

High Dose Colistimethate Sodium (Colistin) in Adults – Consensus Guidance

Background:

Colistimethate sodium (CMS) exhibits concentration-dependent bactericidal killing (AUC/MIC = area under curve/minimum inhibitory concentration)) and is often used in combination with other antibiotics against Carbapenemase producing enterobacteriaceae (CPE) bacteria.

Traditional dosing regimens for CMS do not attain serum concentrations that would be sufficient for the treatment of infections caused by pathogens with minimum inhibitory concentration (MIC) higher than 0.5 mg/L.

Studies have shown that high dose regimens are more effective with limited increase in irreversible nephrotoxicity.¹ Many patients do experience nephrotoxicity but the majority recover renal function. The risk of nephrotoxicity must be balanced against the severity and potential mortality rate of the infection being treated.

The content of this guidance is based on the current UK CMS license and experience of UK specialist pharmacists using it in clinical practice.²

N.B. Always seek specialist advice before initiating treatment with CMS.

This guidance does not cover use of CMS for respiratory infections in cystic fibrosis patients.

Terminology:

Colistimethate sodium (CMS) is a non-active pro-drug of colistin which is converted in vivo to the active colistin. 1mg colistin base activity is contained in 2.4mg CMS which is equivalent to 30,000 IU of CMS. Therefore, 100mg of colistin sulphate base is equivalent to 240mg of CMS and to 3 MU CMS.¹ Vials of Promixin® and the generic products contain 1 million International Units (IU) i.e. 1MU equivalent to 80mg CMS.³ In adults 1MU vials are used.

Adult Loading Dose (normal and impaired renal function including renal replacement therapy):^{3,4,7,8,9}

Body weight	Loading Dose	Notes
Over 60kg	9 MU	<ul style="list-style-type: none"> Use actual body weight unless BMI > 30 In obese patients (BMI > 30) dosing should be based on Ideal Body Weight as use of actual body weight is associated with increased incidence of nephrotoxicity. A loading dose of up to 12 MU may be used in critically ill patients The loading dose is unaffected by renal impairment.
50 - 60kg	8 MU	
40 – 50kg	7 MU	

Adult Maintenance Dose:^{3,4,7,10,11}

Creatinine Clearance (mL/min)	Dose and frequency	Starting time after loading dose
> 50	3 MU every 8 hours	12 hours
30 – 49.9	3 MU every 12 hours	24 hours
10 – 29.9	2.5 MU every 12 hours	24 hours
< 10	1.75 MU every 12 hours	24 hours
Haemodialysis (HD)	1.5 MU every 12 hours 2 nd dose given post-HD on dialysis days	24 hours
Peritoneal dialysis (CAPD)	2.5 MU every 12 hours	24 hours
Continuous veno-venous haemodiafiltration (CVVHD)	Dosing as per Cr Cl > 50 mL/min	24 hours

NB: Increasing maintenance dose to 6 MU 12 hourly may be considered in critically ill patients with good renal function depending on patient response, trough concentration and MIC.

Higher dosage may also be considered in critically ill patients with renal impairment.

Always discuss with an Infection Specialist and review daily.

Administration:

- Reconstitute each 1 MU vial with 10ml of WFI or 0.9% sodium chloride³ and dilute in 100ml 0.9% sodium chloride for infusion.
- Infuse over 30 – 60 minutes via a rate-controlled infusion device.^{3,4} Start infusion immediately after preparation to reduce risk of microbial contamination and hydrolysis.³
- Flush before and after administration with 0.9% sodium chloride.

October 2018

For review October 2021 Original version developed by the Association of Scottish Antimicrobial Pharmacists

Monitoring:

Renal function should be monitored daily for the first week and adjustments made according to the table above if required. If the patient's renal function is stable or stabilises, monitoring can be reduced to every 2-3 days.

Patients should also be monitored for evidence of neurotoxicity which are more common with high doses e.g. apnoea, peri-oral and peripheral paraesthesia, vertigo, headache, muscle weakness; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances. Some may not be apparent if patient is ventilated.

Plasma trough concentrations are required especially in patients with renal impairment and are measured at Bristol Southmead laboratory. The first sample should be taken immediately before the second maintenance dose (i.e. at 24 hours for 12 hourly dosing). Trough concentration measurements of 2- 4mg/L are suggested. Retesting is recommended after 14-28 days if target concentration is achieved or sooner if not at target.¹²

NB: Other antibiotics can interfere with the assay therefore the laboratory will require these details.

References:

- 1 Levy HG, Gould I et al. [Detection, Treatment and Prevention of Carbapenemase-Producing Enterobacteriaceae: Recommendations for an International Working Group](#). Journal of Chemotherapy 2013, 25 (3): 129-140
- 2 Personal communication, Mark Gilchrist, Consultant Pharmacist Imperial Healthcare NHS Trust
- 3 [Summary of Product Characteristics for colomycin \(colistimethate sodium\)](#)
- 4 Guidelines for Administration of Intravenous Colistin as Therapy for Multi- drug resistant *Pseudomonas aeruginosa* in Adults Patients on Wigan ICU February 2010. Personal correspondence. [Copy kept by NHSG Antibiotic Pharmacists.]
- 5 Pogue JM, Lee J et al. [Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system](#). Clin Infect Dis 2011; 53:879-84.
- 6 Dalfino L, Puntillo F et al. [High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study](#). Clin Infect Dis. 2012; 54:1720-6.
- 7 Gauthier et al. [Incidence and Predictors of Nephrotoxicity Associated with Intravenous Colistin in Overweight and Obese Patients](#). Antimicrob Agents Chemother 2012; 56 (5): 2392-2396
- 8 Garonzik SM, Li J et al. [Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients](#). Antimicrob Agents Chemother 2011; 55:3284-94
- 9 Visser Kift E et al, [Systematic review of the evidence for rational dosing of colistin](#) SAMJ March 2014, Vol. 104, No. 3, 183 – 186
- 10 Using Colistimethate Sodium Intravenously in Critically Ill Patients at Tallaght Hospital 2012 Personal correspondence. [Copy kept by NHSG Antibiotic Pharmacists.]
- 11 Antimicrobial Reference Laboratory, North Bristol NHS Trust, Southmead Hospital.
<http://www.bcare.nbt.nhs.uk/wp-content/uploads/Antibiotic-Assay-Guideline-Ranges-20151.pdf>

Additional References:

- 12 The Renal Drug Handbook 3rd Edition. Edited by Ashley C and Currie A, UK Renal Pharmacy Group.
- 13 Hartzell JD et al. [Nephrotoxicity Associated with Intravenous Colistin Treatment at a Tertiary Care Medical Center](#) Clinical Infectious Diseases 2009; 48:1724–8
- 14 Karvanen M, Palchouras D, Friberg LE et al. [Colistin Methanesulfonate and colistin pharmacokinetic in critically ill patients receiving Continuous Venovenous Hemodiafiltration](#). Antimicrobial Agents Chemotherapy. 2013, 57 (1):668.
- 15 Honore et al. [Colistin dosing for treatment of multidrug-resistant *Pseudomonas* in critically ill patients – please, be adequate!](#) Critical care 2014;18:412
- 16 Falagas & Kasiakou. [The Use of Intravenous and Aerosolized Polymyxins for the Treatment of Infections in Critically Ill Patients: A Review of the Recent Literature](#). Clin Infect Dis 2005; 40 (9): 1333-1341
- 17 Nation RL, et al. [Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus](#). The Lancet 2015 15(2); 225–234
- 18 European Medicines Agency completes review of polymyxin-based medicines. [Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics](#) EMA/643444/2014.
- 19 Rocco M et al, [Dose of colistin: a work in progress?](#) Critical Care (2015) 19:65
- 20 Cornelia B et al, Colistin: [How should It Be Dosed for the Critically Ill?](#) Semin Respir Crit Care Med 2015; 36(01): 126-135
- 21 Karaïkos et al, [Colistin Population Pharmacokinetics after Application of a Loading Dose of 9 MU Colistin Methanesulfonate in Critically Ill Patients](#), Antimicrob Agents Chemother 59:7240–7248