



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 in 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.

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.

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:

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