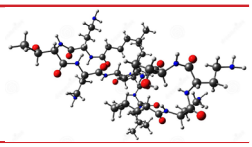
THE PATHCARE NEWS

POLYMYXIN GUIDELINES



International Consensus Guidelines for the Optimal Use of the Polymyxins.

Due to a rapid increase in serious infections related to especially carbapenemase producing Enterobacterales, the clinical use of the polymyxin antibiotics colistin (polymyxin E), and polymyxin B has recently resurged as salvage therapy for otherwise untreatable Gram-negative infections. Both polymyxins demonstrate rapid bactericidal killing against susceptible strains of *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. However, an inoculum effect was demonstrated for polymyxin monotherapy with bacterial killing activity significantly attenuated at inoculates consistent with both ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HAP).

Polymyxin B

Compared to colistin, polymyxin B has superior pharmacokinetic (PK) characteristics in humans where it is important to achieve rapid and reliable plasma concentrations. Polymyxin B also has a decreased potential to cause nephrotoxicity compared to colistin, as it is predominantly cleared by non-renal mechanisms with a median urinary recovery of only 4%. It is therefore the **preferred agent for routine systemic use in invasive infections**.

A loading dose of 2.0 - 2.5 mg/kg for polymyxin B based on total body weight (TBW) (equivalent to 20,000 - 25,000 IU/kg) infused over 1 hour is recommended. The maintenance dose is 1.25 - 1.5 mg/kg (equivalent to 12,500 - 15,000 IU/kg TBW) every 12 hours, infused over 1 hour. Daily **maintenance doses of polymyxin B should not be adjusted if the patient has renal impairment.**

Colistin

Even with a loading dose of colistin at the initiation of therapy, it may take several hours to achieve plasma colistin concentrations that may be effective. PK of colistin methanesulfonate (CMS) and formed colistin are subject to substantially greater interpatient variability than occurs with polymyxin B. Given renal clearance of the prodrug (CMS) that then converts to the active moiety colistin, **colistin is the preferred polymyxin for the treatment of lower urinary tract infections.**

Initiate IV therapy with colistin at a loading dose of 9 - 12 million IU infused over 0.5 - 1 hour and administer the first maintenance dose 12 - 24 hours later. For a patient with normal renal function, administer a dose of 4.5 million IU 2x/d infused over 0.5 - 1 hour. Monitor renal function and adjust the daily dose accordingly.

Polymyxin combination therapy with another active agent might be advantageous. Plasma concentrations of colistin are suboptimal in a substantial proportion of patients, even when daily doses of colistin are at the upper limit of the approved dosage. Similarly, plasma polymyxin B concentrations achieved among patients receiving the current upper limit daily dose are not likely to be reliably efficacious especially in respiratory tract infections. It is also recommended that patients requiring IV polymyxin therapy for XDR Gram-negative HAP or VAP, receive adjunctive polymyxin aerosol therapy.

Conclusion

Until further evidence becomes available, clinicians should consider polymyxin B as the preferred polymyxin to decrease the risk of colistin associated acute kidney injury. An exception to this would be for the treatment of urinary tract infections, where colistin may be the preferred agent.

Further reading: *Pharmacotherapy* 2019;39(1):10-39, *Southern African Journal of Infectious Diseases* 2016;1(1):1–5

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