Optimising the Dosing of Antibiotics: Colistin and vancomycin updates

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ABSTRACT
Multidrug resistant gram-negative nosocomial infection in intensive care units has resulted in an increased use of antibiotics like Colistin and Tigeicycline that the end user may have little experience with. Mechanism of drug resistance, when understood, leads to the correct choice and combination of antibiotics. Understanding the pharmacokinetics of Colistin and proper dosing with a correct loading dose is vital to treatment success. Issues regarding renal toxicity may be important factors in critically ill children and much of the dosing is extrapolated form adult studies.

Key words: Colistin. Multidrug resistance. Gram negative bacteria.

Part 1: Colistin update
The intravenous use of polymyxins has been considered to be associated with considerable nephrotoxicity and neurotoxicity. For this reason, the systemic administration of polymyxins had been abandoned for about 20 years in most areas of the world. However, the problem of infections due to multidrug-resistant (MDR) Gram-negative bacteria such as Pseudomonas aeruginosa and Acinetobacter baumannii has led to a resurgence in the use of polymyxins.

Multidrug resistant (MDR) gram-negative nosocomial infection in intensive care units is a global health problem1-2 (Table 1). Dissemination of enterobacteriaceae producing carbapenemases such as Klebsiella pneumonia carbenemase (KPC), New Delhi Metallo-β lactamase (NDM1), Verona Integron-encoded Metallo beta-lactamases (VIMs) and active on Imipenem Metallo beta lactamases (IMPs) occurs rapidly via plasmids. The other mechanisms of antibiotic resistance in these organisms are porin mutations leading to altered outer membrane permeability, efflux pumps, restricted access of drug to target and enzymatic modification or elimination of the cellular target (Figure 1)3. Carbenem Resistant Enterobacteriaceae (CRE) are usually also resistant to fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole. KPC infections which were originally reported with Klebsiella pneumonia, have been reported in Escherichia, Acinetobacter and pseudomonas species, with an estimated mortality of 27-44%4. Polymyxins are increasingly being used to treat CRE.

Table 1. Acquired resistance category definitions. (Intrinsic resistance to any specific antimicrobial agent would automatically eliminate that agent from being included in defining resistance.)

| Multi Drug Resistant (MDR) | Resistant to more than 1 agent in 3 or more antimicrobial categories |
| Extremly Drug Resistant (XDR) | Resistant to more than 1 agent in all but 2 categories |
| Pan Drug Resistant (PDR) | Resistant to all categories |

Figure 1: a) Impermeable barriers. Some bacteria are intrinsically
resistant to certain antibiotics (blue squares) simply because they have an impermeable membrane or lack the target of the antibiotic. b | Multidrug resistance efflux pumps. These pumps secrete antibiotics from the cell. Some transporters, such as those of the resistance–nodulation–cell division family (pink), can pump antibiotics directly outside the cell, whereas others, such as those of the major facilitator superfamily (red), secrete them into the periplasm. c | Resistance mutations. These mutations modify the target protein, for example by disabling the antibiotic-binding site but leaving the cellular functionality of the protein intact. Specific examples include mutations in the gyrase (green), which cause resistance to fluoroquinolones, in RNA polymerase subunit B (orange), which cause resistance to rifampicin, and in the 30S ribosomal subunit protein S12 (encoded by rpsL) (yellow), which cause resistance to streptomycin. d | Inactivation of the antibiotic. Inactivation can occur by covalent modification of the antibiotic, such as that catalysed by acetyltransferases (purple) acting on aminoglycoside antibiotics, or by degradation of the antibiotic, such as that catalysed by β-lactamases (brown) acting on β-lactam antibiotics. Ac, acetyl group.

Colistin (polymyxin E) and Polymyxin B are cationic polypeptide antibiotics which act by binding to lipopolysaccharide on the outer membrane, leading to altered membrane permeability and cell death. Colistin is active against most gram negative bacteria except for serratia, proteus and proveidencia species which have intrinsic resistance. The breakpoints for colistin susceptibility are defined differently by two main societies: as per US Clinical and Laboratory Standards Institution (CLSI), ≤2 mg/L as the susceptibility breakpoint and >2 mg/L as the resistance breakpoint, while as per British Society for Antimicrobial Chemotherapy (BSAC), ≤4 mg/L as susceptible and ≥8 mg/L as resistant. Colistin is administered as its prodrug, colistin methanesulfonate (CMS), which then undergoes hydrolysis to form a mixture of partially sulphonmethylated as well as active colistin. The half-life of CMS is 2.2 hours, and that of colistin is approximately 14-18.5 hours. Colistin exhibits rapid, concentration-dependent bacterial killing with negligible post-antibiotic effects. Recent studies have shown that use of a loading dose helps achieving desired therapeutic levels rapidly and prolongs the MICs of many organisms that require Colistin therapy. The maximum predicted concentration at steady state was 2.3 mg/liter and achieved after 2-3 days of therapy, Garonzik et al. conducted an open label population pharmacokinetic study on 105 patients of whom 16 were on renal replacement therapy. They then derived loading and maintenance dosing suggestions. (see Table 2). However, a recent study by Grégoire et al on 73 patients found a typical maximum concentration of drug in serum (Cmax) close to 2mg/l 3 hours after a dose of 2 MU CMS, with a colistin half life of 3.1 hours.11.

### Table 2: Suggested loading and maintenance doses of Colistin (Modified from Ref. 7)

<table>
<thead>
<tr>
<th>IV loading dose (as Colistin Base Activity)</th>
<th>T (Target needed) X 2 X Ideal Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Dose</td>
<td>Daily dose of CBA (mg)= T X (1.5 X Cr Cl (ml/min/1.73m2) X 30).</td>
</tr>
<tr>
<td>Recommended pediatric maintenance dose (As colistin base)</td>
<td>3-5 mg/kg/day as BD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>T (Target needed) X 2 X Ideal Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading can be calculated from Ref. 7</td>
<td></td>
</tr>
</tbody>
</table>

Combination therapy: In vitro studies have shown that monotherapy with Colistin may lead to bacterial regrowth and resistance while combination therapy increases antimicrobial activity reduces development of resistance. A retrospective cohort study from 5 ICUs in Italy15 looked at treatment and outcome in patients with infections with KPC-producing bacteria. It was found that combination therapy with at least two drugs displaying in vitro activity against the isolate was associated with lower mortality (OR, 0.52; 95% CI, 0.35-0.77), especially in patients with BSI, lung infections or high APACHE III scores and/or septic shock at infection onset. Analyses of retrospective
studies have shown similar results\cite{16,17,18}. Various drugs such as Tigecycline, Rifampicin, Azithromycin and Dorapenem have been used in combination therapy. Carbapenem resistant KPC infections can still be used in combination therapy with the following caveats: MIC of the carbapenem should be \( <4 \text{mg/l} \), and the drug should be infused over a prolonged period at the maximum possible dose\cite{18}. The mechanisms of positive interaction between these agents are not known, with few exceptions. The combined action of polymyxins and imipenem appears to exist primarily against bacterial strains in which a permeability barrier, created by the loss of an effective outer membrane porin channel, is responsible for relatively low-level imipenem resistance. That polymyxin increases bacterial membrane permeability appears to explain its enhancement of imipenem’s activity. The effect of sulbactam alone or in combination with other agents appears to be due to its attachment to penicillin-binding proteins, specifically in A. baumannii. The enhancing action of rifampin and macrolides against multidrug-resistant gram-negative pathogens remains relatively unknown\cite{19}.

Pediatric data is limited to predominantly retrospective studies and shows that Colistin has a role in treating life threatening MDR infection with nephrotoxicity of 2.8%\cite{20,21,22}. Colistin is poorly distributed to the bones, cerebrospinal fluid, lung parenchyma, and pleural cavity\cite{23}. In a study by Imberti et al, Colistin was undetectable in bronchoalveolar lavage fluid 2 hours after IV Colistin methanesulphate administration. Two recent meta-analyses found significant improvement in clinical response when aerosolized Colistin was added to IV Colistin\cite{24,25}. However, there was no difference in mortality. Valachis et al.\cite{26} included 8 studies (690 patients) and found a statistically significant improvement in clinical response as well as microbiological eradication, when AS colistin was added to the standard antimicrobial therapy in comparison with patients who received IV colistin (OR, 1.57; 95% CI, 1.14–2.15; \( p = 0.006 \) and OR, 1.61; 95% CI, 1.11–2.35; \( p = 0.01 \), respectively). Resistance to Polymyxins is currently around 10% worldwide with higher rates being reported from South East Asia and the Mediterranean\cite{27}. The first International Conference on Polymyxins at Prato identified the following issues\cite{28}.

1. Uniformity in expression of the amount of drug in a parenteral vial by different manufacturers should be expressed as mg of colistin base activity (CBA) or number of International Unit (IU).
2. Uncertainties regarding susceptibility testing and breakpoints (currently under review jointly by the Clinical and Laboratory Standards Institute, CLSI and the European Committee on Antimicrobial Susceptibility Testing, EUCAST).
3. Need of therapeutic drug monitoring in routine clinical practice
4. Suggested research areas are prospective studies using therapeutic drug monitoring, pharmacokinetic studies in special patient populations, randomized controlled trials on combination versus monotherapy, nebulized Colistin, polymyxin B versus Colistin.

**Aerosolised (AS) Colistin**

As only Colistin sensitive (COS) and XDR GNB become more common organisms for Ventilator associated events, the addition of AS colistin to the IV regimen may be a value addition. In an RCT\cite{29} of IV vs IV + AS dosing, a dosage regimen of IV-Colistin at 1,000,00 iu/kg/day in 2-3 divided doses plus AS Colistin in the treatment group 1 million units 8 hrly. Clinical cure rates were significantly higher (69.2% vs 54.8%) in the IV+AS group. (\( p \) value 0.03) The median duration of post VAP ventilation was shorter in the IV+AS group (8 vs 12 days \( p \) value = 0.001). AKI onset during colistin therapy was associated with treatment failure. This could be an add on in the treatment of XDR VAP.

**Toxicity**

In 19 cases in a Greek study, over 4 weeks of Colistin treatment, the median creatinine value increased by 0.25 mg/dl during the treatment compared to the baseline (\( p < 0.001 \)) but returned close to the baseline at the end of treatment (higher by 0.1 mg/dl, \( p = 0.67 \)). No evidence of neuromuscular blockade was seen in any of these patients\cite{30}. In a study by Basso in Texas Children’s Hospital in 21 courses of colistin therapy in children with cystic fibrosis, with MDR Pseudomonas infection, there was one case of renal
toxicity with 6 cases of neurotoxicity31. Neurotoxicity was characterized by perioral paraesthesia with or without ataxia. All toxicities were reversed. Recent experience from all studies continue to show that the fear of renal failure appears to be largely exaggerated and the drug can be safely used in the higher dosages needed for MDR strains with good monitoring. In critically ill patients with nosocomial infection, local epidemiology should be taken into account while starting empirical antibiotic therapy. In an ICU setting where MDR organisms may rule, the clinician often has no choice but to start a carbapenem on suspicion of a serious Gram negative infection. Once culture results are available, specific therapy can be started: Carabepenem for Carbapenem sensitive MDR organism and combination therapy for Carbapenem resistant MDR organism. However, as is often the case, empirical therapy may be needed if the child deteriorates especially in the setting of a febrile neutropenic immunocompromised child with invasive lines.

**Caveats on Colistin**

1. Use a loading dose
2. Slow infusions may help sustain levels
3. Use combination therapy always
4. Use Polymixin when there is a poor response to the colistin methanesulfonate salt

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Part 2: Vancomycin: “Mississippi Mud” - An update

A 6 year old boy is admitted with septic shock and pyomyositis of the right thigh. He undergoes incision and drainage of the thigh abscess and drainage of septic arthritis of the left knee. Blood and pus culture grow Methicillin Resistant *Staphylococcus aureus* (MRSA) with Minimum Inhibitory Concentration (MIC) =1. Five days later, he continues to be febrile and bacteremic Antibiotic coverage from admission includes Vancomycin, and Clindamycin. (Sensitive with D test negative) Multiple trough vancomycin levels remain <10 despite increasing Vancomycin doses to 70 mg/kg/day. The question arises- what is the optimum dosing and monitoring of Vancomycin. Vancomycin was isolated from Streptomyces orientalis in 1952. Its impure form also known as “Mississippi Mud” due to its brown colour was responsible for increased adverse effects and nephrotoxicity. Better purification methods have lowered the incidence of nephrotoxicity. Vancomycin use has increased with the emergence of MRSA. Early recommendations were to aim for trough vancomycin levels of 5-10 mg/L and peak levels of 30-40 mg/L.

Table 1. Trough levels and Vancomycin dosing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients (samples)</th>
<th>Age</th>
<th>Dose</th>
<th>Target trough (μg/ml)</th>
<th>% achieving target trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim, 2010</td>
<td>309 1-16 yrs</td>
<td></td>
<td>40 mg/kg/day</td>
<td>&gt;10</td>
<td>14% 49%</td>
</tr>
<tr>
<td>Broome, 2011</td>
<td>25 1 mth - 18 yrs</td>
<td></td>
<td>45 mg/kg/day</td>
<td>10-15, 15-20</td>
<td>0 0</td>
</tr>
<tr>
<td>Frymover, 2011</td>
<td>182 1mth - 12 yrs</td>
<td></td>
<td>45 mg/kg/day</td>
<td>15-20</td>
<td>7% 14%</td>
</tr>
<tr>
<td>Eiland, 2011</td>
<td>295 (435) 1 mth - 18 yrs</td>
<td></td>
<td>40-60 mg/kg/day</td>
<td>5-15 10-20</td>
<td>78% 49%</td>
</tr>
<tr>
<td>Geer, 2014</td>
<td>159 2 mths - 17 years</td>
<td></td>
<td>60 mg/kg/day</td>
<td>15-20</td>
<td>6.9%</td>
</tr>
<tr>
<td>Durham, 2015</td>
<td>75 1 mth - 18 yrs</td>
<td></td>
<td>15 mg/kg 6 hourly</td>
<td>15-20</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

For effective treatment with vancomycin, a serum concentration well above the minimum inhibitory concentration of the bacteria being treated is required. Recent studies have shown that exposure to trough concentrations <10 mg/l can produce strains with Vancomycin intermediate Sensitivity *Staphylococcus aureus* like characteristics. Current guidelines recommend maintenance of trough levels greater than 10 mg/l to avoid development of resistance. For complicated infections such as bacteremia, endocarditis, osteomyelitis and meningitis due to MRSA, a trough level of 15-20 mg/l is recommended.

Recent pediatric studies have shown that current pediatric dosing recommendations do not achieve the target levels, needing multiple dosage adjustments (Table 1).

This has been our observation as well (Unpublished data, Figure 1). Of 42 children studied, only 5% of children receiving 45 mg/kg/day of vancomycin achieved levels between 15 to 20 μg/ml, and 24% of children receiving 60 ml/kg/day achieved target levels. Eiland et al suggested a higher dose of 85 mg/kg/day, when the target trough is 15 mg/L. Other authors have suggested higher doses in children aged 2 to 12 years.

There are concerns about toxicity with vancomycin with currently recommended trough levels. Van Hal et al performed a meta analysis of 15 studies to determine the nephrotoxicity associated with maintaining higher troughs (>15 mg/l)12. 14 studies involved adults and one study involved children. Maintaining trough concentrations greater than 15 mg/L was associated with increased risk of a nephrotoxic event (OR 2.74; 95% CI 1.94–3.88, p
b 0.01) compared to trough concentrations less than 15 mg/L\(^2\). The probability of a nephrotoxic event was also found to increase as a function of treatment duration, with most episodes occurring after seven days of therapy.

There is a lack of data to support a clear relationship between specific serum concentrations and patient outcome. To date, 7 studies have looked at the relationship between trough Vancomycin levels and clinical outcome; 6 studies found no correlation between trough levels and clinical outcome\(^14\). Only one study found that trough <15 mg/l and > 20 mg/l was associated with Vancomycin failure\(^15\).

Recent Literature suggests that 24-hour Area Under the Concentration-time Curve (AUC) of Vancomycin correlates better with drug efficacy and toxicity compared to trough values. AUC reflects the cumulative exposure for a defined time period while the trough is a single point exposure measurement at the end of the dosing interval. Data from animal models, in vitro studies, and limited human studies suggests that microbiologic success is optimized when the vancomycin AUC/MIC BMD (Minimum Inhibitory Concentration by Broth Micro Dilution) ratio exceeds 400\(^16\)–\(^20\). A retrospective study by Moise-Broder\(^18\) et al looked at 108 patients with MRSA lower respiratory tract infection and found a significant association between clinical cure and an AUC/MIC more than 400. There was no correlation with time above MIC, which was 100% in all patients. AUC can be calculated by pharmacokinetic modeling, Bayesian approach\(^21\) or extrapolation from total Vancomycin dose and creatinine clearance\(^22,23\). Pharmacokinetic modeling needs post distributional peak and trough. The Bayesian approach is based on a single trough level (need not be at steady state) and patient data such as creatinine clearance; it can be done at the bedside and software programmes with Bayesian analysis are available\(^24\). Since vancomycin is primarily cleared by glomerular filtration, its clearance correlates well with creatinine clearance. The 24-hour vancomycin AUC is calculated using the formula\(^22,23,25\):

\[
\text{AUC} = \frac{\text{total vancomycin dose in mg over 24 h}}{\left(\text{Cl Cr} \times 0.79\right) + 15.4} \times 0.06
\]

and creatinine clearance (Cl Cr) is calculated using the Cockcroft-Gault equation\(^26\):

\[
\text{Cl Cr} = \frac{\left(140 - \text{age in years}\right) \times \text{weight in kg}}{0.85 \text{ if female}} \times \frac{\text{S. Creatinine in mg/dl} \times 72}{\text{BSA} \times 1.73 \text{ M}^2}
\]

Trough concentration at steady state has been suggested as a surrogate for achieving an AUC/MIC ratio ≥400. However studies have not consistently shown correlation between the measured trough concentration and the actual AUC value. Pai et al studied the relationship between vancomycin area under the curve over 24 h (AUC24) and trough vancomycin concentration using an established adult population PK model of 5000 subjects and found poor correlation (R\(^2\)=0.409) and suggested that one cannot rely only on the vancomycin trough concentration range of 15-20 mg/l to achieve an AUC/MICBMD ratio ≥400 for S. aureus isolates with MIC values more than 1 mg/L\(^21\)–\(^27\). Frymover\(^6\) et al found that a trough concentration of 7–10 lg/mL predicted achievement of an AUC/MIC = 400 in more than 90 % of MRSA-infected children with an MIC of 1 lg/mL\(^28\). Le et al studied 702 patients aged 3 months to 21 years, with 1660 Vancomycin trough levels and found that a minimum dosage of 60–70 mg/kg/day was necessary to achieve an AUC/MIC C400 in 75 % of patients\(^29\). They correlated an AUC/MIC of 400 to a similar serum trough concentration of approximately 8–9 lg/mL.

Loading doses of Vancomycin have been suggested for rapid attainment of therapeutic levels. A recent systematic review looked at 6 adult studies and 2 studies in children. Only 4 adult studies found that loading dose of vancomycin led to significantly more patients achieving troughs of 15-20 mg/l\(^30\). A randomized controlled trial of loading dose in 46 children showed that loading dose of 30 mg/kg did not lead to earlier attainment of therapeutic trough levels\(^31\). Two of nineteen (11%) loading dose recipients had a trough 15-20 mg/L before the second dose, compared with 0 of 27 in the conventional dose group (P=0.17).

Continuous infusion Vancomycin has been studied in adults and neonates, but data is limited in children. A meta-analysis of adult studies by Waineo et al concluded that continuous infusion vancomycin produces clinical outcomes that are comparable to
intermittent infusion but may be associated with a lower relative risk of kidney injury than intermittent infusion therapy.\(^3\)\(^2\)

Besides pharmacokinetics and pharmacodynamics, other issues may play a role in the response to Vancomycin. Vancomycin acts by inhibiting incorporation of monomers into the peptidoglycan chain which is the backbone of the cell wall; cell death occurs by osmotic cytolysis and may take as long as 24 hours. Studies have shown poor penetration of Vancomycin in many tissues- 0%–18% of serum concentrations in uninflamed meninges, 36%–48% in inflamed meninges, a maximum of 41%–51% in the lung, and 10%–30% in diabetic and normal skin and soft tissues.\(^1\) The bactericidal activity of vancomycin is weak in the presence of a high inoculum, known as the inoculum effect, and in the case of biofilm-associated infections, defined as biofilm resistance.\(^3\)\(^3\)

Vancomycin resistance may occur due to alteration in peptides in the peptidoglycan chain or gradual clogging of the antibiotic into a thickened staphylococcal cell wall.

At present, there is no clarity on the optimal dosing regime for Vancomycin, or how to monitor therapy. It is important to restrict the use of Vancomycin to serious infections (complicated skin infections, bloodstream infections, endocarditis, bone and joint infections, and meningitis) caused by MRSA. Alternatives to Vancomycin like Daptomycin, should be considered in the following scenarios: Vancomycin MIC > 1 mg/ml, or vancomycin treatment failure (positive blood cultures after 48 hours of vancomycin therapy without a focus of infection and after good source control).

In our patient as he had continued to be febrile and bacteremic on day 5 of illness, we planned to maintain higher vancomycin trough levels. Hence the total daily dose of vancomycin required to achieve an AUC of 400 was calculated as follows:\(^3\)\(^4\)

\[
\text{AUC} = \frac{\text{total vancomycin dose in mg over 24 h}}{[(\text{Cl Cr X 0.79}) + 15.4] \times 0.06}
\]

Total vancomycin dose in mg over 24 hrs = AUC X \{(Cl Cr X 0.79) + 15.4\} X 0.06

For our patient’s Dose, we used the AUC as 400 and then worked backwards to find the total daily dose. 400 = \(x / \{(\text{Cl Cr X 0.79}) + 15.4\} \times 0.06\). This resulted in the total daily dose being 2 gms. If the MIC had been 2, the AUC of 400 would not have been reached with this dose and the calculated does would have been double.

Despite this high dose, the trough levels remained <15 mg/l with positive blood cultures and Daptomycin was added. He improved after that.

Another method of adjusting the dose is by using the trough levels. There are several calculators that can be used online. Some require one trough level and some require two. These are not tested for weights below 20Kg, for patients on dialysis or with unstable renal function, and where MICs are >2.\(^3\)\(^3\) There has been shown to be good correlation between these two methods by Holmes et al.

**Summary**

In seriously ill children with MRSA infection Vancomycin loading doses need to be used.

As far as possible trough levels need to be measured before the 4th dose and the ideal total dose calculation made for an AUC of 400.

If the blood culture does not clear in 48-72 hours after all source control, alternative treatment must be considered.

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Optimising the Dosing of Antibiotics: Colistin and Vancomycin Updates

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