COLISTIMETHATE SODIUM (CMS) PRESCRIBING AND MONITORING GUIDELINE IN ADULTS

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INTRODUCTION

The polymyxin antibiotic Colistimethate Sodium (CMS) is indicated for the treatment of serious infections caused by selected, extensively resistant Gram-negative bacteria (for example; primarily extensively resistant *Pseudomonas*, *Acinetobacter* and *Enterobacterales)* in patients with limited treatment options. It is often used in combination with another antibiotic.

CMS is a non-active pro-drug which is converted to the active drug Colistin following intravenous administration. It is a restricted antibiotic and can only be prescribed **after discussion with Microbiology**.

Please note: Nebulised Colistin is also used in the management of chronic respiratory conditions, which are outside the scope of these guidelines. Consult local treatment guidelines for further information.

PURPOSE OF GUIDELINE

This guideline forms part of the All Wales Antimicrobial Pharmacists Group quality improvement strategy for antimicrobial stewardship and patient safety, providing a framework for staff to follow to optimise antibiotic use and help reduce inappropriate prescribing.

SCOPE

This guideline is for all clinical, pharmacy and nursing staff involved in the prescribing and administration of intravenous CMS to adult patients requiring treatment with Colistin.

IV CMS can be used for Carbapenem Resistant Organisms (CROs) / Carbapenemase Producing Enterobacteriaceae (CPE) infections rather than colonisation, but is not the treatment of choice for CRO/CPE in Wales. Treatment of patients with an infection caused by CRO/CPE should be undertaken under the advice of a medical Microbiologist.

TREATMENT PRINCIPLES AND RECOMMENDATIONS

The statements below are based on best practice for management of infection and national guidance;

- If CMS is indicated start treatment promptly.
- Treatment should be guided by susceptibility results. These may vary between strains, including samples obtained from a single patient during a single infection.
- Only treat if patient has symptoms of infection *(Patients may be colonised with CRO/CPE - usually identified by a rectal swab or stool sample but patients may also be colonised at other sites)*
- Review treatment daily to confirm effectiveness and check for adverse effects.

- For advice on isolation and screening please refer to your local screening policy or the PHE '*Framework of actions to contain carbapenemase-producing Enterobacterales*' Available at: https://www.gov.uk/government/publications/actions-to-contain-carbapenemase-producing-enterobacterales-cpe

PRESENTATION OF MEDICINE

Colistimethate Sodium (CMS) is available as a 1 Million Unit (MU) vial suitable for injection.

Some literature refers to Colistimethate Sodium (CMS) in milligrams (mg) or Colistin base activity (CBA). **Confusion and medication errors have occurred** because of the different expressions of dose in terms of potency. The conversion is below;

TABLE 1: CONVERSION OF COLISTIMETHATE SODIUM (CMS)

		Potency	**≈ mass of CMS (mg)***
IU	**MU**	**≈ mg CBA**	
12,500	0.0125	0.4	1
150,000	0.15	5	12
1,000,000	1	34	80
4,500,000	4.5	150	360
9,000,000	9	300	720
	* Nominal potency of the drug substance = 12,500 IU/mg		

Doses should always be prescribed in Million Units (MU)

TREATMENT GUIDELINE

The dose to be administered and the treatment duration should take into account the severity of the infection as well as the clinical response.

Consideration should be given to co-administration with another antibacterial agent whenever this is possible.

CALCULATING THE INITIAL LOADING DOSE

The initial loading dose is based on the patient's **actual** body weight. In obese patients (BMI ≥ 30kg/m^2) dosing should be based on **Ideal** Body Weight as use of **actual** body weight is associated with increased incidence of nephrotoxicity.

Weight	Loading Dose	Notes
>40kg	9 Million Units (MU) *(**Please note**;- In critically ill patients a loading dose of 9-12 Million Units (MU) should be given)*	The loading dose applies to patients with normal and impaired renal function including those on renal replacement therapy. Modelling suggests that loading and maintenance doses of up to 12 MU may be required in patients with good renal function. Clinical experience with such doses is however extremely limited and safety has not yet been established.

CALCULATING THE MAINTENANCE DOSES

Maintenance doses of Colistimethate Sodium (CMS) should be adjusted according to the creatinine clearance (CrCl) using the Cockcroft and Gault equation:

Estimated CrCl (mL/min):

Male: 1.23 x (140-age (years)) x Weight (kg) / Serum creatinine

Female: 1.04 x (140-age (years)) x Weight (kg) / Serum creatinine

TABLE 2: ADULT MAINTENACE DOSING OF COLISTIMETHATE SODIUM (CMS)

CrCl (mL/min)	Dose and Frequency of Maintenance Dose	Time interval between loading dose and first maintenance dose
>50	4.5 Million Units (MU) 12 hourly	12 hours
30-50	2.75 - 3.75 Million Units (MU) 12 hourly	24 hours
10-30	2.25 – 2.75 Million Units (MU) 12 hourly	24 hours
<10	1.75 Million Units (MU) 12 hourly	24 hours
Patients undergoing continuous venovenous haemodiafiltration (CVVHDF)	3 Million Units (MU) 8 hourly	8 hours

Please note:

- Maintenance doses up to 6 MU 12 hourly may be considered in critically ill patients depending on response. **Please discuss with a medical Microbiologist** as clinical experience with such doses is limited and safety has not yet been established.

ADMINISTRATION

1. Reconstitute each 1 MU vial with 10mL of 0.9% sodium chloride or Water for injection and dilute in 100ml 0.9% sodium chloride for infusion.
2. Infuse over 30 - 60 minutes via a rate-controlled infusion device. Start infusion immediately after preparation to reduce risk of microbial contamination and hydrolysis.
3. Flush before and after administration with 0.9% sodium chloride.

For further advice please refer to the Injectable Medicines Guide (IMG), available for guidance on administration and rate of infusion: http://medusa.wales.nhs.uk/

THERAPEUTIC DRUG MONITORING

Plasma concentration monitoring is advised for all patients prescribed Colistimethate Sodium (CMS). Renal function should be monitored at the start of treatment and regularly throughout treatment in all patients.

Concomitant use of intravenous CMS with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.

A trough (pre-dose) level should be taken prior to the 2nd **maintenance dose** and sent to Microbiology. **Please ensure pre-dose levels are clearly marked with time last dose was given and time that level was taken**.

CMS assays are performed at a laboratory in Bristol and **will not** be reported on the same day.

Do not withhold doses whilst waiting for the results.

Target Range: 2-4mg/L (Suggested re-assay interval: 5-7 days)

CAUTIONS AND CONTRAINDICATIONS

CMS is contra-indicated in patients with hypersensitivity to the active substance or other polymyxins. In case of an allergic reaction, treatment with CMS must be discontinued and appropriate measures implemented.

CMS is known to reduce the presynaptic release of acetyl-choline at the neuro-muscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed.

CMS should be used with extreme caution in patients with acute porphyria.

Safety of CMS during pregnancy has not been established and breastfeeding is **not** recommended during treatment.

DRUG INTERACTIONS

Concomitant use of intravenous CMS with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with caution.

Please be aware of the potential for drug-drug interactions when CMS is co-administered with drugs known to inhibit or induce drug metabolising enzymes or drugs known to be substrates for renal carrier mechanisms.

- Due to the effects of Colistin on the release of acetylcholine, non-depolarising muscle relaxants should be used with caution in patients receiving CMS as their effects could be prolonged.
- Co-treatment with CMS and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as ciprofloxacin should be undertaken with caution in patients with myasthenia gravis.
- Concomitant use of CMS with other medicinal products of neurotoxic and/or nephrotoxic potential should be avoided. These include the aminoglycoside antibiotics such as gentamicin, amikacin, and tobramycin.
- There may be an increased risk of nephrotoxicity if CMS is given concomitantly with cephalosporin antibiotics.

For a further list of potential drug interactions please refer to the latest version of the British National Formulary.

ADVERSE EFFECTS

The likelihood of adverse events may be related to the age, renal function and condition of the patient.

High serum concentrations of CMS, which may be associated with over-dosage or failure to reduce the dosage in patients with renal impairment, have been reported to cause neurotoxic effects such as facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea.

Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose.

Hypersensitivity reactions including skin rash and drug fever have been reported. If these occur treatment should be promptly withdrawn.

Local irritation at the site of injection may occur.

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ABBREVIATIONS

CMS	Colistimethate Sodium
CPE	Carbapenemase-producing Enterobacterales
CRO	Carbapenem-resistant Organisms
CBA	Colistin base activity
MU	Million Units
mg	Milligrams
BMI	Body Mass Index
CrCl	Creatinine Clearance
IMG	Injectable Medicines Guide
IBW	Ideal Body Weight
SPC	Summary of Product Characteristics