Oral Step-Down Therapy for Infections Caused by Enterobacterales at Moderate to High Risk for Inducible AmpC Production

Viet Nguyen, PharmD, BCPS, BCACP
Northwest Medical Homes

Objectives

1. Describe the mechanisms of AmpC production in Enterobacterales
2. Identify Enterobacterales at moderate to high risk for clinically significant AmpC production
3. Recognize key considerations for selecting appropriate antibiotics for infections caused by organisms with moderate to high risk of clinically significant AmpC production
4. Understand the role of trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones as oral step-down therapy for infections caused by Enterobacterales at moderate to high risk for clinically significant AmpC production

AmpC β-Lactamases

- Class C serine β-lactamase enzymes produced by some Enterobacterales and glucose non-fermenting Gram-negative bacteria[1]

- AmpC production mechanisms[2,3]
  - Inducible chromosomal resistance
  - Stable chromosomal de-repression
  - Via plasmid-mediated *ampC* genes

Ambler Classification

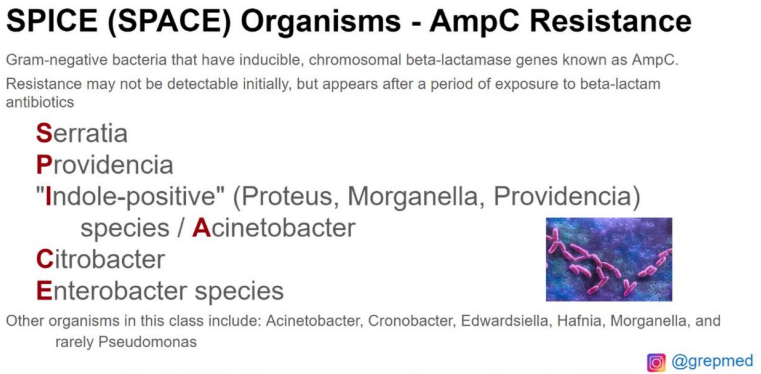
Table 1. β-Lactamases (Ambler Classification).

Type	Ambler Molecular Class	Characteristics	Examples of Enzymes
Narrow-spectrum β-lactamases[12,18,19]	A	Hydrolyze penicillin; produced primarily by *Enterobacteriaceae*	Staphylococcal penicillinase, TEM-1, TEM-2, SHV-1
Extended-spectrum β-lactamases[20]	A	Hydrolyze narrow and extended-spectrum β-lactam antibiotics	SHV-2, CTX-M-15, PER-1, VEB-1
Serine carbapenemases[20]	A	Hydrolyze carbapenems	KPC-1, IMI-1, SME-1
Metallo-β-lactamases[21,22]	B	Hydrolyze carbapenems	VIM-1, IMP-1, NDM-1
Cephalosporinases[10,23,24]	C	Hydrolyze cephamycins and some oxyimino β-lactams; inducible; chromosomally mediated	AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
OXA-type enzymes[25-27]	D	Hydrolyze oxacillin, oxyimino β-lactams, and carbapenems; produced by *Pseudomonas aeruginosa* and *Acinetobacter baumannii*	OXA enzymes

Ann Pharmacother. 2015 Jan;49(1):86-98.

Moderate to High Risk AmpC Producing Enterobacterales

- Moderate to high risk for clinically significant AmpC production[4]
  - Resistance to ceftriaxone may occur in 8-40% of infection post-exposure
  - *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*
- SPACE/SPICE mnemonics[5,6]
  - No longer accurate
  - "Undercalling" and "overcalling"
    - *Citrobacter freundii* versus *Citrobacter koseri*
    - Indole positive *Proteus* species
    - *Serratia marcescens*, *Morganella morganii*, and *Providencia* species
- Less commonly encountered pathogens[7]
  - *Hafnia alvei*, *Citrobacter youngae*, *Yersinia enterocolitica*
  - Limited information on AmpC production



Key Considerations for Antibiotic Selection (1)

- **β-lactam antibiotics**
  - Some are at relatively high risk of inducing *ampC* genes
  - **Aminopenicillins, cephalosporins, and cephamycins**[8,9]
    - Potent AmpC inducers
  - **Imipenem, ertapenem, and meropenem**[8,10]
    - Resistance to AmpC hydrolysis
  - **Piperacillin, ceftriaxone, ceftazidime, and aztreonam**[9]
    - Weak AmpC inducers
    - Susceptible to hydrolysis
    - Unlikely to be effective in treating infections caused by organisms at moderate to high risk for clinically significant inducible AmpC production
  - **Cefepime**[11,12]
    - Weak AmpC inducer and resistance to AmpC hydrolysis
  - **Fluoroquinolones, aminoglycosides, TMP-SMX, tetracycline and other non-beta-lactam antibiotics**[1]
    - Non-AmpC inducers
    - Not substrates for AmpC hydrolysis

Key Considerations for Antibiotic Selection (2)

- **Cefepime**[13]
  - Preferred treatment option for *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*
    - Cefepime MICs ≤ 2 mcg/mL

- **Ceftriaxone or ceftazidime**[14]
  - Not recommended for invasive infections caused by *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*
  - Could be considered for uncomplicated cystitis once susceptibility has been demonstrated

Key Considerations for Antibiotic Selection (3)

- **Piperacillin-tazobactam**[1,15-17]
  - "Not suggested" for serious infections caused by *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*
  - Limited ability of tazobactam to inhibit AmpC hydrolysis *in vitro*
  - Increased mortality in patients receiving piperacillin-tazobactam in two observational studies

- **Newer β-lactam and β-lactam-β-lactamase inhibitor combinations**[1,19-21]
  - Cefiderocol, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and meropenem-vaborbactam
    - Reserved for treating carbapenem-resistant organisms
  - Ceftolozane-tazobactam
    - Unknown activity and limited clinical outcomes against AmpC β-lactamase-producing Enterobacterales (AmpC-E)
    - Not recommended

Oral Step-Down Therapy

- **TMP-SMX or fluoroquinolones**[22,23]
  - Non-substrates for AmpC hydrolysis
  - High bioavailability and sustained serum concentrations
  - Reasonable oral step-down therapy for AmpC-E infections if:
    - Susceptibility has been demonstrated
    - Patients are hemodynamically stable
    - Reasonable source control measures have occurred
    - No concerns about insufficient intestinal absorption

- **Nitrofurantoin, fosfomycin, doxycycline, or amoxicillin-clavulanate**[1,24-25]
  - Poor or unreliable serum concentrations
  - Avoid using for AmpC-E bloodstream infections

- **Nitrofurantoin or TMP-SMX**[24,26]
  - Preferred treatment for AmpC-E uncomplicated cystitis

- **Fosfomycin**[27]
  - Exclusively for *Escherichia coli* cystitis
  - Intrinsic *fosA* gene
  - Not recommended for AmpC-E uncomplicated cystitis

Quiz

TRUE or FALSE

TMP-SMX or fluoroquinolones can be used as oral step-down therapy for infections caused by Enterobacterales at moderate to high risk for clinically significant inducible AmpC production.

Quiz

TMP-SMX or fluoroquinolones can be used as oral step-down therapy for infections caused by Enterobacterales at moderate to high risk for clinically significant inducible AmpC production.

Answer: True

Questions?

References

1. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0. Published March 31, 2022. Accessed March 21, 2022. https://www.idsociety.org/practice-guideline/amr-guidance-2.0/#
2. Sears CL, File TM, Alexander BD, et al. Charting the Path Forward: Development, Goals and Initiatives of the 2019 Infectious Diseases of America Strategic Plan. Clin Infect Dis 2019; 69(12): e1-e7.
3. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum beta-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis 2021; 72(7): e169-e83.
4. Jacobson KL, Cohen SH, Inciardi JF, et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I beta-lactamase-producing organisms. Clin Infect Dis 1995; 21(5): 1107-13.
5. Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev 2009; 22(1): 161-82, Table of Contents.
6. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ, Antibacterial Resistance Leadership G. A Primer on AmpC beta-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. Clin Infect Dis 2019; 69(8): 1446-55.
7. Kohlmann R, Bahr T, Gatermann SG. Species-specific mutation rates for ampC derepression in Enterobacterales with chromosomally encoded inducible AmpC beta-lactamase. J Antimicrob Chemother 2018; 73(6): 1530-6.
8. Sanders CC, Bradford PA, Ehrhardt AF, et al. Penicillin-binding proteins and induction of AmpC beta-lactamase. Antimicrob Agents Chemother 1997; 41(9): 2013-5.
9. Weber DA, Sanders CC. Diverse potential of beta-lactamase inhibitors to induce class I enzymes. Antimicrob Agents Chemother 1990; 34(1): 156-8.
10. Livermore DM, Oakton KJ, Carter MW, Warner M. Activity of ertapenem (MK-0826) versus Enterobacteriaceae with potent beta-lactamases. Antimicrob Agents Chemother 2001; 45(10): 2831-7.
11. Hancock RE, Bellido F. Antibacterial in vitro activity of fourth generation cephalosporins. J Chemother 1996; 8 Suppl 2: 31-6.
12. Negri MC, Baquero F. In vitro selective concentrations of cefepime and ceftazidime for AmpC beta-lactamase hyperproducer Enterobacter cloacae variants. Clin Microbiol Infect 1999; 5 Suppl 1: S25-S8.
13. Harris PN, Wei JY, Shen AW, et al. Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by Enterobacter, Citrobacter or Serratia species: a systematic review with meta-analysis. J Antimicrob Chemother 2016; 71(2): 296-306.
14. Cheng MP, Lee RS, Cheng AP, et al. Beta-Lactam/Beta-Lactamase Inhibitor Therapy for Potential AmpC-Producing Organisms: A Systematic Review and Meta-Analysis. Open Forum Infect Dis 2019; 6(7): ofz248.
15. Papp-Wallace KM, Bethel CR, Caillon J, et al. Beyond Piperacillin-Tazobactam: Cefepime and AAI101 as a Potent beta-Lactam-beta-Lactamase Inhibitor Combination. Antimicrob Agents Chemother 2019; 63(5): e00105-19.
16. Chaubey VP, Pitout JD, Dalton B, Gregson DB, Ross T, Laupland KB. Clinical and microbiological characteristics of bloodstream infections due to AmpC beta-lactamase producing Enterobacteriaceae: an active surveillance cohort in a large centralized Canadian region. BMC Infect Dis 2014; 14: 647.
17. Cheng L, Nelson BC, Mehta M, et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC beta-Lactamase-Producing Enterobacteriaceae. Antimicrob Agents Chemother 2017; 61(6): e00276-17.
18. Toussaint KA, Gallagher JC. β-lactam/β-lactamase inhibitor combinations: from then to now. Ann Pharmacother. 2015 Jan;49(1):86-98. doi: 10.1177/1060028014556652. Epub 2014 Oct 31. PMID: 25361682.
19. Tato M, Garcia-Castillo M, Bofarull AM, Canton R, Group CS. In vitro activity of ceftolozane/tazobactam against clinical isolates of Pseudomonas aeruginosa and Enterobacteriaceae recovered in Spanish medical centres: Results of the CENIT study. International Journal of Antimicrobial Agents 2015; 46(5): 502-10.
20. Robin F, Auzou M, Bonnet R, et al. In Vitro Activity of Ceftolozane-Tazobactam against Enterobacter cloacae Complex Clinical Isolates with Different beta-Lactam Resistance Phenotypes. Antimicrob Agents Chemother 2018; 62(9): e00675-18.
21. Stewart AG, Harris PNA, Chatfield MD, Littleford R, Paterson DL. Ceftolozane-tazobactam versus meropenem for definitive treatment of bloodstream infection due to extended-spectrum beta-lactamase (ESBL) and AmpC-producing Enterobacterales ("MERINO-3"): study protocol for a multicentre, open-label randomised non-inferiority trial. Trials 2021; 22(1): 301.
22. Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med 2019; 179(3): 316-23.
23. Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral Fluoroquinolone or Trimethoprim-sulfamethoxazole vs. beta-lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. Open Forum Infect Dis 2019; 6(10): ofz364.
24. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. JAMA 2018; 319(17): 1781-9.
25. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother 2006; 58(2): 256-65.
26. Fox MT, Melia MT, Same RG, Conley AT, Tamma PD. A Seven-Day Course of TMP-SMX May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis. Am J Med 2017; 130(7): 842-5.
27. Ito R, Mustapha MM, Tomich AD, et al. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal fosA Gene. mBio 2017; 8(4): e00749-17.