Optimising the administration of antibiotics in critically ill patients

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Optimal outcome and a reduction in the potential for resistance require that appropriate pharmacokinetic (PK) targets are achieved. Consequently, we need to target drug concentrations that are significantly higher than those conventionally presumed to be adequate. Drug exposure varies according to the molecular weight, degree of ionisation, protein binding and lipid solubility of each agent. In critically ill patients, hypoalbuminaemia increases the free fraction of hydrophilic drugs, which in turn increases the volume of distribution and clearance (CL), both of which result in reduced drug levels. Similarly, augmented renal clearance (ARC), defined as a creatinine clearance (CLcr) of >130 mL/min/1.73 m², which occurs frequently in critically ill patients, particularly younger patients with normal or near-normal creatinine levels, may also significantly reduce drug exposure. Studies have demonstrated a greater mortality and lower clearance with ARC, particularly with the additive effects of obesity, hypoalbuminaemia and increasing resistance, if conventional dosages are used. These concepts apply to antibiotics targeting Gram-negative and positive organisms. Knowledge of PK and the resistance profiles of organisms in each environment is necessary to prescribe appropriately. This article discusses these issues and the doses that should be used.


Factors impacting on antibiotic exposure

Drug exposure varies according to molecular weight, degree of ionisation, protein binding and lipid solubility. Lipophilic antibiotics, e.g. the fluoroquinolones, have a large volume of distribution (Vd) owing to significant tissue and intracellular penetration. Hydrophilic agents, however, distribute into the extracellular space only and have a much lower Vd. The latter is influenced by a number of factors, such as serum albumin level, augmented renal clearance (ARC) and fluid losses as occurs with an open abdomen and major surgery with blood loss.

Albumin level is of particular relevance for highly protein-bound antibiotics such as teicoplanin (90 - 95% bound), especially in critically ill patients in whom hypoalbuminaemia frequently occurs. In this setting, the Vd and clearance (CL) of the unbound/free fraction are increased. These PK changes could result in suboptimal drug exposure, which may necessitate dose adjustments to ensure that therapeutic exposures are achieved. In this regard, Mimoz et al.
utilising a high-dose regimen of teicoplanin (12 mg/kg 12-hourly for 48 hours, followed by 12 mg/kg once daily) in critically ill patients with ventilator-associated pneumonia (VAP) and severe hypoalbuminaemia (median albumin concentration 16.1 g/L), observed variations in the fraction of unbound teicoplanin of 8 - 42%.

ARC is defined as a creatinine clearance (CLcr) >130 mL/min/1.73 m². The prevalence varies from 30% to 85% in critically ill and trauma patients and a normal or near-normal creatinine level may represent a higher glomerular filtration rate (GFR). At-risk populations are those with good physiological reserve, of a younger age and with lower illness severity scores. In this setting, dose increases are appropriate as the potential for subtherapeutic dosing is high. Increased β-lactam clearance in patients with sepsis, but without organ dysfunction, can lead to subtherapeutic levels for significant periods.[14-17] CLcr should be routinely measured if there is doubt about the GFR and evidence that an 8-hour collection may be just as accurate as a 24-hour one. A recent prospective, single-centre observational study of patients with VAP treated with doripenem or imipenem demonstrated a greater mortality and lower cure with CLcr >150 mL/min. Separate PK/pharmacodynamic (PD) modelling suggested that daily doripenem doses (up to 2 g 8-hourly) might be required for adequate drug exposure, particularly with resistant organisms.[17-19] In 128 surgical and medical patients encompassing 599 antibiotic days, ARC, defined as more than one 24-hour CLcr >130 mL/min/1.73 m², was present in 51.6% of patients and in 12% it occurred throughout the hospital stay. The median CLcr was 144 mL/min/1.73 m² (interquartile range (IQR) 98 - 196), the ARC patients were significantly younger (p<0.001) and treatment failure occurred more frequently: 27.3% v. 12.9%; p=0.04.[17] We investigated ertapenem PK in 8 patients with severe sepsis (all of whom had normal renal function) after the administration of the conventional dose of 1 g daily. These patients had a lower maximum concentration (Cmax), AUIC (0→∞), and higher Vd (26.8 L v. 5.7 L) than healthy volunteers, and in 4 patients time above 2 mg/L (the MIC breakpoint for Enterobacteriaceae) of the unbound fraction was <40% and in 2 it was <20%. These lower levels correlated negatively with low albumin, open abdomen and ARC.[20]

In summary, systemic inflammation increases the Vd of hydrophilic agents through capillary leak, large-volume crystalloid resuscitation and low albumin levels. Furthermore, altered organ perfusion and therapeutic use of inotropes and vasopressors increase the potential for ARC. The additive effects of obesity and extracorporeal circuits reduce drug exposure in an environment where MICs are increasing inexorably. The overall effect is to increase the potential for treatment failure and select for resistance.[21]

What should be done to limit the impact of reduced drug exposure?

There are two obvious approaches, firstly to increase the dose and secondly to alter the methods of administration (infusion for time-dependent agents and, where possible, larger single daily doses for concentration-dependent drugs), both preferably guided by therapeutic drug monitoring (TDM).

β-lactams

In the abovementioned study by Claus et al.[17] doripenem was administered at four times the recommended dose – with good outcome. There have been many similar case studies of the outcomes when treating resistant organisms. In a patient with cystic fibrosis infected with multidrug-resistant Burkholderia cepacia, who was treated with meropenem 2 g
8-hourly as a 3-hour infusion, concentrations >8 μg/mL were achieved for 52% of the dosing interval, with subsequent improvement.[22] In a study of 348 patients using β-lactam therapy (the Defining Antibiotic Levels in ICU (DALI) study – a PK point prevalence study using empirical therapy in the ‘worst case’ scenario), T>MIC was <50% of the dosing interval in 19.2% and <100% in 41.4% of patients. Intermittent infusion significantly increased the likelihood of reaching the target, whereas increased CLcr was independently associated with not reaching the 100% T>MIC target for free drug.[23] Similarly, using a Monte Carlo simulation, Nicasio et al.[24] determined that 3-hour infusions of cefepime or meropenem, both at 2 g three times daily, would be most likely to achieve optimal bactericidal Pseudomonas aeruginosa exposure. When this was implemented, infection-related mortality decreased by 69% (8.5% v. 21.6%; p=0.029), length of stay was reduced (11.7±1 v. 26.1±18.5; p=0.001), there were fewer superinfections, and many ‘non-susceptible’ P. aeruginosa infections were successfully treated.

Tigecycline

The efficacy of tigecycline (TGC) has often been questioned. Meta-analyses of monotherapy v. comparators such as the meta-analysis by Yahav et al.[25] have been done. The latter included 15 trials (N=7654) where overall mortality was higher (relative risk (RR) 1.29 (1.02 - 1.64)), regardless of infection type; clinical and microbiological failure were higher (RR 1.16 (1.06 - 1.27) and 1.13 (0.99 - 1.30), respectively); and development of infection type; clinical and microbiological failure were higher (RR 1.16 (1.06 - 1.27) and 1.13 (0.99 - 1.30), respectively); and development of overall mortality was higher (relative risk (RR) 1.29 (1.02 - 1.64)), regardless of infection type; clinical and microbiological failure were higher (RR 1.16 (1.06 - 1.27) and 1.13 (0.99 - 1.30), respectively); and development of.

Fluoroquinolones and aminoglycosides

With regard to the concentration-dependent antibiotics, optimising the AUIC of fluoroquinolones reduced the development of resistance and was more likely to eradicate the pathogen.[28,29] Aminoglycosides are generally used suboptimally. To achieve appropriate targets, a much larger dose based on age and weight must be administered once per day and the MIC should be low.[30] In general, aminoglycosides are administered for short periods as empirical therapy to decrease the likelihood of inappropriate therapy for hospital-acquired infections. Peak and trough levels and the MIC of the organism (where possible) should be documented and subsequent doses titrated accordingly.[31] As with other hydrophilic agents where the Vd is increased and in the presence of ARC, concentrations may be suboptimal. Amikacin 15 mg/kg, for example, did not reach effective concentrations, with MICs of 8 mg/L, and it is possible that inconsistent concentrations may have contributed to the lack of effect in studies that investigated whether β-lactam-aminoglycoside combinations confer additional efficacy compared with β-lactams only.[22,33] Some reviewers have suggested that doses as high as 25 - 30 mg/kg for amikacin and 7 - 9 mg/kg for gentamicin or tobramycin should be administered initially, and thereafter a Cmax/MIC ratio of 8 - 10 should be targeted.[34] Even then, levels might not be adequate; 33% of patients receiving 25 mg/kg total body weight amikacin load had a Cmax of 60 mg/L, with positive fluid balance being the major negative predictive factor. To complicate matters further, Monte Carlo simulation of conventional v. high-dose extended-interval administration found resistance to be higher against pathogens with high MICs if T>MIC was <60%, even if Cmax/MIC was high, and that treatment efficacy may not be guaranteed.[35] Illustrative dosing schedules for Gram-negative agents may be seen in Table 1.

Colistin

Colistin is a last-line drug and if used inappropriately resistance will develop rapidly. The form available in South Africa is a prodrug, colistimethate sodium or colistin methanesulfonate (CMS), which makes a bolus dose necessary to achieve therapeutic effect. It is effective against most Gram-negative bacilli, except Proteus spp., B. cepacia, Providencia spp., Serratia marcescens and Morganella spp.[36] The appropriate dose must exceed an MIC of 2 mg/L rapidly to prevent regrowth of more resistant organisms in heteroresistant populations, in which the PK target achieved would be insufficient for eradication.[37]

Consequently, a loading dose of 12 million units (MU) administered intravenously over 1 - 2 hours followed by 9 MU daily (4.5 MU twice daily or 3 MU three times daily) administered 12 hours after the loading dose is required.[38,39,40] Colistin is predominantly cleared by unknown non-renal mechanisms and undergoes extensive renal tubular reabsorption.[41] In renal dysfunction, elimination of CMS is decreased and a greater fraction of the administered dose is converted to colistin; however, a loading dose of 12 MU is still required, but maintenance doses are reduced according to CLcr (Table 2).[40] From murine AUC/MIC colistin data, it is estimated that an AUIC of total colistin of 60 is the average achieved without exceeding the dose recommended in the package insert (10 MU), particularly where CLcr is >70 mL/min.[42] Therefore, in an attempt to

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<tr>
<th>Table 1. Illustrative dosing and administration schedules for Gram-negative bacilli: Normal renal function</th>
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<td><strong>Drug</strong></td>
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<td>Meropenem</td>
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<tr>
<td>Imipenem</td>
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<td>Doripenem</td>
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<td>Ertapenem</td>
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<td>Cefepime</td>
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<td>Ceftazidime</td>
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<td>Piperacillin-tazobactam</td>
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*Temperature ≤27°C.

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<tr>
<th>Table 2. Dosing of colistin</th>
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<tr>
<td><strong>Load with 12 MU</strong></td>
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<tr>
<td>60 kg: 3 MU 8-hourly/4.5 MU 12-hourly</td>
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<tr>
<td>Renal impairment – load with 12 MU, then:</td>
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<tr>
<td>CLcr 20 - 50: 1 - 2 MU 8-hourly</td>
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<tr>
<td>CRRT (RRT) – full dose; intermittent HD 1 MU 12-hourly and 1 MU after dialysis</td>
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<tr>
<td>Never use colistin on monotherapy</td>
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MU = million units; CRRT = continuous renal replacement therapy; HD = haemodialysis.
reduce resistance, colistin is not administered as monotherapy and options include the carbapenems (provided the MIC is ≤32 mg/L [for carbapenem-resistant Enterobacteriaceae]), tigecycline (Acinetobacter), fluoroquinolones, rifampicin and others, even if the organism is resistant to these drugs.[41–45]

The glycopeptides, vancomycin and teicoplanin

These concepts regarding dosing are similar when using agents active against Gram-positive organisms. Vancomycin MICs have gradually been increasing, which appears to impact on outcome. In 158 patients with hospital-, ventilator- or healthcare-associated pneumonia caused by methicillin-resistant Staphylococcus aureus, 72.8% had vancomycin MIC ≥1.5 μg/mL. All-cause mortality at day 28 was 32.3%, but this increased as the MIC increased (p = 0.001). Although controversial, it is recommended that other therapies be considered with MICs of 1 – 2 μg/mL.[46–48] Studies using higher troughs (15 – 20 μg/L), loading doses or continuous infusions differ with regard to improved clinical or microbiological outcome; however, it is hoped that higher dosing may delay resistance by not selecting those organisms with higher MICs.[49–51] In another study from the DALI group, 42 patients either received continuous infusions (CIs) (57%) or intermittent doses (43%) of vancomycin. The PK targets were a Cmin ≥15 mg/L or an AUIC >400 (assuming the MIC was 1 mg/L). The Cmin was highly variable and achieved in only 57% overall, and Cmin ≥15 mg/L or an AUIC >400 (assuming the MIC was 1 mg/L).

The CI might significantly improve AUIC.[52] This is not a review of TDM, and it seems reasonable to utilise TDM where available; where not, essential, the dose and method of administration must be optimised, but numerous other studies have proven its worth and it is probably the way of the future.[53,54] Illustrative dosing schedules for Gram-positive agents may be seen in Table 3.

**Conclusion**

There is currently a crisis with regard to antibiotic resistance. Every day that we delay ensures that we are further from a solution. We have to use antibiotics in an appropriate manner, reduce inappropriate use by all possible means, and reduce the incidence of infection, particularly in hospital. We are at the end of the antibiotic era—perhaps we can make it last a few more years to allow the introduction of new agents, particularly β-lactam antibiotics combined with β-lactamase inhibitors, or until new strategies can be devised.

**References**


