Management of chromosomal AmpC producing enterobacterales

The AmpC β-lactamase confers resistance to penicillins and most β-lactamase inhibitor combinations, 1st – 3rd generation cephalosporins, ceftaroline, and aztreonam. Chromosomal AmpC β-lactamases are present in a variety of species of both enterobacterales and non-fermenting gram-negative organisms. These can appear susceptible to 3rd generation cephalosporins and piperacillin/tazobactam initially, but induced resistance on treatment confers clinical failure in as much as 40% of cases involving moderate-risk spp. Cefepime is preferred for empiric treatment of invasive infections with moderate-risk pathogens.

Moderate risk of AmpC production (*E. cloacae, K. aerogenes, C. freundii)*		
Site of infection	Therapy options	Notes
Serious systemic infections	Cefepime Carbapenems are acceptable, but not preferred	SMX-TMP and fluoroquinolones may be appropriate for step down treatment based on patient specific factors and susceptibility
Urine: asymptomatic bacteriuria	No treatment	It is always important not to treat asymptomatic bacteriuria, in order to prevent further resistance among colonizing flora
Urine: cystitis	Appropriate β-lactams (potentially ceftriaxone), SMX-TMP, nitrofurantoin, aminoglycosides, or fluoroquinolones with sensitivity	Of the tetracycline class, only tetracycline achieves sufficient concentrations in the urine to reliably treat cystitis; minocycline and doxycycline do not. Duration of therapy is related to choice of drug.

Low risk of AmpC production (*M. morganii, S. marcescens, Providencia spp.* etc.)		
Site of infection	Therapy options	Notes
Bloodstream infections	Ceftriaxone Cefepime if prior resistance demonstrated or hemodynamic instability	SMX-TMP, fluoroquinolones, or oral 3rd generation cephalosporins may be appropriate once cultures are negative and the source control is achieved, based on patient specific factors
Urine: asymptomatic bacteriuria	No treatment	It is always important not to treat asymptomatic bacteriuria, in order to prevent further resistance among colonizing flora
Urine	Ceftriaxone, SMX-TMP, aminoglycosides, or fluoroquinolones with sensitivity, nitrofurantoin for cystitis only	Of the tetracycline class, only tetracycline achieves sufficient concentrations in the urine to reliably treat cystitis; minocycline and doxycycline do not. Duration of therapy is related to choice of drug.

Enterobacter cloacae, Klebsiella aerogenes (formerly *Enterobacter aerogenes)*, and *Citrobacter freundii* are the moderate-risk pathogens, i.e. the mostly likely enterobacterales spp. to harbor AmpC β-lactamase with clinical relevance. Other enterobacterales spp., including *Morganella morganii, Providencia* sp., and *Serratia marcescens* have the potential for chromosomal induction of AmpC β-lactamase, but the frequency is less than 5%.

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Treatment with 3rd generation cephalosporins and piperacillin/tazobactam should be avoided, even with susceptibility data, for invasive infections with *E. cloacae, K. aerogenes,* or *C. freundii.* For localized infections (e.g., uncomplicated cystitis) with susceptibility data, or systemic infections with potential, but low risk, of AmpC production (*M. morganii, S. marcescens*, etc.), treatment with 3rd generation cephalosporins is reasonable, depending on patient specific factors.

Previously, co-production of ESBL and AmpC in moderate-risk pathogens was thought to be predicted by cefepime MICs of 4-8 (i.e., susceptible dose dependent). Available data do not support this association. For enterobacterales spp. at moderate risk of AmpC production with cefepime MICs from 4-8, cefepime dosed at 2 grams every 8 hours, infused over 3 hours, is suggested.

Some AmpC producing enterobacterales are loosely aligned with acronyms like SPICE, SPACE, SPACE-M etc. These acronyms should be avoided as tools identifying moderate-risk pathogens, as none are reliably inclusive or exclusive. Chromosomal AmpC can also be present on non-enterobacterales spp. like *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, leading some to change the acronym to SPACE or SPACE-M and omit *Providencia*, however treatment considerations for non-fermenters like these should incorporate other factors in addition to AmpC production.

Currently, there is some debate as to the utility of piperacillin/tazobactam for serious infections, and whether it is appropriate to use 3rd generation cephalosporins for mild to moderate infections. Piperacillin/ tazobactam does not have reliable activity against stably de-repressed AmpC-producing pathogens, however it is a poor inducer of AmpC. With susceptibility data, it is likely safe and appropriate to use for localized infections such as cystitis, if use of other appropriate agents is precluded. For localized infections (e.g. cystitis) with moderate-risk pathogens and sensitivity data, or for invasive infections in stable patients with lower risk pathogens, ceftriaxone is reasonable. For these patients who worsen on treatment with ceftriaxone or piperacillin/tazobactam, consideration should be given to switching to cefepime. For infections with low-risk pathogens and physiologic propensity for selection of resistance (high bacterial burden and inadequate source control, i.e. infective endocarditis) it is reasonable to consider treatment with cefepime.

Chromosomal AmpC producing organisms in clinical practice (not inclusive; these are the most common ones):

- ***Citrobacter freundii*** (moderate risk)
- *Citrobacter braakii* (lowest risk)
- ***Enterobacter cloacae*** (moderate risk)
- ***Klebsiella aerogenes*** (moderate risk - formerly *Enterobacter aerogenes*)
- *Halfnia alvei* (lowest risk)
- *Morganella morganii* (lowest risk)
- *Providencia stuartii* (lowest risk)
- *Serratia marcescens* (lowest risk)

Proteus mirabilis and *vulgaris*, as well as *Citrobacter koseri* and *amalonaticus*, **do not** harbor chromosomal AmpC beta lactamases, and may be treated with any susceptible β-lactam.

Tamma PD et al. IDSA 2024 guidance on the treatment of antimicrobial resistant gram-negative infections: Version 4.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/ accessed July 2024.