Prescribing Protocol – SESLHDPR/608

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	Antibacterial for the treatment of **proven urinary tract infections due to susceptible gram negative bacilli** including *E.coli*, *Klebsiella sp*, *Pseudomonas sp*, *Acinetobacter sp* lacking susceptibility to all of cefepime or ceftazidime, imipenem or meropenem, piperacillin-tazobactam, and ciprofloxacin. **Polymixin B is the preferred polymyxin for infections outside of the urinary tract.** Some gram-negative rods are intrinsically resistant to colistin i.e. *Burkholderia cepacia, Serratia marescens, Moraxella catarrhalis, Proteus spp, Providencia spp,* and *Morganella morganii*.
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	Combination therapy with a carbapenem is no longer recommended for treatment of carbapenem-resistant Enterobactorales, Acinetobacter and P. aeruginosa. Dosing is expressed in many forms: 1 million units colistimethate (CMS) ~ 80mg colistimethate (CMS) ~ 30mg colistin base (CBA) Neurotoxic: facial paresthesias, vertigo, abnormal vision, confusion, ataxia, neuromuscular blockade with respiratory failure. Nephrotoxic: Risk increased by concomitant nephrotoxins, hypotension. Reversible. Higher doses of colisitin (>5mg/kg ideal body weight per day) are associated with increased risk of nephrotoxicity and should be reserved for critically ill patients Each vial contain 0.54 mmol of sodium. In patients with creatinine clearance >80mL/min, it is not possible to reliably achieve an average steady-state plasma colistin concentration of 2mg/L Superinfection: Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhoea Synonym: Polymyxin E
Pregnancy Category	B2

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Proposed Place in Therapy	Proven urinary tract infections due to multi-drug resistant gram negative bacilli, eg. *E.coli*, *Klebsiella sp*, *Pseudomonas sp*, *Acinetobacter sp* where other agents are unsuitable or unavailable
Dosage **Dosage (cont.)**	Colistimethate sodium (CMS) is an inactive pro-drug of colistin base (CBS). It is hydrolysed to colistin base (CBA) in the body. 1 million units colistimethate (CMS) ~ 80mg colistimethate (CMS) ~ 30mg colistin base (CBA) **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. Calculated doses are higher than the package insert dosing; need to avoid under-dosage in the critically ill. **Doses are expressed in terms of mg of colistin base (CBA)** **Severe Systemic Infections:** **Loading dose:** colistin 4 mg/kg (use lower of ideal or actual weight) up to a maximum of 300mg as a single loading dose **Maintenance dose (start 12 hours after loading dose):** see appendix 1 for dose recommendation. 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.
Duration of therapy	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.
Important Drug Interactions	Aminoglycosides: may increase risk of neuromuscular blockade, nephrotoxicity Nephrotoxic drugs (e.g. amphotericin, aminoglycosides, cidofovir, foscarnet): may increase risk of nephrotoxicity. Avoid co-administration Non-depolarizing muscle relaxants (atracurium, vecuronium, pancuronium, tubocurarine): neuromuscular blockade may be enhance with IM or IV use

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Administration Instructions

Reconstitute each vial prior to administration, **do not prepare in advance**.

IV route is preferred over IM.

Reconstitute the 150mg vial with 3 mL water for injection to give a concentration of 50mg/mL. Swirl gently to avoid frothing.

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	50mg/mL	3.4mL
180mg	Add 3mL WFI	50mg/mL	3.6mL
300mg	Add 3mL WFI	50mg/mL	6mL

WFI=Water for injection

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 30 minutes.

Monitoring requirements

Safety

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

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.

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Health
South Eastern Sydney
Local Health District

Basis of Protocol/Guideline: (including sources of evidence, references)	The Sanford Guide to Antimicrobial Therapy Web Edition. Available at: webedition.sanfordguide.com. Accessed February 8, 2023 UptoDate. Available at: https://www.uptodate.com.acs.hcn.com.au/contents/polymyxins-an-overview. Accessed February 15, 2023. Colistimethate Sodium. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: www.micromedexsolutions.com . Accessed February 14, 2023. Lancet Infect Dis 2018; 18:391-495 Clin Infect Dis 2013, 57:349 Epidemiol Infect 2013, 141:1214 Antimicrob Agents Chemother 2018; 62;e01631-18 Tsuji 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. 3rd 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. 6th 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

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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.

Colistin loading dose: 4 mg/kg (use lower of ideal or actual weight) up to a maximum of 300mg

Colistin maintenance dose: Commence 12 hours after giving loading dose

Formula for calculating maintenance dose: $C_{ss\ avg}$ target (mg/L) x $10^{(0.0048 \times CrCl + 1.825)}$

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
<5	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

Once daily dosing not recommended due to potential for toxicity and lack of efficacy data

Receiving intermittent haemodialysis
On non-HD days: 65mg 12-hourly (dose as for CrCl <5)
On dialysis day: add 30-40% (40-50mg) 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 – Add 10% (of 130mg) per hour of CRRT to the baseline daily dose of 130mg. Thus, after 24 hours the suggested daily dose is 440mg or 220mg 12 hourly. Seek expert advice (ID or pharmacy) (Refer to Table 2 in CID 2017; 64 (5): 565-71)

1. 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.
2. Creatinine clearance, is creatinine clearance normalised for BSA ($CrCl_n$ = CrCl x BSA in m^2/1.73m^2)
3. 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).
4. 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.