BC Provincial Antimicrobial Clinical Expert (PACE)Committee

Treatment of Carbapenemase–Producing Enterobacterales (CPE) Infections

This CPE 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

Carbapenemase-producing Enterobacterales (CPEs) are a heterogeneous group of pathogens with multiple mechanisms of resistance to the carbapenem class of antibiotics, ertapenem, imipenem-cilastatin and meropenem.

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, OXA-48-like)

Less common carbapenemases include Verona integron-encoded metallo-β-lactamases (VIM) and imipenem-hydrolysing metallo-β-lactamases (IMP).

Initial treatment of confirmed or suspected CPE infections depends on infection severity, organism susceptibility and availability of preferred antibiotics. Antibiotic susceptibility depends on the specific type of CPE enzyme and reported by the microbiology laboratory. In patients with serious infections, such as septic shock, caused by suspected CPEs, empiric antibiotic therapy should be started while awaiting microbiological identification of the causative organism(s) and susceptibility (see Table 1).

Risk factors for CPE infections include:

- Colonization or history of infection with a CPE
- Recent hospitalization in or visit to a region or country with high CPE endemicity (e.g. South Asia).

Some preferred antibiotics are currently 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 hospital pharmacy for antibiotic availability and procurement procedures. When microbiological identification is available, refine therapy accordingly. Table 2 lists directed therapy options for CPE infections. Infectious Diseases consultation is strongly recommended.

Table 1. Empiric Therapy – CPE Infections

High suspicion of CPE infection and awaiting culture and susceptibility results

Dosing based on normal renal function

Septic Shock	*Preferred:* [ceftazidime-avibactam[SAP] 2.5 g IV Q8H; *infused over 3 hours* AND aztreonam[SAP] 2 g IV Q8H; *infused simultaneously over 3 hours]* **OR** cefiderocol[SAP] 2 g IV Q8H; *infused over 3 hours* *If the above options are not available:* meropenem 2 g IV Q8H; *infused over 3 hours* AND amikacin 15 mg/kg IV Q24H; **±** [fosfomycin [NF] 12-24 g/day IV in 2-3 divided doses OR colistimethate 300 mg (equivalent to 300 mg colistin base activity) IV x 1 dose, then 150 mg IV Q12H] Switch to preferred antibiotics when these are available
Sepsis	meropenem 2 g IV Q8H; *infused over 3 hours* **AND** one or more of: 1. amikacin 15 mg/kg IV Q24H **OR** 2. fosfomycin[NF] 12-24 g/day IV in 2-3 divided doses **OR** 3. colistimethate 300 mg (equivalent to 300 mg colistin base activity) IV x 1 dose, then 150 mg IV Q12H **OR** 4. tigecycline 200 mg IV x 1 dose, then 100 mg IV Q12H

Notes:

1. *The Health Canada SAP antibiotics, ceftazidime-avibactam plus aztreonam or cefiderocol, should only be used in patients with suspected CPE infection **and** septic shock or patients with a confirmed CPE infection demonstrating susceptibility to these agents. See Table 2. for directed therapy options.*
2. *Add metronidazole 500 mg PO/IV Q12H to ceftazidime-avibactam/aztreonam or cefiderocol if anaerobic coverage needed (e.g. for an intra-abdominal infection). Meropenem provides anaerobic coverage.*
3. *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*
4. *Aztreonam associated with a moderate to high incidence of reversable hepatic enzyme elevation. Monitor ALT, AST, prothrombin time and INR.*
5. *Meropenem PLUS colistimethate preferred if NDM and oxacillinase (e.g. OXA-48) producing Enterobacterales suspected.*
6. *Meropenem PLUS amikacin preferred if KPC producing Enterobacterales suspected.*
7. *Tigecycline not recommended for urinary tract or bloodstream infections.*

Table 2. Directed Therapy - CPE Infections with KPC, NDM or oxacillinase (e.g. OXA-48) based on confirmed susceptibility

Dosing based on normal renal function

Uncomplicated UTI (Acute Simple Cystitis)	
Any CPE enzyme	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 Q24H x 1 dose
Alternatives: ceftazidime-avibactam[SAP] +/- aztreonam[SAP], cefiderocol[SAP]	
Complicated UTI and infections outside the urinary tract	
KPC	*Preferred:* meropenem-vaborbactam[NF] 4 g (meropenem 2 g + vaborbactam 2 g) IV Q8H; *infused over 3 hours* *Alternatives:* imipenem-relebactam [NF] 1.25 g IV Q6H; *infused over 30 minutes* **OR** ceftazidime-avibactam[SAP] 2.5 mg IV Q8H; *infused over 3 hours* **OR** cefiderocol[SAP] 2 g IV Q8H*; infused over 3 hours*
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 is needed (e.g intra-abdominal infection)*	
OXA-48 or 48-like	*Preferred*: ceftazidime-avibactam[SAP] 2.5 g IV Q8H; *infused over 3 hours* **OR** *Alternative*: cefiderocol[SAP] 2 g IV Q8H; *infused over 3 hours*
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 is needed (e.g. intra-abdominal infection)*	
NDM or NDM/OXA-48 or 48-like	*Preferred*: [ceftazidime-avibactam[SAP] 2.5 g IV Q8H; *infused over 3 hours* **AND** aztreonam[SAP] 2 g IV Q8H; *infused concurrently over 3 hours]* **OR** *Alternatives*: cefiderocol[SAP] 2 g IV Q8H; *infused over 3 hours* OR aztreonam-avibactam[SAP] 2 g (aztreonam 1.5 g + avibactam 0.5 mg) IV Q6H; *infused over 3 hours*
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 intra-abdominal infection)* *3. Aztreonam associated with a moderate to high incidence of reversable hepatic enzyme elevation. Monitor ALT, AST, prothrombin time and INR.*	