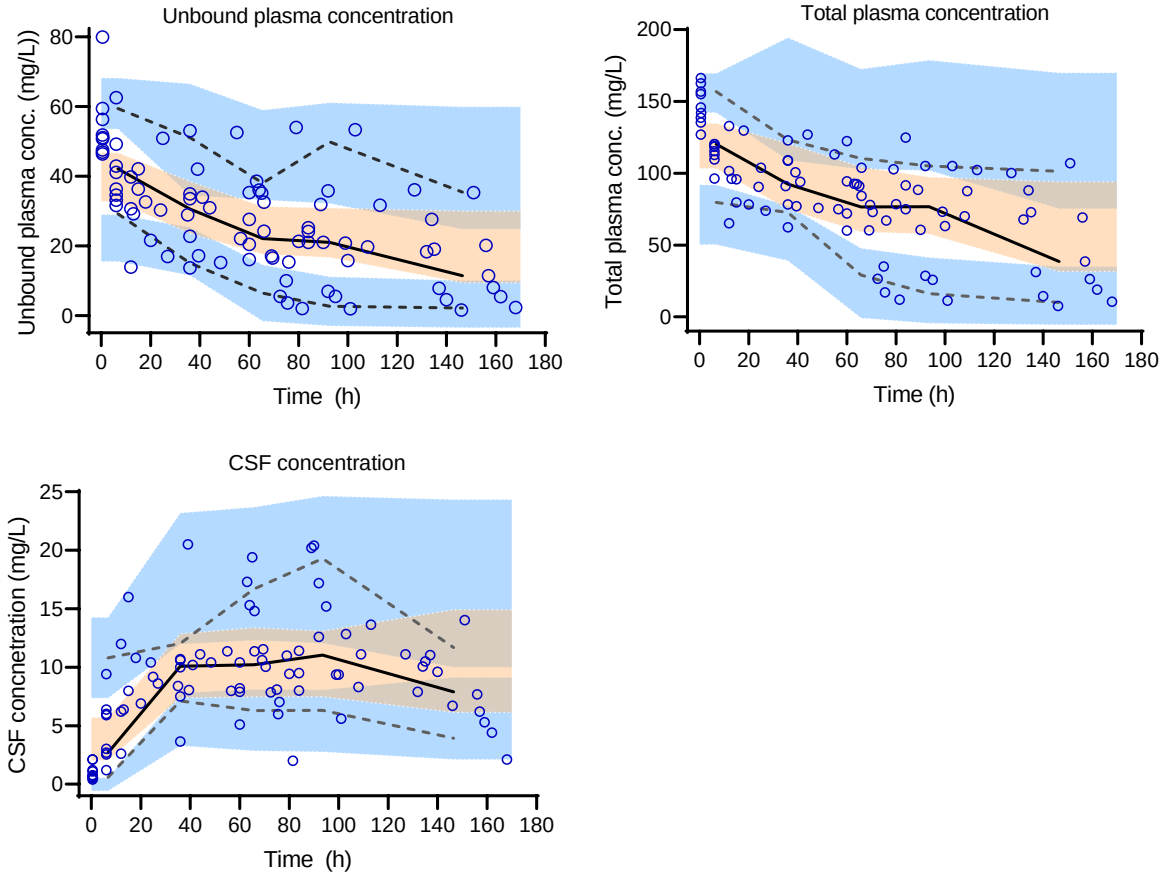

IWRES
Time (h)
NPDE
Time (h)
IWRES
Population Predicted CSF Conc.(mg/L)
NPDE
Individual Predicted CSF Conc.(mg/L)

Figure S4. Visual predictive check (VPC) for unbound (A) and total (B) concentration in plasma and concentration in CSF (C). Symbols (small circles) are observed concentrations, the dashed lines represent the 10th and 90th percentile, and the solid lines represent the 50th percentile of the observed values. The shaded area represents the spread of 90% prediction intervals given by the model for the 10% (in blue), 50% (in brown) and 90% percentile (in blue)**.** Note that the decrease over time is due to the fact that the elimination phase was followed during 12h after the last dose for half of the patients.

Note: the decline of concentrations over time in these plots reflects the fact that data from samples collected after the end of the continuous infusion (in 5 patients) were included in this analysis.



references

1. Matzneller P, Ngougni Pokem P, Capron A *et al.* Single-dose pharmacokinetics of temocillin in plasma and soft tissues of healthy volunteers after intravenous and subcutaneous administration: a randomized crossover microdialysis trial. *J.Antimicrob.Chemother.* 2020; **75:** 2650-6.

2. Briggs RJ, Nicholson R, Vazvaei F *et al.* Method transfer, partial validation, and cross validation: recommendations for best practices and harmonization from the global bioanalysis consortium harmonization team. *AAPS.J.* 2014; **16:** 1143-8.

3. Feinberg M, Boulanger B, Dewe W *et al.* New advances in method validation and measurement uncertainty aimed at improving the quality of chemical data. *Anal.Bioanal.Chem.* 2004; **380:** 502-14.

4. 2018. *Guidance for Industry: Bioanalytical Method Validation, U.S. Department of Health and Human Services*. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf