Open Forum Infectious Diseases

MAJOR ARTICLE

Pharmacokinetic Evaluation of Cefazolin in the Cerebrospinal Fluid of Critically Ill Patients

Alison R. Novak,[1] Martin Krsak,[2] Tyree H. Kiser,[3] Robert T. Neumann,[4] Luis Cava Prado,[4] Kyle C. Molina,[1,2,3] and Scott W. Mueller[1,3]

[1]Department of Pharmacy, UCHealth - University of Colorado Hospital, Aurora, Colorado, USA, [2]Division of Infectious Diseases, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA, [3]Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, and [4]Division of Neurosurgery, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA

Background. The relative distribution of cefazolin into the cerebrospinal fluid (CSF) remains debated. Determining the distribution of cefazolin into the CSF in noninfected adults may allow for further treatment applications of cefazolin. This prospective pharmacokinetic study aimed to determine the pharmacokinetic parameters of cefazolin in serum and CSF from external ventricular drains (EVDs) in neurologically injured adults.

Methods. Blood and CSF were collected, using a biologic waste protocol, for cefazolin quantification and trapezoidal rule–based pharmacokinetic analysis in a total of 15 critically ill adults receiving 2000 mg intravenously every 8 hours or the renal dose equivalent for EVD prophylaxis.

Results. A median (range) of 3 (2–4) blood and 3 (2–5) CSF samples were collected for each patient. The most common admitting diagnosis was subarachnoid hemorrhage (66.7%). The median calculated cefazolin CSF C_{max} and C_{min} values (interquartile range [IQR]) were 2.97 (1.76–8.56) mg/L and 1.59 (0.77–2.17) mg/L, respectively. The median (IQR) CSF to serum area under the curve ratio was 6.7% (3.7%–10.6%), with time-matched estimates providing a similar estimate (8.4%). Of those receiving cefazolin every 8 hours, the median and minimum directly measured CSF cefazolin concentration ≥4 hours following administration were 1.87 and 0.78 mg/L, respectively.

Conclusions. Cefazolin dosed for EVD prophylaxis achieved CSF concentrations suggesting viability as a therapeutic option for patients with meningitis or ventriculitis due to susceptible bacteria such as methicillin-susceptible *Staphylococcus aureus*. Further clinical trials are required to confirm a role in therapy for cefazolin. Population-based pharmacokinetic–pharmacodynamic modeling may suggest an optimal cefazolin regimen for the treatment of central nervous system infections.

Keywords. cefazolin; cerebrospinal fluid; cerebrospinal fluid shunts; critical care; critical illness; distribution; pharmacokinetics.

The current Infectious Disease Society of America recommendation for the treatment of meningitis or ventriculitis due to methicillin-susceptible *Staphylococcus* spp., including *S. aureus* (MSSA), is intravenous nafcillin or oxacillin, with the provisional addition of rifampin in cases involving foreign bodies (eg, shunts) [1, 2]. The cerebrospinal fluid (CSF) and brain tissue penetration estimates of specific antistaphylococcal β-lactams have remained an area of debate for decades [3–8]. Recent studies have suggested that cefazolin is as effective as, potentially better tolerated than, and has a more favorable dosing schedule than antistaphylococcal penicillins for the treatment MSSA infections from non-CSF sources [9, 10]. The absence of cefazolin as a treatment option for highly susceptible isolates in CSF is due to a lack of clinical evidence and a presumed inability to achieve therapeutic CSF concentrations at conventional doses. In part, this is due to relatively high protein binding compared with most cephalosporins, low lipophilicity, and affinity for blood–brain barrier efflux pumps [11].

Many of the original studies describing the limited central nervous system (CNS) penetration of cefazolin were based on single-dose pharmacokinetics and not entirely reflective of clinical practice and individual patient characteristics [11–13]. Animal and limited human reports indicate that there may be CNS penetration of cefazolin at therapeutically used doses [12, 14]. Further, a recent case report and case series suggested that continuous infusion of cefazolin can achieve therapeutic CSF concentrations resulting in bacterial eradication with the aid of therapeutic drug monitoring (TDM) [6, 7]. If cefazolin adequately penetrates into the CSF and clinical trials confirm safety and efficacy for targeted susceptible central nervous system infections, clinicians would be presented with another treatment option.

The purpose of this study was to describe the pharmacokinetic (PK) parameters of cefazolin in CSF and serum in

Received 10 November 2021; editorial decision 17 December 2021; accepted 24 December 2021; published online 25 December 2021.

Correspondence: Scott Mueller, PharmD, FCCM, FCCP, 12850 East Montview Boulevard, Mail Stop C238, Aurora, CO 80045 (scott.mueller@uchealth.org).

Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofab649

noninfected adults with actively draining external ventricular drains (EVDs). By determining the distribution and PK profile of cefazolin in CSF at approved and commonly used doses, further treatment applications of cefazolin for infections involving the central nervous system and regimen optimization may be determined.

METHODS

Setting/Patient Consent

This single-center, prospective observational PK analysis was conducted at UCHealth, a 662-bed academic medical center. The Colorado Multiple Institutional Review Board reviewed the study (COMIRB 19-2069) and waived the requirement of consent under a biological waste secondary use collection protocol, which allowed for secondary deidentified analysis of data once collected and analysis of biological samples once they were deemed waste.

Population

Hospitalized patients >18 years of age who had a non-antibiotic-coated EVD open to drain, who were receiving cefazolin for EVD prophylaxis and had ≥2 planned clinical laboratory tests ordered requiring blood draws within a cefazolin dosing interval, were eligible for inclusion.

Sample Collection

The blood samples were obtained from the clinical laboratory after the clinically indicated tests were completed as permitted under the biological waste protocol. Samples were obtained at multiple time points within the dosing interval for analysis. As waste samples were generated as part of routine care, blood sample timing in relation to cefazolin administration was variable and not controlled by investigators. Biological waste blood was handled under a routine protocol at the clinical laboratory until it was released to an investigator for processing and storage.

The CSF samples were taken from actively draining EVDs just before collecting bags and volumes recorded as to not interfere with routine care and documentation of total CSF drain volume. CSF drainage was considered waste if the attending physician determined that no clinical use would be expected except for the documentation of volume, which was not interrupted. Typically, 1–3 mL of CSF was collected at various time points that attempted to match the timing of clinical lab blood draws in the anticipation of recovering waste blood from the clinical laboratory. It was anticipated that patients would rarely be identified and assessed during the first dose upon admission to the neurosurgical intensive care unit or perioperatively; therefore, no first-dose cefazolin intervals were pursued. At our institution, it was common practice for patients to receive systemic cefazolin for EVD infection prophylaxis when antimicrobial-impregnated drains were not utilized. All collected samples were analyzed for cefazolin and used for PK analysis. All the samples were centrifuged at 2500 rpm for 20 minutes, supernatant-pipetted, and stored at −80°C in triplicate in 0.3–1-mL microcentrifuge tubes until assay.

Data Collection

Patients included in the data analysis were evaluated manually by a single study investigator to assess eligibility based on previously described inclusion and exclusion criteria. Demographic and outcome data for all patients were then extracted via manual chart review from the electronic medical record.

Sample Analysis and Materials

Cefazolin was quantified, after protein precipitation, by a high-performance liquid chromatography–tandem mass spectrometry method developed by iC42 Clinical Research and Development (University of Colorado Anschutz Medical Campus, Aurora, CO, USA; bioanalytics.us). In brief, analytical grade cefazolin (C242500; Lot #25-SSR 120-1) and internal standard N15,2C13-Cefazolin (C242502; Lot #8-XAL 141010) were purchased from Toronto Research Chemicals (North York, ON, Canada). A cefazolin standard curve was constructed in both serum and CSF using a quadratic fit after 1/x weighting. Cefazolin concentrations were quantitated by plotting analyte peak area/internal standard peak ratios against the standard curve. All calculations were carried out using AB Sciex Analyst software (version 1.6.2). The lower limit of quantification was 0.025 mg/L, and calibration curves had a coefficient of determination >0.99. Intrabatch accuracy during analysis was between 85% and 115%, with a coefficient of variance ≤15%. Blank/zeroed samples showed no significant interference.

Statistical Analysis

Descriptive statistics were used to describe the population. Cefazolin PK were generated using 1-compartment estimations for serum by plotting concentrations and time of documented clinical blood draw relative to the documented cefazolin dose. A log linear best fit trapezoidal rule was used to estimate the elimination rate, peak (C_{max}), trough (C_{min}), and area under the curve (AUC) values for the dosing interval. Although limited, this method was used to generate similar estimates for CSF concentrations. Estimated AUC_{CSF}:AUC_{Serum} within the same interval was used to estimate the CSF distribution. Time-matched concentrations were analyzed in a point-by-point CSF:serum concentration ratio to provide a secondary measurement of CSF distribution. In this ratio, CSF samples collected 1–180 minutes following a recovered blood draw, for clinical purposes, were used to provide a reasonable second estimate of cefazolin CSF penetration.

RESULTS

A total of 15 patients (80% female) were included in the study, with a respective median age, weight, body mass index, and creatinine clearance of 56 years, 71.7 kg, 26.3 kg/m^2, and 115 mL/min. The baseline demographics of patients are presented in Table 1. All but 1 patient had an EVD placed subsequent to an intracranial hemorrhage, and 66.7% involved a subarachnoid hemorrhage. One patient had an EVD placed following a brain tumor resection for intracranial pressure relief. The median (interquartile range [IQR]) daily EVD output on the day of CSF sampling was 126 (89–186) mL. All patients were prescribed cefazolin intravenously (IV) for EVD prophylaxis without suspected infection adjusted for renal function at 2000 mg IV every 8 hours (n = 13), 2000 mg IV every 12 hours (n = 1), and 500 mg IV every 24 hours (n = 1). A total of 39 serum samples and 44 CSF samples were obtained, with a median of 3 each per sample per patient, at a median (IQR) of 2.5 (1.5–7) days from first cefazolin dose. No samples were obtained following the first cefazolin dose or on the first calendar day of cefazolin initiation. One patient receiving 2000 mg IV every 8 hours did not have at least 2 serum samples recoverable within the same dosing interval; therefore, systemic AUC and AUC_{CSF}:AUC_{Serum} estimation was not calculated. For this patient, 3 CSF samples within a dosing interval were analyzed and reported, and 1 CSF sample was timed to a matched serum concentration for point-by-point analysis.

Table 1. Patient Demographics

Characteristic	All Patients (n = 15)
Female sex	12 (80)
Age, y	56 (51–60)
Height, cm	167.6 (163.9–172.7)
Weight, kg	71.7 (65–89)
Race/ethnicity	
White	10 (66.7)
Black or African American	2 (13.3)
Other	3 (20.0)
Creatinine clearance, mL/min[a]	115 (84–174)
Creatinine clearance, cefazolin dose, and interval	
>50 mL/min, 2000 mg every 8 h	13 (86.7)
11–49 mL/min, 2000 mg every 12 h	1 (6.7)
<10 mL/min, 500 mg every 24 h	1 (6.7)
EVD placement	
Left frontal	2 (13.3)
Right frontal	11 (73.3)
Other	2 (13.3)
Admission diagnosis[b]	
Subarachnoid hemorrhage	10 (66.7)
Intraparenchymal hemorrhage	4 (26.7)
Intraventricular hemorrhage	4 (26.7)
EVD output in 24 h, mL	126 (89–186)

Data reported as No. (%) or median (interquartile range).

Abbreviation: EVD, external ventricular drain.

[a]Calculated via Cockcroft-Gault equation.

[b]Some patients had multiple hemorrhage locations/diagnoses.

Estimated PK parameters for cefazolin serum and CSF concentrations are presented in Table 2. All CSF samples were within the limit of assay quantification developed at the iC42 laboratory, with a directly measured median (IQR) concentration of 1.99 (1.28–3.14) mg/L. The maximum and minimum directly measured CSF concentrations were 11.5 mg/L and 0.78 mg/L, respectively. Cohort-extrapolated median (IQR) C_{max} and C_{min} concentrations were 2.97 (1.76–8.56) mg/L and 1.59 (0.77–2.17) mg/L, respectively. Within the 2000 mg IV every 8 hours group, 16 CSF samples were obtained >4 hours after infusion, with a median and minimum directly measured concentration of 1.87 and 0.78 mg/L. The median (IQR) distribution ratios of CSF to serum by estimated $AUC_{interval}$ was 6.7% (3.9%–11.3%). A total of 29 CSF samples were obtained within 1–180 minutes after a recovered blood sample for a time-matched CSF distribution analysis. The median (IQR) CSF:serum ratio in matched times was 8.4% (5%–11%). We did not observe a relationship between time from first cefazolin dose to sample obtainment and CSF:serum ratio for AUC analysis or average point-by-point analysis (R^2 = 0.0004 and 0.095, respectively).

Table 2. Pharmacokinetics for Both Serum and Cerebrospinal Fluid

Variable	All Patients	Creatinine Clearance >50 mL/min
Interval dose, mg	Variable	2000
Serum pharmacokinetic parameters		
No. of patients	14[a]	12[a]
C_{max}, mg/L	77.6 (54.4–176.2)	75.9 (52.7–90.3)
C_{min}, mg/L	10.8 (8.3–27.2)	10.2 (8.1–24.2)
Elimination constant, h^{-1}	0.21 (0.13–0.27)	0.22 (0.14–0.28)
Half-life, h	3.37 (2.6–5.4)	3.18 (2.5–4.9)
Clearance, L/h	6.61 (4.1–9.7)	7.48 (5.4–9.9)
Volume of distribution, L	31.42 (13.8–49.8)	33.39 (23.9–61.6)
Weight adjusted volume of distribution, L/kg	0.42 (0.19–0.74)	0.56 (0.29–0.83)
$AUC_{dosing\ interval}$, mg*h/L	302.4 (206–501)	270.6 (201–372)
CSF pharmacokinetic parameters		
No. of patients	15	13
C_{max}, mg/L	2.97 (1.6–11)	2.88(1.4–5.2)
C_{min}, mg/L	1.59 (0.7–2.2)	1.07 (0.6–2.2)
CSF elimination constant, h^{-1}	0.11 (0.05–0.13)	0.08 (0.05–0.12)
CSF half-life, h	6.46 (5.5–13.1)	8.39 (5.7–13.7)
CSF $AUC_{dosing\ interval}$, mg*h/L	18.19 (10–32)	15.95 (9–28)
CSF:serum estimated ratios		
CSF:serum AUC ratio,[a] %	6.7 (3.9–11.3)[a]	4.1 (3.8–12.9)[a]
CSF:serum time matched ratio, %	8.4 (5–11)	8.3 (4.8–11.2)

Data are reported as No. (%) or median (interquartile range).

Abbreviations: AUC, estimated area under the curve; C_{max}, extrapolated maximum concentration; C_{min}, extrapolated minimum concentration; CSF, cerebrospinal fluid.

[a]One patient was excluded from serum pharmacokinetic evaluation as multiple blood samples from a dosing interval were not recovered, n = 14 for all and n = 12 for creatinine clearance >50 mL/min.

DISCUSSION

In this prospective cohort of neurosurgical patients with EVDs receiving cefazolin for prophylaxis, we observed variable yet reasonable CSF distribution at commonly used doses. Cefazolin is an effective agent for many susceptible gram-positive and gram-negative bacterial infections. It is likely as effective as and possibly better tolerated than antistaphylococcal penicillins for most infections due to MSSA [9, 10, 15–17]. Our analysis provides important estimates of cefazolin CSF concentrations in a cohort of noninfected patients. These estimates may be useful in the design of therapeutic studies evaluating cefazolin for infections involving the central nervous system while minimizing the risk of cefazolin-related neurotoxicity.

The ability of cefazolin to reach therapeutic CSF concentrations has been debated. Historically, cefazolin not been recommended for the majority of infections involving the CNS [1, 2]. Early studies reported undetectable cefazolin CSF concentrations after a single 1000-mg dose but brain tissue concentrations of 2–40 mcg/g after a single 2000-mg dose [3, 4]. Conversely, significant CSF accumulation and neurotoxicity were reported by others after multiple doses [12]. More recently, potentially therapeutic concentrations of cefazolin in CSF samples have been reported in less well-defined or smaller populations, though some reports rely on the low MSSA minimum inhibitory concentration (MIC) of 0.5 mg/L, which is an important caveat [6, 7, 18, 19]. Of interest, 1 report used serial therapeutic drug monitoring and continuous infusion cefazolin of 10 or 8 g daily to effectively treat MSSA ventriculitis [6]. This case report found a median CSF concentration of 12 mg/L with a CSF:plasma ratio of 12% during a 10-g/d continuous infusion and a median CSF concentration of 6.1 mg/L with a CSF:plasma ratio of 10% during an 8-g/d continuous infusion. These investigators conducted a retrospective analysis of patients treated with cefazolin continuous infusion and CSF therapeutic drug monitoring for staphylococcal meningitis. In 14 CSF samples analyzed in 8 patients treated with a median (range) continuous infusion of 8 (6–12) g/d, they reported a median (IQR) cefazolin concentration of 2.8 (2.1–5.2) mg/L and a corresponding CSF:plasma ratio of 4.3% (2.9%–8.4%). In 4 patients without meningitis, these investigators observed lower median CSF concentrations and distribution ratios of 0.95 (0.5–1.4) mg/L and 2.1% (0.9%–5.2%), respectively [7]. Although intriguing, the safety of higher total daily doses of cefazolin remains to be established. Our data concur with these reports, providing an estimate of CSF distribution that is within the variations reported by that study group [6, 7]. These differences may be explained by dosing strategies and patient-specific factors. As an observational study, we assessed standard intermittent doses of cefazolin adjusted for renal function, not high-dose continuous infusion. It is possible that greater drug and dose exposure led to an increased CSF distribution ratio. This may explain a ratio decrease from 12% to 10% in the same patient after the dose was decreased secondary to therapeutic drug monitoring in plasma and CSF in the case report [6]. Additionally, we assessed CSF distribution in EVD output during prophylaxis and not in patients suspected to have ventriculitis. The additional inflammation occurring from ventriculitis would be expected to increase blood–brain barrier permeability perhaps beyond that of EVD placement alone. In the retrospective study, CSF inflammation was likely a factor in lower CSF distribution ratios, as reported in those without meningitis [7]. Regardless, our estimates of CSF distribution, combined with recently published reports, provide independent evidence that cefazolin can reach therapeutic concentrations in the CSF. Although the CSF distribution ratio may be variable, it is likely within the estimate ranges discussed above.

The Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) eliminated cefazolin interpretive breakpoints for *S. aureus* [20]. However, the EUCAST $MICs_{50/90}$ for MSSA are 0.5 and 1 mg/L, respectively, with an epidemiologic cutoff of 2 mg/L [21]. Although a CSF pharmacodynamic (PD) target for meningitis or ventriculitis has not been established, our study and previous reports suggest that cefazolin is viable to meet commonly used PD targets of time above MIC >35% or 100% for $MIC_{50/90}$ values. Nevertheless, caution is warranted, as the lower quartile estimated trough in our standard dosing cohort was <1 mg/L. Similarly, it is unlikely that standard cefazolin doses would meet PD targets for pathogens with higher MICs, and alternative dosing strategies or agents should be considered. Determining the pathogen MIC for an antibiotic of interest, as is the case for *Streptococcus pneumoniae* meningitis, before instituting targeted definitive therapy remains prudent. If possible, therapeutic drug monitoring could provide additional information regarding drug penetration at the site of infection, allowing for alternative dosing strategies to optimize efficacy while minimizing overexposure. This strategy has been reported for other β-lactams beyond the therapeutic drug monitoring of cefazolin [7, 18]. Importantly cefazolin, among other antibiotics, has been reported to have increased MICs in the presence of a large number of organisms (MSSA in particular), occasionally leading to clinical failure in deep-seated infections [22, 23]. This phenomenon, coined the cefazolin inoculum effect (CIE), is a result of MSSA producing β-lactamases encoded by the blaZ gene [24, 25]. The clinical significance of the CIE is not entirely clear, as while some studies show higher rates of clinical failure and mortality in the presence of the CIE, other studies do not show poorer outcomes with cefazolin as compared with antistaphylococcal penicillins. In certain conditions, potential complications with high bacterial burden may be mitigated by appropriate source control [16, 20]. Source control in the CNS would include infected device removal and prompt abscess drainage of any formed abscess.

Comparatively, other antistaphylococcal penicillins have variable CSF penetration, in some cases less than that of cefazolin. Le Turnier et al. reported lower median (IQR) CSF:plasma ratios and steady state CSF concentrations of 1.8% (1.7%–2.8%) and 0.66 (0.5–0.9) mg/L, respectively, with cloxacillin 12 g IV daily compared with cefazolin [7]. A 3% ratio of CSF:unbound plasma concentration for cloxacillin has been estimated by others [26]. Flucloxacillin 2000 mg IV every 4 hours resulted in CSF concentrations of 0.3 mg/L, and others report very low CSF concentrations even when utilizing continuous infusions [27]. Conversely, nafcillin CSF concentrations are reported as adequate to treat MSSA CSF infections. Daily nafcillin doses of 100–200 mg/kg resulted in adequate CSF concentrations for MSSA [28]. However, a single nafcillin dose of 40 mg/kg IV in 8 patients resulted in a mean CSF concentration of 0.12 mg/L at 2 hours postdose and a mean CSF concentration of 0.03 mg/L at 4 hours postdose in patients with no meningeal inflammation [29]. In 7 patients with bacterial ventriculitis, CSF nafcillin was reported as 0.8%–20.4% peak serum concentrations [30]. Brain tissue concentrations following 2000 mg IV of nafcillin in 13 patients resulted in a mean of 2.7 mcg/g, whereas cefazolin 2000 mg IV resulted a mean of 10.6 mcg/g, suggesting comparable brain penetration of both nafcillin and cefazolin [4].

This study has several important limitations. We assessed cefazolin distribution using 2 methods through a biological waste secondary use protocol. As such, these values should be viewed as estimates, as a formal PK study was not possible and somewhat unsophisticated single-compartment trapezoidal calculations were used to provide estimates, which did not account for delayed CSF distribution. However, both AUC_{CSF}:AUC_{Serum} and matched point estimates resulted in serum to CSF distribution concordant values in line with previous reports. Nevertheless, significant variability around CSF penetration exists within our cohort of patients. This variability has also been reported by others, suggesting an IQR spread similar to the estimated median CSF percent distribution ratio [7]. This observation is also true of extrapolated CSF C_{min} values and was of concern in our cohort as values approached commonly reported MICs of targeted pathogens when 2 g IV every 8 hours dosing (with renal adjustment) was used. In the 16 CSF samples obtained >4 hours after infusion with a median and minimum directly measured concentration of 1.87 and 0.78 mg/L, we are reminded that an appropriate dosing schedule selection is critical, especially in individuals with potential augmented renal clearance and/or individuals at high risk for treatment failure due to high-inoculum MSSA infection or retained hardware. Given the free drug time above MIC PD target of cefazolin, alternative dosing strategies such as more frequent dosing, extended interval dosing, or continuous infusion, especially in those with high renal clearance, may be required to optimize efficacy and safety. Future PK/PD modeling beyond the limited trapezoidal estimates in the CSF compartment and clinical studies is required to provide more insight into optimized dosing strategies, target CSF concentrations, and the overall efficacy and safety of cefazolin as a targeted therapy compared with standard of care before use can be widely adopted. In addition, we did not assess meningeal inflammation in our cohort. Our patients were not suspected to have meningitis or ventriculitis, which may increase blood–brain barrier permeability. Although the insertion of an EVD is traumatic and our population had underlying reasons for meningeal inflammation, we cannot comment on the relative difference in inflammation and drug distribution expected in those with meningitis. Lastly, CSF samples were obtained from a single EVD after a median of 2.5 days from cefazolin initiation. These estimates assume both steady state in CSF distribution and homogenous mixing between EVD output and the CSF compartment.

CONCLUSIONS

In a prospective cohort of 15 critically ill neurosurgical patients with EVDs, we observed variable cefazolin CSF concentrations and relative CSF distribution. These estimates suggest that cefazolin may be a viable option for the treatment of meningitis or ventriculitis due to susceptible bacteria. Optimal dosing regimens for this indication require further study and may be aided by therapeutic drug monitoring. Ultimately, clinical studies evaluating the efficacy and safety of cefazolin, with or without additional antimicrobials, are needed to define a role in therapy.

Acknowledgments

We acknowledge Deborah Sherman, PharmD, for assistance in identifying patients and the Neurosurgical Interdisciplinary Team (MDs, RNs, and Advanced Practitioners) for assistance with biological waste sample collection.

Financial support. This work was partially supported by seed grants from University of Colorado Skaggs School of Pharmacy, Department of Clinical Pharmacy and the Associate Dean of Research (S.W.M.).

Potential conflicts of interest. All investigators are supported by the National Institutes of Health (NIH)/National Center for Advancing Translation Sciences (NCATS) Colorado CTSA (Grant Number UL1 TR002535). The authors declare no other disclosures or conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. M.K., R.T.N., L.C.P., K.C.M., S.W.M. designed the study; A.R.N., S.W.M. collected patient samples; A.R.N., T.H.K., K.C.M., S.W.M. pharmacokinetic analysis and statistics; M.K. and S.W.M. obtained seed funding; A.R.N., M.K., T.H.K., R.T.N., L.C.P., K.C.M., S.W.M. prepared and made substantial comments to the manuscript.

References

1. Tunkel AR, Hasbun R, Bhimraj A, et al. Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis **2017**; 64:e34–65.
2. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis **2004**; 39:1267–84.
3. Bassaris HP, Quintiliani R, Maderazo EG, et al. Pharmacokinetics and penetration characteristics of cefazolin into human spinal fluid. Curr Ther Res Clin Exp **1976**; 19:110–20.
4. Frame PT, Watanakunakorn C, McLaurin RL, et al. Penetration of nafcillin, methicillin, and cefazolin into human brain tissue. Neurosurgery **1983**; 12:142–7.

5. Thys JP, Vanderkelen B, Klastersky J. Pharmacological study of cefazolin during intermittent and continuous infusion: a crossover investigation in humans. Antimicrob Agents Chemother **1976**; 10:395–8.
6. Grégoire M, Gaborit B, Deschanvres C, et al. High-dosage cefazolin achieves sufficient cerebrospinal diffusion to treat an external ventricular drainage-related staphylococcus aureus ventriculitis. Antimicrob Agents Chemother **2019**; 63:e01844-18.
7. Le Turnier P, Grégoire M, Deslandes G, et al; NAMPA study group. Should we reconsider cefazolin for treating staphylococcal meningitis? A retrospective analysis of cefazolin and cloxacillin cerebrospinal fluid levels in patients treated for staphylococcal meningitis. Clin Microbiol Infect **2020**; 26:1415 e1–4.
8. Chew R, Woods M. Flucloxacillin does not achieve therapeutic cerebrospinal fluid levels against methicillin-sensitive *Staphylococcus aureus* in adults: a case report and review of the literature. Int J Antimicrob Agents **2016**; 47:229–31.
9. Miller MA, Fish DN, Barber GR, et al. A comparison of safety and outcomes with cefazolin versus nafcillin for methicillin-susceptible *Staphylococcus aureus* bloodstream infections. J Microbiol Immunol Infect **2020**; 53:321–7.
10. Lecomte R, Bourreau A, Deschanvres C, et al. Comparative outcomes of cefazolin versus antistaphylococcal penicillins in methicillin-susceptible *Staphylococcus aureus* infective endocarditis: a post hoc analysis of a prospective multicentre French cohort study. Clin Microbiol Infect **2021**; 27:1015–21.
11. 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.
12. Moore TD, Bechtel TP, Ayers LW. Effect of multidose therapy on cerebrospinal fluid penetration of cefazolin. Am J Hosp Pharm **1981**; 38:1496–9.
13. Cherubin CE, Eng RH, Norrby R, et al. Penetration of newer cephalosporins into cerebrospinal fluid. Rev Infect Dis **1989**; 11:526–48.
14. Tsai TH, Chen YF. Simultaneous determination of cefazolin in rat blood and brain by microdialysis and microbore liquid chromatography. Biomed Chromatogr **2000**; 14:274–8.
15. Loubet P, Burdet C, Vindrios W, et al. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemia: a narrative review. Clin Microbiol Infect **2018**; 24:125–32.
16. Li J, Echevarria KL, Traugott KA. Beta-Lactam therapy for methicillin-susceptible *Staphylococcus aureus* bacteremia: a comparative review of cefazolin versus antistaphylococcal penicillins. Pharmacotherapy **2017**; 37:346–60.
17. Allen JM, Bakare L, Casapao AM, et al. Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with methicillin-susceptible *Staphylococcus aureus* infection: a meta-analysis with trial sequential analysis. Infect Dis Ther **2019**; 8:671–86.
18. Bellouard R, Deslandes G, Morival C, et al. Simultaneous determination of eight beta-lactam antibiotics in human plasma and cerebrospinal fluid by liquid chromatography coupled to tandem mass spectrometry. J Pharm Biomed Anal **2020**; 178:112904.
19. Klekner A, Ga'spa'r A, Kardos S, et al. Cefazolin prophylaxis in neurosurgery monitored by capillary electrophoresis. J Neurosurg Anesthesiol **2003**; 15:249–54.
20. Dein Bard J, Hindler JA, Gold HS, et al. Rationale for eliminating *Staphylococcus* breakpoints for β-lactam agents other than penicillin, oxacillin or cefoxitin, and cefaroline. Clin Infect Dis **2014**; 58:1287–96.
21. European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website. Available at: https://mic.eucast.org/search/?search%5Bmethod%5D=mic&search%5Bantibiotic%5D=-1&search%5Bspecies%5D=449&search%5Bdisk_content%5D=-1&search%5Blimit%5D=50. Accessed 2 August 2021.
22. Lenhard JR, Bulman ZP. Inoculum effect of beta-lactam antibiotics. J Antimicrob Chemother **2019**; 74:2825–43.
23. Sabath LD, Garner C, Wilcox C, et al. Effect of inoculum and of beta-lactamase on the anti-staphylococcal activity of thirteen penicillins and cephalosporins. Antimicrob Agents Chemother **1975**; 8:344–9.
24. Carvajal LP, Rincon S, Echeverri AM, et al. Novel insights into the classification of staphylococcal beta-lactamases in relation to the cefazolin inoculum effect. Antimicrob Agents Chemother. **2020**; 64:e02511-19.
25. Rincon S, Carvajal LP, Gomez-Villegas SI, et al. A test for the rapid detection of the cefazolin inoculum effect in methicillin-susceptible *Staphylococcus aureus*. J Clin Microbiol. **2021**; 59:e01938-20.
26. Schievink HI, Mattie H, Thomeer R, et al. The passage of cloxacillin into cerebrospinal fluid in the absence of meningitis. Br J Clin Pharmacol **1993**; 36:57–60.
27. Chew R, Woods ML. Flucloxacillin does not achieve therapeutic cerebrospinal fluid levels against methicillin-sensitive *Staphylococcus aureus* in adults: a case report and review of the literature. Int J Antimicrob Agents **2016**; 47:229–31.
28. Kane JG, Parker RH, Jordan GW, et al. Nafcillin concentration in cerebrospinal fluid during treatment of staphylococcal infections. Ann Intern Med **1977**; 87:309–11.
29. Fossieck BE, Kane JG, Diaz CR, et al. Nafcillin entry into human cerebrospinal fluid. Antimicrob Agents Chemother **1977**; 11:965–7.
30. Yogev R, Schultz WE, Rosenman SB. Penetrance of nafcillin into human ventricular fluid: correlation with ventricular pleocytosis and glucose levels. Antimicrob Agents Chemother **1981**; 19:545–8.