



## Penicillins for *Staphylococcus aureus*: Aye or Nay?

*Staphylococcus aureus* is a gram-positive coccus that can cause infections ranging from mild skin and soft tissue infections to life threatening infections. A clinically significant distinction is made between methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), where MSSA is treatable by beta-lactams such as [nafcillin](#) or [cefazolin](#) and MRSA is resistant to beta-lactams with some exceptions (e.g. ceftaroline, ceftobiprole). Since MSSA is susceptible to nafcillin, can other penicillins be used?

### How often is penicillin active against MSSA?

When penicillin was first introduced, penicillin resistance in *S. aureus* was rare. However, by the early 2000's  $\geq 90\%$  of *S. aureus* isolates were penicillin resistant. Penicillin resistance in *S. aureus* is mediated by a [beta-lactamase](#), often referred to as a penicillinase.<sup>1</sup>

### How is penicillin-susceptible *S. aureus* (PSSA) identified?

In addition to standard susceptibility testing, The Clinical and Laboratory Standards Institute (CLSI) recommends an additional beta-lactamase detection test in *S. aureus* isolates that test susceptible to penicillin to confirm susceptibility before reporting. However, some isolates may harbor a penicillinase gene despite testing negative by the beta-lactamase test.<sup>2</sup> Microbiology laboratories may not be readily able to perform the additional testing if not previously validated.

### Which penicillins are active against PSSA and MSSA?

If PSSA is confirmed with susceptibility testing and negative beta-lactamase testing, then penicillinase-labile penicillins are expected to be active. These include penicillin, amoxicillin, ampicillin, and piperacillin. However, due to the susceptibility testing reliability concerns, the 2015 American Heart Association Endocarditis guidelines recommend nafcillin or cefazolin over penicillin for penicillin-susceptible staphylococcal endocarditis.<sup>3</sup>

When penicillin susceptibility cannot be confirmed for MSSA, a penicillinase-labile penicillin can only be used if paired with a beta-lactamase inhibitor. The beta-lactam/beta-lactamase combination antibiotics amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam will be stable against MSSA if a penicillinase is present.<sup>2</sup>

**Key Takeaway:** MSSA should be considered resistant to penicillin, amoxicillin, and ampicillin unless unique susceptibility testing has confirmed penicillin activity. Even when confirmed, penicillin is not recommended in some severe infections such as endocarditis. Amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam are considered active against MSSA.

### References:

1. Livermore DM. Antibiotic resistance in staphylococci. *Int J Antimicrob Agents*. 2000;16 Suppl 1:S3-S10. doi:10.1016/s0924-8579(00)00299-5
2. Clinical and Laboratory Standards Institute. M100: performance standards for antimicrobial susceptibility testing. 35 ed. 2025
3. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation*. 2015;132(15):1435-1486. doi:10.1161/CIR.0000000000000296