Sepsis in Known or Suspected CPO Infections

MICROBIOLOGY

- Terminology:
  - CPO = Carbapenemase-producing organism
  - CPE = Carbapenemase-producing *Enterobacteriaceae*
  - CRO = Carbapenem-resistant organism
  - CRE = Carbapenem-resistant *Enterobacteriaceae*
- Other mechanisms of resistance to carbapenems (CRO) exist apart from carbapenemases (CPO), e.g., drug efflux pumps. This resource is specific to known or suspected **CPO** infections. Other treatment options may exist for CRO infections that lack carbapenemases.
- Carbapenemases are a group of beta-lactamase enzymes that confer resistance to carbapenems and most other beta-lactams. Several common CPO enzymes are seen in FH hospitals:
  - NDM (New Delhi Metallobetalactamase) is the most common (~70%).
  - OXA-48 is the second most common (~15%).
  - KPC (*Klebsiella pneumoniae* Carbapenemase) is the third most common (~10%). Other less common types include IMP and VIM, amongst others.
- Antibiotic susceptibility is dependent on the specific type of CPO enzyme.
- All patients with known CPO colonization should have their specific CPO enzyme identified in relevant prior microbiology results.

Fraser Health CPE Susceptibilities

	Percentage of isolates susceptible to listed antimicrobial						
***E. coli*, *Klebsiella*, and other Enterobacteriaceae (CPE)**	**Amikacin**	**Colistin**	**Tigecycline**	**Ciprofloxacin**	**SXT**	**Aztreonam**	**Fosfomycin**
NDM Enzyme	34 %	97 %	50 %	12 %	19 %	9 %	67 %
KPC Enzyme	94 %	86 %	62 %	18 %	35 %	R	82 %
OXA-48 Enzyme	41 %	100 %	38 %	18 %	35 %	R	69 %

Based on clinical isolates from 2013-2019. R = inherently resistant.
Insufficient data for FH CPO *Pseudomonas* and *Acinetobacter* antibiograms.

EMPIRIC THERAPY

Step #1 Is the patient's CPO status relevant to the suspected infection?		
Infections where having a history of CPO colonization is unlikely to be of relevance: • Community acquired pneumonia (non-severe) • Cellulitis		
Step #2 Is the severity of infection such that empiric CPO coverage should be given?		
Empiric therapy for CPO infections requires combinations of antimicrobials, with significant toxicity and side effects. In non-severe infections, standard empiric therapy (refer to relevant ASP Handbook chapter) can be given while waiting for culture results.		
Step #3 Empiric antibiotic regimen determined by suspected organism and CPO enzyme		
Organism	**CPO Enzyme**	**Empiric Therapy**
***E. coli*, *Klebsiella*, and other *Enterobacteriaceae* (CPE)**	NDM, OXA-48, and other non-KPC	**meropenem** 2 g IV q8h AND **colistin** IV*
	KPC Only	**meropenem** 2 g IV q8h AND **amikacin** IV*
Pseudomonas	Any CPO	**meropenem** 2 g IV q8h AND **colistin** IV*
Acinetobacter	Any CPO	**meropenem** 2 g IV q8h AND **colistin** IV* *Combination therapy with meropenem not beneficial in proven Acinetobacter infections. Discontinue meropenem if CPO Acinetobacter infection confirmed.*
Step #4 Empiric MRSA therapy where indicated		
First Line: **vancomycin** IV* Second Line: **linezolid** IV/PO (consider if tenuous renal function) *See syndrome-specific ASP Handbook chapters for further guidance.*		
Step #5 Review antibiotics DAILY		
Review antibiotics DAILY for potential step-down, directed therapy, and duration. Empiric antibiotic regimen above may no longer be appropriate once culture results are available.		

* Refer to relevant ASP Handbook chapter for dosing.

DIRECTED THERAPY AND DURATION

- Infectious Diseases consultation recommended for **ALL** confirmed CPO infections
- Duration of therapy generally reflects underlying source of infection, not presence of specific resistance

Role of carbapenem combination therapy

- Carbapenems are often used as part of combination treatment regimens for CPO infections despite being resistant. The role of carbapenem combination therapy is controversial.
- The evidence of benefit is greatest for KPC-producing *Enterobacteriaceae* when MIC is ≤8. Those who are critically ill benefit most from carbapenem-containing regimens, while those with urinary tract source of infection benefit least.
- Consider extended infusion of carbapenems (e.g., meropenem 2 g IV q8h, each dose infused over 3 hours) where logistically feasible.
- A randomized controlled trial showed no benefit to carbapenem combination therapy for carbapenem-resistant *Acinetobacter* infections. Monotherapy with colistin is equally effective in this case.

APPENDIX

E. coli, Klebsiella, and other Enterobacteriaceae (CPE)

- Non beta-lactam agents may have activity against CPE, refer to antibiogram above: **aminoglycosides**, **fluoroquinolones**, **cotrimoxazole**, **colistin**, **tigecycline**, and **fosfomycin**
- **Aztreonam** may be effective against some CPE with the NDM enzyme. However, **aztreonam** is inactivated in the presence of ESBL, AmpC, or other CPE enzymes.
- Several novel antimicrobials are only active against CPE with the KPC enzyme: **ceftazidime-avibactam**, **meropenem-vaborbactam**, and **imipenem-relebactam**.
- CPE with the OXA-48 enzyme may retain susceptibility to **ceftazidime** and **ceftazidime-avibactam**.
- **Ceftolozane-tazobactam** is not active against CPE.

CPO Pseudomonas

- Non beta-lactam agents may have activity against CPO *Pseudomonas*: **aminoglycosides**, **fluoroquinolones**, **colistin**, **fosfomycin**
- **Ceftazidime-avibactam** may retain activity in CPO *Pseudomonas* with the KPC enzyme.
- **Aztreonam** may retain susceptibility against CPO *Pseudomonas* with the NDM enzyme.
- **Tigecycline** is not effective against *Pseudomonas*
- **Ceftolozane-tazobactam** is not effective against CPO *Pseudomonas*. However, it may be effective against multi-drug resistant *Pseudomonas* that lack carbapenemases.

CPO Acinetobacter

- Non beta-lactam agents may have activity against CPO *Acinetobacter*: **aminoglycosides**, **fluoroquinolones**, **cotrimoxazole**, **colistin**, **minocycline**, and **tigecycline**.
- **Aztreonam** and **fosfomycin** are not effective against CPO *Acinetobacter*