Consensus Guidance on High Dose Colistimethate Sodium (Colistin) in Management of Carbapenemase producing enterobacteriaceae (CPE) in Adults

**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. Recent studies have shown that high dose regimens are more effective with limited increase in irreversible nephrotoxicity. 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.

**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.*

**Contra-indications:** Myasthenia Gravis or allergy to CMS  
**Cautions:** Acute porphyria

**Interactions:** Check BNF. Use with caution when combining with other drugs which may potentiate nephrotoxic or neurotoxic side effects - antibiotics e.g. gentamicin, vancomycin, cephalosporins, amphotericin; neuromuscular blocking agents; rifampicin

**Side-effects:**
- Neurotoxicity especially with high doses e.g. apnoea, peri-oral and peripheral paraesthesia, vertigo, headache, muscle weakness; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances
- Nephrotoxicity
- Rash

**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. Vials of Promixin® and the generic Forest Laboratories product contain 1 million International Units (IU) i.e. 1MU equivalent to 80mg CMS. In adults 1MU vials are used.

**Adult Loading Dose:**

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Loading Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 50kg</td>
<td>9 million units (MU)</td>
<td>• In obese patients (BMI&gt;30) dosing should be based on Ideal Body Weight. Use of actual body weight in these patients is associated with increased incidence of nephrotoxicity.</td>
</tr>
<tr>
<td>50kg or under</td>
<td>6 million units (MU)</td>
<td>• In critically ill patients a dose of 9MU should be used. The loading dose is unaffected by renal impairment.</td>
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</tbody>
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Adult Maintenance Dose: ²,³,⁷,¹⁰,¹¹

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose and Frequency (based on SPCs)</th>
<th>Starting time after loading dose</th>
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</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>4.5MU 12 hourly</td>
<td>12 hours</td>
</tr>
<tr>
<td>30-50</td>
<td>3 MU 12 hourly</td>
<td>24 hours</td>
</tr>
<tr>
<td>10-30</td>
<td>2.5MU 12 hourly</td>
<td>24 hours</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1.75MU 12 hourly</td>
<td>24 hours</td>
</tr>
<tr>
<td>Patient undergoing continuous venovenous haemodiafiltration (CVVHDF)</td>
<td>3MU 8 hourly</td>
<td>8 hours</td>
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NB: Increasing maintenance dose to 6 MU 12 hourly may be considered in critically ill depending on patient response, and MIC – discuss with an Infection Specialist and review daily.

Administration

- Reconstitute each 1 MU vial with 0·9% sodium chloride ² and make doses of 4-5 MU to 9MU up to 100ml with 0·9% sodium chloride for infusion.
- Infuse over 30minutes via a rate-controlled infusion device. ²,³ Start infusion immediately after preparation to reduce risk of microbial contamination and hydrolysis. ²
- Flush before and after administration with 0·9% sodium chloride.
- Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of up to 2 million units in 10ml given over a minimum of 5 minutes. ³

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.

Plasma levels are required and are measured at Bristol Southmead laboratory. From 2015 trough levels of 2-4mg/L are suggested and retesting after 14-28 days. ¹²

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

Monitor for signs of neurotoxicity, 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 in ICU.
References


2. Promixin Solution for Infusion SPC (Profile Pharma Limited) Last updated on the eMC: 21/01/2016

3. Colomycin Injection SPC (Forest Laboratories UK Ltd) Last updated 06/02/2016.

4. British National Formulary www.bnf.org Accessed online 31/03/16

5. 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.]


11. Using Colistimethate Sodium Intravenously in Critically Ill Patients at Tallaght Hospital 2012 Personal correspondence. [Copy kept by NHSG Antibiotic Pharmacists.]


Additional References


14. Hartzell JD et al. Nephrotoxicity Associated with Intravenous Colistin Treatment at a Tertiary Care Medical Center Clinical Infectious Diseases 2009; 48:1724–8


Developed by members of the Association of Scottish Antimicrobial Pharmacists
Approved by the Scottish Antimicrobial Prescribing Group

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