Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Beta-lactamase Basics

Beta-lactamases are bacterial protein enzymes that inactivate beta-lactam antibiotics (i.e. penicillins, cephalosporins, monobactams, and carbapenems), rendering them ineffective. Many beta-lactamases exist and can be found in gram-positive, gram-negative, and anaerobic bacteria.[1] Beta-lactamases are a major cause of antimicrobial resistance and certain types of beta-lactamases have been identified as major threats as genes encoding for them can be transferred horizontally between bacteria (e.g. extended spectrum beta-lactamases [ESBL]).

How do beta-lactamases differ?

Different beta-lactamases inactivate different beta-lactam antibiotics. For example, methicillin susceptible *Staphylococcus aureus* (MSSA) often produces a narrow-spectrum beta-lactamase that only inactivates penicillins, but *E. coli* and other gram-negative bacteria can produce an ESBL which confers resistance to penicillins and cephalosporins.[1] There are thousands of beta-lactamases produced by bacteria making identification and classification of these proteins challenging.[2]

What beta-lactam antibiotics can I use if a bacteria is producing a beta-lactamase?

Some beta-lactam antibiotics are stable against beta-lactamases. For example, anti-staphylococcal penicillins like oxacillin and nafcillin are not inactivated by the beta-lactamase produced by MSSA. Similarly, carbapenem antibiotics are not inactivated by ESBLs. Additionally, some beta-lactams come in combination with a beta-lactamase inhibitor. Beta-lactamase inhibitors may inhibit beta-lactamase enzymes and allow the beta-lactam antibiotic to work again. For example, all *Klebsiella pneumoniae* are resistant to aminopenicillins like ampicillin due a beta-lactamase that is always expressed. Sulbactam and clavulanate inhibit the beta-lactamase therefore ampicillin-sulbactam and amoxicillin-clavulanate can be active against *Klebsiella pneumoniae*.[3]

In most cases, a beta-lactam or beta-lactam/beta-lactamase inhibitor combination can be used if it is reported as susceptible on a microbiology report. There are exceptions to this where use of a beta-lactam antibiotic to treat severe infections due to beta-lactamase producing bacteria may be discouraged. For example, the use of piperacillin-tazobactam for the treatment of bacteremia caused by ESBL producing gram-negative bacteria is controversial. The Infectious Diseases Society of America currently recommends against using piperacillin-tazobactam for infections outside of the urinary tract caused by ESBL producing bacteria even when susceptibility has been demonstrated.[4] More studies on this topic are underway.

Key Takeaway: Beta-lactamases are a major cause of antimicrobial resistance. Most beta-lactam antibiotics and beta-lactam/beta-lactamase inhibitor combinations can be used based on susceptibility testing.

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. Bush K. Past and present perspectives on β-lactamases. Antimicrob Agents Chemother. 2018:62(10);e01076-18.
3. Doi, Y. Penicillins and β-Lactamase Inhibitors. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia, PA: Elsevier, Inc.; 2020: 251-67
4. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America **2022**; Version 1.1. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed 15 Feb 2023.

Created on February 15th, 2023