NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINES

SAPG Guidance on the Intravenous use of Colistimethate sodium (Colistin) in adults

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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SAPG Guidance on the Intravenous use of colistimethate sodium (colistin) in adults

Always seek specialist advice before initiating treatment with colistimethate sodium

This guidance does not cover use for respiratory infections in patients with cystic fibrosis

Note: terminology – colistimethate sodium is often referred to as colistin (the active drug) or abbreviated to CMS

Please be aware that the dosing recommendations in this guideline may not be adequate for the treatment of critically ill patients with lung infections.[1]

1. Introduction

This guidance is for healthcare professionals and should be used along with advice from an infection specialist. This guidance provides helpful advice on how best to start a patient on intravenous colistimethate sodium therapy. Colistimethate sodium (CMS) is rarely used and dosing recommendations can vary. This guidance is based on the International Consensus Guidelines for the Optimal Use of the Polymyxins[1] and the experience of Scottish specialist pharmacists using it in clinical practice.

2. Background

Colistimethate sodium is an inactive prodrug of colistin which is converted in the body to colistin, the active drug. Colistimethate sodium is often used in combination with other antibiotics against carbapenemase producing Enterobacteriaceae bacteria. Colistin exhibits rapid concentration-dependent bactericidal killing and free drug AUC/MIC (area under curve/minimum inhibitory concentration) is the pharmacokinetic/pharmacodynamic index best associated with efficacy.[1]

Colistimethate sodium is associated with nephrotoxicity in 20–50% of patients,[1] but for most patients nephrotoxicity is mild and reversible.[2] Studies have shown that high dose regimens are more effective with limited increase in irreversible nephrotoxicity.[3] Risk factors for nephrotoxicity are shown in box 1. The risk of nephrotoxicity must be balanced against the severity and potential mortality rate of the infection being treated.

Patients with good renal clearance have been shown to require higher dosing.

Box 1: Risk factors for nephrotoxicity [1, 4-7]

The following risk factors are associated with increased nephrotoxicity:

- advanced age
- BMI (Body mass index) >31.5kg/m^2

- chronic co-morbidities eg diabetes, hypoalbuminemia
- other nephrotoxic drugs, and
- longer duration of therapy.

3. Terminology

Colistimethate sodium is an inactive prodrug of colistin which is converted in vivo to active colistin. In the UK colistimethate sodium dosing should always be prescribed using international units (IU).

1 million unit and 2 million unit vials are available.

1 million international units of CMS = 80mg CMS = 33mg of colistin base activity (CBA) [1]

4. Prescribing

There is more than one recognised dosing regimen for colistimethate sodium.[8] The Scottish Antimicrobial Prescribing Group (SAPG) endorses the doses recommended in the International Consensus Guideline[1] (see tables 1 and 2). UK licensed dosing differs; information is available at www.medicines.org.uk. Always discuss dosing with an infection specialist before prescribing and review daily.

Step 1: Calculate creatinine clearance (see renal function calculation for colistimethate sodium guidance)

- the creatinine clearance result is only valid when creatinine is stable
- do not use eGFR (estimated glomerular filtration rate)
- where renal function is changing, consider using 8 or 24 hour urine collections to obtain a more accurate reflection of creatinine clearance

Step 2: Choose the most appropriate dosing regimen (see dosing regimens below)

- prescribe a loading dose
- prescribe a maintenance dose

Step 3: Make a plan for monitoring (see section 6)

- monitor for nephrotoxicity and neurotoxicity

- take the first pre-dose plasma sample for therapeutic drug monitoring at 24 hours (before the second maintenance dose if 12 hourly dosing)

Dosing Regimen: International Consensus Guidelines

Tables 1, 2 and 3 show the recommended International Consensus Guidelines dosing for colistimethate sodium. Compared to UK licensed dosing regimens, the dose increases for patients with good renal clearance and there is an increased number of dosing bands for different stages of renal impairment.[1]

Table 1

International Consensus adult loading dose (normal and impaired renal function including renal replacement therapy) [1,9]

Loading Dose	Notes
9 million international units	• If patient is 60kg or less see calculation of colistimethate sodium loading dose for low weight patients • Loading dose is unaffected by renal impairment

Table 2

International Consensus adult maintenance dose[1]

Creatinine Clearance (mL/min)	Dose and frequency	Starting time after loading dose
≥ 90	5.5 million international units every 12 hours	12 hours
80–89	5.2 million international units every 12 hours	12 hours
70–79	4.5 million international units every 12 hours	12 hours
60–69	4.2 million international units every 12 hours	12 hours
50–59	3.7 million international units every 12 hours	12 hours
40 – 49	3.3 million international units every 12 hours	12 hours
30–39	3 million international units every 12 hours	12 hours
20–29	2.6 million international units every 12 hours	12 hours
10–19	2.4 million international units every 12 hours	12 hours
5 – 9	2.2 million international units every 12 hours	12 hours
0–4	2 million international units every 12 hours	12 hours

Table 3

Renal replacement therapy

Renal replacement therapy	Dosing	Starting time after loading dose
Intermittent haemodialysis (HD)	On non-dialysis days 2 million international units every 12 hours. On dialysis days add an extra 1.2 million international units for every 3 hour dialysis session or 1.6 million international units for every 4 hour dialysis session to the next regular dose following dialysis. Conduct dialysis sessions as late as possible in the CMS dosage interval to minimise the amount of CMS and active colistin lost to the extracorporeal system	12 hours
Sustained low-efficiency dialysis (SLED)	Add 10% of CMS dose to the baseline daily dose for every hour of SLED	
Continuous renal replacement therapy (CVVH/ CVVHDF)	6.6 million international units every 12 hours	12 hours

5. Administration

- Reconstitute each 1 million international units vial with 5mL and each 2 million international units vial with 10mL of water for injection or 0.9% sodium chloride[5] and dilute in 50ml 0.9% sodium chloride for infusion[10]
- Infuse over 30 – 60 minutes via a rate-controlled infusion device[4,5,10]
- Start infusion immediately after preparation to reduce risk of microbial contamination and hydrolysis[4,5]
- Flush before and after administration with 0.9% sodium chloride[10]
- Monitor for pain and irritation at injection site, dizziness and visual disturbance[10]

6. Monitoring

Renal function

- Monitor renal function daily for the first week
- If required adjust dosing according to table 2
- If renal function is stable, reduce monitoring to every 2-3 days after the first week
- For risk factors for nephrotoxicity see box 1
- If the patient develops an acute kidney injury, consider stopping colistimethate sodium if the infection diagnosis is uncertain or an alternative less nephrotoxic agent is available[1]

Nervous system function

- Neurotoxicity is more common with high doses and in the first few days of therapy
- Monitor for signs and symptoms, for example: apnoea, peri-oral and peripheral paraesthesia, vertigo, dizziness, headache, muscle weakness; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances, partial deafness, seizures and ataxia[11,12]
- Some signs and symptoms may not be apparent if the patient is sedated

Therapeutic drug monitoring

- Monitor plasma pre-dose (trough) concentrations, especially in patients with renal impairment
- Contact your local microbiology laboratory to discuss how to arrange samples and the time frame and reporting arrangements for results
- Samples are sent to the Antimicrobial Reference Laboratory (Southmead Hospital, Bristol)
- If a loading dose has been given, the first sample can be taken at 24 hours (immediately before the second maintenance dose if 12 hourly dosing)
- The therapeutic window for colistin is very narrow and therapeutic levels overlap with those that can cause nephrotoxicity
- Pre-dose (trough) level range is 2–4mg/l
- Re-assay after 5-7 days or if the normal range is not achieved at first sample or concerns about toxicity[13]
- Seek specialist advice (from an antimicrobial pharmacist if available) on dose adjustment as the pharmacokinetics are still not well understood

Dosing adjustment should be based on patient's response to treatment, side effects, pre-dose level, renal function and the minimum inhibitory concentration (MIC) of the pathogen(s) (if known).

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