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Cefazolin in the Treatment of Central Nervous System Infections: A Narrative Review and Recommendation

Running title: Cefazolin in the Treatment of CNS Infections

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Abstract

Infections of the central nervous system (CNS) are complex to treat and associated with significant morbidity and mortality. Historically, antistaphylococcal penicillins such as nafcillin were recommended for the treatment of staphylococcal CNS infections. However, the use of antistaphylococcal penicillins present challenges, such as frequent dosing administrations and adverse events with protracted use. This narrative reviews available clinical and pharmacokinetic/pharmacodynamic (PK/PD) data for cefazolin use in CNS infections and produces a recommendation for use. Based on the limited available evidence analyzed, dose optimized cefazolin is likely a safe and effective alternative to antistaphylococcal penicillins for a variety of CNS infections due to methicillin-susceptible *Staphylococcus aureus*. Given the site of infection and wide therapeutic index of cefazolin, practitioners may consider dosing cefazolin regimens of 2 g IV every 6 hours or a continuous infusion of 8-10 grams daily instead of 2 g IV every 8 hours to optimize PK/PD properties.

Keywords: CNS, central nervous system infection, cefazolin, nafcillin, antistaphylococcal penicillins

Introduction

Infections of the central nervous system (CNS), including meningitis, encephalitis, ventriculitis, and brain abscesses, are particularly complex to treat and are generally associated with significant morbidity and mortality. CNS infections pose a significant treatment challenge due to the deep-seated condition, uncertainty regarding antibiotic exposure targets, and potential for adverse effects during antibiotic therapy.[1] Understanding the CNS penetration of antimicrobials is essential for therapeutic effectiveness and optimizing treatment outcomes, since the potential for adverse consequences is high with improper treatment.

Historically, antistaphylococcal penicillins have been preferred as the drug of choice for serious methicillin-susceptible *Staphylococcus aureus (*MSSA)infections, including bloodstream infections (BSI) and infective endocarditis[2]. However, this preference is primarily due to clinician experience and lack of comparative trials with clinically meaningful outcomes between antistaphylococcal penicillins and other antimicrobials. Among beta-lactams, antistaphylococcal penicillin antibiotics such as nafcillin and oxacillin are currently recommended in tertiary references and guidelines for treatment of CNS infections due to MSSA, while cefazolin is not preferred.[2,3] However, the use of antistaphylococcal penicillins presents challenges with both administration and adverse events (e.g., fluid retention, elevated liver enzymes, interstitial nephritis) with protracted use.[4] The use of cefazolin for CNS infections has become a topic of increased interest given superior tolerability, less frequent dosing, and mounting clinical data showing at least equivalent, if not improved, outcomes in the treatment of BSI and endocarditis when compared to antistaphylococcal penicillins.[5-8] The objectives of this narrative review are to summarize the available data and produce a recommendation for cefazolin use in CNS infections.

Drug Characteristics for Optimal CNS Penetration

The ability of an antibiotic to enter the CNS depends on multiple factors such as degree of meningeal inflammation, molecular size, charge, degree of protein binding, lipophilicity, and affinity for active transport mechanisms at the blood brain barrier. Ideal molecular characteristics of agents utilized for CNS infections include small molecular size, low degree of protein binding, moderate lipophilicity, and a weak affinity for efflux pumps in the CNS.[9,10]

It is important to clarify what CNS penetration means; penetration is often defined as cerebrospinal fluid (CSF) or parenchymal concentrations relative to plasma concentrations or simply "percent penetration". However, even parenchymal concentrations are comprised of various matrices combined (e.g., inter-cellular, interstitial fluids, red blood cells remaining, etc). Biodistribution (and governing kinetics that define transfer rates) into each of these separate anatomical sites is not well described in the literature, especially in human studies. Complicating the matter, parenchymal tissue is notoriously hard to obtain in humans which limits understanding of pharmacokinetic transfer rates.[11,12] It is not clear that transfer to and from these separate anatomic locations is governed by a single first order process, nor characterized by a single steady state. Additionally, relative, proportional penetration of a drug into the CSF as a single point of reference does not accurately reflect drug concentrations in the CNS compartment, given that in some cases low serum concentrations may impact this number significantly. Simply put, a low "percent penetration" (e.g., nafcillin or cefazolin) does not reflect inadequate concentrations of a drug, and vice versa, in the CNS as well as with other deep-seated infections. Molecular characteristics of cefazolin, oxacillin, and nafcillin are shown in Table 1.

Overview of Beta Lactam Pharmacokinetic/Pharmacodynamic Principles

Beta-lactams are commonly recommended in guidelines for invasive CNS infections, however understanding how to optimize beta-lactam dosing is important for effectively treating such infections. In general, the serum half-life for most beta-lactams is 1 to 2 hours, with a few outliers such as ceftazidime (4-6 hours) and ceftriaxone (8-10 hours). These agents are mostly eliminated through glomerular filtration and a few through the hepatobiliary system, such as ceftriaxone and oxacillin.[14] Further pharmacokinetic/pharmacodynamic (PK/PD) parameters of commonly used beta-lactams are summarized in Table 2.

The primary pharmacodynamic determinant for beta-lactam effectiveness is the proportion of a 24-hour time period that the unbound (free) drug concentration remains above the minimum inhibitory concentration (*f*T>MIC). For the class of cephalosporins, animal and human studies have suggested a *fT*>MIC requirement of 50 to 70% for efficacy, with higher targets proposed for more serious infections.[20,21] In order to maximize the *f*T>MIC of beta-lactams in the blood, various strategies have been utilized, including extended and continuous infusion. Clinical

studies with extended infusion cefazolin are relatively limited (and are non-existent for CNS infections); however, as with other beta-lactams, maximizing *f*T>MIC with extended infusion cefazolin has been associated with improved outcomes such as higher tissue concentrations, decreased incidence of infection, and decreased patient burden during outpatient therapy.[22-24]

Antistaphylococcal Penicillins Pharmacokinetics

Relevant antistaphylococcal penicillins have both renal and non-renal clearance. Nafcillin is primarily excreted via the feces and urine (~30% excreted as unchanged drug in urine), and is highly protein bound (~90% serum protein binding), with a half-life of 0.5-1 hour and a volume of distribution (Vd) of ~1 L/kg.[4] Oxacillin, an additional intravenous antistaphylococcal penicillin, is primarily excreted via bile and urine (~50% of dose is metabolized in the liver to active and inactive metabolites), similarly highly protein bound (~94% serum protein binding), with a half-life of 20 to 30 minutes, and a Vd of 0.4 L/kg.[25]

Early animal models showed that both nafcillin and oxacillin achieved comparable antibiotic concentrations within the CNS. In a rabbit model where antibiotics were administered at doses between 25-125 mg/kg/hour for three or more doses, nafcillin penetrated the CNS to nearly the same extent as oxacillin, producing mean CSF concentrations 1.4-2.0% and 1.0-2.8% of serum concentrations, respectively. As a comparator in this study, methicillin CSF concentrations ranged from 3.6% to 5.9% of serum concentrations.[26]

In a small cohort of 18 critically ill adult patients who received nafcillin 40 mg/kg in the absence of meningeal inflammation, mean CSF concentrations at 1, 2, 3, and 4 hours post infusion were 0.1-0.2%, 0.4-0.9%, 1.3-2.5%, and 1-1.4% of mean serum concentrations, respectively.[27] Furthermore, in a case report of a 69-year-old patient with *S. aureus* meningitis, the CSF concentration 45 minutes post a 3 g IV dose of nafcillin (administered over 5 minutes) was 9.5 mg/L.[28] An additional study analyzed nine patients treated with nafcillin for staphylococcal infections. Nafcillin concentrations were greater than the MIC for *S. aureus* in eight of the nine patients. In patients who had CSF pleocytosis, nafcillin concentrations ranged from 7.5 – 88 mg/L in the CSF. In patients without CSF pleocytosis, nafcillin concentrations ranged from 0.13 – 2.7 mg/L in the CSF. [29]

First-generation Cephalosporin Pharmacokinetics

Cefazolin is primarily eliminated via the kidney (70-80% excreted in urine as unchanged drug), is highly protein-bound (80% serum protein binding), with a half-life of 1.8 hours and a Vd of 0.19 L/kg.[30] Cephalothin, a first-generation cephalosporin developed prior to cefazolin, has a half-life of 0.47 hours, a Vd of 0.25 L/kg, and is 65% protein bound.[31] Cephalothin has a reported low degree of CNS penetration in a rabbit model, with CSF concentrations 1.4-2.1% of serum concentrations.[31] As detailed in the next section, the relatively low CNS penetration was corroborated with reports of clinical failures in bacterial meningitis.

When comparing the PK properties of nafcillin, oxacillin, and cefazolin with literature reported values, all three agents exhibit constrained CSF penetration in the absence of meningeal inflammation (Table 3). A rabbit model for pneumococcal meningitis was used to analyze cefazolin CSF concentrations at 2, 4, 6, and 8 hours after a continuous 30 mg/kg/hr dose of cefazolin. This analysis showed that cefazolin had a CSF penetration of 3.1%, which was similar to the penicillin G CSF penetration of 2.8%.[32] Cefamandole and cephalothin had similar degrees of CSF penetration to penicillin G and cefazolin, likely a function of the high degree of serum protein binding (>50%) among these four agents.[32]

Despite lower proportional blood-to-CSF penetration (ie., "percent penetration"), emerging data in humans has shown that cefazolin achieves therapeutic concentrations within the CSF. A case report of a patient with MSSA ventriculitis being successfully treated with high-dose cefazolin at 10 g/day followed by 8 g/day reported mean CSF concentrations of 11.9 mg/L and 6.1 mg/L, respectively, with no worsening in glomerular filtration rate.[33] Both of these concentrations achieved 100% *f*T>MIC when considering the approved breakpoint for cefazolin (as surrogate to oxacillin/penicillin) against MSSA is ≤ 2 mcg/mL per the Clinical and Laboratory Standards Institute (CLSI).[34] Another study among adult patients undergoing craniotomy reported that cefazolin achieved higher concentrations in homogenized brain tissue (mean: 10.6 mcg/g) than nafcillin or methicillin (mean: 2.7 mcg/g and 2 mcg/g), at 30 to 225 minutes after a 2 g IV dose.[35] Considering the cefazolin CLSI breakpoint of ≤ 2 mcg/mL for MSSA, all measured cefazolin concentrations at steady state were above the breakpoint throughout treatment.[34] In an analysis of six adult patients receiving cefazolin at doses ranging from 1-3 g q4-6h IV, CSF and serum concentrations drawn at steady state showed five of six patients had notable CSF concentrations (11.3% $\pm$ 2.7% of serum concentration).[36]

A recent prospective PK study analyzed the concentration of cefazolin in CSF and serum in non-infected adults with external ventricular drains (EVDs).[37] Fifteen adult patients (with a median of three CSF samples obtained from each patient) received 2 g IV Q8 of cefazolin, or a renally-adjusted equivalent dose. Directly measured CSF maximum concentration (Cmax) and minimum concentration (Cmin) were 11.5 mg/L and 0.78 mg/L, respectively. When analyzing only patients who received 2 g IV Q8, median and minimum CSF concentrations (n=16 samples) obtained 4 hours after administration were noted to be 1.87 mg/L and 0.78 mg/L, respectively. The median CSF:serum area under the curve (AUC) ratio was 6.7% (inner quartile range 3.9% - 10.6%). For demonstrative purposes, cefazolin simulations were created in PK-Sim [Open Systems Pharmacology, Wuppertal, Germany] by author (MS) to represent n=500 females and n=500 males between the ages of 30 and 100 years, weighing 60-120 kg with a body mass index of 18-35 kg/m^2. The following parameters were defined for cefazolin as a compound.[38] The cefazolin free fraction was set at 0.2 with an estimated plasma clearance of 0.92 mL/min/kg (from a plasma half-life of 1.8 hours and a Vd of 0.15 L/kg). Gaussian simulated GFRs ranged from 5 to 41 mL/min/100 g kidney weight (i.e. 16 to 131 mL/min for 320 g of kidney).[39] Cefazolin 2 g every 8 hours was simulated for five doses as a 30-minute infusion to illustrate concentrations that are expected initially and at steady state (Figure 1). The estimated concentrations at specific sites within the brain were generated from base settings in Open Systems Pharmacology.[38] Median peak interstitial brain concentrations after a single 2-g dose were ~21 mg/L (total) and 9 mg/L (free). After five doses, approximately steady state, concentrations of ~39 mg/L (total) and 16 mg/L (free) were achieved. However, brain tissue concentrations are predicted to be much lower with a peak of 0.1 mg/L after a single dose and 0.18 mg/L at steady state. Thus, understanding the exact site of infection and predicted concentrations is necessary (e.g. are interstitial predicted concentrations the correct target for extracellular pathogens?). Additionally, understanding how assays are functionally conducted is important. Tissues are often homogenized, resulting in mixed inter- and intra-cellular drug concentrations. It is also important to be aware of available therapeutic drug monitoring capabilities, as many clinical laboratories can only quantify total drug concentrations for a given sample.[40]

Few PK studies exist for cefazolin, and longstanding dogma that cefazolin does not reach the CNS in sufficient concentrations has limited research efforts. Data from PK studies should be

interpreted with caution, given the general limitations of such research. With expected (and largely unmeasured) significant heterogeneity in the inter- and intra-individual CNS exposures of antibiotics, it is important to know concentrations of cefazolin at the site of infection, and this remains a gap in knowledge.

Cefazolin Clinical Data in CNS Infections

As alluded to above, the first-generation cephalosporin cephalothin, has reported negative outcomes for treatment of meningitis. A case series of five patients developed breakthrough meningitis while receiving cephalothin therapy, although all infections were caused by pathogens other than *Staphylococcus aureus* (two cases of *Streptococcus pneumoniae*, one case of *Neisseria meningitidis*, one case of *Klebsiella pneumoniae*, and one case of *Listeria monocytogenes*- all sensitive to cephalothin except unknown in Listeria case).[41] Historically, early development of second- and third-generation cephalosporins was driven in part by the desire to use beta-lactam agents to treat resistant gram-positive and gram-negative CNS infections. Although breakthrough meningitis cases have not been reported with cefazolin, it has likely been avoided as an agent for treating CNS infections by its association with other first-generation cephalosporins, such as cephalothin.[27]

The successful use of cefazolin in BSI and endocarditis raises intrigue related to its effectiveness in treating other deep-seated infections. A literature review identified nine case reports of the use of cefazolin for spinal epidural abscesses (SEAs) (Table 4).[42-50] Seven patients had MSSA, one had Group G *Streptococcus*, and one had methicillin-susceptible *Staphylococcus lugdunensis*. Only one case described the use of cefazolin for empirical therapy, five described cefazolin as definitive therapy after culture results were available, and three did not specify. Six patients had cefazolin monotherapy, and three patients had combination therapy with either clindamycin or rifampin. Duration of cefazolin therapy ranged from 2 to 6 weeks, and the dose of cefazolin was specified in some, but not all, of the case reports. Eight of the patients had improvement in neurologic function and/or imaging findings documenting no relapse. One report did not comment on the outcome of the patient. Some limitations of these case reports include lack of controls, small sample size, and perhaps publication bias.

One potential barrier to the widespread adoption of cefazolin for treatment of CNS infections is concern regarding the cefazolin inoculum effect (CIE) for MSSA. The inoculum effect is an *in vitro* phenomenon, described as a significant rise in cefazolin MIC when bacterial inoculum size increases from 10^5 to 10^7 CFU/mL.[51] Inoculum effect has been associated with the *blaZ* gene, which allows for the production of staphylococcal beta-lactamases. One study of MSSA clinical isolates found a 26% prevalence of type A beta-lactamase, with 19% of isolates displaying a pronounced inoculum effect ($MIC_{90} \geq 16$ mcg/mL with 10^7 CFU/mL).[52] For this reason, some have postulated that an inoculum effect may be of particular concern in CNS infections where high bacterial loads are expected and antibiotic exposures are lower. This *in vitro* effect is not as frequently seen in nafcillin in comparison to cefazolin. In an article studying the inoculum effect in 118 clinical isolates of *S. aureus* in 13 antibiotics, nafcillin was more resistant to the inoculum effect, whereas benzylpenicillin and cefazolin were most susceptible to the inoculum effect in comparison to the other cephalosporins.[53] However, data suggests that cefazolin is an effective treatment option for infective endocarditis, further suggesting that the inoculum effect is solely an *in vitro* phenomenon.[7,8,28] Literature reports that resistance to clindamycin (OR: 3.55, 95% CI: 1.62-7.80) and erythromycin (OR: 5.00, 95% CI: 2.50-9.99) predicts the presence of CIE with high sensitivity (92.9%) and relatively high negative predictive value (82.3%).[54] However, these concerns are largely theoretical; the CIE may be an *in vitro* phenomenon.

Recent *in vivo* data bring the CIE into question by showing low prevalence of inoculum effect and positive clinical outcomes with cefazolin use in BSIs.[55] A pivotal study in South Korea, prompted by a nafcillin shortage, was among the first to demonstrate effectiveness of cefazolin for MSSA BSI. In this retrospective, propensity score-matched, cohort study, mortality and hospital length of stay were comparable in patients with MSSA BSI who received nafcillin before the shortage or cefazolin during the shortage. Patients with suspected CNS infections were excluded from this study. Patients treated with cefazolin had less drug-related adverse events, particularly interstitial nephritis.[56] After this landmark study, several other larger cohorts confirmed these findings in systematic reviews and meta-analyses. The collective results of these studies reassure clinicians that cefazolin is not only a practical alternative to nafcillin, but also a drug of choice for MSSA BSI. [7,57,58] A randomized, controlled, non-inferiority clinical trial (CloCeBa) comparing cloxacillin versus cefazolin efficacy and safety in patients with MSSA

BSI is currently enrolling.[59] Many patients in these aforementioned cohort studies had complicated MSSA BSI including left-sided infective endocarditis. Accordingly, the American Heart Association infective endocarditis guidelines for native valve endocarditis caused by methicillin-susceptible strains of *Staphylococcus spp.* further elaborate on the clinical application of cefazolin by recommending it as a potential first-line alternative to nafcillin or oxacillin.[60] Notably, the European guidelines specifically recommend that nafcillin should be used in the presence of a brain abscess.[61]

Only a few published studies provide direct comparisons of cefazolin and antistaphylococcal penicillins in the treatment of CNS infections. A recent multicenter study of 79 adult patients with MSSA SEAs received either cefazolin or antistaphylococcal penicillins. There were no differences in failure rates at 12 weeks defined as requiring antibiotic extension in the cefazolin or antistaphylococcal penicillin group (33.3% vs. 44.1%), respectively. Similarly, no differences were found in epidural abscess-related death (0% vs. 0%), mortality (15.6% vs. 11.8%, p=0.75), or 90-day recurrence rates (11.4% vs. 9.4%, p=1) between the cefazolin and antistaphylococcal penicillin treatment groups, respectively. Notably, the median duration of total antibiotic therapy in both groups was approximately 8 weeks, with equal incidence of treatment interruptions due to adverse events.[62] A recent retrospective cohort study examined the effectiveness of cefazolin versus cloxacillin in 98 patients with MSSA SEA.[63] Mortality at 90 days was comparable between those who received cefazolin (n=50) and those who received cloxacillin (n=48) (8% vs 13%, p=0.52, respectively). Antibiotic failure rate was 12% and 19%, respectively (p=0.41). Recurrence rates (2% vs 8%) and adverse events rate (0% and 4%) were numerically higher but not statistically significant in the cloxacillin cohort. An additional retrospective cohort study examined cefazolin effectiveness for acute bacterial meningitis due to MSSA confirmed by CSF cultures or polymerase chain reaction (PCR) from 2009 to 2019. Included patients had received either cefazolin or cloxacillin, and CSF drug concentrations were measured. Greater than 70% of patients had combination therapy, most commonly the addition of levofloxacin. Eight of the 17 patients received cefazolin with a median daily dose of 8 g (range of 6-12 g) via continuous infusion. All CSF samples were drawn at least 24 hours after initiation of antibiotics. Median CSF concentration for cefazolin was 2.8 mg/L, confirming therapeutic CSF concentration in these patients, and 0.66 mg/L for cloxacillin. All patients included in this study had full recovery, although two of the cloxacillin patients had persistently

positive CSF cultures and were switched to a different agent. No therapeutic failures were noted in the cefazolin group.[64]

The evidence summarized above for cefazolin in the treatment of CNS infections is mainly limited by the retrospective, observational nature of clinical studies with small sample sizes. This limits our ability to extrapolate existing data to more serious infections that require higher doses and/or longer durations of treatment.

Cefazolin Dosing Considerations

It is often a balance of attempting to ensure sufficient CNS concentrations of beta-lactams are achieved while avoiding toxicity. The typical dosage of cefazolin ranges from 1 to 2 grams intravenously every 8 hours, with higher doses recommended for more serious infections caused by MSSA and *Streptococcus* spp. Although the United States Food and Drug Administration approved maximum dose for cefazolin is 6 grams per 24 hours in patients with normal renal function[30], commonly documented experience of doses up to 10 grams per day has been used without significantly increasing rates of adverse reactions. Similarly, tertiary references frequently utilized by clinicians state 12 g/day as the maximum cefazolin dose.[30,65] Compared to traditional dosing schemes, high-dose cefazolin (i.e., > 6 grams per day) has been associated with lower rates of treatment failure in obese patients, while not increasing rates of renal or neurological adverse effects. [66,67] Approved breakpoints for cefazolin (as surrogate to oxacillin/penicillin) against MSSA and *Streptococcus spp.* are ≤ 2 mcg/mL and ≤ 0.12 mcg/mL, respectively, from the CLSI, though notably these breakpoints do not consider site-specific PK/PD for cefazolin. If one focuses on interstitial brain concentrations for cefazolin, it appears that these targets are achievable for susceptible organisms.

Beta-lactams are frequently given in extended infusion schemes to maximize fT>MIC in other infection settings. Although intermittent dosing allows for higher peak serum concentrations, beta-lactams demonstrate time-dependent killing, maximizing the time in which drug levels exceed the MIC. This suggests that dosing cefazolin via continuous infusion may correlate with increased bacterial eradication. Although the beta-lactams in general have a reasonable number of studies supporting extended dosing schemes, few studies have been conducted for cefazolin. Some insight may be garnered from studies with other infections.

Superiority of continuous infusion versus standard intermittent infusion has been demonstrated in rats with hemorrhagic shock. Rats receiving continuous infusion cefazolin had significantly higher concentrations in subcutaneous abscess tissues and 56% fewer abscesses, compared to rats in the intermittent infusion group.[22] The safety and efficacy of continuous infusion cefazolin for the treatment of bone and joint infections has also been evaluated in human patients. One retrospective study among 100 patients with bone and joint infections reported high rates of overall cure (82/88) [93%] with continuous infusion cefazolin along with only two incidences of moderate-grade adverse events requiring dose adjustment.[68] The median daily dose was 6 g and the median serum cefazolin concentration was 63 mg/L between days 2 to 10.

Cefazolin Safety Data

Cefazolin is generally well-tolerated, with the infrequent adverse reactions reported as hypersensitivity reactions, neutropenia, thrombocytopenia, and diarrhea. In cases of renal impairment and drug accumulation, CNS toxicity can occur in the form of encephalopathy, seizures, and even coma in the severe setting. Encephalopathy induced by a cephalosporin generally occurs 1 to 10 days following initiation of the medication. Treatment consists of discontinuing the offending agent and a need for hemodialysis in certain cases, and symptoms generally resolve in 2 to 7 days following discontinuation.[69] The reversible encephalopathy is generally associated with EEG abnormalities, and may be required for diagnosis of cephalosporin-induced encephalopathy. Anticonvulsants can temporarily alleviate symptoms if necessary. Side effects of antistaphylococcal penicillins include hypersensitivity reactions, interstitial nephritis, hepatotoxicity, fluid retention, phlebitis, and bone marrow suppression. In a study comparing the efficacy and safety of nafcillin verses cefazolin for MSSA bacteremia, nafcillin was associated with more nephrotoxicity (25.3% vs. 2%), hepatotoxicity (11.4% vs. 0%), and allergic reactions (11.4% vs. 0%) in comparison to cefazolin, respectively.[70]

Cefazolin, like other cephalosporins, has a wide therapeutic index with rare reports of intolerability in patients with normal kidney function.[30] Few case reports analyze cefazolin concentrations after patients had experienced seizures following a course of cefazolin therapy. One case report describes a 60-year-old woman with impaired renal function who received cefazolin 1.5 g IV every 4 hours. On day 12, the patient experienced a tonic-clonic seizure and subsequent cefazolin serum and CSF concentrations were 470 and 64 mcg/mL, respectively. A

second case describes a 70-year-old man with impaired renal function who received cefazolin 1 g IV every 12 hours, followed by 1 g IV every 6 hours. Cefazolin serum and CSF concentrations were 360 and 34 mcg/mL, respectively, after the patient suffered tonic-clonic seizures on day 8. Of note, both of these patients had acute kidney injury and their cefazolin dose was not adjusted accordingly.[71] Similarly, another case series of six patients noted that cefazolin serum concentrations above 300 mcg/mL and CSF concentrations above 34 mcg/mL were associated with seizure events, whereas CSF penetration without seizures occurred at serum concentrations of 90 mcg/mL or CSF concentrations of 16 mcg/mL.[36] If dosed appropriately in conjunction with the patient's renal function, cefazolin toxicity is uncommon. It is important to note that cefazolin, like other beta-lactams, should never be administered intraventricularly or directly into the CNS due to the very high potential for seizure induction.[72]

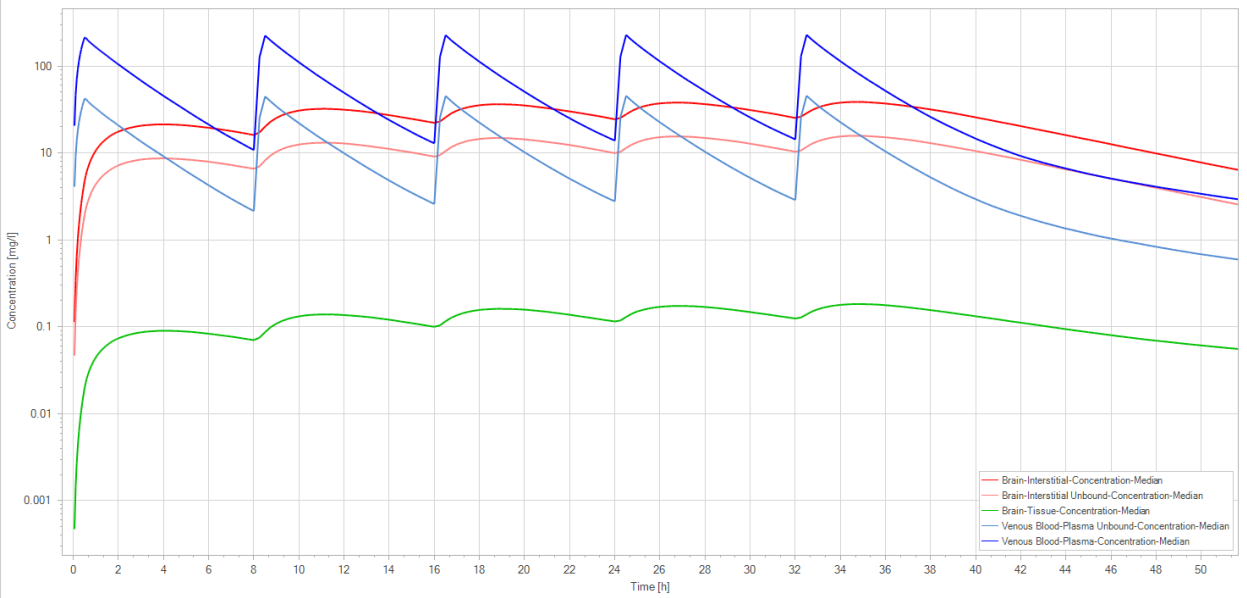
Recommendation and Conclusion

Based on the limited available evidence, cefazolin is likely a safe and effective alternative to antistaphylococcal penicillins for a variety of CNS infections due to MSSA. Based on measured concentrations from a number of CNS matrices (e.g. CSF, interstitium, etc.), pathogens such as MSSA appear to be treatable with cefazolin. Cefazolin may be preferred over antistaphylococcal penicillins in patients who develop intolerable side effects on nafcillin therapy and those who require less frequent dosing administrations. Given the site of infection and wide therapeutic index of cefazolin, practitioners may consider dosing cefazolin regimens of 2 g IV every 6 hours or a continuous infusion of 8-10 grams daily instead of 2 g IV every 8 hours to optimize time above the MIC; however, it would be best to ensure that plasma concentrations do not greatly exceed population norms with this approach via therapeutic drug monitoring (TDM), if available. In patients with altered PK parameters such as obesity or augmented renal clearance, monitoring cefazolin plasma and CSF concentrations may be beneficial to ensure efficacy and safety. Although TDM of beta-lactams is not routine practice at many institutions, TDM of cefazolin can play an important role in both achievement of therapeutic serum/CSF concentrations and prevention of adverse effects when this agent is used for CNS infections.[68] A recent systematic review and meta-analysis analyzing the impact of TDM-guided dosing in critically ill patients showed TDM-guided dosing was associated with improved clinical cure,

microbiological cure, treatment failure, and target attainment.[73] Based on retrospective observational data, preliminary total drug concentration thresholds for effectiveness (≥ 2 mcg/mL) and neurotoxicity (≥ 300 mcg/mL serum, ≥ 30-34 mcg/mL CSF) may be utilized to monitor cefazolin therapy. It is important to note that concentrations should be obtained at steady state.

Although more research is needed to directly compare cefazolin to antistaphylococcal penicillins for CNS infections, current data support that dose optimized cefazolin may be a reasonable and potentially superior alternative therapy.

Figure 1. Median total and free interstitial brain and venous cefazolin concentrations and brain tissue concentrations with cefazolin given as 2 g over a 30-minute infusion every 8 hours.



Description: Simulations were generated using PK-Sim [Open Systems Pharmacology, Wuppertal, Germany] as described in the text.

Table 1. Molecular characteristics of nafcillin, oxacillin, and cefazolin[13]

Antibiotic	Molecular weight	Protein binding	Lipophilicity LogP
Nafcillin	454.5	90-94%	2.9
Oxacillin	401.4	90-94%	2.4
Cefazolin	476.5	73-87%	-0.58

Table 2. Summary of Key Pharmacokinetic Parameters of Select Beta-Lactams[15-19]

Beta-lactam	Vd[a]	Protein Binding	CSF % relative to serum
Ampicillin	0.33 L/kg	18%	1-2%
Penicillin G	0.35 L/kg	46-58%	2 -6%
Nafcillin	0.5-1.5 L/kg	90-94%	9-20% (therapeutic CSF levels at high dose)
Oxacillin	0.4 L/kg	90-94%	10-15% (therapeutic CSF levels at high dose)
Cefazolin	0.19 L/kg	73-87%	1-4%
Cefuroxime	0.3-1.1 L/kg	33-35%	33%
Ceftriaxone	0.08-0.2 L/kg	85-95%	~14%
Cefepime	0.26 L/kg	20%	4-34%
Ceftaroline	0.26-0.30 L/kg	20%	2-7%
Piperacillin/tazobactam	0.24 L/kg	26-33%	~22% (piperacillin)
Ampicillin/sulbactam	0.25 L/kg	38%	--
Ertapenem	0.12 L/kg	85-95%	2-7%
Meropenem	0.21-0.28 L/kg	2%	9%

[a]standardized to a 70-kg patient; Vd: volume of distribution; CSF: cerebrospinal fluid

Table 3: Summary of cefazolin Pharmacokinetic/Pharmacodynamic data in CNS infections

Study	Study type	Population/ sample	Dose/ regimen	Objectives/ End points	Results	Notes
Sande, et al. 1978.[32]	In-vitro, rabbit model	n= 3-5	30 mg/kg/hr continuous infusion	Cefazolin concentration in serum and CSF	-Concentrations obtained at 0,2,4,6,8 hours -Mean cefazolin concentration in serum = 82 ± 14 mcg/mL and in CSF 2.5 ± 1.4 mcg/mL -Percent CSF penetration 3.1%	
Gregoire M, et al. (2019)[33]	Human, case report, efficacy	n=1	Continuous infusion: 8 g/day and 10 g/day IV	Cefazolin plasma concentrations at day 2 to day 21 after cefazolin initiation	- Median total plasma concentrations (n=5) -10g cefazolin: 118 mg/L -8 g cefazolin: 66.5 mg/L - Median total CSF concentrations (n=5) -10 g cefazolin: 12 mg/L -8 g cefazolin: 6.1 mg/L	Free concentrations at steady state in CSF was above MIC throughout treatment
Frame PT, et al (1983)[35]	Human, efficacy	n=7	2 g q24h IV	Cefazolin concentration in brain tissue and serum	- Post-infusion serum concentrations: 61-100 mcg/mL (mean 77 mcg/mL) - Normal brain tissue mean concentrations: 4.3 mcg/g - Abnormal brain tissue mean concentrations: mean 15.9 mcg/g - Concentrations were 7 to 143 times the average MIC (0.38 mcg/mL)	Cefazolin > nafcillin, methicillin in tissue concentration
Moore TD, et al. (1981)[36]	Human, efficacy and safety	n=6	1-3 g q4-6h IV x 1-13 days	Cefazolin concentration in serum/CSF	- 5/6 patients had notable CSF concentrations (11.3 ± 2.7% of serum concentration)- CNS penetration without seizures occurred in patients with a serum concentration of 90 mcg/mL or CSF	

					concentration of 16 mcg/mL - Serum concentrations above 300 mcg/mL or CSF concentrations above 34 mcg/mL were associated with seizure events	
Novak, et al. 2022[37]	Prospective, PK study	n=15	2 g IV Q8, or renally adjusted dose	Cefazolin serum and CSF concentrations	-Median calculated CSF Cmax and Cmin values were 2.97 mg/L and 1.59 mg/L -CSF:serum AUC 6.7%	
Bechtel TP, et al. (1980)[71]	Human, case series	n=3	Case 1: 1.5 g q4h IV + gentamicin Case 2: 1 g q6h IV Case 3: 2 g q6h IV+ gentamicin	Cefazolin concentrations in CSF s/p seizure while on therapy	- Case 1: 27 hours post-dose serum and CSF 470 and 64 mcg/mL, respectively - Case 2: 7.5 hours post-dose serum and CSF 360 and 34 mcg/mL, respectively - Case 3: 28 hours post-dose serum and CSF 1000 and 106 mcg/mL, respectively	Case patients 1 and 2 had AKI and dose was not adjusted
Ries K, et al. (1973)[77]	In vitro	n=26	1-3 g q6-12 hrs IM	Cefazolin concentration in serum	- Serum concentrations 1 hr after IM injection was 36.4 mcg/mL in patients with normal renal function - Serum concentrations 4 hrs after IM injection was 16.1 mcg/mL	Only analyzed concentrations in serum/urine
Tsai TH, et al. (2000)[78]	Animal, efficacy	n=6	10 mg/kg	Cefazolin AUC in serum/brain	- Blood AUC 0.78 □ 0.21 (mg*min/mL) - Brain AUC 0.047 □ 0.018 (mg*min/mL) - Brain AUC percentage relative to blood AUC: 6%	Used microdialysis sampling from blood and brain tissue

AUC: area under the curve; CSF: cerebrospinal fluid; s/p: status post; AKI: acute kidney injury; CNS: central nervous system; MIC: minimum inhibitory concentration; Cmax: maximum concentration; Cmin: minimum concentration; PK: pharmacokinetic

Table 4: Summary of cefazolin clinical data in CNS infections

Study First author (year)	**Pathogen**	**HPI**	**CNS diagnosis**	**Clinical course/intervention**	**Antibiotics**	**Outcome**
Winter, J (1991)[37]	MSSA	27y/F with IVDU, 22 weeks gestation with flaccid paraplegia and urinary retention	T1-T6 epidural abscess	Decompressive laminectomy (T1 to T6)	Empiric nafcillin → cefazolin monotherapy for 6 weeks for definitive therapy (unspecified dose)	No improvement in neurologic status but learned to function independently
Sarubbi, F (1997)[43]	MSSA	72y/F with reflex sympathetic dystrophy of left foot who had lumbar catheter for bupivacaine drip for 5 days – fever and purulent material	Lumbar epidural abscess	Catheter removed, treated with antibiotics	Initially oral cefadroxil therapy → cefazolin monotherapy for 1 month after culture results (unspecified dose)	Fever and back pain resolved on cefazolin, returned to baseline 3 months later
Panagiotopoulos, V (2004)[44]	MSSA	80y/M with fever, low	Multiple cervico-	Bilateral limited laminectomies at	Empiric ciprofloxacin,	Full neurological recovery after 3

		back pain, and bilateral leg weakness	lumbar epidural abscesses, consisting of 3 distinct collections	T2–T3, right hemilaminectomy at L1–L2 with catheter placement	vancomycin, and clindamycin → transition to cefazolin 2 g IV q8h plus clindamycin 600 mg q8h combination therapy for 6 weeks	weeks, no abscess on MRI after 3 months
Patel, D (2008)[45]	MSSA	55y/M with recent complicated dental procedure with severe back pain	T8-T10 epidural abscess	CT-guided biopsy followed by open biopsy and debridement	6 weeks of IV cefazolin monotherapy (unspecified dose)	Neurologic baseline at 1 year
Smith, A (2008)[46]	MSSA	49y/M with PMH of psoriatic arthritis had neck pain, paralysis, and urinary retention	C2–T7 Epidural abscess with cord compression	C3–6 and T3–5 laminectomies	Empiric vancomycin → IV cefazolin + PO rifampin combination therapy for 6 weeks (unspecified doses)	Normal strength and urinary function; still has some lower extremity sensory changes; repeat MRI at 4 months with no abscess
Sales G (2013)[47]	MSSA	15y/M with urinary retention, back pain, bilateral leg	L2-L3 lumbar epidural abscess	L2- L3 laminectomy	"Intravenous antibiotic (cefazolin 1 g, unspecified frequency) was	Normal neurologic function 3 months post-operatively; no

		numbness and weakness			administered for 2 postoperative weeks then oral antibiotic (cephalexin 500 mg every 6 hours) were continued for 4 weeks."	recurrence of infection
Wittig, J (2018)[48]	MSSA	15y/M with increasing trismus for 3 days	Suspected pericoronitis of an impacted wisdom tooth, TMJ abscess penetrating epidural temporal region	Drainage of infratemporal abscess with subsequent craniotomy for drainage of epidural abscess	Initially on cefazolin → broadened to vancomycin post-operatively for a few days → de-escalated to cefazolin monotherapy (unspecified dose and duration)	6-week follow-up MRI normal scar tissue, physical exam & labs unremarkable without signs of infection
Fujii, M (2020)[49]	Group G strep	81y/M with fever, back pain, bilateral leg progressive weakness	T6-L3 epidural abscess	Fluoroscopy-guided percutaneous epidural drainage	Empiric meropenem, clindamycin, and vancomycin for 3 days → de-escalate to cefazolin and clindamycin combination therapy for 28 days (unspecified doses)	Slow improvement in pain and weakness, resolution of abscess on MRI 3 weeks post-operatively

Noh, T (2019)[50]	Methicillin-susceptible *Staphylococcus lugdunensis*	58y/F no PMH with neck and left arm pain/weakness	Cervical epidural abscess	Partial anterior cervical decompression	8 weeks cefazolin 2 g IV Q8 and oral rifampin 600 mg daily, followed by cephalexin 500 mg twice daily for 6 months	Numerous follow up visits over 8 weeks, 100% compliance reported, resolution of symptoms and inflammatory markers
Campioli, CC (2021)[62]	MSSA	79 adult patients with spinal epidural abscesses	Spinal epidural abscess	Aspiration or IR guided drainage, surgical debridement	N=45 patients treated with cefazolin 2 g IV Q8 N=29 patients treated with nafcillin 2 g IV Q4 N=5 patients treated with oxacillin 2 g IV Q4	No significant difference between cefazolin and oxacillin/nafcillin in treatment failure, overall mortality, or 90-day recurrence rates
Bai, AD (2021)[63]	MSSA	98 patients with spinal epidural abscess	Spinal epidural abscess	Drainage by IR, 1-3 surgeries for source control	N=50 patients treated with cefazolin N=48 patients treated with cloxacillin	90-day mortality 8% vs. 13% (p=0.52) in cefazolin and cloxacillin group, respectively Antibiotic failure rate 12% cefazolin vs. 19% cloxacillin (p=0.41)

HPI: history of present illness; M: male; F: female; PMH; past medical history; MSSA: methicillin susceptible S. aureus; IVDU: intravenous drug use; PMH: past medical history; MRI: magnetic resonance imaging; CT: computed tomography; CNS: central nervous system; IR: interventional radiology; TMJ: temporomandibular joint

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