Prescribing Protocol SESLHDPR/573

Polymyxin B IV for infections outside of the urinary tract

Health
South Eastern Sydney
Local Health District

Areas where Protocol/Guideline applicable	Inpatient ward areas including intensive care
Authorised Prescribers:	Infectious Diseases specialist or Microbiologist
Indication for use	Antibacterial for the treatment of **proven infections due to susceptible gram negative bacilli** including *E.coli*, *Klebsiella sp*, *Pseudomonas sp*, *Acinetobacter sp* resistant to all of cefepime or ceftazidime, imipenem or meropenem, piperacillin-tazobactam, and ciprofloxacin. Some gram-negative organisms are intrinsically resistant to polymixin B i.e. *Serratia spp., Proteus spp., Morganella spp., Burkholderia Cepacia,* and *Providencia spp.* Note: POLYMYXIN B IV is a highly restricted drug that requires specific approval from the Infectious Diseases or Microbiology service and the TGA Special Access Scheme (SAS) prior to use.
Clinical condition Patient selection: Inclusion criteria	Diagnosis of infection from susceptible gram negative organism with no susceptibility to all of cefepime, ceftazidime, imipenem or meropenem, piperacillin-tazobactam, ciprofloxacin. **Do not use for infections arising from the urinary tract** (polymyxin E/colistin is the preferred polymyxin for UTI)
Contra-indications	Known hypersensitivity to polymyxin B, or its excipients. Not recommended for inhalation therapy due to potential for damage to lung epithelial cells
Precautions	Combination therapy with a carbapenem is no longer recommended for treatment of carbapenem-resistant Enterobactorales, Acinetobacter and P. aeruginosa Dosing is expressed in many forms: **1mg = 10,000 units** Nephrotoxic: Acute tubular necrosis (reversible) Neurotoxic: circumoral and peripheral paresthesia, vertigo, dizziness, blurred vision, ataxia, slurred speech, irritability, extremity numbness Neuromuscular blockade (can manifest as respiratory arrest) May exacerbate or unmask myasthenia gravis
Pregnancy Category	C

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Proposed Place in Therapy	Used for multi-drug resistant gram-negative infections only when susceptibility of the organism or drug availability mean there are no more suitable treatment options. Polymyxin B has a “detergent effect” on the cell membrane that allows restoration of antibacterial activity of drugs considered resistant as monotherapy.
Dosage (for age 2 and above)	For pathogens with MIC of 2mcg/ml or less: Loading dose (based on total body weight (TBW)*): 2.5mg/kg (25,000 units/kg) IV over 2 hours Maintenance dose (based on TBW*): (*12 hours post loading dose*) 1.5 mg/kg (15,000 units/kg) over 1 hour IV 12-hourly No dose adjustment required for patients with renal insufficiency. *Obesity: If obese (BMI≥30), suggest loading dose and maintenance dose based on adjusted body weight (ABW). There is limited experience with doses of >200mg (and >400mg in 24 hours) and increased risk of adverse effects with higher doses (including thoracic pain, paraesthesias, dizziness, dyspnoea and hypoxemia). Please consult with antimicrobial stewardship (AMS) pharmacist in morbid obesity.
Duration of therapy	Duration should be based on bacterial cultures and the patient’s clinical response. In general, therapy should continue for at least 5 days after the last negative blood culture.
Important Drug Interactions	Nephrotoxic drugs (e.g. amphotericin, aminoglycosides, cidofovir, foscarnet, vancomycin): may increase risk of nephrotoxicity. Rifampicin co-administration may also increase nephrotoxicity. Where co-administration cannot be avoided, exercise caution when co-administering polymyxin B and other nephrotoxins, and monitor renal function closely. Non-depolarizing muscle relaxants (atracurium, vecuronium, pancuronium, tubocurarine): neuromuscular blockade may be enhanced with IM or IV use.
Administration Instructions	Dilute each 500,000 unit vial in 300-500 mL of glucose 5% and infuse over 60 to 120 minutes. The reconstituted solution should be used as soon as possible but is stable for 72 hours at 2-8°C. *Do not freeze.* In fluid restricted patients: Doses of 1.5mg/kg have been diluted in 50 mL (Glucose 5% in water or Sodium chloride 0.9%) and infused over 60 minutes. High doses should be infused over 1-4 hours to minimize risk for adverse effects.

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Monitoring requirements	Check renal function prior to therapy initiation. Daily electrolytes and urea, full blood count. Daily blood cultures until negative if bacteraemic. Regular monitoring of non-invasive blood pressure, pulse, temperature measurements. **Monitor for signs and symptoms:** **Neuromuscular blockage:** depressed respiration, muscle weakness, apnoea. **Neurologic**: peri-oral paresthesias, numbness of extremities, blurred vision, ataxia, drowsiness, irritability, dizziness. **Nephrotoxicity:** dose dependent reversible tubular necrosis. Increased risk nephrotoxicity with high daily dose, cumulative dose, and length of therapy. Also concomitant nephrotoxins (see "Important drug interactions"), obesity, age, diabetes mellitus, and hypertension. Skin hyperpigmentation reported (skin darkness of face, ears, neck and upper chest and head during therapy). Effectiveness is determined by clinical response and bacterial cultures Polymyxin B therapeutic drug monitoring (TDM) is not routinely done however may be available and helpful, especially for dosing uncertainty/obesity. Please contact AMS Pharmacist for assistance.
Management of Complications	Consideration of discontinuation of therapy and management of the specific complication, if severe.

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Basis of Protocol/Guideline: (including sources of evidence, references)	The Sanford Guide to Antimicrobial Therapy Web Edition. Available at: webedition.sanfordguide.com. Accessed February 8, 2023. Pharmacotherapy 2019; 39(1): 10-39. International Journal of Infectious Diseases. 2015; 30: 125-132. Antimicrobial Agents and Chemotherapy. 2018; 62(3): e01475-17. Antimicrobial Agents and Chemotherapy 2017; 61:e20690-16. Polymyxin B. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: www.micromedexsolutions.com. Accessed February 8, 2023. Johns Hopkins ABX Guide 2012. 3rd ed. Lancet ID 2015; 15: 225-34. CID 2008; 47: 1298. JAC 2010; 65: 2231. CID 2013; 57: 524 CID 2014; 59(1): 88-94. CID doi:10.1093/cid/civ717
Groups consulted in development of this guideline	ID pharmacist, ID Department, Microbiology Department, Antimicrobial Stewardship Committee for Prince of Wales Hospital and St George Hospital, Clinical Applications Advisory Committee

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GOVERNANCE	
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