

Colistimethate (Colistin) IV (Polymyxin E) for Urinary Tract Infections



Areas where applicable	Inpatient ward areas including intensive care
Authorised Prescribers:	Infectious Diseases physician or Microbiologist
Indication for use	<p>Antibacterial for the treatment of proven urinary tract infections due to susceptible gram negative bacilli including <i>E.coli</i>, <i>Klebsiella sp</i>, <i>Pseudomonas sp</i>, <i>Acinetobacter sp</i> lacking susceptibility to all of cefepime or ceftazidime, imipenem or meropenem, piperacillin-tazobactam, and ciprofloxacin.</p> <p>Polymixin B is preferred for infections outside of the urinary tract.</p> <p>Some gram-negative rods are intrinsically resistant to colistin i.e. <i>Burkholderia cepacia</i>, <i>Serratia marescens</i>, <i>Moraxella catarrhalis</i>, <i>Proteus spp</i>, <i>Providencia spp</i>, and <i>Morganella morganii</i>.</p>
Clinical condition	Infection due to susceptible gram negative organism with resistance to all of cefepime, ceftazidime, imipenem or meropenem, piperacillin-tazobactam, ciprofloxacin.
Contra-indications	Known hypersensitivity to colistimethate, colistin, or its excipients.
Precautions	<p>Do not use as monotherapy (combine with carbapenem or tigecycline or rifampicin)</p> <p>Dosing is expressed in many forms: 1 million units colistimethate (CMS) ~ 80mg colistimethate (CMS) ~ 30mg colistin base (CBA)</p> <p>Neurotoxic: circumoral paresthesia, vertigo, abnormal vision, confusion, ataxia, neuromuscular blockade with respiratory failure.</p> <p>Nephrotoxic: Risk increased by concomitant nephrotoxins, hypotension. Reversible.</p> <p>Higher doses of colistin (>5mg/kg ideal body weight per day) are associated with increased risk of nephrotoxicity and should be reserved for critically ill patients</p> <p>Each vial contain 0.54 mmol of sodium.</p> <p>In patients with creatinine clearance >80mL/min, it is not possible to reliably achieve an average steady-state plasma colistin concentration of 2mg/L</p> <p>Synonym: Polymyxin E</p>
Proposed Place in Therapy	Used in combination with either a carbapenem, tigecycline, or rifampicin for multiresistant gram negative infections
Dosage	<p>Colistimethate sodium (CMS) is an inactive pro-drug of colistin base (CBS). It is hydrolysed to colistin base (CBA) in the body.</p> <p>1 million units colistimethate (CMS) ~ 80mg colistimethate (CMS) ~ 30mg colistin base (CBA)</p>

**Colistimethate (Colistin) IV
(Polymyxin E) for Urinary Tract Infections**



<p>Dosage (cont.)</p>	<p>Potential for dosing errors due to lack of standardization in literature when referring to product and dose. Colistimethate and colistin base strengths are not interchangeable. Prescribed dose must be expressed in terms of colistin base.</p> <p>Calculated doses are higher than the package insert dosing; need to avoid under-dosage in the critically ill.</p> <p>Doses are expressed in terms of mg of colistin base (CBA)</p> <p>Severe Systemic Infections:</p> <p>Day 1: colistin 4 mg/kg (use ideal body weight (IBW)) up to a maximum of 300mg as a single loading dose</p> <p>Day 2 onwards: see appendix 1 for dose calculation.</p> <p>No dose adjustment is required for patients with mild, moderate or severe hepatic impairment. Dose adjustment for patients with renal insufficiency based on algorithm in appendix 1.</p>																																																				
<p>Duration of therapy</p>	<p>Duration should be based on bacterial cultures and the patient’s clinical response. In general, therapy should continue for at least 5 days after the last negative blood culture.</p>																																																				
<p>Important Drug Interactions</p>	<p>Aminoglycosides: may increase risk of neuromuscular blockade, nephrotoxicity</p> <p>Nephrotoxic drugs (e.g. amphotericin, aminoglycosides, cidofovir, foscarnet): may increase risk of nephrotoxicity. Avoid co-administration</p> <p>Non-depolarizing muscle relaxants (atracurium, vecuronium, pancuronium, tubocurarine): neuromuscular blockade may be enhance with IM or IV use</p>																																																				
<p>Administration Instructions</p>	<p>Reconstitute each vial prior to administration, do not prepare in advance.</p> <p>Reconstitute with 3 mL water for injection to give a concentration of 50mg/mL. Swirl gently to avoid frothing. Reconstitute each vial with an appropriate volume of water for injection to extract the required dose accurately.</p> <table border="1" data-bbox="513 1402 1439 2024"> <thead> <tr> <th>Dose of colistin</th> <th>Reconstituting 150mg vials</th> <th>Concentration</th> <th>Volume to be extracted for dose</th> </tr> </thead> <tbody> <tr> <td>65mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>1.3mL</td> </tr> <tr> <td>75mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>1.5mL</td> </tr> <tr> <td>80mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>1.6mL</td> </tr> <tr> <td>87.5mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>1.75mL</td> </tr> <tr> <td>100mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>2mL</td> </tr> <tr> <td>110mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>2.2mL</td> </tr> <tr> <td>125mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>2.5mL</td> </tr> <tr> <td>137.5mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>2.75mL</td> </tr> <tr> <td>150mg</td> <td>Add 3mL WFI</td> <td>50mg/mL</td> <td>3mL</td> </tr> <tr> <td>170mg</td> <td>Add 3mL WFI to each vial</td> <td>50mg/mL</td> <td>3.4mL</td> </tr> <tr> <td>180mg</td> <td>Add 3mL WFI to each vial</td> <td>50mg/mL</td> <td>3.6mL</td> </tr> <tr> <td>300mg</td> <td>Add 3mL WFI to each vial</td> <td>50mg/mL</td> <td>6mL</td> </tr> </tbody> </table> <p>WFI=Water for injection</p>	Dose of colistin	Reconstituting 150mg vials	Concentration	Volume to be extracted for dose	65mg	Add 3mL WFI	50mg/mL	1.3mL	75mg	Add 3mL WFI	50mg/mL	1.5mL	80mg	Add 3mL WFI	50mg/mL	1.6mL	87.5mg	Add 3mL WFI	50mg/mL	1.75mL	100mg	Add 3mL WFI	50mg/mL	2mL	110mg	Add 3mL WFI	50mg/mL	2.2mL	125mg	Add 3mL WFI	50mg/mL	2.5mL	137.5mg	Add 3mL WFI	50mg/mL	2.75mL	150mg	Add 3mL WFI	50mg/mL	3mL	170mg	Add 3mL WFI to each vial	50mg/mL	3.4mL	180mg	Add 3mL WFI to each vial	50mg/mL	3.6mL	300mg	Add 3mL WFI to each vial	50mg/mL	6mL
Dose of colistin	Reconstituting 150mg vials	Concentration	Volume to be extracted for dose																																																		
65mg	Add 3mL WFI	50mg/mL	1.3mL																																																		
75mg	Add 3mL WFI	50mg/mL	1.5mL																																																		
80mg	Add 3mL WFI	50mg/mL	1.6mL																																																		
87.5mg	Add 3mL WFI	50mg/mL	1.75mL																																																		
100mg	Add 3mL WFI	50mg/mL	2mL																																																		
110mg	Add 3mL WFI	50mg/mL	2.2mL																																																		
125mg	Add 3mL WFI	50mg/mL	2.5mL																																																		
137.5mg	Add 3mL WFI	50mg/mL	2.75mL																																																		
150mg	Add 3mL WFI	50mg/mL	3mL																																																		
170mg	Add 3mL WFI to each vial	50mg/mL	3.4mL																																																		
180mg	Add 3mL WFI to each vial	50mg/mL	3.6mL																																																		
300mg	Add 3mL WFI to each vial	50mg/mL	6mL																																																		

**Colistimethate (Colistin) IV
(Polymyxin E) for Urinary Tract Infections**



Administration Instructions (cont.)	Administration: IV injection: Administer by direct IV injection over 3-5 minute IV infusion: Add extracted volume to 100mL of sodium chloride 0.9% or glucose 5% infusion bag and infuse over 15-30 minutes. Do not add to burette.
Monitoring requirements Safety Effectiveness	Daily electrolytes and urea, full blood count, urine output. Daily blood cultures until negative if bacteraemic. Signs and symptoms of neuromuscular blockade (i.e. depressed respiration, muscle weakness, apnoea). Non-invasive blood pressure, pulse, temperature measurements. Effectiveness is determined by clinical response and bacterial cultures
Management of Complications	Consideration of discontinuation of therapy and management of the specific complication, if severe.
Basis of Protocol/Guideline: (including sources of evidence, references)	The Sanford Guide to Antimicrobial Therapy 2020. 50 th ed. Tsuiji BT, Pogue JM, Zavascki AP, et al. Pharmacotherapy 2019; 39(1): 10-39. Nation RL et al. CID 2017; 64(5): 565-71. Johns Hopkins ABX Guide 2012. 3 rd ed. Garonzik SM, et al. AAC 2011; 55(7): 3284. Plachouras D, et al. AAC 2009; 53: 3430. Bergen PJ, et al. AAC 2010; 54: 3783. Nation RL, et al. Lancet ID 2015; 15: 225-34. Australian Injectable Drug Handbook. 6 th Ed. Nation RL, et al. CID 2015; online Oct Nation RL, et al. CID 2014; 59(1): 88-94.
Groups consulted in development of this guideline	ID pharmacist, ID Department, Microbiology Department, POWH & SGH, Guidance Management Committee

AUTHORISATION	
Author (Name)	Adriana Chubaty ¹ Jeffrey Post ²
Position	1 - Senior Pharmacist - Antimicrobial Stewardship 2 - Senior Staff Specialist Infectious Diseases
Department	1 - Pharmacy Department, Prince of Wales Hospital 2 - Department of Infectious Diseases
Department Contact	Adriana Chubaty Adriana.chubaty@health.nsw.gov.au Jeffrey Post Jeffrey.post@health.nsw.gov.au
GOVERNANCE	
Enactment date	15 April 2016
<i>Reviewed (Version 2)</i>	February 2018
<i>Reviewed (Version 3)</i>	July 2019
<i>Reviewed (Version 4)</i>	March 2021
Expiry date:	March 2023
Ratification date by SESLHD QUM Committee	25 March 2021
Chairperson, QUM Committee	Ms Amy Murray
Version Number	4

Colistimethate (Colistin) IV (Polymyxin E) for Urinary Tract Infections



Appendix 1

In Australia, colistin is available as an inactive prodrug, colistimethate sodium (CMS). The dosage units are expressed in colistin base activity (CBA).

Calculated doses are higher than the package insert due to the need to avoid under dosing in the critically ill.

Day 1: Colistin loading dose

4 mg/kg (ideal body weight (IBW)) up to a maximum of 300mg

Day 2: Colistin maintenance dose¹

Commence 12 hours after giving loading dose

Formula for calculating maintenance dose:

$$C_{ss \text{ avg}} \text{ target (mg/L)} \times 10^{(0.0048 \times CrCl + 1.825)}$$

Not on renal replacement:

CrCl (ml/min/1.73m ²) ²	Daily dose required for C _{ss avg} = 2mg/L ⁴ (expressed as CBA)	Recommended Dose
0	130 mg	65 mg 12-hourly
5 to <10	150 mg*	75 mg 12-hourly
10 to <20	160 mg	80 mg 12-hourly
20 to <30	175 mg	87.5 mg 12-hourly
30 to <40	200 mg*	100 mg 12-hourly
40 to <50	220 mg	110 mg 12-hourly
50 to <60	250 mg*	125 mg 12-hourly
60 to <70	275 mg	137.5 mg 12-hourly
70 to <80	300 mg ³	150 mg 12-hourly ³
80 to <90	340 mg ³	170 mg 12-hourly ³
≥90	360 mg ^{1,3}	180 mg 12-hourly ^{1,3}

*Dose varies slightly from CID 2017;64(5):565 and Pharmacotherapy 2019; 39(1): 10-39. Has been rounded for practicality of administration

Receiving intermittent haemodialysis

On non-HD days: 65mg 12-hourly (dose as for CrCl =0)

On dialysis day: add 30-40% to baseline daily dose after a 3 or 4 hour session; dialyse towards end of dosage interval and administer a supplemental dose of 40-50mg with next regular dose, after the dialysis session has ended.

Receiving continuous renal replacement

CRRT – Suggested dose depends on hours on CRRT up to 440mg per day or 220 mg 12-hourly. Seek expert advice (ID or pharmacy) (Refer to Table 2 in CID 2017; 64 (5): 565-71)

- Maximum recommended dose is 360 mg in 24 hours. Higher doses of colistin (>5mg/kg of ideal body weight per day) are associated with increased risk of nephrotoxicity and should be reserved for critically ill patients. Higher doses might be considered by ID Department if there are concerns 180 mg 12-hourly is not adequate to treat an infection. The benefit of using a higher daily dose must outweigh the risk of toxicity.
- Creatinine clearance, is creatinine clearance normalised for BSA (CrCl_n = CrCl x BSA in m²/1.73m²)
- If CrCl is >80ml/min, there is a risk of under dosing (due to increased clearance of CMS before being converted to colistin). Avoid monotherapy (combine with carbapenem, tigecycline or rifampicin).
- This nomogram assumes a target colistin steady state level (C_{ss avg}) of 2mg/L. The likelihood of a decline in kidney function increases with plasma colistin concentrations of more than about 2.5mg/L. If it is not possible to achieve a colistin concentration of about 2mg/L or if the infecting pathogen has an MIC greater than 1mg/L, combination therapy is advised.