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### Antibiotic Management in the ICU



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Antimicrobial management in the intensive care unit (ICU) represents an ongoing challenge for critical care clinicians. In the ICU setting broad-spectrum antibiotic consumption is often unavoidably high, and antimicrobial resistance rates are increasing in many parts of the world (Brusselsaers et al. 2011). Early and appropriate antimicrobial administration is paramount in critically ill patients with suspected or confirmed infection and sepsis (Kumar et al. 2006). However, in hospitals with high rates of multi-drug-resistant pathogens, appropriate antimicrobial choices are limited to few options like carbapenems, colistin and tigecycline. Moreover, critically ill patients present profound pathophysiological changes, altering the pharmacokinetics of the administered antimicrobials, and failure to achieve target serum concentrations is not uncommon (Lipman and Boots 2009; Roberts and Lipman 2009). Lastly, apart from procalcitonin-based algorithms, other validated diagnostic and prognostic biomarkers that could assist in determining antimicrobial treatment duration and guide de-escalation strategies are lacking. The problem of reduced antibiotic development in combination with growing antimicrobial resistance calls for better use of currently available antibiotics. The goal of this review is to focus on strategies aimed at optimising antimicrobial use within intensive care units.

### General Principles of Antibiotic Use in the ICU

#### 1. Timing

When clinically indicated, antibiotics should be administered as soon as possible. A retrospective analysis of the Surviving Sepsis Campaign database, which included 17,990 patients with sepsis and septic shock from 160 ICUs in Europe, South America and the United States, confirmed the association between mortality and timing of antibiotic administration. The study results showed that in-hospital mortality risk increased linearly for each hour delay before the administration of the first antimicrobial dose (Ferrer et al. 2014). Guidelines recommend that the first antimicrobial dose is administered within 1 hour after the onset of hypotension in sepsis (Kumar et al. 2006; Dellinger et al. 2013), and within 4 hours of arrival to the hospital in community-acquired pneumonia (Blot et al. 2007).

#### 2. Appropriate Antimicrobial Selection

For serious infections it is appropriate to start with **broad spectrum antibiotics** in order to ensure adequate coverage for possible resistant pathogens, with de-escalation of antimicrobials targeted to the causative agents once cultures and susceptibility data are available (Leone et al. 2014). The choice of antibiotics used should account for the identity and susceptibility pattern of the bacteria commonly isolated in that unit, as there is considerable variability in the spectrum of potential pathogens and the susceptibility patterns between different ICUs, even within the same institution. Inadequate initial antibiotic therapy is associated with elevated mortality, which in the case of sepsis has been shown to be 8 times higher than the risk in those who receive adequate coverage (Garnacho-Montero et al. 2003).

#### 3. Combination Therapy

The use of **combination therapy**, including two antimicrobial agents from different classes, in order to achieve synergistic or additive effects has been a controversial topic for years. Most studies evaluating the benefit of combination therapy have not shown a mortality benefit, with the only exception being *Pseudomonas* bacteremia and carbapenemase-producing *Klebsiella pneumonia* bacteremia (Hilf et al. 1989; Paul et al. 2004; Leibovici et al. 1997; Safdar et al. 2004; Daikos et al. 2014). However, in critically ill patients combination therapy may be appropriate for empiric

treatment, especially in cases where infections due to resistant organisms are suspected. In such cases, combination therapy increases the chance that the empiric antimicrobial coverage is adequate. Patient **risk factors** for colonisation or infection with multi-drug resistant pathogens should be taken into account, including recent antibiotic use and hospitalisation, prolonged hospital stay, dialysis and the presence of invasive devices (Kollef 2001).

## 4. Dosing

### a. Loading Dose

Deciding on the **first dose of antibiotic** in a septic patient is probably equally important as timing. Loading doses are frequently needed in order to ensure therapeutic concentrations, as in the setting of increased volume of distribution (Vd) standard doses may result in suboptimal drug exposure. Higher initial doses should therefore be considered, particularly in the case of hydrophilic antimicrobials such as aminoglycosides, vancomycin, colistin, glycopeptides and add hyphen between beta-lactams (Udy et al. 2013).

### b. Individualised Approach

The **dosing strategy** for antibiotics should take into account the mode of action of the drug and individual patient characteristics that influence pharmacodynamics and pharmacokinetic factors, in order to maximise bacterial killing, prevent the development of antimicrobial resistance, and avoid concentration-related adverse drug reactions.

## i. Dosing Intervals

Evaluation of the antibiotic kill characteristics in experimental models suggests different **dosing intervals** for different classes of antibiotics.

1. For concentration-dependent agents (such as aminoglycosides, colistin, quinolones, vancomycin) the antimicrobial effect is maximal when the free drug peak concentration in a dosing interval exceeds the minimum inhibitory concentration (MIC) by 8-10 times ( $C_{max}/MIC > 8-10$ ). This has been translated into single daily (or extended interval) dosing for aminoglycosides (Buijk et al. 2002; Hatala et al. 1996; Mavros et al. 2011; Barza et al. 1996).

2. For time-dependent agents (such as betalactams) the killing effect is almost entirely related to the time for which levels in tissue and plasma exceed the MIC of the offending pathogen ( $fT > MIC$ ). Penicillin and monobactams are reported to require at least 50-60%  $fT > MIC$ , cephalosporins need a 60-70%  $fT > MIC$ , whereas carbapenems require a 40%  $fT > MIC$  (Craig 1998). These antibiotics lack a post-antibiotic effect, and, once the levels fall below the MIC, bacterial growth immediately resumes, leading to treatment failure and promotion of bacterial resistance. Modifying antibiotic delivery in order to improve the probability of obtaining  $fT > MIC$  targets has been shown to decrease mortality. Hence, dosing regimens for beta-lactams are being re-evaluated, and, at least for critically ill patients with resistant pathogens, extended or continuous dosing is recommended (Dulhunty et al. 2013; Falagas et al. 2013; Roberts et al. 2014b; Goncalves-Pereira and Pova 2011; Seyler et al. 2011).

For concentration-dependent with time dependence agents (such as quinolones, daptomycin, glycopeptides, tigecycline, linezolid), the antimicrobial effect is defined by the area under the curve (AUC) of free drug over a 24 hour period over the MIC. For example, contemporary vancomycin dosing regimens target an  $AUC/MIC \geq 400$  for serious methicillin resistant *Staphylococcus* infections (Liu et al. 2011).

## ii. Pharmacokinetic Profile

Current antibiotic dosing recommendations are based on patient populations that were not critically ill. However, critical illness is characterised by multiple organ dysfunctions, inciting pathophysiological changes that may alter significantly the antibiotic pharmacokinetic profile (Blot et al. 2014). Without dose adjustments, suboptimal dosing may lead to therapeutic failure and increased mortality. Therefore, in the context of guidelines, individual patient characteristics should be considered:

### 1. Increased Volume of Distribution (Vd)

The Vd is a proportionality constant that relates the amount of drug in the body to the observed concentration in the plasma. The Vd in critically ill patients is commonly altered as a result of the pathophysiology of sepsis and severe illness, hypoalbuminaemia and reduced protein binding, frequently performed interventions such as cardiopulmonary bypass and mechanical ventilation and specific pathologies such as pancreatitis (Felton et al. 2014).

As an example, sepsis and septic shock are characterised by increased volume of distribution due to vasodilation, increased capillary permeability leading to capillary leak and fluid shifts to the interstitium. Aggressive intravenous fluid resuscitation leads to further increase in the volume of total body water and Vd (Hosein et al. 2011).

The clinical importance of increased Vd is particularly important for hydrophilic antimicrobials, such as beta-lactams, aminoglycosides, vancomycin and colistin that have a low Vd. If loading doses are not increased, sub-therapeutic antimicrobial levels will lead to therapeutic failure. On the other hand, no major influence is expected for lipophilic antimicrobials such as quinolones as their Vd is high (Roberts and Lipman

2009).

## 2. Hypoalbuminaemia

Hypoalbuminaemia, defined as albumin < 2.5 mg/dl, results in increased levels of unbound drug. The unbound drug, which is the pharmacodynamically active form, is available for distribution and elimination resulting in increased Vd and augmented clearance respectively, leading to failure to maintain high plasma concentrations (Uldemolins et al. 2011). The effect of hypoalbuminaemia in the PK/PD is important for drugs with increased protein binding such as daptomycin, ceftriaxone and ertapenem, as their volume of distribution in the view of hypoalbuminaemia may increase up to 100% (Roberts et al. 2014a).

## 3. Clearance

The clearance of a drug is defined as the volume of plasma cleared by the drug per unit time. Critical illness and sepsis frequently involve multiple organ dysfunction, including acute kidney injury leading to decreased clearance of antimicrobials, accumulation and toxicity. The impact of acute kidney injury (AKI) on the antimicrobial concentrations depends on the extent of renal function compromise. Dose reductions for renally cleared antimicrobials are recommended; however, underdosing may be a significant risk as other pathophysiologic parameters, such as the increased Vd that frequently is combined with AKI in cases of sepsis, major surgery and extensive burns often compensate for the reduced clearance, particularly in the first 48 hours of treatment. Furthermore, alternative elimination pathways may compensate for the decreased renal clearance (Blot et al. 2014).

On the other hand, renal clearance of antimicrobials, may be augmented by hyperdynamic conditions including sepsis, volume overload, high cardiac output and use of positive inotropes leading to suboptimal antimicrobial concentrations. In such cases clearance of antimicrobials may increase up to three-fold (Udy et al. 2011). Additional pathophysiologic parameters such as hypoalbuminaemia may further increase clearance, as stated before.

Renal replacement therapy (RRT) is commonly applied in patients with AKI, but marked unpredictability in antimicrobial clearance has been described. In general hydrophilic antimicrobials, with low protein binding and increased renal clearance, are more efficiently removed. High interpatient variability limits the applicability of general guidelines, and calls for locally established dosing regimens during RRT, based on the type of RRT performed (Blot et al. 2014).

Hepatic dysfunction can affect the elimination of antimicrobials, which are metabolised by the liver or undergo transintestinal clearance. In general livers' metabolic capacity have to be reduced by >90% before drug metabolism is significantly affected (Park 1996).

## iii. Therapeutic Drug Monitoring

It is evident that predicting antimicrobial concentrations in the critically ill patient is nearly impossible, which calls for the application of therapeutic drug monitoring (TDM) in daily practice in order to optimise dosing. TDM relies on direct measurement of serum antibiotic concentrations, which are then interpreted in the context of therapeutic ranges. TDM is routinely used in the administration of antimicrobials, characterised by a narrow therapeutic window and substantial risk of toxicity, such as aminoglycosides and glycopeptides. However, it has been supported that TDM is likely to be beneficial for other agents such as beta-lactams, quinolones and linezolid (Roberts et al. 2010; Scaglione et al. 2009).

## 5. Source Control

Importantly, together with antimicrobials adequate source control encompassing abscess drainage, wound debridement, surgical excision of necrotic tissue and device removal is paramount for the successful control of an infection (Marshall and al Naqbi 2009).

## 6. Duration

Administration of early empiric broad-spectrum antimicrobial coverage for all epidemiologically relevant and possibly resistant pathogens implies daily reassessment of treatment, and transition to a narrower-spectrum regimen once culture results and susceptibilities are available. Provided that the infection source is controlled, short antibiotic courses (< 7 days) are sufficient for most infections in the critically ill patient, with a few exceptions (Lipman and Boots 2009). More specifically, shorter (3-8 days) rather than longer (10-21 days) antimicrobial courses have been shown to be equally efficacious in the treatment of ventilator-associated pneumonia (Singh et al. 2000; Ibrahim et al. 2001).

Biomarker-based algorithms are often used to guide antibiotic de-escalation strategies (Pierrakos and Vincent 2010). Procalcitonin (PCT) is the most widely studied biomarker in antibiotic initiation and de-escalation algorithms in the critical care setting. PCT has some diagnostic and prognostic utility in the management of critically ill patients, since it is elevated in patients with severe sepsis, septic shock and bacteraemia, and its decline is associated with better prognosis (Reinhart and Meisner 2011). PCT-based algorithms are associated with shorter duration of antibiotic treatment without compromising ICU outcomes (Bouadma et al. 2010; Schuetz et al. 2012; Pova and Salluh 2012).

## Surveillance and Stewardship

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Surveillance of nosocomial infections, antibiotic use and antimicrobial resistance rates in the ICU is an essential tool for infection control measures and antimicrobial stewardship strategies (Bergmans et al. 1997; De Bus et al. 2014). Knowledge of the prevalence of infections and the indication-based antibiotic prescribing rates in a certain unit can help guide preventive interventions that aim to reduce both antimicrobial use and resistance. Researchers from Belgium compared two antibiotic treatment algorithms with the actual empiric therapy for hospital-acquired pneumonia regarding the proposed regimens' spectrum of activity and appropriateness of treatment. The study, which was performed in a 36-bed tertiary centre ICU with a moderate prevalence of MDR pathogens, involved one strategy based on overall bacterial resistance rates (local ecology-based algorithm [LEBA]) and another based on individual patient respiratory surveillance cultures (surveillance culture-based algorithms [SCBA]). While both strategies conferred similar rates of appropriate antimicrobial coverage, SCBA was associated with the use of less overall and broad-spectrum antibiotic prescribing (De Bus et al. 2014).

## Conclusion

Prompt and appropriate management of infections in critically ill patients is vital in order to limit mortality and morbidity. Antibiotic dosing requires special considerations because of altered drug pharmacokinetics in these patients, and therapeutic monitoring is often needed in order to achieve maximal efficacy, decrease the risk of antimicrobial resistance and minimise toxicity.

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