Colistin = colistimethate sodium (inactive prodrug) = Polymixin E

MOA: Colistimethate is hydrolyzed to colistin which binds to the outer cell membrane of gram negative bacteria. Colistin acts 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.

Use for MDR Gram Negative Bacilli

- Activity: Most commonly used for MDR Acinetobacter, Carbapenem Resistant Enterobacteriaceae (CREs), *P.aeruginosa*
  - also active vs Enterobacter, E.coli, Citrobacter
- No activity: Morganella morganii, Proteus spp, Providencia spp, Serratia spp
- BEWARE the emergence of heteroresistance = no monotherapy
  - Colistin monotherapy is unlikely to generate reliably efficacious plasma levels
  - Should be used as part of a highly active combination therapy
    - Carbapenems may be considered as part of the combination therapy despite in vitro susceptibility
- Colistin is a restricted agent and use for this indication may require ID consultation

PK/PD[1]:

- Concentration dependent, bactericidal, efficacy correlates with AUC: MIC ratio
- Inactive pro-drug is renally cleared
  - Correlation between CrCl and colistin levels (e.g. as GFR decreases, there is more prodrug available to convert to colistin)
- Active drug is cleared via non renal clearance (deep tissue depot)
- Both efficacy and nephrotoxicity are dose dependent[2]

Dosing:

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. The label expresses the strength as 150 mg of colistin base per vial. Colistin should ONLY be prescribed in terms of colistin base activity (CBA) with a daily dose of 5 mg/kg/day in patients with normal renal function.[3]

CBA	CrCL ≥ 50 mL/min	CrCL 49 - 30 mL/min	CrCL 29 - 10 mL/min	CrCL ≤ 10 mL/min or iHD
Loading Dose	5 mg/kg x1			
Maintenance dose	2.5 mg/kg Q12	1.75 mg/kg Q12	2.5 mg/kg Q24	1.25 mg/kg Q24 given post HD on dialysis days
	Begin 12-hrs after loading dose	Begin 12-hrs after loading dose	Begin 24-hrs after loading dose	Begin 24-hrs after loading dose

Patients on SLED for > 8 hours may have higher requirements than iHD patients and this should be evaluated on an individual basis.

- Loading doses are necessary for rapid achievement of therapeutic levels[4,5]
- All doses should be calculated using the lesser of actual or ideal body weight
  - Use of an adjusted body weight may be considered for critically ill, obese patients. Risk vs benefit should be weighed as total doses exceeding 5 mg/kg/day IBW are associated with a higher incidence of nephrotoxicity[6,7]

Colistin base activity (CBA)

400 mg vial of colistemethate sodium → remove 5 sodium atoms = 375 mg colistemethate
375 mg colistemethate→remove the 5 methanesulfonates = 267 mg colistin base
267 mg colistin base → ~50% conversion to active drug = 150 mg CBA

1 mg CBA = 30,000 IU of CBA = 2.4 mg colistin prodrug (colistemethate sodium)

---

[1] Bergen PJ, Bulman ZP, Saju S, Bulitta JB, Landersdorfer C, et al. Polymyxin combinations: pharmacokinetics and pharmacodynamics for rationale use. Pharmacotherapy. 2015;35(1):34-42.

[2] Vicari G1, Bauer SR, Neuner EA, Lam SW. Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia. Clin Infect Dis. 2013;56(3):398-404

[3] http://www.ashp.org/DocLibrary/Policy/PatientSafety/NANAlert-Colistimethatesodium.aspx

[4] Rao GG, Ly NS, Haas CE, Garonzik S, Forrest A, et al. New Dosing Strategies for an Old Antibiotic: Pharmacodynamics of Front-Loaded Regimens of Colistin at Simulated Pharmacokinetics in Patients with Kidney or Liver Disease. Antimicrob Agents Chemother. 2014; 58(3): 1381–1388

[5] Grégoire N, Mimoz O, Mégarbane B, Comets E, Chatelier D, et al. New colistin population pharmacokinetic data in critically ill patients suggesting an alternative loading dose rationale. Antimicrob Agents Chemother. 2014 Dec;58(12):7324-30.

[6] Pogue JM, Lee J, Marchaim D, Yee V, Zhao JJ, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. Clin Infect Dis. 2011;53(9):879-84.

[7] Ortwine JK, Kaye KS, Li J, Pogue JM. Colistin: understanding and applying recent pharmacokinetic advances. Pharmacotherapy. 2015;35(1):11-6.