Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Higher Cefazolin Urine Breakpoint

Antibiotics need to achieve therapeutic concentrations at the site of infection to work. Many antibiotics will concentrate in the urine, but the Clinical Laboratory Standards Institute (CLSI) does not differentiate most breakpoints based on site of infection, however cefazolin for uncomplicated urinary tract infections (UTIs) is an exception. The 2025 IDSA guidelines define uncomplicated UTIs as infections limited to the bladder without systemic signs of infection (e.g. fever).[1] How should a higher urine cefazolin breakpoint be used?

What does CLSI recommend?

For uncomplicated UTI due to *E. coli*, *K. pneumoniae*, and *P. mirabilis*, the CLSI recommends a cefazolin breakpoint of 16 µg/mL, which is 3-fold dilutions higher than the non-urinary breakpoint of 2 µg/mL.[2] This breakpoint may also act as a surrogate for oral cephalosporins including cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef. This higher cefazolin urine breakpoint may overcall resistance to cefuroxime, cefpodoxime, and cefdinir, which may be susceptible if tested individually.

What concentrations do cephalosporins achieve in the urine?

Cephalosporins in general reach high concentrations in the urine.[3] For example, the average urine cefazolin concentration was ~290 µg/mL obtained 8 hours after a single 500 mg cefazolin IM dose in 10 volunteers with varying renal function.[4] The average urine cephalexin concentration was ~ 1290 µg/mL obtained 4-6 hours after a single 1 g PO cephalexin dose given with and without food to 6 volunteers.[5]

What antimicrobial stewardship benefits are there with the higher urine breakpoint?

A higher breakpoint will decrease the % of isolates categorized as resistant thereby increasing the role of empiric and definitive cefazolin and narrow spectrum oral cephalosporins (e.g. cephalexin) in the treatment of uncomplicated UTIs.[6] This can aid in preserving the activity of broader spectrum agents like ceftriaxone which are often used empirically in more complicated infections such as complicated UTIs and complicated intra-abdominal infections and lower the risk for *C. difficile* infection.

How can this be implemented?

The Food and Drug Administration did not endorse the higher urine breakpoints recommended by CLSI due to a lack of clinical outcomes data.[7] However, some have argued that it is unlikely that these studies will be done and they are not critical due to known PK-PD profiles and cephalosporin abilities for concentrating in the urine.[3] Microbiology labs can implement the CLSI breakpoints over FDA breakpoints if they are able (e.g. have the correct concentration of wells on their susceptibility panels, resources to validate, etc) and chose to do so.[3]

Key Takeaway: Using higher urine breakpoints for cefazolin allows for more frequent use of narrow-spectrum antibiotics for uncomplicated UTIs, which reduces risk of resistance and *C. difficile* infections.

References:

1. Trautner BW, Cortes-Penfield NW, Gupta K, et al. Clinical practice guideline by Infectious Diseases Society of America (IDSA): 2025 guideline on management and treatment of complicated urinary tract infections. Available at https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/. Accessed March 11, 2025.
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 36th ed. CLSI supplement M100. 2026
3. Bryson AL, Bhalodi A, Liesman RM, Mathers AJ. Cefazolin as a predictor of urinary cephalosporin activity in indicated Enterobacterales. *J Clin Microbiol.* 2024;62(4):e0078821. doi:10.1128/jcm.00788-21
4. Rein, Michael F., Frederic B. Westervelt, and Merle A. Sande. "Pharmacodynamics of cefazolin in the presence of normal and impaired renal function." Antimicrob Agents Chemother 4.3 (1973): 366-371.
5. Gower, P. E., and C. H. Dash. "Cephalexin: human studies of absorption and excretion of a new cephalosporin antibiotic." Br J Pharmacol 37.3 (1969): 738.
6. Yetsko A, Draper HM, Eid K, Jameson AP, Dumkow LE. Two Times Versus Four Times Daily Cephalexin Dosing for the Treatment of Uncomplicated Urinary Tract Infections in Females. *Open Forum Infect Dis*. 2023;10(9):ofad430. Published 2023 Aug 11. doi:10.1093/ofid/ofad430
7. Rationale for FDA's position on the use of cefazolin breakpoints as a surrogate for determining breakpoints for oral cephalosporins for the treatment of uncomplicated urinary tract infections. Food and Drug Administration. October 24, 2022. Accessed March 10, 2026. https://www.fda.gov/drugs/development-resources/rationale-fdas-position-use-cefazolin-breakpoints-surrogate-determining-breakpoints-oral.

Created 3.11.26