Approach to treatment of infections due to drug-resistant gram-negative organisms: ESBL, AmpC β-lactamase and CPE producers

Gram-negative bacteria can be resistant to broad-spectrum β-lactam antibiotics through a variety of mechanisms, notably through the production of β-lactamases, which can inactivate penicillins, cephalosporins, and, in some cases, carbapenems. Examples of these enzymes in enteric gram-negative organisms include:

- **Extended spectrum β-lactamases (ESBL)**
- **AmpC β-lactamases**
- **Carbapenemase Producing Enterobacterales (CPE)**

ESBL

- Inactivate most penicillins, cephalosporins, and monobactams (eg. aztreonam) but not carbapenems or non-beta lactam agents
- Resistance to ceftriaxone is often used as proxy for ESBL production
- Often test susceptible to β-lactam/ β-lactamase inhibitors (BL-BLI) combinations (ex: piperacillin-tazobactam), but treatment with such agents may not be appropriate under all conditions (eg: high-burden infections with bacteremia)

AmpC

- Inactivate most penicillins, cephalosporins and monobactams but not carbapanems.
- **May initially appear susceptible to cephalosporins,** but exposure to these agents induces resistance to cephalosporins (i.e. *inducible ampC*).
- Organisms at moderate to high-risk of *inducing A*mpC production :
    - *Hafnia alvei, Enterobacter cloacae*, *Citrobracter freundii* (not C. *koseri*), *Klebsiella aerogenes*, Yersinia enterocolitica (acronym HECK-Yes)
- Older acronyms (SPICE, SPACE or ESKAPE)refer to organisms at lower risk for inducible AmpC production (*Serratia marcescens*, *Providencia* spp., *Proteus* spp., *Morganella* morganii)

CPE

- CPE inactivate penicillins, cephalosporins, carbapenems, monobactams, and some beta-lactam-beta-lactamase inhibitors (BL-BLI)
- Resistance to meropenem and all other beta-lactams is used as a proxy for CPE production.
- Isolates are all sent to for testing for CPE type (KPC, NDM, etc.), and for susceptibility to reserve drugs.

MUHC antibiogram (2024):

	% susceptible to ceftriaxone	**% susceptible to piperacillin-tazobactam**
E. coli	85%	90%
Klebsiella spp	85%	90%
Enterobacter spp	<50%	75%
Citrobacter spp	< 50%	90%
Pseudomonas aeruginosa	NONE	85%

Recommended Antibiotic treatment for ESBL, AmpC, CPE producers

Suspected mechanism	Usual Organism	Antibiogram[1]	Management based on scenario[2]
ESBL	*E. Coli, Klebsiella spp*	R to ceftriaxone and/or R ceftazidime	**Uncomplicated UTI:** Treat as per sensitivity profile, favor **nitrofurantoin** if S **Complicated UTI / Pyelo (without bacteremia)** **Piperacillin/Tazobactam 4.5 g IV q6h** **Bacteremia, sepsis:** **Meropenem[2]* 1g IV q8h over 3-4h *AND*** **** CONSULT ID ****
Amp C	*E. cloacae; K. aerogenes; C. freundii*	R to piperacillin, cefazolin, aztreonam May appear as S to ceftriaxone (inducible ampC)	**Uncomplicated UTI:** Treat as per sensitivity profile, favor nitrofurantoin **Complicated UTI / Pyelo (without bacteremia)** **Meropenem[3,5] 1 g IV q8h *OR*** **Cefepime[4] 2g IV q8h** **Bacteremia, sepsis:** **Meropenem[3] 1g IV q8h over 3-4h *AND*** **** CONSULT ID ****
CPE	*E. coli, Klebsiella spp, Enterobacter spp, Citrobacter spp, etc*	R to all beta-lactams tested routinely	**** CONSULT ID **** (choice of therapy depends on expanded susceptibility testing to restricted agents)

[1] Antibiogram for current pertinent clinical isolate
[2] For empirical treatment, refer to pertinent syndromic guideline (eg: UTI, sepsis)
[3] Meropenem is restricted to ID, ICU, Hematology/Medical Oncology and Emergency; carbapenems are not interchangeable for treatment of gram-negative infections
[4] Cefepime is restricted to ID
[5] Stepdown to BL-BLI can be considered once patient is clinically stable, if isolate tests susceptible.

References

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