Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

β-lactam/β-lactamase inhibitors for MSSA

Methicillin-susceptible *Staphylococcus aureus* (MSSA) is a gram-positive coccus that causes infections ranging from mild skin and soft tissue infections to life threatening infections. Primary treatment options are typically β-lactams such as nafcillin or cefazolin. Certain penicillins have in vitro activity against MSSA when they are combined with β-lactamase inhibitor. Can β-lactam/β-lactamase inhibitors (BLBLIs) such as piperacillin-tazobactam and ampicillin-sulbactam be used to treat MSSA infections?

What microbiological concerns are there with BLBLIs?

There are concerns with an inoculum effect with MSSA and BLBLIs. Inoculum effect refers to an in vitro phenomenon of increased MIC with increased bacterial inoculum, which theoretically could impact efficacy of an antibiotic for infections with high bacterial burden such as endocarditis.[1] In one study of 302 clinical MSSA isolates, a significant increase in MIC was identified for piperacillin-tazobactam and ampicillin-sulbactam in high inoculums that were 100x larger than standard inoculums (e.g. 10^5 vs 10^7 CFU/mL).[2] The clinical significance of this in vitro phenomenon is unclear. Notably, inoculum effects have also been observed with cefazolin and MSSA, however cefazolin was not associated with inferior clinical outcomes in a randomized controlled trial.[3]

What clinical outcomes data is there?

Data is observational and mixed. Caution should be exercised when interpreting results due to possible confounding from selection of BLBLIs in "sicker" patients due to their broader spectrum.

- Empiric therapy with a BLBLI in inpatients with MSSA bacteremia has been associated with higher 30-day mortality (adj OR: 2.68; 95% CI 1.23 – 5.85) relative to oxacillin/cefazolin after multivariate logistic regression.[4]
- Inpatients receiving definitive therapy for MSSA bacteremia had lower 30-day mortality in the nafcillin/oxacillin/cefazolin group when compared to a propensity-score matched piperacillin-tazobactam group (HR: 0.10; 95% CI 0.01 – 0.78).[5]
- In a small retrospective study of inpatients with MSSA bacteremia, no significant difference in 90-day mortality was found between definitive therapy with ampicillin-sulbactam versus cefazolin. More patients who received ampicillin-sulbactam experienced liver dysfunction.[6]

Key Takeaway: BLBLIs are active against MSSA, but microbiological and observational clinical data suggest worse outcomes compared to anti-staphylococcal penicillins or cefazolin. Potentially improving efficacy is another reason to de-escalate from broader spectrum BLBLIs in serious MSSA infections.

References:

1. Lenhard JR, Bulman ZP. Inoculum effect of β-lactam antibiotics. *J Antimicrob Chemother.* 2019; 74(10):2825-43. doi: 10.1093/jac/dkz226.
2. Song KH, Jung SI, Lee S, et al. Inoculum effect of methicillin-susceptible *Staphylococcus aureus* against broad-spectrum beta-lactam antibiotics. *Eur J Clin Microbiol Infect Dis*. 2019; 38(1):67-74. doi: 10.1007/s10096-018-3392-6.
3. Burdet C, Saïdani N, Dupieux C, et al. Cloxacillin versus cefazolin for meticillin-susceptible *Staphylococcus aureus* bacteraemia (CloCeBa): a prospective, open-label, multicentre, non-inferiority, randomised clinical trial. *Lancet*. 2025; 406(10517):2349-59. doi: 10.1016/S0140-6736(25)01624-1.
4. Paul M, Zemer-Wassercug N, Talker O, Lishtzinsky Y, Lev B, Samra Z, Leibovici L, Bishara J. Are all beta-lactams similarly effective in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia? *Clin Microbiol Infect.* 2011; 17(10):1581-6. doi: 10.1111/j.1469-0691.2010.03425.x.
5. Beganovic M, Cusumano JA, Lopes V, LaPlante KL, Caffrey AR. Comparative effectiveness of exclusive exposure to nafcillin or oxacillin, cefazolin, piperacillin/tazobactam, and fluoroquinolones among a national cohort of veterans with methicillin-susceptible *Staphylococcus aureus* bloodstream infection. *Open Forum Infect Dis*. 2019; 6(7):ofz270. doi: 10.1093/ofid/ofz270.
6. Hirai J, Asai N, Hagihara M, et al. Comparative effectiveness of ampicillin/sulbactam versus cefazolin as targeted therapy for bacteremia caused by beta-lactamase-producing methicillin-sensitive *Staphylococcus aureus*: a single-center retrospective study. *Antibiotics (Basel)*. 2022; 11(11):1505. doi: 10.3390/antibiotics11111505.

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