Introduction

According to the World Health Organisation (WHO), antimicrobial resistance is threatening the effective prevention and treatment of a variety of infections that are on the increase.\(^1\) Antimicrobial resistance is a global threat with new mechanisms of resistance that are emerging rapidly. In addition, nosocomial infections are typically caused by bacteria that are either highly-resistant (such as methicillin-resistant *Staphylococcus aureus*; MRSA), or by multi-drug-resistant gram-negative bacteria (such as *Acinetobacter baumannii*). Carbapenem-resistance (in organisms such as *Klebsiella pneumoniae* and *Enterobacter* spp.) is emerging in South Africa and high resistance levels are currently seen in *Pseudomonas aeruginosa* and *A. baumannii*. From 2007 to 2011 there has been a decline in susceptibility to the carbapenems from 35% to 17% for *A. baumannii*.\(^2\) The inappropriate use of antibiotics in intensive care units (ICUs) is common and contributes to the poor outcomes.

Since the approval of tigecycline by the United States Food and Drug Administration (FDA), there has not been any new marketing authorisation for any novel antimicrobial agents against gram-negative infections. Many of the multi-drug resistant (MDR) gram-negative bacteria are, therefore, only sensitive to colistin.

Colistin is an old antibiotic, discovered in the late 1940s and introduced in 1959, produced by *Bacillus polymyxa* var. *colistinus*. However, after concerns were raised about reports of nephrotoxicity, the drug was withdrawn from the market in the 1970s.\(^3\) Currently there is insufficient pharmacokinetic and pharmacodynamic data on colistin, which makes it difficult to use safely and effectively in critical care patients.\(^2\) Currently, colistin often provides the only viable antimicrobial treatment option to manage these infections. It should be a general lack of agreement with regard to the rational use and dosing of colistin on a worldwide scale, and in South Africa there are no officially recognised or endorsed guidelines to follow.

Disagreement exists about the correct dosing and interpretation of the various dosing units since the dosing units of colistin are not standardised amongst manufacturers. Colymycine\(^6\), containing colistimethate sodium (CMS), is used in South Africa, and is available in vials that are measured in international units. Colymycine\(^6\) (colistin/CMS) is not registered in South Africa, but is obtainable via the Medicines and Related Substances Act, through the Section 21 application process to the Medicines Control Council (MCC). This guideline will provide South African healthcare providers with a standard approach to using colistin as colistimethate sodium (CMS), referred to as colistin (CMS), rationally and effectively, and to clear confusion and questions about this medicine (Appendix 1). Therefore, the aim of the document is to provide clear guidance and a standardised approach to the properties, dosing, reconstitution and administration of colistin (CMS), for use in both adult and paediatric patients.

Overview of colistin

**Properties and mechanism of action**

Colistin (CMS) is a fermentation product consisting of both polymyxin E\(_1\) and E\(_2\), and is both a cyclic polypeptide and cation at physiological pH.\(^7\) CMS is the inactive prodrug which is hydrolysed to colistin, which acts as a cationic detergent and damages the bacterial cytoplasmic membrane causing leakage of intracellular substances and cell death.\(^8\) Colistin displays a high binding affinity for lipopolysaccharides (LPS) molecules. The electrostatic interaction between these molecules causes a competitive displacement of the divalent cations (Ca\(^{2+}\) and Mg\(^{2+}\)) from phosphate groups, causing a disruption of the membrane. The end result is an increase in the permeability of the bacterial cell, leakage of the cell contents and subsequent cell death.

**Antibacterial activity**

Colistin (CMS) is mainly used for its activity against MDR gram-negative strains of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Stenotrophomonas*


pathogens with a susceptibility breakpoint of 2 μg/ml, and can result in the emergence of resistant strains.12

Synergistic effects were seen when colistin (CMS) was used in combination with the carbapenems in 77% of A. baumannii strains.13 An increase in the bactericidal effect was seen with colistin-carbapenem combination therapy.14 Combination antimicrobial therapy is used for maximum antimicrobial activity and to decrease the chances of resistance.1

**Loading dosage**
During life-threatening infections, it is important to achieve therapeutic concentrations of colistin (CMS) rapidly. Patients who are critically ill have capillary leakage, which increases their volume of distribution 4-15 fold.2 According to Landersdorfer & Nation (2015) CMS is converted to colistin slowly.3 This fact, combined with the long half-life of formed colistin, may result in a time interval of 2-3 days to reach an adequate therapeutic plasma concentration, in the absence of a loading dosage. Therefore, it is very important to initiate colistin (CMS) therapy with a loading dosage of 12 MU – regardless of kidney function – to reach therapeutic concentrations quicker. The high loading dosage does not affect the renal function; only the subsequent maintenance dosages would need to be adjusted.

**Adult dosing guideline**
The recommended dosage is based on the patient’s actual body weight (ABW). However, if a patient weighs >20% their ideal body weight (IBW), the adjusted body weight (AdjBW) should be used. If ABW < IBW, use ABW.

Adjusted body weight, which falls between lean body weight and total body weight, is calculated as follows:

**Adjusted body weight = LBW + 0.4(TBW – LBW)**

To calculate Lean Body Weight (LBW) for a MALE:

LBW (kg) = 50 + (0.906 x (height in cm – 152.4))

To calculate Lean Body Weight (LBW) for a FEMALE:

LBW (kg) = 45 + (0.906 x (height in cm – 152.4))

Table 1 provides the adult dosing guideline regarding treatment for MDR gram-negative infections.

Table 2 provides terminology and information regarding the vials of colistin (CMS) used in South Africa.

**Paediatric dosing guideline**
Table 3 illustrates the recommended dosages for paediatrics in susceptible gram-negative infections.

**Reconstitution and administration guideline**
Colymycine® (Colistin/CMS) contains 1 MU per vial. Each vial should be reconstituted with 5 ml of 0.9% sodium chloride. Further dilute to a final volume of 50 ml for maintenance dosages and 100 ml for the loading dosage.

The loading dosage of 12 MU should be given over 60 minutes.

The maintenance dosages may be given over 15-30 minutes.

Table 4 provides an outline of the reconstitution volume, diluent and infusion time to be used.

**Reconstitution of colistin (CMS) for use in Neonates**
For an 80mg (1 MU) vial, reconstitute with 5 ml 0.9% sodium chloride (normal saline) to yield a concentration of 100 000 IU/ml. The dosage should be infused over 30 minutes.

**Reconstitution of colistin (CMS) for use in Paediatrics**
For an 80mg (1 MU) vial, reconstitute with 2 ml sterile water for injection to yield a concentration of 500 000 IU/ml. This should either be further diluted to 10 ml with normal saline (100 000 IU/ml) and infused over 10 minutes, or be further diluted to 50 ml with normal saline (20 000 IU/ml) and infused over 30 minutes.

**Renal failure and renal replacement therapy**
When the patient is in renal failure, dosage adjustments need to be made. During renal failure there is a decreased rate of CMS elimination and, in turn, more CMS is converted to colistin. This results in the impairment of colistin clearance. The CMS plasma concentration is subsequently much higher than the concentration of the formed colistin. During dialysis a large

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**Table 1:** Recommended adult dosages of IV colistin (CMS) in critically-ill patients

<table>
<thead>
<tr>
<th>Normal renal function:</th>
<th>Loading dose: 12 million units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 million units every 8 hours</td>
</tr>
<tr>
<td></td>
<td>Then: 4.5 million units every 12 hours</td>
</tr>
</tbody>
</table>

**Renal impairment:**
- *CrCl* 40-60 ml/min
- *CrCl* 10-40 ml/min
- *CrCl* <10 ml/min

**Renal replacement therapy:**
- Haemodialysis
  As per *CrCl*, with an additional 2 million units after dialysis
- CVVHD**
  Dosing as for normal renal function

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*Creatinine clearance (*CrCL*) based on Cockcroft-Gault equation;
**Continuous veno-venous hemodialysis

**Table 2:** Colistin (CMS) dosages and dosing interval terminology

1 Vial = 1 MU = 80mg CMS = 30mg colistin base
The dosing of aerosolised colistin

amount of the CMS is removed before the conversion to colistin can take place. Colistin is also subjected to extensive carrier-mediated tubular reabsorption in the kidneys, but dialysis does not carry this function and it passively diffuses into the dialysate. These factors imply that careful dosage selection should be done for these patients. Refer to Table 1 for the recommended dosages in renal failure patients.

**Inhaled colistin**

The administration of antibiotics via inhalation is widely used for patients with cystic fibrosis and bronchiectasis. Colistin (CMS) is the preferred drug of choice for aerosolised administration. Although there is lack of data on the efficacy and safety of inhaled colistin from randomised controlled trials, colistin (CMS) may be used as adjunctive therapy to intravenous antimicrobial treatment in critically-ill patients with ventilator-associated pneumonia (VAP) caused by MDR gram-negative bacteria, which are susceptible to colistin (CMS). Table 5 provides an overview of the dosing guidelines of aerosolised colistin.

**Reconstitution and administration**

Add the required amount of colistin (CMS) to 4 ml of 0.9% sodium chloride (normal saline) or sterile water. The solution should be nebulised at an oxygen flow rate of 8 l/min via a face mask.

**Side-effects of inhaled colistin**

The side-effects include bronchoconstriction (due to histamine release), coughing and a feeling of tightness in the chest and apnoea (due to neuromuscular blockade). To prevent bronchoconstriction and cough, treat the patient with a β2-agonist before colistin inhalation. Inhaled colistin is generally well tolerated, as demonstrated by the fact that there are only minimal changes in the FEV1 before and after the inhalation. There is minimal renal and/or neurotoxicity with this route of administration. Good infection control measures are recommended to prevent the spread of MDR bacteria through nebulisation devices.

**Table 3: Recommended paediatric dosages for colistin (CMS)**

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Dosing recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 kg</td>
<td>500 000 IU 12-hourly</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>1 000 000 IU 12-hourly</td>
</tr>
<tr>
<td>Recurrent/severe pulmonary infections</td>
<td>2 000 000 IU 8-hourly</td>
</tr>
</tbody>
</table>

**Table 4: Colistin (CMS) reconstitution outline information**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Final volume</th>
<th>Diluent</th>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 MU loading dose</td>
<td>100 ml</td>
<td>0.9% sodium chloride (normal saline)</td>
<td>60 minutes</td>
</tr>
<tr>
<td>3 MU 8 hourly</td>
<td>50-100 ml</td>
<td>0.9% sodium chloride (normal saline)</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td>4.5 MU 12 hourly</td>
<td>50-100 ml</td>
<td>0.9% sodium chloride (normal saline)</td>
<td>15-30 minutes</td>
</tr>
</tbody>
</table>

**Table 5: The dosing of aerosolised colistin**

<table>
<thead>
<tr>
<th>Dosage Final volume</th>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 kg</td>
<td>500 000 IU 12-hourly</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>1 000 000 IU 12-hourly</td>
</tr>
</tbody>
</table>

**References**


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APPENDIX 1

COLISTIN USE/DOSAGE CHECKLIST

Approved Indications:

Patients with a history of, suspected, or confirmed multi-drug-resistant gram-negative organism: Please check appropriate organism ☑

<table>
<thead>
<tr>
<th>Organism</th>
<th>☑</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td></td>
</tr>
<tr>
<td>Carbapenem-resistant enterobacteriaceae</td>
<td></td>
</tr>
</tbody>
</table>

Colistin dosing:

**Dosing in normal patients**

<table>
<thead>
<tr>
<th>Dosing mode</th>
<th>Dosing details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose 12 MU</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose 3 MU tds (8-hourly) or 4.5 MU bd (12-hourly)</td>
<td></td>
</tr>
</tbody>
</table>

**Renal impairment:**

<table>
<thead>
<tr>
<th>CrCl* 40-60 ml/min</th>
<th>2 million units, 12-hourly</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl* 10-40 ml/min</td>
<td>2 million units, 24-hourly</td>
</tr>
<tr>
<td>CrCl* &lt;10 ml/min</td>
<td>1.5 million units, 36-hourly</td>
</tr>
</tbody>
</table>

**Renal replacement therapy:**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Dosing instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodialysis</td>
<td>As per CrCl*, with an additional 2 million units after dialysis</td>
</tr>
<tr>
<td>CVVHD**</td>
<td>Dosing as for normal renal function</td>
</tr>
</tbody>
</table>

**Colistin dosing instructions:**

- Reconstitute each vial with 5 ml 0.9% sodium chloride, further dilute to 100 ml for loading dosage and 50 ml for maintenance dosage.
- Infusion loading dose over 60 minutes.
- Infuse maintenance dose over 15-30 minutes.
- Must be given with a second agent (either rifampicin or a carbapenem) – never on its own.

**Additional comments:**

- Very nephrotoxic.
- Need blood results to apply for a Section 21 approval – Very important!!
- Store below 25 degrees Celsius (°C).
- Cannot be stored once mixed – therefore discard any unused portion.