Colistin & Polymyxin B Dosing Recommendations

BACKGROUND:

- Colistin (Polymyxin E) and Polymyxin B are polypeptide antibiotics first discovered in the 1950's. However, their use had fallen out of favor due to high toxicities, such as nephrotoxicity and neurotoxicity.
- With increasing resistance rates, their use have resurged in recent years & they play an important role as salvage therapy for many MDRO gram-negative infections.
- See table below for a comparison between the two agents:

	COLISTIN	POLYMYXIN B
Mechanism of action	Bind to the outer cell membrane of gram negative bacteria, acting as a detergent by displacing divalent cations from the phosphate groups of membrane lipids, which leads to disruption of the outer cell membrane, leakage of intracellular contents, and bacterial death	
Antibacterial activity	Most commonly used for MDR Acinetobacter, Carbapenem Resistant Enterobacteriaceae (CREs), *P. aeruginosa*. Also active vs Enterobacter, E. Coli, Citrobacter	
Administered as	Inactive prodrug colistimethate sodium (CMS) and has variable and slow conversion to active moiety	Active drug and may achieve plasma concentration more rapidly
PK/PD	Concentration dependent, bactericidal, efficacy correlates with AUC: MIC ratio	
Loading Doses	Required for both formulations to achieve therapeutic plasma concentrations as soon as possible	
Clearance	Inactive prodrug (CMS) is renally cleared	Non-renal clearance & extensively resorbed, leading to low polymyxin B concentration in urine
Attainment of therapeutic concentrations	Unreliable in patients with good renal function	Since active drug is administered, it is possible to achieve desired plasma concentrations
Nephrotoxicity risk	Both are potentially nephrotoxic (dose-dependent)	
Renal Dose Adjustments	Yes (CMS eliminated renally)	Not recommended

SUSCEPTIBILITY TESTING:

- Established MIC breakpoints are:

CLSI/EUCAST Breakpoints for Colistin and Polymyxin B			
Organism	**Susceptible**	**Intermediate**	**Resistant**
CLSI			
Acinetobacter sp	---	≤ 2	≥ 4
Pseudomonas aeruginosa	---	≤ 2	≥ 4
Enterobacteriaceae	---	≤ 2	≥ 4
EUCAST			
Acinetobacter sp	(2)*	---	(2)*
Pseudomonas aeruginosa	(4)*	---	(4)*
Enterobacteriaceae	(2)*	---	(2)*

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing

*EUCAST introduced brackets (), which are used to distinguish between bacteria with and without acquired resistance mechanisms, but the drug should not be used in monotherapy for systemic/severe infections.

INDICATIONS:

- **Polymyxin B is preferred over colistin for all MDR-GNB systemic infections outside of the urine tract** due to more predictable pharmacokinetics and decreased potential to cause nephrotoxicity
    - **EXCEPTIONS**: Colistin is preferred over polymyxin B for urinary tract infections, nebulization administration, and intrathecal/intraventricular administration

DOSING & ADMINISTRATION (INTRAVENOUS):

- **Polymyxin B and colistin dosing is NOT interchangeable**
    - Polymyxin B is available in vials of 500,000 units each
        - 10,000 units Polymyxin B = 1 mg Polymyxin B
        - Dilute all doses in D5W or NS and administer loading doses over 1 hour and maintenance doses over 30-60 minutes.
        - Final concentration should NOT exceed 2 mg/mL
    - Colistimethate Sodium (CMS) is available in vials equivalent to 150 mg of colistin base activity (CBA) per vial. In the US, the strength of all FDA-approved colistimethate for injection products is labeled in terms of the colistin base activity (CBA), not the prodrug. Colistin should ONLY be prescribed in terms of colistin base activity (CBA).
        - Administer over 30 minutes
        - Final concentration: 75 mg colistin base activity/mL

Dosing Recommendations for Polymyxin B and Colistin

CrCl (mL/min)	≥ 90 mL/min	80-89 mL/min	70-79 mL/min	60-69 mL/min	50-59 mL/min	40-49 mL/min	30-39 mL/min	20-29 mL/min	10-29 mL/min	5-9 mL/min	<5 mL/min	HD
Colistin[1]	LD: 300 mg x1 for ALL patients											
	180 mg Q12	170 mg Q12	150 mg Q12	138 mg Q12	122 mg Q12	110 mg Q12	98 mg Q12	88 mg Q12	80 mg Q12	72 mg Q12	65 mg Q12	130 mg Q24 + 40 mg x1 (3 hr HD session) or 50 mg x1 (4 hr HD session) after HD on dialysis days
Polymyxin B[2-4]	LD: 2.5 mg/kg x1 for ALL patients (For doses >200 mg, consult ASP Pharmacist)											
	1.25 - 1.5 mg/kg Q12 (For doses >200 mg, consult ASP Pharmacist)											

1. Dosing based on colistin base activity (CBA).
2. Use total body weight. For obesity, use adjusted body weight.
3. Limited data in renal impairment. No dosing adjustment suggested based on PK studies.
4. PK data does not support capping upper absolute doses in obese patients. Clinical studies using doses >200 mg/infusion are limited. Doses up to 300 mg/day have been used in smaller studies with small risk of severe infusion-related adverse events (0.9% of patients).

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