



Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

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Lancet Infect Dis 2014;
14: 498–509

Published Online

April 24, 2014

[http://dx.doi.org/10.1016/S1473-3099\(14\)70036-2](http://dx.doi.org/10.1016/S1473-3099(14)70036-2)

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Infections in critically ill patients are associated with persistently poor clinical outcomes. These patients have severely altered and variable antibiotic pharmacokinetics and are infected by less susceptible pathogens. Antibiotic dosing that does not account for these features is likely to result in suboptimum outcomes. In this Review, we explore the challenges related to patients and pathogens that contribute to inadequate antibiotic dosing and discuss how to implement a process for individualised antibiotic therapy that increases the accuracy of dosing and optimises care for critically ill patients. To improve antibiotic dosing, any physiological changes in patients that could alter antibiotic concentrations should first be established; such changes include altered fluid status, changes in serum albumin concentrations and renal and hepatic function, and microvascular failure. Second, antibiotic susceptibility of pathogens should be confirmed with microbiological techniques. Data for bacterial susceptibility could then be combined with measured data for antibiotic concentrations (when available) in clinical dosing software, which uses pharmacokinetic/pharmacodynamic derived models from critically ill patients to predict accurately the dosing needs for individual patients. Individualisation of dosing could optimise antibiotic exposure and maximise effectiveness.

Introduction

Patients in intensive care units differ considerably from those in general ward environments and have substantially higher mortality rates. These patients are usually critically ill and have a high level of sickness severity that is associated with profound pathophysiological changes requiring aggressive medical interventions.^{1,2} Health-care providers are treating a growing number of critically ill patients, but clinical outcomes for many subgroups of patients are not improving substantially.³ In particular, critically ill patients with sepsis, septic shock, or acute kidney injury, are a substantial challenge to infectious diseases physicians, critical care physicians, nephrologists, and clinical pharmacists and pharmacologists.

In studies of sepsis and septic shock, interventions that optimised antibiotic therapy improved clinical outcomes the most.^{4–9} Early and appropriate antibiotic administration reduces mortality rates,^{6–8} but less information is available about the effect of appropriate dose regimens on clinical outcome.¹⁰ Although robust data are available for exposure effect relations between antibiotics and bacterial killing in vitro and in animals,^{11,12} the effect of antibiotic exposure on mortality has not been defined as precisely, although, some studies of these relations, mostly observational or retrospective in nature, are available.

Results from a randomised controlled trial with aminoglycosides by van Lent-Evers and colleagues¹³ showed that a dedicated therapeutic drug-monitoring intervention (also described as therapeutic drug management) in a general patient cohort in one hospital significantly reduced their length of stay (mean 20.3 days [SD 1.4]), compared with the length of stay for patients who did not have therapeutic drug monitoring (26.3 [2.9]; $p=0.045$).¹³ Studies of quinolones,^{10,14,15} β lactams,^{10,16–19} glycopeptides,^{20,21}

and linezolid²² all have results from at least retrospective cohort analyses that show advantages in terms of clinical cure, mortality, or both, associated with achievement of target pharmacokinetic/pharmacodynamic indices. The major challenge for clinicians is to ensure that dosing achieves these pharmacokinetic/pharmacodynamic targets in all patients.

Information about effective antibiotic dosing specifically for critically ill patients is not usually included in treatment guidelines—product information for the antibiotic usually guides the choice of dose for such patients. However, product information is based on dose-finding studies in patients who are not critically ill, and the results are then extrapolated to critically ill patients, which might not be accurate for this population. Many critically ill patients have severely altered pharmacokinetic characteristics, which might reduce the likelihood that they will achieve the pharmacokinetic/pharmacodynamic targets that are associated with improved likelihood of positive clinical outcomes.^{23,24} Even general dosing guidelines for patients in intensive care units might not be a satisfactory solution because critically ill patients have substantial pharmacokinetic variability. Increased pharmacokinetic variability reduces the ability to predict therapeutic doses of antibiotic for individual patients, which could potentially worsen outcomes for patients.

After many years of dosing antibiotics in critically ill patients with a “one dose fits all” strategy there is a strong rationale to move to an individualised approach to dosing. This change is further supported by the problem of reduced antibiotic development, the need to make better use of currently available antibiotics, and the growing problem of antibiotic resistance.

In this Review, we describe the challenges of changes in pharmacokinetic characteristics caused by

pathophysiological changes often seen in critically ill patients, and the challenges of the reduced susceptibility to antibiotics of bacterial organisms that is frequently encountered in intensive care. Either pharmacokinetics or pharmacodynamics, or both, affect the pharmacokinetic/pharmacodynamic ratio, and in turn, the magnitude of the pharmacokinetic/pharmacodynamic target. Therefore, we considered solutions to these challenges in the form of individualised dosing strategies, supported by different bedside dosing techniques based on software packages.

Challenge 1: effect of critical illness on antibiotic pharmacokinetics

Overview

Dysfunction of one or many organ systems occurs in critical illness and might substantially change antibiotic concentrations from those seen in patients who are not critically ill (figure). Without rational dose adjustment, these changes in drug concentrations can predispose patients to clinical failure, emergence of antimicrobial resistance, or even toxic effects from the drug. Therefore we first review the pharmacokinetic effects caused by dysfunction of the cardiovascular, renal, pulmonary, and hepatic systems.

Cardiovascular system

Critically ill patients frequently have systemic inflammatory response syndrome caused by pathological changes that are either infectious or non-infectious.²⁵ A major consequence of systemic inflammatory response syndrome, particularly in patients with severe sepsis and septic shock, is extreme fluid extravasation into interstitial space from endothelial damage and capillary leakage. This extravasation, known as third spacing,²⁵ results in hypotension; in response clinicians give large volumes of resuscitation fluids that might also distribute into interstitial fluid and thereby substantially increase interstitial volume. For hydrophilic antibiotics, a rise in interstitial volume might lead to a large increase in

volume of distribution.²⁶ By contrast, lipophilic antibiotics (eg, fluoroquinolones and macrolides) have an inherently larger volume of distribution that is often not greatly affected by such fluid movements or administration.²⁷

Volume of distribution for hydrophilic antibiotics such as aminoglycosides,^{28,29} β lactams,^{26,30} glycopeptides,³¹ and linezolid³² can be up to two times greater in critically ill patients, than in patients who are not critically ill.

Hypoalbuminaemia, defined as a serum albumin concentration less than 25 g/L, is a common but frequently neglected disorder in intensive care units (incidence 40–50%³³). Uildemolins and colleagues³⁴ have reviewed hypoalbuminaemia in detail and concluded that its effect on antibiotic pharmacokinetic characteristics in critically ill patients might be clinically important. Reduced concentrations of albumin could raise the unbound fraction of protein-bound drugs such as antibiotics.³⁵ Unbound fractions of antibiotics are available not only for elimination, but also for distribution. For antibiotics that are moderately to highly-protein bound (eg, ceftriaxone,³⁶ flucloxacillin,³⁷ ertapenem,^{38,39} and daptomycin⁴⁰) the volume of distribution rises by up to 100% in critically ill patients with hypoalbuminaemia. Fluid shifts and altered protein-binding, both often seen in mechanically ventilated patients, raise volume of distribution. An increased volume of distribution might reduce the peak concentration of drugs, which might in turn reduce the effectiveness of antibiotics that are concentration-dependent (eg, aminoglycosides). These drugs need a high ratio of maximum concentration of unbound antibiotic to minimum inhibitory concentration and a high ratio of area under the concentration–time curve to minimum inhibitory concentration for maximum bacterial killing.^{41–43} However, for a drug that is highly protein-bound (eg, daptomycin), hypoalbuminaemia will probably lead to a high free fraction of antibiotic in the early part of the dosing interval, which might result in advantageously high unbound concentrations. By contrast, for time-dependent β lactam antibiotics, changes in volume of distribution and protein binding can lead to

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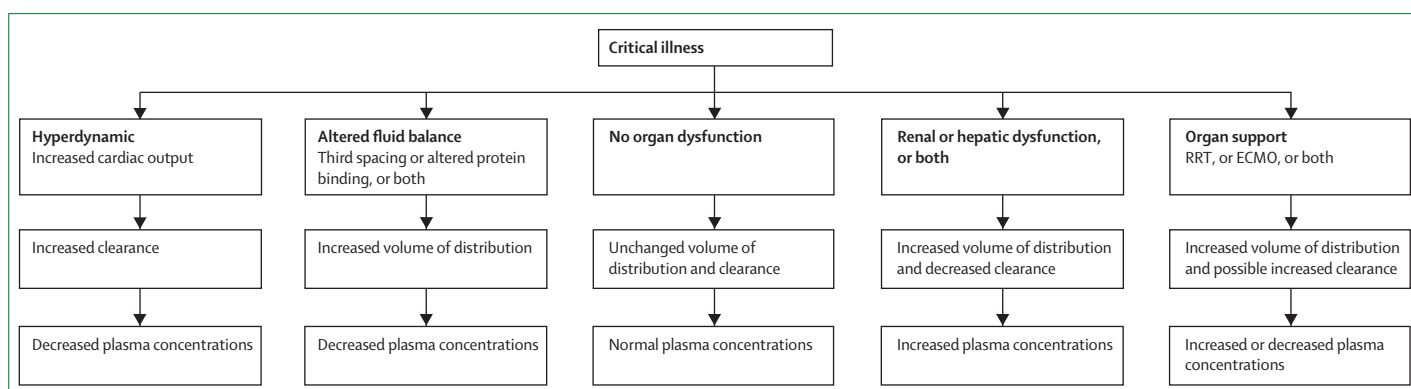


Figure: The range of altered pathophysiology in patients with critical illness, and its effects on drug concentrations
RRT=renal replacement therapy. ECMO=extracorporeal membrane oxygenation.

low unbound concentrations later in the dosing interval in critically ill patients. The concentration of unbound antibiotic in patients who are critically ill could fall to subtherapeutic concentrations and put patients at risk of treatment failure.^{35,36}

Importantly, increased severity of illness is associated with increased volume of distribution, so the most critically ill patients will probably have the least amount of antibiotic exposure if standard dosing is used, at least in the first days of treatment.²⁹ With recovery from infection, volume of distribution returns to normal and, for longer courses of therapy, dose modifications throughout treatment are often needed. For all antibiotic classes, which include concentration-dependent antibiotics, an increased volume of distribution might delay the time taken to reach therapeutic concentrations.

Antibiotics need to reach effective concentrations in the interstitial fluid of tissues, because this is the site of most infections.⁴⁴ However, severe infections can cause vascular dysfunctions such as microvascular failure, which can impair drug delivery into body tissues.⁴⁵ Several studies report impaired tissue penetration for various antibiotics in patients with severe infection. Antibiotics in these studies included cefpirome,⁴⁶ fosfomycin,⁴⁷ piperacillin,^{45,48} and levofloxacin,⁴⁹ and subtherapeutic concentrations in tissue for all these antibiotics are common in the early phase of treatment, particularly in patients with septic shock who are also receiving vasopressors.⁴⁵ Therefore, at least for the antibiotic classes above, plasma concentrations might be an imprecise surrogate for tissue concentrations.

Renal system

Many widely used antibiotics in critically ill patients are cleared renally, and therefore their concentrations will be affected by changes in renal function. Although standard practice is to reduce antibiotic doses in the presence of acute kidney injury to avoid toxic effects, some critically ill patients can develop augmented renal clearance where glomerular filtration is increased in some patients. Augmented renal clearance, defined as a creatinine clearance of at least 130 mL/min, is a potential reason for underdosing, and thus some critically ill patients with renal impairment might actually need more intensive regimens of antibiotics.

Augmented renal clearance is driven by pathophysiological responses to infection and treatment interventions (eg, fluid resuscitation and use of vasopressors) that are also associated with an early increase in cardiac output and enhanced blood flow to major organs.⁵⁰ Increased perfusion to the kidneys enhances drug delivery and therefore substantially raises glomerular filtration and clearance of renally cleared solutes, including some antibiotics, such as aminoglycosides, β lactams, and glycopeptides.^{1,51,52} Augmented renal clearance is frequently seen in critically ill patients with normal serum creatinine

concentrations, and typically happens in younger men (aged less than 55 years) with trauma, sepsis, burns, haematological malignant disease, or pancreatitis.⁵³ In an investigation by Udy and colleagues⁵⁴ up to 82% of patients with augmented renal clearance did not achieve therapeutic antibiotic concentrations with standard doses.

Any reduction in kidney perfusion, including micro-circulatory failure, could lead to acute kidney injury and reduced clearance of renally eliminated antibiotics. Acute kidney injury is identified by raised serum creatinine concentrations or a reduction in urine output⁵⁵ and necessitates an appropriate decrease in antibiotic dose to ensure therapeutic but non-toxic exposure. However, large dose reductions are not needed in the presence of acute kidney injury for drugs with a wide therapeutic index, cleared by several routes, and for which the proportion of clearance through the non-renal route is moderate to high (eg, ceftriaxone, flucloxacillin, and ciprofloxacin have both hepatic and renal clearance pathways).

If severe acute kidney injury occurs, renal replacement therapy could be prescribed for clearance of metabolic waste products or fluid removal. This therapy could consist of continuous renal replacement, or intermittent haemodialysis, or a hybrid form of both, such as sustained low-efficiency dialysis. Continuous renal replacement therapy is the most usual form used in critically ill patients, although hybrid forms are becoming more widely used. Important principles and factors of antibiotic dosing during renal replacement therapy have been discussed in detail in other papers,^{56,57} but in general, drugs with high volumes of distribution (more than 1 L/kg), lipophilic drugs, or drugs that are highly protein bound (more than 80%), or all three, are poorly eliminated by renal replacement therapy.⁵⁶

Sepsis in the presence of renal replacement therapy is associated with a 50% increased probability of death, compared with renal replacement therapy alone.⁵⁸ The increased risk might be partly attributable to the difficulties in antibiotic dosing in patients with sepsis. Renal replacement therapy delivery does not have a standard approach, with the exception of intermittent haemodialysis, therefore antibiotic clearance varies substantially with method and setting. Some reports have emphasised the challenges for dosing with vancomycin, ciprofloxacin, and β lactams, because 10–50% of critically ill patients in these studies did not achieve target antibiotic concentrations.^{59,60} Dosing of antibiotics should ideally be individualised to the patient, method of renal replacement therapy, and setting.

Pulmonary system

Pneumonia is the most common infection in critically ill patients and an important cause of morbidity and mortality in patients in intensive care units (especially as a complication of mechanical ventilation).⁶¹ Provision of optimum antibiotic exposure for ventilated patients with

hospital-acquired pneumonia might be a challenge, especially when various factors associated with the patients, pathological changes, and factors that can affect drug penetration to the site of infection are taken into account.⁶² Alveolar compartments such as epithelial lining fluid are thought to be the closest measurable site where extracellular pathogens accumulate, and thus optimum antibiotic concentrations in the epithelial lining fluid might determine therapeutic success.⁶² After systemic administration, an antibiotic first crosses the alveolar capillary barrier, then reaches and acts within the epithelial lining fluid. The passage across the alveolar capillary barrier could be affected by physicochemical (eg, lipophilicity) and pharmacokinetic characteristics (eg, level of protein-binding) of the antibiotic, and patient-specific characteristics (eg, inflammation or chronic lung disease, or both). The degree of epithelial lining fluid penetration for an antibiotic is characterised by the ratio of exposure in the epithelial lining fluid to exposure in the plasma.

In the context of antibiotic physicochemistry, the more lipophilic antibiotics (eg, fluoroquinolones, macrolides, and oxazolidinones) have an epithelial lining fluid to plasma exposure ratio of at least 1.^{63,64} Such high exposure ratios are not always seen for hydrophilic antibiotics, although ratios might be underestimated because of technical errors.^{63,65,66} Although blood concentrations of antibiotics might seem therapeutic, epithelial lining fluid concentrations might be insufficient, especially with reduced bacterial susceptibility. Therefore, for hydrophilic drugs, some investigators suggest the use of higher doses in patients with severe nosocomial pneumonia.^{67,68} Alternatively, use of different administration approaches such as extended or continuous infusion of β lactam antibiotics,^{63,65} or administration via nebulisation,⁶⁹ could be used to raise antibiotic concentrations in epithelial lining fluid.

Hepatic system

In severe sepsis and septic shock, hepatic dysfunction could reduce drug metabolism and clearance.^{70,71} However, few data are available to guide antibiotic dose adjustments in critically ill patients with liver dysfunction⁷².

Challenge 2: reduced bacterial susceptibility to antibiotics

Knowledge of the minimum inhibitory concentration of an antibiotic against a pathogen is essential to calculate the dose of antibiotic needed. The minimum inhibitory concentration is a critical factor of the pharmacokinetic/pharmacodynamic relationship that defines how much antibiotic exposure is necessary to achieve a predefined pharmacokinetic/pharmacodynamic target that is associated with maximum effectiveness.

Infections in intensive care units are often caused by pathogens with higher minimum inhibitory concentrations than in other clinical settings.^{73,74} For example,

in a German study of predominantly Gram negative isolates⁷⁵, the minimum inhibitory concentrations of doripenem, meropenem, and imipenem needed to kill 90% of the pathogen were all greater in critically ill patients than in patients who were not critically ill (four times greater with doripenem, and eight times greater with meropenem and imipenem).⁷⁵ For an antibiotic, the pharmacokinetic exposure that is needed to achieve the pharmacokinetic/pharmacodynamic ratio threshold rises proportionally with increased minimum inhibitory concentration. For example, if vancomycin is given for health-care-associated pneumonia, a pharmacokinetic/pharmacodynamic target ratio of area under the concentration–time curve from 0 h to 24 h to minimum inhibitory concentration of 400 might be used.⁷⁶ In this case, if a methicillin resistant *Staphylococcus aureus* pathogen has a vancomycin minimum inhibitory concentration value of 0.5 mg/L, then an area under the curve (0–24 h) value of 200 mg/L/h is needed. This concentration could be achieved comfortably with a trough concentration of more than 10 mg/L. However, if the minimum inhibitory concentration is 2 mg/L, then an area under the curve (0–24 h) value of 800 mg/L/h is needed. This concentration would, in turn, need a trough concentration of more than 20–25 mg/L, which would substantially raise the risk of drug-related toxic effects. In the case of high minimum inhibitory concentrations, an alternative antibiotic or combination therapy might be needed.

This example shows some of the challenges that might prevent optimum dosing of antibiotics in the presence of bacteria with reduced susceptibility. Quantitative knowledge of antibiotic susceptibility will help to guide dosing needs in critically ill patients. Another difficulty is reduced bacterial susceptibility to widely used antibiotics, particularly in critically ill patients, and therefore regular surveillance is needed.⁷⁷ Surveillance programmes should report minimum inhibitory concentrations from intensive care units separately from those on regular wards because differences in antibiotic susceptibility are often seen between the two.^{73,74,78,79} Most laboratories routinely report bacterial susceptibility to antibiotics with the classifications susceptible, intermediate-susceptible, or resistant, which are based on minimum inhibitory concentration breakpoints (ie, at which a bacterium is deemed either susceptible or resistant to the specific antibiotic being used). Although this approach is suitable for many clinical situations because it unambiguously delineates when an antibiotic should not be given, it might not be suitable for critically ill patients with altered pharmacokinetic and antibiotic susceptibilities close to the breakpoint of intermediate or resistant. In such patients, the relevant pharmacokinetic/pharmacodynamic target might still not be achieved even if the bacterial organism's breakpoint is classified as susceptible for a particular antibiotic.⁸⁰ Therefore, minimum inhibitory concentration data for a pathogen

in specific patients are essential to accurately calculate the pharmacokinetic exposure needed to achieve the necessary pharmacokinetic/pharmacodynamic targets in that patient—local microbiology laboratories could be engaged to obtain these data.

Another important issue for treatment of infections in critically ill patients is that minimum inhibitory concentration breakpoints reported by groups such as the European Committee on Antimicrobial Susceptibility and Testing and the Clinical and Laboratory Standards Institute are frequently derived from antibiotic exposures in patients who are not critically ill. If the pharmacokinetics for an individual patient are profoundly changed, and the patient is infected by a pathogen with a minimum inhibitory concentration at or near the resistant breakpoint, then a standard fixed regimen could increase the probability of underdosing.

In view of such inherent challenges for antibiotic dosing related to pathophysiology, pharmacokinetics, and reduced bacterial susceptibility, what can be done to possibly strengthen the probability of positive treatment outcomes with antibiotics for critically ill patients?

Possible solution: individualised antibiotic dosing for critically ill patients

Approaches

Best possible outcomes for patients from treatment of infection are most likely when pharmacokinetic/pharmacodynamic targets associated with maximum antibiotic activity are achieved. In-vitro and in-vivo mathematical pharmacokinetic/pharmacodynamic models introduced since the 1980s have enabled an accurate description of the targets that are associated with maximum antibiotic effect. Clinical analyses have attempted to support the results of these studies and have, for the most part, described pharmacokinetic/pharmacodynamic targets that do not differ from targets noted in the preclinical studies.⁸¹ Various targets that have been described in preclinical and clinical studies could be therapeutic targets for optimised dosing in individual patients (table 1).

To increase the probability of achieving therapeutic targets for antibiotics given systemically, two main approaches could be used to adjust standard regimens: altered administration techniques such as once daily dosing or prolonged infusion, which are often based on reported studies of the specific dosing regimen, or dose adjustment guided by therapeutic drug monitoring, or both approaches together.

Improved administration techniques

Many pharmacokinetic studies have applied dosing simulations to identify optimised regimens that can achieve pharmacokinetic/pharmacodynamic targets for infections caused by organisms with higher than normal minimum inhibitory concentrations, or for patients with altered pharmacokinetics. Such an approach to dosing is not individualised when used in a population, but it is a

form of therapeutic adaptation designed to improve antibiotic effectiveness. Dosing based on pharmacokinetic/pharmacodynamic models has changed the way aminoglycosides are prescribed clinically, from three times to once per day, and has improved the safety and effectiveness of these compounds.¹¹⁵ Because of this improvement, extended-interval dosing for aminoglycosides is widely regarded as the standard of antibiotic care.¹¹⁶

Several studies of β lactams have been reported, the results of which collectively suggest that infusion of β lactams should be extended in patients who are critically ill (either for 40–50% of the dosing interval [ie, 3–4 h], or a continuous infusion), because this practice is more likely to achieve pharmacokinetic/pharmacodynamic targets than standard bolus dosing.^{68,117–124} Some studies investigated the clinical value of extended infusions in prospective randomised controlled trials. The results suggest that a continuous infusion of antibiotics is advantageous for critically ill patients with severe sepsis.^{125,126} Although some meta-analyses of these studies have not been able to quantify definitive advantages for either intermittent or extended infusions of β lactams, these studies have often not been stratified for patients with altered pharmacokinetics or reduced susceptibility.^{126,127} For example, an investigation by Arnold and colleagues¹²⁸ changed dosing of β lactams across an intensive care unit from intermittent infusion to extended infusion, but noted this approach was not clinically advantageous. This result was probably because of the high proportion of susceptible pathogens in that particular intensive care unit with low minimum inhibitory concentrations, which meant that standard infusions had already obtained requisite pharmacokinetic/pharmacodynamic ratio thresholds in most patients.¹²⁸ Clinicians should find out whether patients, pathogens, or both, might not respond to a standard fixed regimen, because a different approach to dosing for all patients might not be necessary or confer any therapeutic advantage. In a separate investigation by Lodise and colleagues,¹²⁹ extended infusions of piperacillin–tazobactam for *Pseudomonas aeruginosa* infections were clinically effective in patients who were critically ill with very severe sickness.

A few studies of vancomycin have compared continuous infusion versus intermittent dosing and the results have mostly shown equivalence between the two techniques.¹³⁰ Results from one study only, by Rello and colleagues,¹³¹ have shown potential clinical outcome advantages for continuous versus intermittent infusion of vancomycin. The merit of continuous infusion for vancomycin is probably related to more consistent achievement of pharmacokinetic/pharmacodynamic targets,³¹ although the effect of continuous infusion of antibiotics on antibiotic resistance has not been addressed in these studies.

In general, a change in the dose, frequency, or method of administration of an antibiotic can be implemented

For the European Committee on Antimicrobial Susceptibility and Testing see <http://www.eucast.org>

For the Clinical and Laboratory Standards Institute see <http://www.clsi.org>

Preclinical studies			Clinical studies	
Concentration-dependent				
Aminoglycosides	Maximum killing ⁴³ Resistance suppression ⁸⁷	AUC_{0-24}/MIC 80–100 C_{max}/MIC 10–30	Clinical cure ⁸²⁻⁸⁶ Microbiological cure	C_{max}/MIC 8–10; $AUC/MIC >70$..
Time-dependent				
Carbapenems	Maximum killing ⁸⁸ Resistance suppression ^{90, 91}	40% $T_{>MIC}$ $16 \times MIC$; $C_{min}/MIC >6.2$	Clinical cure ⁸⁹ Microbiological cure ⁹⁷	75% $T_{>MIC}$; C_{min}/MIC 5 54% $T_{>MIC}$
Cephalosporins	Maximum killing ¹¹ Resistance suppression	60–70% $T_{>MIC}$..	Clinical cure ⁹² Microbiological cure ^{16,93}	100% $T_{>MIC}$ 60–100% $T_{>MIC}$; 95% $T_{>4-3MIC}$
Penicillins	Maximum killing ¹¹ Resistance suppression ⁹⁴	40–50% $T_{>MIC}$ 40–50% $T_{>MIC}$	Clinical cure Microbiological cure ⁹⁵	.. 40–50% $T_{>MIC}$
Concentration-dependent and time-dependent				
Fluoroquinolones	Maximum killing ^{119,6} Resistance suppression ^{99,100,101}	$AUC_{0-24}/MIC >30-100$ $AUC_{0-24}/MIC >160$; $AUC_{0-24}/MPC \geq 22$	Clinical cure ^{15,86,96,97,98} Microbiological cure ^{14,86,102}	$AUC_{0-24}/MIC \geq 125-250$; $C_{min}/MIC \geq 8$ $AUC_{0-24}/MIC \geq 34-125$; $C_{min}/MIC \geq 8$
Vancomycin	Maximum killing ¹⁰³ Resistance suppression ¹⁰⁴	AUC_{0-24}/MIC 86–460 $AUC_{0-24}/MIC >200$	Clinical cure ^{20,21} Microbiological cure ²⁰	$AUC_{0-24}/MIC \geq 400-450$ $AUC_{0-24}/MIC \geq 400$
Linezolid	Maximum killing Resistance suppression	Clinical cure ²² Microbiological cure ²²	$AUC_{0-24}/MIC \geq 85$; 85% $T_{>MIC}$ AUC_{0-24}/MIC 80–120; 85% $T_{>MIC}$
Tigecycline	Maximum killing ¹⁰⁵ Resistance suppression	50% $T_{>MIC}$..	Clinical cure ^{106,107,108} Microbiological cure ^{109,110}	$AUC_{0-24}/MIC >12.8-17.9$; $fAUC_{0-24}/MIC \geq 0.9$ AUC_{0-24}/MIC 6.9–17.9
Daptomycin	Maximum killing ^{111,112} Resistance suppression ¹⁰⁴	AUC_{0-24}/MIC 38–442 $AUC_{0-24}/MIC >200$	Clinical cure Microbiological cure
Colistin	Maximum killing ^{113,114} Resistance suppression	AUC_{0-24}/MIC 7–23 ..	Clinical cure Microbiological cure

AUC_{0-24}/MIC =ratio of area under the concentration time curve from 0 to 24 h to minimum inhibitory concentration. C_{min}/MIC =ratio of maximum concentration of antibiotic in a dosing interval to minimum inhibitory concentration. $T_{>MIC}$ =percentage of dosing interval that the antibiotic concentration is maintained above the minimum inhibitory concentration. AUC_{0-24}/MPC =ratio of the AUC_{0-24} to the concentration that prevents mutation. C_{min} =minimum concentration of antibiotic in a dosing interval, f =free concentration or fraction of drug not bound to plasma proteins. *Where the index is reported as a range, data included might have been derived from different infection models with different bacteria. Specific data for the contributing values can be found in the associated references. Data for the various indices has been reported in different studies according to total and free (unbound) concentrations of drug.

Table 1: Studies reporting pharmacokinetic/pharmacodynamic indices from preclinical and clinical assessments, by antibiotic class

across an intensive care unit when minimum inhibitory concentration data are available to justify an empirical change.

Adjustment of antibiotic dose guided by therapeutic drug monitoring

Therapeutic drug monitoring is traditionally used to minimise toxic effects, but in critically ill patients it is also used to optimise dosing in the presence of severely changed pharmacokinetics.^{10,132} Therapeutic drug monitoring relies on direct measurement of serum antibiotic concentrations with timely feedback to clinicians who then interpret results in the context of therapeutic ranges. Adequacy of a measured concentration can be interpreted by either direct comparison of one concentration value to a therapeutic target, or an estimation of antibiotic exposure with non-linear regression or Bayesian techniques. Doses could then be increased or decreased as predicted by the clinician or any dosing software used.

The concentration of unbound drug in a blood sample is important for accurate interpretation of drug exposure, because only free drug is microbiologically active. Knowledge of free concentrations is most important for antibiotics that are highly bound in plasma.¹³³ Likewise, concentration results should be made available in a

timely manner so that rapid dose adjustments can be made. In view of the dynamic nature of pharmacokinetics in patients who are critically ill, long delays can result in inappropriate dose adjustment. For ideal therapeutic drug monitoring, the antibiotic minimum inhibitory concentration values for the organism and pharmacokinetic targets should be available too.

So far, various reports of therapeutic drug monitoring for antibiotics in patients who are critically ill include investigations of aminoglycosides,¹³⁴ glycopeptides,¹³⁵ β lactams,^{10,19,136} linezolid,¹³⁷ and quinolones.¹⁰ However, few studies have compared the clinical outcomes of therapeutic drug monitoring versus outcomes without this intervention, and therefore prospective individualised therapy in patients who are critically ill should be rigorously assessed.

Dosing nomograms for dose adjustment of antibiotics are widely used across many clinical specialties.¹³⁸ These nomograms compare a measured concentration of prescribed antibiotic at a particular timepoint with a graph that shows the therapeutic range of concentrations at the same timepoint. The dose of antibiotic can then be increased or reduced as necessary to ensure the next measured concentration is in the therapeutic range. These nomograms are simple to use and are popular with clinicians. Nomograms for vancomycin and

aminoglycosides are the most widely available^{138–140} because these drugs have high toxicity thresholds (ie, low therapeutic index) and available assays, and they are often targets for therapeutic drug monitoring by pharmacists and physicians. A limitation of many nomograms, however, is that they are rarely designed with pharmacokinetic/pharmacodynamic targets from patients who are critically ill, and rely on clinicians' experience to make appropriate dose adjustments in these circumstances.¹⁴¹

Application of non-linear regression analysis to a series of concentration values at different timepoints can be used to calculate basic pharmacokinetic variables such as area under the curve, clearance, elimination rate constant, maximum concentration in the dosing interval, and trough concentration. To calculate the dose of an antibiotic, the measured or calculated values for area under the concentration–time curve, maximum concentration of antibiotic in a dosing interval or trough concentrations, or both, can be compared against the pharmacokinetic/pharmacodynamic targets for the prescribed antibiotic, and the dose empirically increased or decreased as needed.

Population pharmacokinetic models have been developed for many antibiotics used in patients who are

critically ill. A drawback of many of these models is that the increased pharmacokinetic variability in these patients is unlikely to be captured because the sample size used in many of these studies is usually too small (around ten to 20 patients).^{142,143} However, these population models are probably more accurate than a model derived from another group of patients.¹⁴⁴

Greatest accuracy of dose adaptation based on data for drug concentrations could be ensured with a stochastic control approach, to define the timing and number of samples that should be taken from a patient and then used in dose prediction.¹⁴⁵ This approach is particularly useful for drugs with high pharmacokinetic variability such as voriconazole.⁷² The accuracy of dose prediction improves with more data for antibiotic concentrations across different dosing intervals.⁷²

In Bayesian dose adaptation, the dose of a drug is adjusted to ensure an individual patient's exposure meets pharmacokinetic/pharmacodynamic targets. Information about a specific patient's serum drug concentrations and a population pharmacokinetic model from the relevant population are included. The model contains a series of mathematical equations that include parameter estimates and their distribution for clearance, and volume of distribution.

	BestDose v1.0	ID-ODS	MWPharm	DoseMe	TCI Works	First-dose	WinAUC	CADDy Program v4.e
Method of pharmacokinetic assessment	Bayesian non-parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Population parametric approach	Non-linear regression	Non-linear regression
Adaptive feedback?	Yes	Yes	Yes	Yes	Yes	No	No	No
Web, server, or terminal based?	Terminal	Terminal and server	Terminal and server	Terminal and server	Terminal and server	Web	Terminal	Web or server
Compatibility	Windows	Mac, Windows, Linux, Android, iOS	Windows	Mac, Windows, Linux, Android, iOS	Mac, Windows	Mac, Windows, Linux, Android, iOS	Windows	Mac, Windows, Linux, Android, iOS
Smart phone application?	No	Yes	No	Yes	No	Yes	No	No
Patient covariates in dose predictions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Output from program?	Doses and pharmacokinetic parameter estimates	Dosing regimens, pharmacokinetic parameter estimates, and PTAs	Doses and pharmacokinetic parameter estimates	Doses and pharmacokinetic parameter estimates	Doses and pharmacokinetic parameter estimates	Doses	Pharmacokinetic parameter estimates	Doses
IT support available within 24 h?*	Yes	Yes	No	Yes	Yes	No	No	Yes
Capacity for ICU and non-ICU dosing?	Yes	Yes	Yes	Yes	Yes	No	No	No
Further information	http://www.lapk.org	http://www.optimum-dosing-strategies.org	http://www.mediware.cz/index_en.html	www.doseme.com.au	www.tciworks.info	http://www.firstdose.org/	Contact the developers (Dr Jerome Schentag: schentag@buffalo.edu)	www.jjpreisenberger.de
Cost	Current version is free.	Free	€1250 per license	Dependent on requirements	Free	Free	Free	Free

ICU=intensive care unit. IT=information technology. PTA=probability of target attainment. ID-ODS=Individually Designed Optimum Dosing Strategies. WinAUC=Windows Antibiotic Utilisation Information and Consultation. *Response time often depends on the severity of the problem for the user (for non-urgent issues, responses might exceed 24 h).

Table 2: Characteristics of various antibiotic dosing programs

A critically ill patient could receive the first dose at the clinician's discretion, preferably with a strategy that is likely to achieve pharmacokinetic and pharmacodynamic targets (eg, vancomycin loading dose³¹ or extended infusion β lactam).^{68,117-124} During the first or subsequent dose intervals, one or more blood samples could be taken to estimate the patient's pharmacokinetic variables for the antibiotic. Samples could then be assayed in a timely manner (eg, within 6 h) and, if a software package has been chosen to help to calculate antibiotic dosing, then the dosing history, drug concentrations, pathogen minimum inhibitory concentration, and necessary data for the patient (eg, weight or creatinine clearance) could be entered. The software could then combine the recorded data for the patient plus the population pharmacokinetic model to estimate the Bayesian posterior pharmacokinetic parameter values. The appropriate dose that achieves the pharmacokinetic/pharmacodynamic targets needed for that particular patient could then be calculated and used in the next dosing interval.

Many programs are available that apply different approaches to calculate individualised antibiotic doses for patients. Table 2 shows a summary of various programs, and others are identified by Fuchs and colleagues.¹⁴⁶ Importantly, not all programs contain all relevant antibiotics, although the developers of most state that additional pharmacokinetic models for antibiotics can be included. To ensure that robust antibiotic dosing at the bedside is possible, many of these programs have, or will have, electronic medical record interfaces and smart-phone applications that can be used at the patient's bedside.

On the basis of best available evidence, we suggest the following process for dose individualisation in a critically ill patient: (1) diagnose the infection and select an antibiotic; (2) establish the patient's physiological characteristics (eg, weight, sex, creatinine clearance, serum albumin concentration, fluid overload status, presence of extracorporeal circuits); (3) estimate the first dose of antibiotic on the basis of the patient's characteristics and local baseline data for bacterial susceptibility in the intensive care unit, possibly with the appropriate software; (4) give the dose to the patient in a timely manner after diagnosis; and (5) take blood samples at predefined timepoints and assess them in a timely manner.

The clinician could then enter the concentration-time data from the blood samples and patient's covariate data into software that personalises a dosing regimen for the patient to achieve an evidence-based pharmacokinetic and pharmacodynamic target. When available, susceptibility data for a specific pathogen should be incorporated into the dose estimation process.

Conclusions

Patients who are critically ill have substantially varied pharmacokinetics compared with patients who are not critically ill. Additionally, patients who are critically ill

Search strategy and selection criteria

We searched for English language articles in PubMed (1966 to Feb 2014), Embase (1966 to Feb 2014), the Cochrane Controlled Trial Register, and references from relevant articles, with the key words "antibacterial", "Bayesian", "intensive care unit", "pharmacodynamics", and "pharmacokinetics". Search terms related to antibiotic pharmacokinetics and pharmacodynamics in patients who were critically ill, and dosing software, were also included.

are more likely to be infected by bacteria that are less susceptible to antibiotic treatment. Traditional strategies for dosing with antibiotics in patients who are critically ill are unlikely to consistently achieve the pharmacokinetic/pharmacodynamic targets associated with maximum antibiotic activity. This situation raises the risk of clinical failure, or development of resistance, or both, for a patient who is critically ill. Optimisation of antibiotic dosing in the intensive care unit therefore needs an individualised approach for the patient that takes into account the minimum inhibitory concentration of an antibiotic for the infecting pathogen, and selects a dosing regimen that is likely to obtain the requisite pharmacokinetic/pharmacodynamic ratio predictive of success. Proactive therapeutic management for antibiotics other than vancomycin and aminoglycosides is possible, but should be escalated to the next level and made available to all hospitals. Individualised antibiotic concentrations for patients, combined with software programs that calculate individual doses, could increase the accuracy of antibiotic dosing, and the likelihood that pharmacokinetic and pharmacodynamic targets and favourable clinical outcomes can be achieved in all patients.

Contributors

JAR, JLK, and UT contributed to conception of the Review. JAR and MHA-A were responsible for the literature search, and drafting the tables and figure. JAR, JLK, UT, and MHA-A wrote the manuscript. JL, JWM, AAV, TWF, WWH, AF, MNN, JJS, GD, and ORF were responsible for critical review. All authors contributed to data interpretation and final approval of the Review.

Declaration of interests

AF is involved in the development of the software Individually Designed Optimum Dosing Strategies (ID-ODS). MNN is involved in the development of the software BestDose. JJS is involved in the development of the software WinAUC. ORF is involved in the development of the software CADDy Program. No other authors have competing interests.

Acknowledgments

Judit Preisenberger, Alexander Brinkman, Robert McLeay, Nick Holford, and Sam Holford provided information about specific dosing software programs. JAR is funded by a career development fellowship from the National Health and Medical Research Council of Australia (APP1048652). TWF is a UK Medical Research Council (MRC) Clinical Training Fellow supported by the North West England MRC Fellowship Scheme in Clinical Pharmacology and Therapeutics, which is funded by the MRC (grant number G1000417/94909), ICON, GlaxoSmithKline, AstraZeneca, and the Medical Evaluation Unit. WWH is supported by a National Institute of Health Clinician Scientist Fellowship.

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