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Antibacterial Dosing in Intensive Care

Pharmacokinetics, Degree of Disease and Pharmacodynamics of Sepsis

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Abstract

Treatment of sepsis remains a significant challenge with persisting high mortality and morbidity. Early and appropriate antibacterial therapy remains an important intervention for such patients. To optimise antibacterial therapy, the clinician must possess knowledge of the pharmacokinetic and pharmacodynamic properties of commonly used antibacterials and how these parameters may be affected by the constellation of pathophysiological changes occurring during sepsis.

Sepsis, and the treatment thereof, increases renal preload and, via capillary permeability, leads to 'third-spacing', both resulting in higher antibacterial clearances. Alternatively, sepsis can induce multiple organ dysfunction, including renal and/or hepatic dysfunction, causing a decrease in antibacterial clearance.

Aminoglycosides are concentration-dependent antibacterials and they display an increased volume of distribution (V_d) in sepsis, resulting in decreased peak serum concentrations. Reduced clearance from renal dysfunction would increase the likelihood of toxicity. Individualised dosing using extended interval dosing, which maximises the peak serum drug concentration (C_{max})/minimum inhibitory concentration ratio is recommended.

β-Lactams and carbapenems are time-dependent antibacterials. An increase in V_d and renal clearance will require increased dosing or administration by continuous infusion. If renal impairment occurs a corresponding dose reduction may be required.

Vancomycin displays predominantly time-dependent pharmacodynamic properties and probably requires higher than conventionally recommended doses because of an increased V_d and clearance during sepsis without organ dysfunction. However, optimal dosing regimens remain unresolved. The poor penetration of vancomycin into solid organs may require alternative therapies when sepsis involves solid organs (e.g. lung).

Ciprofloxacin displays largely concentration-dependent kill characteristics, but also exerts some time-dependent effects. The V_d of ciprofloxacin is not altered with fluid shifts or over time, and thus no alterations of standard doses are required unless renal dysfunction occurs.

In order to optimise antibacterial regimens in patients with sepsis, the pathophysiological effects of systemic inflammatory response syndrome need consideration, in conjunction with knowledge of the different kill characteristics of the various antibacterial classes.

In conclusion, certain antibacterials can have a very high V_d, therefore leading to a low C_{max} and if a high peak is needed, then this would lead to underdosing. The V_d of certain antibacterials, namely aminoglycosides and vancomycin, changes over time, which means dosing may need to be altered over time. Some patients with serum creatinine values within the normal range can have very high drug clearances, thereby producing low serum drug levels and again leading to underdosing.

The treatment of sepsis remains a significant challenge to critical care physicians world wide with persisting high mortality and morbidity rates. The incidence of sepsis exceeds that of colon cancer, breast cancer and AIDS, with mortality rates of 30% for mild to moderate sepsis and up to 82% for severe sepsis and septic shock.[1] Up to 50% of all patients diagnosed with severe sepsis will die during their hospital admission.[2] In the US alone, 750 000 patients are diagnosed with sepsis annually,[3,4] resulting in 210 000 deaths at a cost of $US17 billion.[4] The incidence of sepsis is thought to be rising because of the prevalence of increasing age of the population, the number of immuno-compromised patients, the use of invasive procedures and antibiotic resistance.[5] It is not the focus of this review to discuss diagnosis or novel management strategies of sepsis. Suffice to say that compelling evidence suggests that with source control of the pathogen, early and appropriate antibacterial therapy remains the most important intervention that the clinician can implement for such patients.[6-10] Appropriate antibacterial therapy should therefore be a priority in the management of patients with sepsis.

A constellation of pathophysiological changes can occur in patients with sepsis, which complicate antibacterial dosing. Knowledge of the pharmacokinetic and pharmacodynamic properties of the antibacterials used for the management of sepsis is essential for selecting the antibacterial dosage regimens that will optimise patient outcomes.[11] Changes in the volume of distribution (V_d) and clearance of the antibacterials have been noted in sepsis, which will affect the antibacterial concentration at the target site. It follows that the pharmacodynamic parameters that determine antibacterial efficacy, which can vary between antibacterial classes, may also be affected. Further, since the physiology of these patients may change over a relatively short period of time, ongoing evaluations of sickness severity are indicated to allow timely adjustment of antibacterial dosing. Optimisation of these parameters is necessary to maximise the rate of response through patient recovery and minimise antibacterial resistance.[11,12] This review identifies the pathophysiological changes that occur during sepsis in critically ill patients in the intensive care unit (ICU) and the effect this has on the pharmacokinetic behaviour, and the pharmacodynamic effect of commonly used aminoglycoside, β-lactam, glycopeptide and fluoroquinolone antibacterials.

1. Sepsis

1.1 General

The older definitions of sepsis[13] (a systemic inflammatory response syndrome [SIRS] triggered by an overwhelming infection) have recently been refined.[13,14] Severe sepsis occurs upon failure or dysfunction of at least one organ. Septic shock is defined by hypotension in the setting of severe sepsis that is unresponsive to fluid resuscitation. Despite advances in critical care medicine, the prognosis of sepsis and septic shock remain poor. Much

research has been directed at cellular targets to limit the associated inflammatory and coagulation cascades including interleukins, cytokines and tumour necrosis factor-α.[5] None of these interventions have been found to be as important or effective as optimal antibacterial therapy.[5-9,15] However, the appropriate prescription of antibacterials requires a detailed knowledge of the pathophysiological and subsequent pharmacokinetic changes that occur throughout the course of sepsis.[16,17]

1.2 Pathophysiological Changes in Sepsis that Can Affect Drug Distribution

1.2.1 General Pathophysiology of Sepsis without Organ Dysfunction

The pathogenesis of sepsis appears highly complex.[5,14,18,19] Endotoxins, such as lipopolysaccharides (Gram-negative bacteria), or lipoteichoic acid (Gram-positive bacteria) or mannan (fungi) stimulate the production of various endogenous mediators, such as cytokines, interleukins, platelet activating factor, eicosanoids, complement components and kinins.[20] These mediators may affect the vascular endothelium directly or indirectly, resulting in either vasoconstriction or vasodilatation with maldistribution of blood flow, endothelial damage and increased capillary permeability. This capillary leak syndrome results in fluid shifts from the intravascular compartment to the interstitial space,[21,22] which is known as 'third spacing'. This would increase the V_d of water-soluble drugs, which decreases their serum drug concentration.

Increased Creatinine Clearance in Critically Ill Patients without Renal Dysfunction

Patients often present with hypotension from the inflammatory response associated with sepsis. Standard initial management involves administration of intravenous fluids to elevate blood pressure. If hypotension persists, inotropic agents (some of which may be 'inoconstrictors') are prescribed. It is therefore not surprising that patients with sepsis often have higher than normal cardiac indices.[18,23,24] In the absence of significant organ dysfunction, there is often an increased renal preload and consequently increased creatinine and drug clearance.[25-27]

Previous studies have reported that critically ill patients with normal serum creatinine levels may have high creatinine clearance (CL_{CR}).[28,29] This phenomenon is most likely to result from the clinical interventions used to reverse hypotension as described earlier. The implications of the high creatinine clearance, which is probably related to high renal blood flow, will result in supranormal clearance of renally cleared drugs. This increase in clearance is the major reason for the different dosing requirements between ICU and non-ICU patients.[30,31] A similar scenario probably occurs for hepatically cleared antibacterials.

1.2.2 Pathophysiology of Sepsis Causing Organ Dysfunction

As sepsis progresses, significant myocardial depression can occur, which leads to a decrease in organ perfusion.[23] Myocardial insufficiency and abnormalities of the macrovascular circulation are compounded by failure of the microcirculation. This induces end-organ microvascular alterations which may progress to multiple organ dysfunction syndrome.[1] This often includes renal and/or hepatic dysfunction. There is a consequent decrease in antibacterial clearance, which prolongs elimination half-life ($t_{1/2}$) and may increase antibacterial concentrations and/or lead to the accumulation of metabolites.[32]

Figure 1 schematically identifies the pharmacokinetic changes that can occur due to the altered pathophysiology during sepsis.

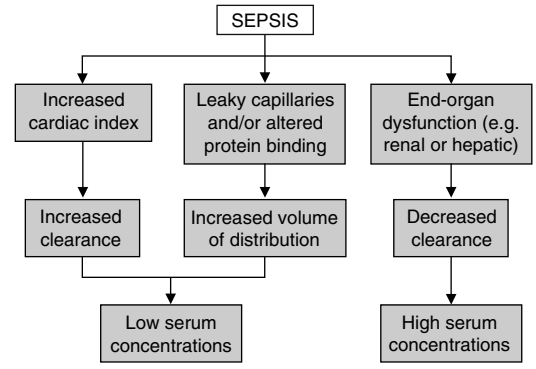

Fig. 1. Schematic representation of the basic pathophysiological changes that can occur during sepsis, and their subsequent pharmacokinetic effects.

When renal dysfunction is present or if the patient needs intermittent haemodialysis, standard texts or review articles[33,34] can be used as a guide for altered dosing. However, if a patient has been commenced on continuous renal replacement therapy (CRRT), a new variable is introduced.[35] While it is not the focus of this review to address this area, when dosing antibacterials in the ICU consideration of this issue is necessary, as illustrated in the next paragraph.

Continuous Renal Replacement Therapy

Septic patients may develop acute renal failure requiring CRRT during sepsis. Various methods of CRRT are available to remove fluid and waste products from the blood of patients with renal insufficiency or failure. CRRT may have an additional effect on antibacterial pharmacokinetics. The effect is complex and each method varies in its extent of drug clearance. Concomitant patient factors to be considered include changes in total body water, albumin and acute phase protein levels, muscle mass, blood pH, bilirubin concentration, renal, hepatic and cardiac function.[36,37] Drug factors include molecular size, protein binding, route of elimination, drug charge and volume of distribution.[36-38] CRRT considerations include the type of filter used, the blood flow rate, the ultrafiltration rate, whether counter current dialysis is used and the volume and dialysate flow rate and any membrane interactions that may occur.[31,35-37,39-44]

With recovery from sepsis, these pathophysiological changes will reverse. The challenge for the clinician and prescribing team is to appropriately alter dosages of antibacterials in line with changes to organ function and third spacing.

2. Applied Clinical Pharmacology

To achieve the 'ideal' treatment of an infection, it is necessary to optimise the possible interactions between the host, the pathogen and the antibacterial.[11] This task becomes more difficult in critically ill patients, where recommended antibacterial regimens have been derived from volunteer studies or other patient groups who were not critically ill. Therefore, consideration of the effect of the pathophysiological changes, caused by sepsis, on the pharmacokinetic and pharmacodynamic parameters of the antibacterial is necessary. Further, since the physiology of these patients may change over a relatively short period of time, ongoing evaluations of sickness severity are indicated to allow timely adjustment of antibacterial dosing.

2.1 Pharmacokinetic Considerations

Pharmacokinetics refers to the study of concentration changes of a drug over a given time period. The primary pharmacokinetic parameters of importance to antibacterials include:

- V_d
- clearance
- $t_{1/2}$
- peak serum drug concentration achieved by a single dose (C_{max})
- minimum serum drug concentration during a dosing period (C_{min})
- area under the serum concentration-time curve (AUC).

These factors can be used to determine whether appropriate concentrations of the antibacterial are being delivered to the target area.[12]

2.2 Pharmacodynamic Considerations

Pharmacodynamics relate pharmacokinetic parameters (measures of drug exposure) and pharmacological effect. For antibacterials, pharmacodynamic parameters relate the pharmacokinetic factors to the ability of the antibacterials to kill or inhibit the growth of the infective organism.

Pharmacodynamic parameters include the following:

- the time for which the serum concentration of a drug remains above the minimum inhibitory concentration for a dosing period (T>MIC);
- the ratio of the antibacterial C_{max} to MIC (C_{max}/MIC);
- the ratio of the AUC during a 24-hour time period to MIC (AUC_{24}/MIC) [see figure 2].

Pharmacodynamically, the rate and extent of the bactericidal activity of an antibacterial is dependent

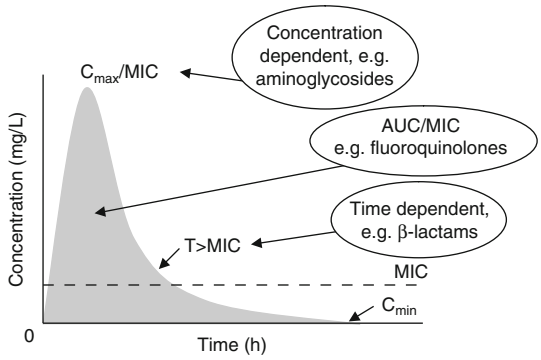

Fig. 2. Pharmacokinetic and pharmacodynamic parameters of antibacterials on a concentration vs time curve. **AUC** = area under the serum concentration-time curve; **C_{max}** = peak serum drug concentration; **C_{min}** = minimum serum drug concentration; **MIC** = minimum inhibitory concentration; **T>MIC** = time for which the serum concentration of a drug remains above the MIC for a dosing period.

on the interaction between drug concentrations at the site of infection, bacterial load, phase of bacterial growth and the MIC of the pathogen.[12] It follows that a change in any of these factors will affect the activity of the antibacterial against a particular pathogen and may affect the outcome of therapy. Developing dosing regimens that maximise the rate of response in patients with sepsis is important for accelerating patient recovery and minimising the development of antibacterial resistance.[12,45] Effective antibacterial therapy is essential to optimise patient outcomes.[6-10]

2.3 Kill Characteristics of Different Antibacterial Classes

Pharmacodynamically, different antibacterial classes appear to have different types of kill characteristics on bacteria (figure 2 and table I). These kill characteristics have been determined from *in vitro* studies and describe the pharmacokinetic measurements that represent optimal bactericidal activity.[12] The β-lactam group of antibacterials have a time-dependent (or concentration-independent) kill characteristic with T>MIC as the best predictor of efficacy.[46] In contrast, aminoglycosides have a concentration-dependent (or time-independent) kill characteristic where effect is determined by C_{max}/MIC.[47] Fluoroquinolones are more complex and were initially reported to be C_{max}/MIC dependent, although subsequent studies have also found that AUC_{24}/MIC is important[45,48] (table II).

2.3.1 Post-Antibiotic Effect

Most antibacterials demonstrate a post-antibiotic effect (PAE). PAE refers to the continued suppression of bacterial growth for prolonged periods when drug concentrations fall below the MIC of the bacteria.[70] β-Lactams demonstrate a modest PAE against Gram-positive organisms, but no PAE (except carbapenems) against Gram-negative organisms.[70,71] Aminoglycosides demonstrate a significant PAE (>3 hours), the duration of which is concentration dependent.[47,72-78] Fluoroquinolones also possess a prolonged PAE.[79,80] Interestingly, the PAE of an antibacterial can change in states of altered immune function, such as neutropenia,[81-83] or in critically ill patients with sepsis, although this has not been widely characterised for all antibacterials. A reduction in leukocyte count has been shown to reduce the efficacy of aminoglycosides.

2.3.2 Post-β-Lactamase Inhibitor Effect

Post-β-lactamase inhibitor effect (PLIE) refers to a period of continued suppression of bacterial growth after removal of a β-lactamase inhibitor (also known as suicide inhibitor).[84] It has been shown

Table I. Pharmacodynamic properties that correlate with the efficacy of selected antibacterials

Antibacterials	Pharmacodynamic kill characteristics	Optimal pharmacodynamic parameter
Aminoglycosides Metronidazole Fluoroquinolones	Concentration dependent	C_{max}/MIC
Fluoroquinolones Azithromycin Tetracyclines Glycopeptides	Concentration dependent with time dependence	AUC_{24}/MIC
β-Lactams Carbapenems Linezolid Erythromycin Clarithromycin Clindamycin	Time dependent	T>MIC

AUC_{24} = area under serum concentration-time curve during 24-hour time period; **C_{max}** = peak plasma drug concentration; **MIC** = minimum inhibitory concentration; **T>MIC** = time for which the serum concentration of a drug remains above the MIC for a dosing period.

Table II. General pharmacokinetic characteristics of selected antibacterial classes and possible changes that can occur during fluid shifts in critically ill patients[a]

Antibacterial class	V_d	Increased V_d with fluid shifts	Decreased C_{max} with fluid shifts	$t_{1/2}$	Protein binding	Altered CL in sepsis	TDM required
Aminoglycosides[49-52]	0.2–0.3 L/kg (consistent with extracellular water)	Yes	Yes	2–3h	Low	Varies proportionately with renal function	Yes – to ensure high C_{max} and adequate CL[53-58]
β-Lactams[29,30,59-61]	Variable but consistent with extracellular water	Yes	Yes	0.5–2h (except ceftriaxone)[62]	Low (except ceftriaxone and oxacillin)	Varies proportionately with renal function (some exceptions; e.g. cefoperazone[63])	No
Carbapenems[64]	Variable but consistent with extracellular water	Yes	Yes	1h (except ertapenem 4h)	Low (except ertapenem)	Varies proportionately with renal function	No
Vancomycin[65]	0.2–1.25 (consistent with extracellular water)	Yes	Yes	4–6h	30–55%	Varies proportionately with renal function	Yes – to ensure serum trough concentrations >15 mg/mL[66]
Fluoroquinolones[67-69]	Variable and often unrelated to extracellular water	No	Yes	3h (increases to 4–5h in the elderly	20–40%	Variable – especially levofloxacin and gatifloxacin with variation proportionate to renal function	No

a All values quoted are for healthy volunteers unless otherwise indicated.

CL = apparent total body clearance; **C_{max}** = peak serum drug concentration; **$t_{1/2}$** = elimination half-life; **TDM** = therapeutic drug monitoring; **V_d** = volume of distribution.

to occur *in vitro* for amoxicillin plus clavulanic acid,[84] and more recently, ceftazidime plus sulbactam.[85] It is thought that a β-lactam and suicide inhibitor (e.g. clavulanic acid or sulbactam) may be combined to utilise this PLIE in extended-spectrum β-lactamases, to enable reduced β-lactam doses.[84] However, to date there is scarce evidence of the clinical effects of PLIE itself.

3. Antibacterial Classes

General pharmacokinetic and pharmacodynamic characteristics is considered for aminoglycosides, β-lactams, glycopeptides and ciprofloxacin (as a representative of the fluoroquinolones) . The clinical application and dosing implications of these properties for critically ill patients is also addressed.

3.1 Aminoglycosides

3.1.1 Pharmacokinetics – General

The debate of aminoglycoside dosing continues because of the narrow therapeutic index of these drugs. There is accumulating evidence to show that administering aminoglycosides as a once-daily dose is associated with less nephro- and ototoxicity than the same total dose administered in small, multiple doses.[86-91] It is therefore considered that the troughs – or more specifically the AUC – are more closely correlated with the well documented adverse renal and ototoxic effects of these drugs.[86-91] Monitoring of serum aminoglycoside concentrations is essential for minimising these adverse effects. The serum half-life of aminoglycosides will increase in renal impairment as they are excreted unchanged almost entirely by glomerular filtration.[49]

3.1.2 Pharmacodynamic Principles of Aminoglycosides

The kill characteristic of the aminoglycosides is concentration dependent.[72-78,92-94] Experimentally, a high C_{max} of an aminoglycoside antibacterial provides a better, faster killing effect on standard bacterial inocula. In a retrospective study, Moore et al.[47] demonstrated, quite unequivocally, that a high C_{max} of an aminoglycoside relative to the MIC for the infecting organism was a major determinant of the clinical response. Aminoglycosides also exhibit a significant PAE, which can prevent bacterial regrowth for prolonged periods should drug concentrations fall below the MIC.[47,70,72-78,91]

To clarify, the properties of aminoglycosides are as follows: (i) high widely spaced doses causing less toxicity than smaller more frequent doses; (ii) high doses producing better kill curves; and (iii) the PAE led to the development of single daily dosing for aminoglycoside antibacterials.[95,96] It has now been shown in prospective clinical trials[53,97-99] and numerous meta-analyses[87-90] that this recommendation is valid, i.e. large, single, daily doses (or more correctly, extended interval dosing) of aminoglycosides produce less toxicity and comparable, if not superior clinical outcomes.

3.1.3 Pharmacodynamic Considerations for Critically Ill Patients with Sepsis

The problem of patient variability in peak aminoglycoside serum concentrations has been observed in critically ill patients.[49,50,100-109] In sepsis without organ dysfunction there is typically increased aminoglycoside clearance.[50,76,107,109] An increase in aminoglycoside V_d has been noted in patients with sepsis, due to the processes described above,[21,22,110] and with patient sickness severity, measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score.[111] Importantly, the critically ill patient with a high APACHE II score and normal renal function will not only have lower trough concentrations, but also lower peak concentrations compared with a patient who has a lower APACHE II score. The effect of sickness severity on aminoglycoside concentrations, resulting in a change in V_d in an individual patient during the course of therapy, may explain in part the wide variability of dosages needed to achieve therapeutic concentrations as reported in published studies.[50,100-109]

The aminoglycoside PAE has been demonstrated in Gram-positive and Gram-negative organisms.[82,112] *In vitro* studies have shown enhanced bacterial phagocytosis by leukocytes after exposure to aminoglycosides, which has been termed the post-antibiotic leukocyte enhancement (PALE).[113]

It follows that in a critically ill patient with neutropenia or a low leukocyte count (as shown in animal models[82]), aminoglycosides may have decreased efficacy. This has been supported by data showing that as the absolute neutrophil count decreases, higher bactericidal activity is required,[83] and this may be obtained by increasing the aminoglycoside C_{max}. The value of once-daily dosing in this population has been studied[81] and randomised trials comparing once-daily and multiple-daily dosing of aminoglycosides have been performed with co-administration of a β-lactam antibacterial. These studies were subjected to a meta-analysis that found no significant differences in efficacy between once-daily and multiple-daily dosing.[114] However, there is reduced toxicity from once-daily dosing.[115] Until there are further studies suggesting otherwise, the evidence supports the administration of high-dose, once-daily aminoglycosides, given with a broad spectrum β-lactam antibacterial, to critically ill patients with sepsis who have a low leukocyte count.

3.1.4 Summary of Aminoglycoside Dosing in Critically Ill Patients with Sepsis

Tobramycin and gentamycin should be initially administered at 7 mg/kg (amikacin 20–30 mg/kg) to enable a high C_{max}/MIC ratio with drug clearance monitored by using either published nomograms[110] or trough serum concentrations if renal dysfunction is suspected. Such dosing should enable a C_{max}/MIC ratio >10, which maximises the PAE and bacterial killing.[70,110,116] Subsequent doses should be individualised.[110] If drug or creatinine clearance is reduced, then maintenance of doses to maximise the C_{max}/MIC ratio at extended intervals is recommended, even if that requires 36- or 48-hourly dosing. In patients with renal function within the reference range, 24-hour dosing using published nomograms could be used.[54,55] Alternate methods of monitoring aminoglycosides after once-daily dosing have also been successfully suggested,[53,56,57] including using Bayesian methods that have shown reduced toxicity profiles.[54,55,58]

3.2 β-Lactam Antibacterials

3.2.1 Pharmacokinetics – General

The β-lactam group of antibacterials consists of penicillins, cephalosporins, carbapenems and monobactams. Evidently, this group encompasses many compounds and variability certainly exists (e.g. ceftriaxone has a longer $t_{1/2}$ [5.8–8.7 hours] in adults, and high protein binding [>80%],[62] table II). In conventional bolus dosing regimens, serum concentrations of these antibacterials fall to low levels between doses.[29,59,117] Renal elimination of these drugs is often linearly related to CL_{CR}, so serum concentrations will increase in the presence of renal dysfunction[30,60] except for those β-lactams that have significant biliary clearance (e.g. ceftriaxone and oxacillin). In contrast, low serum concentrations of these antibacterials can occur in the acute phase of sepsis because of enhanced cardiac and renal (and possibly hepatic) function resulting in high drug clearance.[29,59]

3.2.2 Pharmacodynamic Principles of β-Lactam Antibacterials

Kill characteristics of β-lactam antibacterials differ significantly from those of aminoglycosides. *In vivo* animal experiments have demonstrated that β-lactams have a slow continuous kill characteristic that is almost entirely related to the time for which concentrations in tissue and serum exceed a certain threshold (generally the MIC) of the infecting organism (T>MIC).[46] Once the concentration of the antibacterial falls below this threshold, any remaining bacteria multiply almost immediately.[72-77,92,93,118] This may also facilitate the development of antibacterial resistance, particularly if the serum concentrations fall below the threshold for more than half the dosing interval.[119] It has been proposed that, in the absence of any PAE, the serum concentration of a β-lactam antibacterial should exceed the MIC for the respective organism for 90–100% of the dosing interval.[120] Animal and *in vitro* studies show that β-lactams do confer a PAE on Gram-positive staphylococci, streptococci and enterococci, while only carbapenems have demonstrated a PAE against Gram-negative orga-

nisms.[46,71,112,121-126] Other studies have demonstrated maximum killing of bacteria at 4–5 times MIC, with still higher concentrations providing no added efficacy.[127,128] As such, it has been proposed that concentrations of β-lactam antibacterials should be maintained at 4–5 times the MIC for extended periods during each dosing period.[73-75] It is noteworthy that bolus dosing (e.g. of cephalosporins) produces unnecessary peak and low trough concentrations below the MIC for much of the dosing interval.[29,59,129,130] It follows that an improved antibacterial profile is obtained with either more frequent dosing[59,120] or continuous infusions.[59,118,120,121,127,129-136]

At the clinical level, dosing regimens of β-lactam antibacterials are currently undergoing re-evaluation to ascertain the optimal T>MIC.[117,118,120,128,137] Numerous studies have compared administration of β-lactams by continuous infusion with bolus dosing.[118,127,138-140] The results have largely shown comparable therapeutic efficacy with other literature purporting improved patient survival, decreased length of stay in ICU and decreased resources expended on patient therapy when continuous infusion is used.[7,141] Continuous infusion has also shown a reduction in the total daily dose of drug required.[127,131,142-148] Further research is necessary to quantify the clinical utility of administering β-lactams as a continuous infusion.

3.2.3 Pharmacodynamic Considerations for Critically Ill Patients with Sepsis

It is increasingly apparent that the pharmacokinetics of the β-lactam antibacterials in the critically ill patient with sepsis are different from those in other patients.[149,150] Some studies have shown an increased V_d.[17,29,151] Sepsis without organ dysfunction can lead to increased β-lactam clearance and result in lower serum concentrations than expected.[29,50,59,76,107,109,127,129-131,149,150] High β-lactam clearance has been demonstrated in several other studies.[29,59,127,129-131] One inclusion criterion common to many of these studies was normal serum creatinine. In two of these studies it was shown that the clearance of cefepime and, more recently, cefpirome is linearly related to CL_{CR}.[29,59] As such, CL_{CR} was reported to be an independent predictor of antibacterial clearance. Pharmacokinetic/pharmacodynamic modeling showed that the T>MIC could be predicted by CL_{CR}, and that serum concentrations of these antibacterials were low when using a standard dosing regimen.[29,59] As a result, dosage adjustment according to increased renal function is an important pharmacokinetic consideration to ensure optimal therapy that complies with β-lactam pharmacodynamic properties. This may require increased dosing or preferably increased frequency of dosing to ensure T>MIC is maximised. Preliminary data suggest clinical and bacteriologic superiority when administering ceftriaxone by continuous infusion compared with bolus dosing of ceftriaxone in patients with sepsis.[152]

In severe sepsis with renal and/or hepatic dysfunction, reduced β-lactam clearance can occur. Consequently, serum drug concentrations may be elevated to higher than expected concentrations. Dependent on the infective organism and toxicity profile of the β-lactam, dose reduction may be indicated. Severe sepsis may also lead to an immune system dysfunction evident by the presence of neutropenia. Previous studies with *Klebsiella pneumoniae* have suggested that neutropenia may not reduce the antibacterial effect of β-lactams significantly, but may enable a relapse of infection when antibacterial therapy is ceased.[153,154] It follows that critically ill patients may require β-lactam therapy until the white blood cell count normalises.

3.3 Carbapenems

3.3.1 Pharmacokinetics – General

Carbapenems are a separate class of β-lactam antibacterials that possess good Gram-negative and Gram-positive activity. Like other β-lactams, these antibacterials typically have a minimal adverse-effect profile.[64] Increased seizure activity has been noted with imipenem and as a result has been recorded as a potential adverse event for all carbapenems, particularly in infants, elderly patients and those with renal dysfunction.[155-158] Because of its instability, imipenem is typically combined with cilastatin and betamipron is combined with

panipenem as a renal protectant.[159] These adjuncts have higher protein binding and may accumulate in patients with renal failure, the significance of which is unknown.[64]

In conventional bolus dosing regimens, serum concentrations of carbapenems fall to low concentrations between dosages. Renal elimination of these drugs is directly related to CL_{CR}, so serum concentrations may accumulate in renal dysfunction if dosage adjustments are not made.[64,160-162]

3.3.2 Pharmacodynamic Principles of Carbapenems

Kill characteristics of carbapenems are similar to other β-lactam antibacterials and show time-dependent killing.[120] However, *in vitro* models have shown that carbapenems require a reduced percentage of T>MIC for bacteriostatic activity (20%) and bactericidal activity (40%),[163] which may relate to the carbapenem PAE.[123] Thus, while the apparent need for more frequent dosing or administration by continuous infusion is reduced from this *in vitro* data, concentration-related toxicity can be avoided[46,163] and pharmacoeconomic advantages from a reduced total daily dose may still be conferred.[164] Optimisation of the pharmacodynamic profile of carbapenems has been shown previously by the use of extended infusions,[165-167] although, to date only improved *in vitro* efficacy has been reported.[167,168] Further research to determine the clinical efficacy of administering carbapenems as a continuous infusion is required.

3.3.3 Pharmacodynamic Considerations for Critically Ill Patients with Sepsis

As with other β-lactam antibacterials, the pharmacokinetics of the carbapenems change in critically ill patients with sepsis. Specifically, carbapenems demonstrate decreased $t_{1/2}$ and increased V_d and clearance.[169,170] In sepsis without organ dysfunction, as with aminoglycosides and other β-lactams, increased clearance can occur resulting in lower serum concentrations of carbapenems. Higher dosing or more frequent dosing may, therefore, be indicated for critically ill patients with sepsis without organ dysfunction. Administration by continuous infusion, to maximise T>MIC remains a topical issue for carbapenems. Some research has shown meropenem to be unsuitable for 8-hour infusions in a tropical country, where the room temperature was 32–37°C[171] and that it spontaneously degrades in saline solutions after <6 hours at normal room temperature (25°C).[172] Other research has shown adequate stability for 8-hour infusions to be administered[167,173] and up to 12 hours in a cold pouch.[174] Intermittent 3-hour infusions have also been utilised in previous studies.[175] Some preliminary data suggest clinical superiority of administration by continuous infusion in critically ill patients;[176] however, further studies are needed. Because of the stability concerns associated with meropenem, the use of intermittent 3-hour infusions is suggested to optimise the pharmacodynamic profile.

As with other β-lactams, the impaired immune function of the critically ill patient will most likely have little effect in changing the MIC breakpoints. Therefore, individualised dosing, dependent on the sickness severity, fluid shifts and organ function, is required in this patient population.[153]

3.4 Glycopeptides (Vancomycin and Teicoplanin)

3.4.1 Pharmacokinetics – General

Vancomycin has a V_d of 0.2–1.25 L/kg and a $t_{1/2}$ of 4–6 hours (table II) in patients with normal renal function, which may extend to 19 hours in chronic renal failure. It is 30–55% protein bound and distributes widely into extracellular water.[65,177] It is predominantly renally eliminated and while it has been associated with self-limiting nephrotoxicity, particularly during co-administration of other nephrotoxins,[178,179] its potential to cause nephrotoxicity has been debated.[65] However, Fernandez de Gatta et al.[66] found a relationship between vancomycin exposure and nephrotoxicity and provided evidence that therapeutic drug monitoring of vancomycin led to a reduced incidence of nephrotoxicity.

Teicoplanin has a V_d of 0.9–1.6 L/kg (at steady-state concentrations) and a $t_{1/2}$ of 80–160 hours in patients with normal renal function, which may be

extended in patients with renal failure.[180-182] It is 90% protein bound and distributes widely into extracellular water. It is predominantly renally eliminated. A decrease in albumin level or binding increases the V_d and clearance of teicoplanin.[181] Therapeutic drug monitoring of teicoplanin is not necessary to avoid toxicity, but can be helpful in certain patient groups to ensure therapeutic concentrations are present.[182]

3.4.2 Pharmacodynamic Principles of Glycopeptides

The specific interpretation of the pharmacodynamic properties of glycopeptides is not fully understood. Vancomycin is preferentially discussed as representative of the glycopeptides due to its increased usage. Vancomycin is well known to induce PAE and has pharmacodynamic properties in common with both aminoglycosides and β-lactams. Some data suggest that the bactericidal activity of vancomycin is time-dependent.[183-185] Larsson et al.[183] demonstrated this in an *in vitro* staphylococcal model suggesting that maximising kill rates is achieved by maintaining concentrations above the MIC.[153] Similar results have been obtained for teicoplanin in a rabbit endocarditis model.[186] Interestingly, an *in vitro* study[187] found no difference in rates of killing of *Staphylococcus aureus* by vancomycin when given as various forms of continuous infusion and bolus dosing, suggesting that T>MIC is not the categorical pharmacodynamic factor. C_{max}/MIC was found to be the pharmacodynamic factor correlated with efficacy in a non-neutropenic mouse peritonitis model for *Streptococcus pneumoniae* and *S. aureus* suggesting that glycopeptides might show concentration-dependent killing against some organisms.[188] Whether this pharmacodynamic effect is primarily because of the presence of neutrophils in this model is unknown.

Other studies have proposed that AUC_{24}/MIC is the most important pharmacokinetic/pharmacodynamic parameter correlating with efficacy.[153,177] As such, the optimal dosing regimen for administration of vancomycin remains unknown; continuous infusion ensures the T>MIC property without the benefits of the PAE, while the reverse exists if vancomycin is administered by bolus dosing. Wysocki et al.[189] specifically compared continuous infusion and intermittent dosing of vancomycin in 160 patients and found no significant difference in clinical efficacy. However, recently Rello et al.,[190] described a suggestion of clinical superiority of continuous infusion of vancomycin in a subset of patients treated for ventilator-associated pneumonia caused by methicillin-resistant *S. aureus* (MRSA). Thus, while the economic advantages of reduced dosage of vancomycin by continuous infusion have been described,[189] the possible clinical advantages remain unclear.

3.4.3 Pharmacodynamic Considerations for Critically Ill Patients with Sepsis

Sepsis without organ dysfunction will cause an increased V_d from increased extracellular water and an increased rate of renal excretion of vancomycin. As a consequence, in our experience we have found that higher doses than those conventionally recommended (similar to paediatric doses 40 mg/kg/day[191]) may be needed to optimise serum concentrations. It also seems that the greater the third spacing in the patient, the higher the dose of vancomycin needed to achieve any target concentration.[191] However, with renal dysfunction there will be reduced clearance and drug accumulation.[178,179,192] As a result, diligent monitoring of trough vancomycin serum concentrations (recommended concentration 15–20 mg/L) is currently recommended to ensure efficacy of dose by following the T>MIC pharmacodynamic property.[193] These concentrations can be maintained by dosing 6-, 8- or 12-hourly or by continuous infusion, although the optimal dosing regimen for vancomycin remains unresolved because of the lack of definitive evidence of pharmacodynamic efficacy and evidence linking concentrations to either outcome or toxicity.[184,193] The ongoing debate on the optimal administration of vancomycin[184,187,189,190,194] demonstrates the need for further research in this area. Improved outcomes from dosing glycopeptides by continuous infusion may particularly be found in critically ill patients with neutropenia.

Another factor emerging for the prescribing team to consider when ordering vancomycin, is its poor penetration into solid organs, particularly the lung.[195,196] Thus, if the sepsis is thought to emerge from a lung focus, the co-prescription of rifampicin (rifampin) as dual therapy has been suggested.[195] Therapy with rifampicin as a single agent is not recommended because of its propensity to cause bacterial resistance.[197] Alternatively, high-dose vancomycin (aiming for trough concentrations ≥20 mg/L) has been advocated[197] for sepsis originating in solid organs. Of course, other antibacterial agents do provide better penetration of the epithelial lining fluid of the lung and, thus, therapy with either, linezolid,[198] tigecycline[199] or televancin[200] may be preferred. We believe that teicoplanin does not add many clinical advantages and that newer drugs in production will take its place as vancomycin substitutes.

3.5 Ciprofloxacin (as a Representative of the Fluoroquinolones)

3.5.1 Pharmacokinetics – General

Ciprofloxacin is metabolised in liver to multiple metabolites although dosage adjustment is only recommended, by the product information,[67] in renal dysfunction to prevent accumulation of drug and metabolites.[201] Other research by Jones[202] has shown impaired ciprofloxacin clearance in renal impairment only when the patient had concomitant bowel or liver pathology, suggesting that accumulation will only occur when at least two elimination pathways are compromised. The researcher recommended that in critically ill patients with sepsis and acute renal impairment, dosage adjustment is only necessary if the patient also has intra-abdominal disease. It should be noted that the fluoroquinolones, levofloxacin and gatifloxacin are only moderately lipophilic, which confers a higher rate of renal clearance suggesting that reduced doses are necessary during renal failure (table II).[203-205]

3.5.2 Pharmacodynamic Principles of Fluoroquinolones

Ciprofloxacin displays largely concentration-dependent kill characteristics, but also some time-dependent effects. Previous research has suggested that achieving a C_{max}/MIC ratio of 10 for ciprofloxacin is the critical variable in predicting bacterial eradication.[206] Forrest et al.[48] studied ciprofloxacin in critically ill patients and concluded that achieving an AUC_{24}/MIC >125 is associated with a successful clinical outcome. This result is necessary for Gram-negative organisms with Gram-positive organisms requiring an AUC_{24}/MIC of 30,[48,207-209] although fluoroquinolones should not be used as single agent treatment of Gram-positive infections. Inappropriate low-dose administration of ciprofloxacin has also been associated with the emergence of resistant bacterial strains (particularly enterococci, *Pseudomonas* and MRSA).[210-212] For Gram-negative bacteria, this may occur when the AUC_{24}/MIC is <100.[213,214] Therefore, AUC_{24}/MIC and C_{max}/MIC are pharmacodynamic variables that require close attention for optimal fluoroquinolone usage.

3.5.3 Pharmacodynamic Considerations for Critically Ill Patients with Sepsis

Ciprofloxacin (like other quinolone antibacterials) is commonly used in critically ill patients because of its broad spectrum and good tissue penetration.[215] Pharmacokinetic studies in adult patients with severe sepsis and intra-abdominal sepsis[215] have shown that the V_d of ciprofloxacin is not altered with fluid shifts, or over time, since it distributes intracellularly and binds to structures therein. This characteristic is also maintained for the infant <12 months old,[28] where body water content is greater than that in older children and adults. In contrast, vancomycin and aminoglycosides distribute into the extracellular and intravascular compartments. Thus, changes in the extracellular, intravascular compartment will affect C_{max} and V_d more than if these latter drugs would be distributed throughout all tissues. Ciprofloxacin, on the other hand, is distributed more widely within the body, which allows the V_d for ciprofloxacin to remain relatively unchanged. Thus, while dosage adjustments for altered V_d are not required in critically ill patients, dosage adjustments may be necessary in enhanced or reduced renal function. As stated previously achieving an AUC_{24}/MIC of >125 for Gram-

negative organisms is associated with improved clinical outcomes in critically ill patients. The dosage recommended to achieve these pharmacodynamics is intravenous ciprofloxacin 400mg 8-hourly in adults and this need not be changed during sepsis unless renal dysfunction occurs.[215,216]

4. Conclusion

Current antibacterial regimens have been derived from trials with patients who are not critically ill with conditions such as sepsis. In order to optimise antibacterial regimens in patients with sepsis, the pathophysiological effects of SIRS need consideration, in conjunction with knowledge of the different kill characteristics of the various antibacterial classes. The end result will be dosing and regimens that are more appropriate for use in critically ill patients with sepsis that may differ from more common antibiotic prescribing practices.

Certain antibacterials can have a high V_d during sepsis leading to a reduced C_{max}. It follows then that underdosage may occur if a high C_{max} is needed (e.g. aminoglycosides).

The V_d of antibacterials that distribute primarily into extravascular water, namely aminoglycosides, vancomycin and, to a lesser extent, β-lactams, changes with clinical severity, so dosing may need to be altered during the course of illness; something not described for non-critically ill patients.

Some patients with serum creatinine within the normal range can have higher than normal drug clearances, thereby producing low serum concentrations. If a drug needs to have a minimum serum concentration maintained (e.g. β-lactams), a high drug clearance will lead to underdosage for renally excreted drugs. In other words when CL_{CR} is high, the renal clearance of these drugs will be high. In relation to the aminoglycosides, this means that not only are large doses required to be administered, but because of a high CL_{CR} these antibacterials may also need dosing even more frequently than every 24 hours. As discussed before, all β-lactams should, in such patients, be administered more frequently than suggested in non-sepsis patients. In view of renal clearance of the fluoroquinolones, in the presence of a high CL_{CR} we can assume fluoroquinolone clearance is also high. If this were true these antibacterials would also need to have higher daily doses than proposed in the standard literature. We have shown that in adults with normal renal function ciprofloxacin can be safely administered intravenously at 400mg 8-hourly.

The treatment of sepsis remains a significant challenge given the persisting high morbidity and mortality rates. Data suggest that effective antibacterial therapy remains the most important intervention available to the clinician. In treating sepsis, a clinician must be aware of the impact of the various pathophysiological and subsequent pharmacokinetic changes that can occur during sepsis. In this article we have described the common antibacterial classes and the pharmacodynamic features that must be recognised to optimise clinical efficacy. Facilitation of these pharmacodynamic parameters will optimise antibacterial therapy in patients with sepsis, and augment therapeutic outcomes.

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