**Supplementary Table S1. External PD validation of high-dose cefazolin**

| Literature | ・**Patient information**<br>・**Cefazolin administration** | **CSF observations** | **CSF predicted values** |
|---|---|---|---|
| **Grégoire M et al. [11]** | ・a case report with normal renal function (glomerular filtration rate: 60 to 106 mL/min per 1.73 $m^2$ after six weeks)<br>・continuous infusion of 8 g daily | 6.1 μg/mL) | Median: 5.7 μg/mL<br>(95% CI: 0.5 to 62.4 μg/mL)<br>in typical patients with $CL_{cr}$ = 90 mL/min |
| **Le Turnier P et al. [12]** | ・Eights subjects with normal renal function (the median glomerular filtration: 136 mL/min)<br>・continuous infusions of 8 g daily | Median: 2.8 μg/mL)<br>(ranging from 2.1 to 5.2 μg/mL) | Median: 5.7 μg/mL<br>(95% CI: 0.5 to 62.4 μg/mL)<br>in typical patients with $CL_{cr}$ = 90 mL/min |
| **Novak AR et al. [13]** | ・Fifteen subjects with normal renal function (median $CL_{cr}$: 115 mL/min)<br>・2 g three times daily (6 g/day) | Median: 1.59 μg/mL ($C_{min}$)<br>(ranging from 0.7 to 2.2 μg/mL). | Median: 1.2 μg/mL<br>(95% CI: 0.05-25.1 μg/mL)<br>in typical patients with $CL_{cr}$ = 90 mL/min |

**Supplementary Table S2. Probabilities of exceeding a neurotoxicity-related cefazolin concentration ($C_{min}$ > 64 μg/mL [20]) in CSF. The neurotoxicity-related CSF concentration value was set using the median of cefazolin CSF concentrations in three cases of generalized seizures.**

| Cefazolin regimen | Probabilities (%) of exceeding the neurotoxicity-related CSF concentration ($C_{min}$ > 64 μg/mL [20]) |
|---|---|
| **$CL_{cr}$ = 90 mL/min** | |
| **2 g q.i.d. 0.5-h infusion (8 g/day)** | 1.1 |
| **2 g t.i.d. 4-h infusion (6 g/day)** | 0.8 |
| **2 g q.i.d. 4-h infusion (8 g/day)** | 1.8 |
| **6 g continuous infusion (6 g/day)** | 1.4 |
| **8 g continuous infusion (8 g/day)** | 2.5 |
| **10 g continuous infusion (10 g/day)** | 4.0 |
| **12 g continuous infusion (12 g/day)** | 5.0 |
| **$CL_{cr}$ = 60 mL/min** | |
| **2 g t.i.d. 0.5-h infusion (6 g/day)** | 1.0 |
| **2 g q.i.d. 0.5-h infusion (8 g/day)** | 2.3 |
| **2 g t.i.d. 4-h infusion (6 g/day)** | 1.6 |
| **2 g q.i.d. 4-h infusion (8 g/day)** | 3.0 |
| **6 g continuous infusion (6 g/day)** | 2.6 |
| **8 g continuous infusion (8 g/day)** | 4.3 |
| **10 g continuous infusion (10 g/day)** | 6.1 |
| **$CL_{cr}$ =30 mL/min** | |
| **2 g b.i.d. 0.5-h infusion (4 g/day)** | 1.1 |
| **2 g t.i.d. 0.5-h infusion (6 g/day)** | 3.7 |
| **2 g b.i.d. 4-h infusion (4 g/day)** | 1.8 |
| **2 g t.i.d. 4-h infusion (6 g/day)** | 9.0 |
| **4 g continuous infusion (4 g/day)** | 3.5 |
| **6 g continuous infusion (6 g/day)** | 6.6 |
| **8 g continuous infusion (8 g/day)** | 9.9 |

**Supplementary Table S3 Demographic information of literature data used in this study**

| | **PK model parameter in blood concentrations**<br>・Lanoiselée J et al. [25]) | **Physiological parameters**<br>・Cutler RWP et al. [26] | **Calculation of $KP_{CSF}$**<br>・Ikuno H et al. [18] |
|---|---|---|---|
| **Patient demographics** | | | |
| Study design | Observational study | Observational study | Observational study |
| The number of the subjects | N = 100 (51 males and 49 females) | N = 12 (8 males and 4 females) | N = 8 (4 males and 4 females) |
| Subject characteristics | Adult patients undergoing total hip arthroplasty | Eight patients with subacute sclerosing panencephalitis and four patients with pontine gliomas | adult patients with suspected meningitis. |
| Age (years) | 67 (mean value) (range from 24 to 91) | 8.3 (mean value) (range from 4 to13) | 47.9 (mean value) (range from 38 to 60) |
| Body weight (kg) | 76 (mean value) (range from 48 to 123) | 24.6 (mean value) (range from 16.0 to 37.5) | NA |
| Renal function | Creatinine clearance (mL/min/1.73m$^2$): 83 (range from 17 to 129) | NA | NA |
| Hepatic function | NA | NA | NA |
| **Bioanalytical methods** | Measurement for plasma concentration: liquid chromatography system | NA | Measurement for CSF concentrations: bioassay (B. subtilis ATCC 6633) |
| **PK model structure** | A 2-compartment model best described cefazolin concentrations out of 1-, 2- and 3- compartment models. | NA | NA |
| **Covariate analysis** | Covariate for clearance in final model: Creatinine Clearance (mL/min) according to the CKD-EPI formula<br>Age, total body weight, body mass index, lean body weight, creatinine clearance (mL/min) according to the Cockcroft-Gault formula, and sex were investigated as other covariates with stepwise procedure. | NA | NA |

NA; Not applicable

**Supplementary Figure S1. Hybrid model building using $PRIOR subroutine**

```
-----------------------------------------------------------------------------------------
$PRIOR NWPRI
$THETAP
2.86 FIXED ;(1)CL
0.79 FIXED ;(2)CCR ON CL
5.2  FIXED ;(3)V1
10.9 FIXED ;(4)Q
4.56 FIXED ;(5)V2
0.0525 FIXED ;(6)KCSF
0.021  FIXED ;(7)QCSF
0.092  FIXED ;(8)VCSF

$THETAPV ; informative
0.142
0.0902
0.186
0.360
0.288
0.0548
0.0012
0.0273

$OMEGAP  (0.102 FIXED) (0.325 FIXED) (0.437 FIXED) (0.01 FIXED)(1.387)(1.222)(1.221)
$OMEGAPD (390.5 FIXED) (254.7 FIXED) (89.8 FIXED) (3.92 FIXED) (0.486) (35285.5) (140911.2)
$SIGMAP  0.0144 FIXED
$SIGMAPD (886.4 FIXED)
-----------------------------------------------------------------------------------------
```

**・The comparison of model parameter and RSE% with prior or without prior**

**with prior**

| Interindividual variability (exponential error model) | | | |
|---|---|---|---|
| | **Estimate** | **RSE (%)** | **95%CI** |
| **ηKP$_{CSF}$** | 1.39 | (18.0) | 7.19-1310.6 |
| **ηQ$_{CSF}$** [c] | 1.22 | (0.75) | 115.3-1133.2 |
| **ηV$_{CSF}$** [c] | 1.22 | (0.38) | 134.7-925.8 |

**without prior**

| Interindividual variability (exponential error model) | | | |
|---|---|---|---|
| | **Estimate** | **RSE (%)** | **95%CI** |
| **ηKP$_{CSF}$** | 1.39 | (203.0) | 0.0188-43.6 |
| **ηQ$_{CSF}$** [c] | 1.22 | (0.75) | 0.00245-172.7 |
| **ηV$_{CSF}$** [c] | 1.22 | (0.38) | 0.00443-178.4 |

CI, confidence interval determined from sampling importance resampling algorism; RSE, relative standard error; η, random variable which is normally distributed with a mean of zero and variance