BC Provincial Antimicrobial Clinical Expert Committee (PACE)

Treatment Recommendations for Confirmed or Suspected CPO Infections

This CPO treatment guidance has been developed by PACE, based on evidence-based recommendations and the expert opinion of practitioners, recognizing that some potential preferred drugs may be in short supply or unavailable. This living document will be updated as more information and evidence is gathered, and as new drugs and treatment options are approved and added to the BC Formulary.

Introduction

- Initial treatment of confirmed or suspected CPO infections depends on infection severity, organism susceptibility and availability of preferred antibiotics.
- Some preferred antibiotics are non-formulary (NF) in BC Health Authorities or only available through the Health Canada – Special Access Program (SAP). Procurement delays of NF and SAP antibiotics can be expected.
- Contact the local hospital pharmacy for antibiotic availability and procurement procedures.
- The most common carbapenemases reported in British Columbia are:
    - New Delhi metallo-β-lactamases (NDM)
    - *Klebsiella pneumoniae* carbapenemases (KPC) which is not limited to *K. pneumoniae* isolates
    - Oxacillinases (e.g. OXA-48-like).
- In patients with serious infections, such as septic shock, caused by suspected CPO Enterobacterales, empiric antibiotic therapy should be started while awaiting microbiological identification of the causative organism(s) (see Table 1).
- Risk factors for CPO Enterobacterales infections include:
    - Colonization or history of infection with CPO Enterobacterales;
    - Recent hospitalization in or visit to a region or country with high CPO Enterobacterales endemicity (e.g. South India);
- When microbiological identification is available, de-escalate therapy accordingly. Table 2 lists directed therapy options for CPO Enterobacterales infections.

Table 1. Empiric Therapy – CPO Enterobacterales Infections –

(based on normal renal function)

Septic Shock	Meropenem 2 g IV Q8H; *each dose infused over 3 hours* AND amikacin 15 mg/kg IV Q24H; **OR if available;**
	Ceftazidime-avibactam[SAP] 2.5 g IV Q8H AND aztreonam[SAP] 2 g IV Q8H; *must be infused simultaneously over 3 hours* **OR;**
	Cefiderocol[SAP] 2 g IV Q8H; *must be infused over 3 hours*

Notes:

1. *Add metronidazole 500 mg PO/IV Q12H to the ceftazidime-avibactam/aztreonam or cefiderocol options if anaerobic coverage needed (e.g. for an intra-abdominal infection). Meropenem provides anaerobic coverage.*
2. *aztreonam is associated with a moderate to high incidence of reversable hepatic enzyme elevation. Monitor ALT, AST, prothrombin time and INR.*

Table 2. Directed Therapy - CPO Enterobacterales Infections

(based on normal renal function)

KPC, NDM or oxacillinase (e.g. OXA-48) Producing Enterobacterales Urinary tract infections	
Acute simple cystitis	fosfomycin 3 g PO x 1 dose (E. coli only)(can repeat Q2 days x 2 doses); **OR** nitrofurantoin 100 mg PO BID x 5 days; **OR** gentamicin OR tobramycin 5-7 mg/kg IV x 1 dose **OR** amikacin 15 mg/kg IV x 1 dose
Additional alternatives: ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole	
Complicated UTI	gentamicin OR tobramycin 5-7 mg/kg IV Q24H **OR** amikacin 15 mg/kg IV Q24H x 7 days
Alternatives: ceftazidime-avibactam^{SAP} +/- aztreonam^{SAP}, cefiderocol^{SAP}, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole	
KPC, NDM or oxacillinase (e.g. OXA-48) Producing Enterobacterales Infections outside the urinary tract	
KPC or OXA	Preferred: ceftazidime-avibactam 2.5 g IV Q8H^{SAP}; infused over 3 hours **OR** Alternative: cefiderocol 2 g IV Q8H^{SAP}
Note: 1. *add metronidazole 500 mg PO/IV Q12H if anaerobic coverage is needed (e.g. for an intra-abdominal infection)*	
NDM or NDM/OXA	Preferred: ceftazidime-avibactam^{SAP} 2.5 g IV Q8H **AND** aztreonam^{SAP} 2 g IV Q8H; infused concurrently over 3 hours **OR** Alternative: cefiderocol^{SAP} 2 g IV Q8H
Notes: 1. *In patients with augmented renal clearance, increase cefiderocol to 2 g IV Q6H* 2. *Add metronidazole 500 mg PO/IV Q12H if anaerobic coverage needed (e.g. for an intra-abdominal infection)* 3. *aztreonam is associated with a moderate to high incidence of reversable hepatic enzyme elevation. Monitor ALT, AST, prothrombin time and INR.*	

Sepsis	Meropenem 2 g IV Q8H; infused over 3 hours **AND** one or more of: 1. amikacin 15 mg/kg IV Q24H **OR** 2. colistin-base activity 300 mg IV x 1 dose, then 150 mg PO Q12H **OR** 3. fosfomycin 12-24 g/day IV in 2-3 divided doses[NF] **OR** 4. tigecycline 200 mg IV x 1 dose, then 100 mg IV Q12H

Notes:

1. *Meropenem PLUS colistin preferred for NDM and oxacillinase (e.g. OXA-48) producing Enterobacterales*
2. *Meropenem PLUS amikacin preferred for KPC producing Enterobacterales*
3. *Tigecycline inferior to aminoglycosides against complicated UTIs and inferior to other agents (e.g. colistimethate) to treat bloodstream infections; tigecycline not recommended for bloodstream infections*
4. *Colistimethate (colistin) causes acute kidney injury and neurotoxicity (e.g. dizziness, facial and peripheral paresthesia, vertigo, visual disturbances, confusion, ataxia and neuromuscular blockage that may lead to respiratory failure or apnea). Monitor kidney and neurological function frequently.*