Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Beta-lactamases: Focus on AmpC

What is an AmpC?

AmpC beta-lactamases are enzymes found in gram-negative bacteria that inactive penicillins and many cephalosporins including the cephamycins (cefoxitin & cefotetan). However, carbapenems and cefepime are stable to inactivation by AmpC beta-lactamases.[1] Tazobactam is a poor inhibitor of AmpC beta-lactamses whereas avibactam has good AmpC inhibition.[2] Non-beta-lactam antibiotics are unaffected by AmpC beta-lactamases. Genes encoding for AmpC beta-lactamases can be transferred vertically through chromosomes (i.e. bacteria are born with it) or horizontally through plasmids (i.e. bacteria acquire it later in life). AmpC beta-lactamases can either be derepressed (i.e. turned on all the time) or inducible (i.e. not on currently on but can be turned on).[3]

Clinically relevant inducible AmpC expression

Organisms with inducible AmpC genes may initially test susceptible to some beta-lactams (e.g. ceftriaxone) but may become resistant while on treatment. *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii* are the highest risk organisms for induced resistance. *Serratia marcescens*, *Morganella morganii*, and *Providencia* spp are lower risk.[4]

Treatment options for inducible AmpC organisms

Treatment selection should take into consideration risk for AmpC beta-lactamase expression along with susceptibility results, source of infection, and clinical status of the patient. The Infectious Diseases Society of American provides recommendations for the management of infections due to high risk inducible AmpC beta-lactamase organisms and are summarized in the table below[4]:

Treatment for *E. cloacae, K. aerogenes, & C. freundii*	
Beta-lactam Options	**Non-Beta-lactam Options**
• Cefepime* • Carbapenems **Uncomplicated Cystitis Only:** • Ceftriaxone or Ceftazidime • Piperacillin-tazobactam **Active, but not recommended due to broad spectrum activity. Reserve for carbapenem-resistant organisms:** • Cefiderocol • Ceftazidime-avibactam • Carbapenem/beta-lactamase inhibitor combinations	• Trimethoprim-sulfamethoxazole (TMP-SMX) • Fluoroquinolones **Uncomplicated Cystitis:** • Nitrofurantoin • One-time dose of aminoglycoside • TMP-SMX

*A carbapenem is recommended if the cefepime MIC ≥ 4 mcg/mL due to risk for ESBL co-production

Key Takeaway: Cefepime, a carbapenem, TMP-SMX, or a fluoroquinolone are the preferred treatment options for severe infections due to *E. cloacae*, *K. aerogenes*, and *C. freundii*, even if ceftriaxone, ceftazidime, or piperacillin-tazobactam test susceptible. Susceptibility results can be followed for uncomplicated cystitis with any AmpC producing organism.

References:

1. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Ninth Edition. Chapter 18. Molecular Mechanisms of Antibiotic Resistance in Bacteria
2. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-Lactamase Inhibitor Combinations [published correction appears in Clin Microbiol Rev. 2021 Jan 27;34(2):]. *Clin Microbiol Rev*. 2020;34(1):e00115-20. Published 2020 Nov 11. doi:10.1128/CMR.00115-20
3. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ; Antibacterial Resistance Leadership Group. A Primer on AmpC β-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. *Clin Infect Dis*. 2019;69(8):1446-1455. doi:10.1093/cid/ciz173
4. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Infectious Diseases Society of America **2022**; Version 2.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance-2.0/. Accessed 8 March 2023.

Created on 3.8.23