Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Pick your Team: Are you #TeamASPs or #TeamCefazolin for MSSA Infections?

β-lactam antibiotics are associated with reduced mortality and are preferred over vancomycin in the definitive treatment of severe methicillin-susceptible *Staphylococcus aureus* (MSSA) infections.[1-2] Commonly used anti-MSSA β-lactams include anti-staphylococcal penicillins (ASPs) and cefazolin. When it comes to treating a severe MSSA infection, how do you pick your poison?

Safety

Cefazolin is usually better tolerated than ASPs. ASPs have higher rates of discontinuation due to rash, phlebitis, hyperkalemia, hyponatremia, neutropenia, allergic interstitial nephritis, or liver enzyme elevations.[3,4] However, cefazolin is broader spectrum with unneeded gram-negative activity compared to ASPs. This results in cefazolin carrying a higher risk of *Clostridioides difficile* infection. Cefazolin can also be given safely to patients with a history of anaphylaxis to penicillin.

Efficacy

Inoculum Effect - Historically, cefazolin was reserved as an alternative to ASPs due to concern with an "inoculum effect." *In vitro* data showed reduced efficacy of cefazolin in deep-seated/high-burden infections (e.g. endocarditis) that was not observed with ASPs.[3] However, observational studies comparing cefazolin to ASPs in bloodstream infections have found no difference in treatment failure and in some cases, lower mortality[4-5]. Mortality benefits should be interpreted with caution as these studies are potentially limited by selection bias (e.g. picking ASPs over cefazolin in endocarditis).[3] To hopefully address this, two on-going, prospective, clinical trials will further evaluate ASPs vs cefazolin in MSSA bacteremia.[6]

CNS Infections - Cefazolin has been historically avoided in CNS infection due to older data demonstrating poor CNS penetration and breakthrough infections with other 1st generation cephalosporins (e.g. cephalothin). More recent pharmacokinetic, case, and observational data demonstrate that high doses of cefazolin (8-10 g/day) will give optimal pharmacodynamic exposures for the treatment of CNS infections.[7]

Table 1. Summary of considerations for selecting between ASPs and cefazolin

	Nafcillin, Oxacillin	Cefazolin
Dosing	1 – 2 g IV every 4 hours (six times a day) or as continuous infusion	1 – 3 g IV every 8 hours (three times a day) or as continuous infusion
Dose adjustments	No renal or hepatic dose adjustments	Dose reductions in renal impairment required May be given with intermittent hemodialysis session (e.g. thrice weekly)
Tolerability[3]	Higher rates of adverse drug reactions.	Fewer discontinuations compared with ASPs Patients not tolerating ASPs usually tolerate cefazolin
***C. difficile* infection risk**	Low - Moderate	Moderate
Antimicrobial Resistance Considerations	Narrow spectrum with activity against only *Staphylococcus* and *Streptococcus* spp.	Broader spectrum with activity against *Staphylococcus* spp, *Streptococcus* spp, *E. coli*, *Klebsiella* spp (excluding *K. aerogenes*), and *Proteus* spp.
Role in CNS Infections[7]	Regarded as drug of choice for severe MSSA CNS infections	Not recommended first line, but higher doses (8-10 g/day) may achieve adequate exposures.

Key Takeaway: Despite theoretical concerns for inferior efficacy, observational data demonstrates cefazolin has outcomes at least as good as anti-staphylococcal penicillins in the treatment of severe MSSA infections. Cefazolin may be better tolerated and easier to administer but is broader spectrum and probably higher risk for *C. difficile* infection.

References:

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7. Antosz K, Battle S, Chang J, et al. Cefazolin in the Treatment of Central Nervous System Infections: A Narrative Review and Recommendation. Pharmacotherapy. 2023;43(1):85-95.