Cefazolin Dosage Considerations for Methicillin-Susceptible *Staphylococcus aureus* (MSSA) Central Nervous System Infections: Exploring Optimal Regimens

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Background

- Historically, cefazolin (CFZ) has not been considered an appropriate agent to treat central nervous system (CNS) infections. However, recent studies have shown that standard CFZ dosing achieves concentrations above the typical minimum inhibitory concentration (MIC) for methicillin-susceptible *Staphylococcus aureus* (MSSA).
- Literature to highlight appropriate CFZ treatment regimens for MSSA CNS infections is lacking.

Objective

- To identify CFZ dosing regimens necessary to achieve adequate probability of target attainment (PTA) for treatment of an MSSA CNS infection.

Methods

- Monte Carlo simulations were performed based on CFZ plasma and cerebral spinal fluid (CSF) pharmacokinetic (PK) parameters and CNS penetration data obtained from a previous published study (**Table 1**).[1]
- Pharmacodynamic (PD) targets of 40%*f*T>MIC for intermittent infusions and 100%*f*T>MIC and 100%*f*T>4xMIC for continuous infusions (CI) were analyzed for MICs of 0.5 mg/L, 1 mg/L, and 2 mg/L based on $MIC_{50/90}$ and epidemiologic cutoff values used in historical breakpoint standards.[2]
- Treatment regimens included 2g q8h, q6h, and q4h infused over 30 minutes, and 6g, 8g, 10g, and 12g as CI over 24 hours.
- **Primary Outcome:** Probability of target attainment (PTA).
  - Red - <80%
  - Yellow – 80%-89%
  - Green - ≥90%

Results

- Standard intermittent regimen of 2g q8h did not achieve ≥90% PTA for any MIC evaluated (**Table 2**).
- All other CFZ regimens achieved ≥90% PTA when the MIC remained ≤ 0.5 mg/L (**Table 2 and Table 3**).
- Only the 10 g and 12 g CI regimens achieved ≥90% PTA for 100%*f*T>MIC when the MIC was 1 mg/L (**Table 3**).
- No continuous infusion regimen achieved ≥90% PTA when using the PD target of 100%*f*T>4xMIC (**Table 4**).

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Standard cefazolin dosing (2g q8h) does not achieve adequate target attainment for MSSA CNS infections.

When comparing the same total daily dose administered as an intermittent versus continuous infusion, continuous infusions are more likely to achieve PD target attainment for MSSA CNS infections.

Questions?

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Table 1: Baseline Characteristics and PK Parameters[1]

	Overall N=15
Age, median (IQR)	56 (51-60)
Gender, female (%)	12 (80)
Weight, kg (IQR)	72 (65-89)
CSF half-life (hour) ± SD	6.5 ± 5.6
CSF: serum AUC ratio (%) ± SD	6.7 ± 5.5
Volume of Distribution (L) ± SD	31.4 ± 26.7
Clearance (L/h) ± SD	6.6 ± 4.1
Creatinine Clearance (mL/min), median (IQR)	115 (84-174)

Table 2: PTA of 40%*f*T>MIC for Intermittent Infusions

Dosing Regimen	MIC = 0.5	MIC = 1	MIC = 2
2 grams every 8 hours	86%	67%	39%
2 grams every 6 hours	91%	76%	49%
2 grams every 4 hours	96%	84%	58%

Table 3: PTA of 100% *f*T>MIC for Continuous Infusions

Dosing Regimen	MIC = 0.5	MIC = 1	MIC = 2
6 grams	95%	82%	56%
8 grams	98%	89%	68%
10 grams	99%	93%	76%
12 grams	99%	95%	82%

Table 4: PTA of 100%*f*T>4xMIC for Continuous Infusions

Dosing Regimen	4x > MIC of 0.5	4x > MIC of 1	4x > MIC of 2
6 grams	56%	27%	9%
8 grams	68%	39%	15%
10 grams	76%	48%	21%
12 grams	82%	56%	27%

References

1. Novak AR, Krsak M, Kiser TH et al. 2022. Pharmacokinetic evaluation of cefazolin in the cerebrospinal fluid of critically ill patients. *Open Forum Infect Dis* 9:ofab649.
2. European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website.