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CONFERENCE REPORT AND EXPERT PANEL

Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper#

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Abstract

Purpose: This Position Paper aims to review and discuss the available data on therapeutic drug monitoring (TDM) of antibacterials, antifungals and antivirals in critically ill adult patients in the intensive care unit (ICU). This Position Paper also provides a practical guide on how TDM can be applied in routine clinical practice to improve therapeutic outcomes in critically ill adult patients.

Methods: Literature review and analysis were performed by Panel Members nominated by the endorsing organisations, European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/Pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and International Society of Antimicrobial Chemotherapy (ISAC). Panel members made recommendations for whether TDM should be applied clinically for different antimicrobials/classes.

Results: TDM-guided dosing has been shown to be clinically beneficial for aminoglycosides, voriconazole and ribavirin. For most common antibiotics and antifungals in the ICU, a clear therapeutic range has been established, and for these agents, routine TDM in critically ill patients appears meritorious. For the antivirals, research is needed to identify therapeutic targets and determine whether antiviral TDM is indeed meritorious in this patient population. The Panel

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#Societies: European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and International Society of Antimicrobial Chemotherapy (ISAC)

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Members recommend routine TDM to be performed for aminoglycosides, beta-lactam antibiotics, linezolid, teicoplanin, vancomycin and voriconazole in critically ill patients.

Conclusion: Although TDM should be the standard of care for most antimicrobials in every ICU, important barriers need to be addressed before routine TDM can be widely employed worldwide.

Keywords: Antibacterials, Antifungals, Antivirals, Pharmacokinetics, Pharmacodynamics, Sepsis

Introduction

Despite numerous therapeutic innovations, infection-related mortality in critically ill patients persists as a significant healthcare concern. Given the corresponding high burden of infection, it is unsurprising that the consumption of antimicrobial agents (antibacterials, antifungals and antivirals) in the intensive care unit (ICU) is ten times higher than in other wards [1]. It is essential to optimise the use of antimicrobial agents not only to maximise therapeutic success but also to prolong the clinical lifespan of these currently available drugs by limiting the emergence of resistance [2]. However, the process of optimising antimicrobial therapy (including both spectrum and therapeutic exposure) is a massive challenge in ICU patients, who often manifest extreme inter- and intra-individual pharmacokinetic (PK) variability [3]. It follows that conventional antimicrobial dosing may risk clinical failure in this patient population as most dose-finding studies only included non-ICU populations. Indeed, perhaps more than in any other patient population, non-optimised antimicrobial dosing may more commonly lead to low drug exposure and therapeutic failure and/or antimicrobial resistance [4], or high drug exposure, leading to an increased risk of toxicity.

With an expanding knowledge on the relationships between antimicrobial dosing, pharmacokinetic/pharmacodynamic (PK/PD) exposure and patient outcomes, there is now a strong rationale to individualise antimicrobial dosing in critically ill patients with the aid of therapeutic drug monitoring (TDM). Traditionally, TDM was only employed to minimise the likelihood of toxicity in drugs with narrow therapeutic indices (e.g. aminoglycosides and vancomycin) and in drugs with complex pharmacokinetics (e.g. voriconazole) and has been hitherto underused for other antimicrobials. However, the recent surge in multidrug-resistant pathogens causing infections, combined with a declining antimicrobial pipeline, is causing a need to revise this approach. TDM of antimicrobials, even for those with a wide therapeutic index, is becoming more common [5, 6], whilst TDM for the "traditional" drugs, such as aminoglycosides and glycopeptides, is continually being studied for further improvement.

Take-home message:

The Panel Members recommend routine TDM to be performed for aminoglycosides, beta-lactam antibiotics, linezolid, teicoplanin, vancomycin and voriconazole in critically ill patients.

Currently, there is significant variation across institutions on how TDM is applied in terms of antimicrobial and patient selection, sampling time points and antimicrobial assays for concentration monitoring, as well as PK/PD targets and the approach to dose modification [5, 6]. This Position Paper aims to review and discuss the available data on TDM of antibacterials, antifungals and antivirals in critically ill adult patients. This Paper will also provide a practical guide on how antimicrobial TDM can be applied in everyday clinical practice to improve therapeutic outcomes in critically ill adult patients. Finally, the Panel aims to recommend antimicrobials for which TDM should be routinely performed in critically ill patients.

Methods

Position Paper Panel composition

The Position Paper Panel members were nominated by the endorsing organisations including European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/Pharmacodynamic (PK/PD) and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and International Society of Antimicrobial Chemotherapy (ISAC).

Literature review and analysis

This Position Paper was developed following a review of studies published in English before 1 July 2019. A literature search was performed on PubMed with no date restrictions using the following MeSH terms: ("antibacterial agents" OR "antifungal agents" OR "antiviral agents") AND ("drug monitoring" OR "pharmacokinetics" OR "pharmacodynamics") AND ("critical care" OR "critical illness" OR "intensive care units"). The search was also performed for each antimicrobial (e.g. meropenem) and antimicrobial class of interest (e.g. carbapenems). For clinical efficacy and toxicity, only studies on

critically ill adult patients were reviewed and included in the analysis.

Process overview

The Panel members held face-to-face meetings and teleconferences to formulate the structure and content of this Position Paper. Members were divided into groups consisting of a lead author and co-authors for each section. Each group was tasked to review the literature, evaluate the available data and summarise their findings in a draft document addressing whether TDM is indicated for a particular antimicrobial/antimicrobial class in critically ill patients. All members reviewed the full draft document, and discrepancies were discussed and resolved by consensus.

Panel consensus for use of TDM

A seven-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = somewhat disagree, 4 = neutral, 5 = somewhat agree, 6 = agree and 7 = strongly agree) was used to score the recommendation of the Panel for performing TDM for each antimicrobial/antimicrobial class in critically ill patients. Consensus was achieved when the sum of 1 and 2 (negative consensus) or 6 and 7 (positive consensus) was $\geq 75\%$.

Pharmacokinetic and pharmacodynamic issues in critically ill patients

Pharmacokinetic changes

Critically ill patients are those patients whose conditions are life-threatening and require specialised care in the ICU. Such patients require intensive monitoring and treatment due to failure of vital organ functions (due to acute and/or chronic disease) or due to the sequelae of surgical or other intensive treatment associated with life-threatening conditions. Critical illness is characterised by marked homoeostatic changes, driven by both the underlying disease process and the interventions required. These features profoundly affect organ function, resulting in a pathophysiological state that is not encountered in an ambulatory setting. Moreover, the presence of chronic comorbidity can further exacerbate the pathophysiological changes commonly encountered during critical illness. All of these factors will significantly influence antimicrobial PK in the critically ill and can be broadly considered in terms of altered volume of distribution (V_d) and drug clearance (CL).

Altered volume of distribution

Endothelial dysfunction is common in critical illness and is characterised by expansion of the interstitial space through "capillary leakage". This is closely linked to the severity of the underlying disease process and the degree of systemic inflammation. Sepsis and major burn injury are classic examples. This is then further exacerbated by intravenous (IV) fluid loading, a near-ubiquitous intervention in the ICU. For hydrophilic antimicrobials (e.g. acyclovir, aminoglycosides, beta-lactams, daptomycin, fluconazole and glycopeptides), this can result in a significantly expanded V_d [7]. Changes in protein binding associated with hypoalbuminaemia will also potentially influence antimicrobial PK [8]. Indeed, hypoalbuminaemia is commonly encountered (as a negative acute phase reactant), resulting in an increase in the V_d for highly protein-bound antimicrobials, such as ceftriaxone, daptomycin, ertapenem, flucloxacillin and teicoplanin [8]. In these scenarios, the free (or unbound) fraction is increased, resulting in both greater distribution and potentially CL. Finally, extremes of body size and composition (typically obesity) will also influence V_d, although the magnitude of any such change will depend on the physicochemical properties of the antimicrobial (e.g. molecular weight, lipid solubility and degree of ionisation) [9].

Altered drug clearance

Many commonly prescribed antimicrobials are principally cleared by renal elimination. In this context, critical illness can have a profound impact on renal function and therefore drug CL. Augmented renal clearance (ARC) is being increasingly noted in critically ill sub-populations (incidence of 14–80%) [10]. ARC is defined as an increased creatinine clearance > 130 mL/min/1.73 m^2 measured by 8–24-h urine collection and refers to the enhanced renal elimination of circulating solute (such as metabolic waste and drugs) [11]. The underlying mechanisms are uncertain, although increased solute delivery related to a hyperdynamic high cardiac output state, in combination with tubular and/or neuroendocrine changes, is likely implicated [10]. Identifying patients with ARC is challenging as these patients may have elevated renal function despite normal serum creatinine concentrations [12], and importantly, commonly used glomerular filtration rate mathematical estimates, such as the Cockcroft–Gault and Modified Diet in Renal Disease equations, are unlikely to be reliable as compared to urinary creatinine clearance data [13]. Younger patients with multiple trauma are at the highest risk [12], but ARC has also been described in other patient categories. Moreover, the presence of ARC has been associated with sub-optimal plasma antimicrobial concentrations [11], although the implications in terms of clinical outcomes remain unclear [14].

In contrast, many critically ill patients will develop acute kidney injury, requiring the use of renal replacement therapy (RRT). In the acute setting, continuous veno-venous techniques are most frequently used, with

variable fractions of filtration and/or dialysis. Factors such as molecular weight, protein binding, hydrophilicity, mode of RRT, filter porosity, surface area, blood flow rate and total effluent rate will all influence extracorporeal drug handling [15]. Given the heterogeneity in clinical practice and pathophysiology, antimicrobial dosing is generally empiric, resulting in substantial intra- and inter-patient variability in drug concentrations [16]. The intensity of RRT and any residual native renal function are likely to be the most important variables in determining renal drug CL in this setting [17].

Other extracorporeal circuits (such as extracorporeal membrane oxygenation) may also contribute to altered drug CL, depending on the degree of adsorption, and any co-existing renal dysfunction [18].

Pharmacodynamic changes

For antimicrobials, PD links PK exposure with its ability to kill or inhibit the growth of a pathogen. This relationship can be described by relating the PK exposure of an antimicrobial to the minimum inhibitory concentration (MIC) of the offending pathogen. Antimicrobials classically have different PK/PD indices [19], and these can be categorised as: (a) the ratio of maximum drug concentration (C_{max}) to MIC (C_{max}/MIC); (b) the duration of time (T) that the free drug concentration remains above the MIC during a dosing interval ($fT_{>MIC}$); and (c) the ratio of the area under the concentration–time curve during a 24-hour period to MIC (AUC_{0-24}/MIC) [20]. However, it is also important to note that individual MICs were rarely measured in most of the earlier studies and parameters such as MIC_{50} and MIC_{90} were used instead to describe the PK/PD relationships. For antivirals, in particular, measures other than the MIC have been used as the denominator of the PK/PD index such as the in vitro concentration required to obtain 50% of the maximum effect (EC_{50}). The denominator in these indices is an important consideration because when it increases, the corresponding PK exposure should also be increased to ensure that the optimal PK/PD index is still achieved. This is mostly relevant in the ICU as at least bacterial pathogens may demonstrate higher MICs, as much as 2–4 times higher, when compared to the general wards [21].

Importantly, a recent review by Mouton et al. highlights that the use of an individual MIC to guide antibacterial dosing may not be appropriate due to imprecise and highly variable (varying by 1–2 dilutions in both directions) measurements associated with MIC determination [22]. Therefore, an individual MIC measurement should only be regarded as an estimate and not a "true" value of a pathogen's susceptibility. MIC may vary according to determination methods (e.g. broth microdilution vs. E-test®), and it is therefore important to aim for an appropriate MIC method-specific target, with broth microdilution (BMD) MIC being the preferred method, if they are available. Any potential dosing adjustments with the aid of TDM must consider MIC variation and should be interpreted in the context of assay variation, species identification and wild-type distributions. Measures of MIC distributions such as epidemiologic cut-off (ECOFF) values, which separate bacterial populations into those of a wild-type population and those with either a low- or high-level phenotypically detectable resistance, can be more useful to guide antibacterial dosing. Mouton et al. proposed several practical solutions in their review to optimise antibacterial dosing for patients, and one of the important recommendations included the use of ECOFF values as the PD target for dosing purposes when the measured MIC for the bacterial strain is within the wild-type distribution [22]. If the MIC is slightly above the ECOFF, a two-fold dilution of the MIC can be assumed for dosing purposes, whilst MIC-guided therapy should not be an option if the measured MIC is clearly far above the ECOFF and clinical resistance breakpoint.

Basic principles of therapeutic drug monitoring

An antimicrobial should fulfil certain criteria for TDM to be of potential benefit and some of these criteria include: (a) a significant intra- and/or inter-individual PK variability; (b) a defined exposure range associated with pharmacological responses (clinical responses and toxicities); (c) defined relevant sampling time points; and (d) accurate and timely bioanalytical assay methods for drug measurement.

Critically ill patients often demonstrate extreme variability in antimicrobial PK, which can be partly explained by patient covariates (e.g. body weight and renal function). Unexplained PK variability can be observed across patients (i.e. inter-individual variability) and also, within a patient (i.e. intra-individual PK variability). TDM-based dosing adjustment is clinically useful for an antimicrobial if the unexplained inter-individual PK variability exceeds the intra-individual variability. Otherwise, solely applying covariate-based dosing strategies would be sufficient, as is the case with Product Information and nomogram-based dosing.

PK sampling for antimicrobial TDM is traditionally performed at the end of each dosing interval to obtain a trough sample (minimum concentration in dosing interval, C_{min}). Whilst C_{min} provides some information on drug CL, determination of V_d requires an additional sample earlier in the dosing interval. For the estimation of derived PK parameters, such as the AUC, and PK/PD targets, such as the $fT_{>MIC}$, an optimised PK sampling schedule is suggested for unbiased and precise parameter estimation. A limited sampling strategy (LSS), which uses

the most "informative" concentration–time points (commonly 1–3 sampling time points) to describe a drug's PK, is relatively easy to be performed and may provide accurate estimates of full drug exposure [23, 24]. The optimal sampling time points for a drug can be identified during "limited sampling" studies where these time points will be estimated or calculated using PK models and Monte Carlo simulations. The time points can then be used to predict AUC_{0-24}, and as such, this approach is beneficial for those antimicrobials in which AUC_{0-24}/MIC ratios are the major determinants for efficacy. For example, although 10–15 time points are conventionally needed to calculate 80% of the total AUC, Alsultan et al. demonstrated that these can be reduced to only 2 time points (sampling at 4 and 6 h post-dose) with LSS to estimate levofloxacin AUC [25]. For antibacterials that are administered via continuous infusion, a sample at any given time during administration can be used.

Ideally, measuring antimicrobial concentration at the site of infection (e.g. epithelial lining fluid in pneumonia and cerebrospinal fluid in meningitis) is preferred as most antimicrobial–pathogen interactions are thought to occur here. However, due to practical limitations, most centres have been using plasma concentrations as a surrogate for concentrations at the actual site of infection. Importantly, some antimicrobials are unevenly distributed and plasma concentration does not always reflect concentrations at the infected tissues.

Bioanalytical assays for measuring antimicrobial concentrations should be precise, accurate, highly selective for a particular drug and, importantly, available in a timely manner (e.g. turnaround times of < 8 h, preferably shorter or within the same day of sampling). Regular quality control exercises through proficiency testing programs are recommended to ensure that the assays have sufficient accuracy, precision and specificity for routine TDM and patient management [26, 27]. Ideally, free drug concentrations should be measured at physiologically relevant conditions [28] and reported, but due to practical limitations, most laboratories report only total concentrations. Further to this, exposure targets for some drugs have only been defined in terms of total exposure (e.g. vancomycin).

TDM-based dosing adjustments can be performed in several different ways. Whilst it is still popular to compare and evaluate a single drug concentration (e.g. C_{min}) against a therapeutic target range, and this method is the easiest, it is the least accurate method for dosing adjustment. Dosing nomograms, on the other hand, can integrate PK/PD data with measures of organ function (e.g. renal function described using creatinine clearance) and have demonstrated to be superior to conventional antimicrobial dosing [29, 30]. However, separating the sources of PK variability and incorporating > 1 covariate for dosing adjustments (e.g. creatinine clearance and weight) are not possible with a single dosing nomogram. Additionally, the dose prediction from such nomograms would be inaccurate if the pre-defined PK sampling/dosing schedule is not strictly adhered to. The use of dosing software overcomes these limitations [2], and these methods have been shown to be superior over conventional antimicrobial dosing for vancomycin [31], particularly in the context of:

(a) the first dose can initially be individualised for patients by using Monte Carlo simulations;
(b) the sources of PK variability can be separated into intra- and inter-individual variability;
(c) PK sampling before reaching steady state is possible; and
(d) through Bayesian estimation, the entire antimicrobial PK profile can be estimated from a single PK sample. Bayesian estimation is most accurate when an optimal sampling time is chosen to provide the most information about the drug's PK behaviour in the patient and a suitable population PK model matching the target population to serve as the Bayesian prior model [32]. After initial TDM, it is recommended to repeat TDM (within 1–2 days for most drugs) to confirm therapeutic exposures have been achieved and again thereafter if there are concerns of significant changes to PK (e.g. enteral absorption, renal function).

The following sections describe the specific TDM data relating to various antimicrobial classes. Tables 1, 2 and 3 describe optimal PK/PD indices and magnitudes associated with clinical efficacy and toxicity of antibacterials, antifungals and antivirals, respectively. TDM recommendations for each antimicrobial are summarised in Table 4. Table 5 highlights relevant studies/data that demonstrate clinical outcome benefits of antimicrobial TDM. The primary data that support each recommendation and the suggested empirical dosing of these antimicrobials in critically ill patients are included in Supplementary Tables. We highly recommend readers to use the information presented in the following sections in conjunction with the data presented in Tables 1, 2, 3, 4 and 5, as well as those presented in Supplementary Tables 1–5, for specific suggestions on how TDM can be performed for a particular antimicrobial/antimicrobial class in critically ill patients.

Table 1 Pharmacokinetic/pharmacodynamic (PK/PD) indices and the magnitudes associated with antibacterial clinical efficacy and toxicity

Antibacterial class	PK/PD index	Pre-clinical PK/PD target for efficacy	Clinical PK/PD target for efficacy	Clinical PK/PD threshold for toxicity
Aminoglycosides				
Amikacin	AUC_{0-24}/MIC	AUC_{0-24}/MIC: 80–100	C_{max}/MIC ≥ 8–10	C_{min} > 5 mg/L[a]
Gentamicin/tobramycin	AUC_{0-24}/MIC	AUC_{0-24}/MIC: 80–100	AUC_{0-24}/MIC ≥ 110 C_{max}/MIC ≥ 8–10	C_{min} > 1 mg/L[a]
Beta-lactams				
Carbapenems	% $fT_{>MIC}$	40% $fT_{>MIC}$	50–100% $fT_{>MIC}$	C_{min} > 44.5 mg/L[b]
Cephalosporins	% $fT_{>MIC}$	60–70% $fT_{>MIC}$	45–100% $fT_{>MIC}$	C_{min} > 20 mg/L[c]
Penicillins	% $fT_{>MIC}$	50% $fT_{>MIC}$	50–100% $fT_{>MIC}$	C_{min} > 361 mg/L[d]
Co-trimoxazole	Unclear	Unclear	Unclear	Unclear
Daptomycin	AUC_{0-24}/MIC	AUC_{0-24}/MIC ≥ 517	AUC_{0-24}/MIC ≥ 666 mg/L	C_{min} > 24 mg/L[e]
Fluoroquinolones	AUC_{0-24}/MIC	AUC_{0-24}/MIC ≥ 100 C_{max}/MIC ≥ 8	AUC_{0-24}/MIC ≥ 125–250 C_{max}/MIC ≥ 12	Unclear
Glycopeptides				
Teicoplanin	AUC_{0-24}/MIC	AUC_{0-24}/MIC ≥ 610	C_{min} ≥ 10 mg/L	Unclear
Vancomycin	AUC_{0-24}/MIC	AUC_{0-24}/MIC: 86–460	AUC_{0-24}/MIC ≥ 400 C_{min} > 10–20 mg/L	AUC_{0-24} > 700 mg h/L[f] C_{min} > 20 mg/L[f]
Linezolid	AUC_{0-24}/MIC	AUC_{0-24}/MIC ≥ 100	AUC_{0-24}/MIC: 80–120 ≥85% $T_{>MIC}$	AUC_{0-24} > 300[g] C_{min} > 7[g]
Polymyxins				
Colistin	AUC_{0-24}/MIC	$fAUC_{0-24}$/MIC: 6.6–13.7[h] $fAUC_{0-24}$/MIC: 3.5–17.6[i]	No data	C_{min} > 2.4 mg/L[f]
Polymyxin B	AUC_{0-24}/MIC	$fAUC_{0-24}$/MIC: 3.7–28.0	No data	AUC_{0-24} > 100[f]

AUC_{0-24}/MIC = the ratio of the area under the concentration–time curve during a 24-hour period to minimum inhibitory concentration; C_{max}/MIC = the ratio of maximum drug concentration to minimum inhibitory concentration; C_{min} = trough drug concentration; $fAUC_{0-24}$/MIC = the free (unbound drug concentration) ratio of the area under the concentration–time curve during a 24-h period to minimum inhibitory concentration; $fT_{>MIC}$ = the duration of time that the free drug concentration remains above the MIC during a dosing interval; PK/PD = pharmacokinetic/pharmacodynamic

[a] Nephrotoxicity or ototoxicity

[b] Data only available for meropenem and related to nephrotoxicity or neurotoxicity

[c] Data only available for cefepime and related to neurotoxicity

[d] Data mostly on piperacillin and related to nephrotoxicity and neurotoxicity

[e] Myopathy indicated by creatine phosphokinase elevation

[f] Related to nephrotoxicity

[g] Related to haematological toxicity

[h] Exposure against *Pseudomonas aeruginosa*

[i] Exposure against *Acinetobacter baumannii*

Antibacterials

Aminoglycosides

Pharmacokinetics

Aminoglycosides are hydrophilic with a low V_d and CL that is proportional to glomerular filtration rate. Significant V_d and CL alterations have been widely described in critically ill patients.

Pharmacodynamics

Aminoglycosides demonstrate "concentration-dependent" bactericidal activity, which is optimal when the C_{max} is ≥ 8–10 × MIC [33–35]. Recent data, however, have suggested that the AUC_{0-24}/MIC ratio might be a better predictor of activity and is better suited to judge target attainment in extended-interval dosing of aminoglycosides. High C_{min} and AUC exposures over days have been associated with oto- and nephrotoxicity.

Dosing in critically ill patients

High, single-dose, extended-interval dosing should be used in patients with Gram-negative infections. Recent data suggest that higher-than-standard aminoglycoside dosing regimen may be required for critically ill patients [36, 37].

TDM in critically ill patients

The Panel recommends that TDM be routinely performed when aminoglycosides are used in critically ill patients.

Table 2 Pharmacokinetic/pharmacodynamic (PK/PD) indices and the magnitudes associated with antifungal clinical efficacy and toxicity

Antifungal class	PK/PD index	Pre-clinical PK/PD target for efficacy	Clinical PK/PD target for efficacy	Clinical PK/PD threshold for toxicity
Echinocandins	AUC_{0-24}/MIC	$fAUC_{0-24}$/MIC: 10–20	AUC_{0-24}/MIC > 3000[a]	No data
Fluconazole	AUC_{0-24}/MIC	AUC_{0-24}/MIC: 25–44	AUC_{0-24}/MIC ≥ 55–100	Unclear
Flucytosine	$fT_{>MIC}$	≥ 20–45% $fT_{>MIC}$	No data	C_{max} > 100 mg/L[b]
Isavuconazole	AUC_{0-24}/MIC	$fAUC_{0-24}$/MIC: 25–50	No data	No data
Itraconazole	AUC_{0-24}/MIC	C_{max} > 6 mg/L[c]	C_{min} ≥ 0.25–0.5 mg/L (Prop) C_{min} ≥ 1 mg/L (Tx)	C_{ave} ≥ 17.1 mg/L[d]
Posaconazole	AUC_{0-24}/MIC	$fAUC_{0-24}$/MIC: 25–50	C_{min} > 0.5 (Prop) C_{min} > 1 mg/L (Tx)	No data
Voriconazole	AUC_{0-24}/MIC	$fAUC_{0-24}$/MIC: 25–50	C_{min} ≥ 1–2 mg/L	C_{min} ≥ 4.5–6 mg/L[e]

AUC_{0-24}/MIC = the ratio of the area under the concentration–time curve during a 24-h period to minimum inhibitory concentration; C_{ave} = average drug concentration; C_{min} = trough drug concentration; $fAUC_{0-24}$/MIC = the free (unbound drug concentration) ratio of the area under the concentration–time curve during a 24-hour period to minimum inhibitory concentration; $fT_{>MIC}$ = the duration of time that the free drug concentration remains above the MIC during a dosing interval; PK/PD = pharmacokinetic/pharmacodynamic; Prop = prophylaxis; Tx = treatment

[a] In patients receiving micafungin for invasive candidiasis/candidemia

[b] Related to haematological toxicity and hepatotoxicity

[c] Concentration determined by bioassay

[d] Mostly related to gastrointestinal toxicity

[e] Mostly related to hepatotoxicity and neurotoxicity

Table 3 Pharmacokinetic/pharmacodynamic (PK/PD) indices and the magnitudes associated with antiviral clinical efficacy and toxicity

Antivirals	PK/PD index	Pre-clinical PK/PD target for efficacy[a]	Clinical PK/PD target for efficacy	Clinical PK/PD threshold for toxicity
Aciclovir/valaciclovir	Unclear	Unclear	Unclear	Unclear
Foscarnet	Unclear	Unclear	Unclear	No data
Ganciclovir/valganciclovir	AUC	Unclear	AUC: 40–60 mg h/L (Prop)	Unclear
Oseltamivir/oseltamivir carboxylate	Unclear	Unclear	Unclear	Unclear
Ribavirin	AUC	Unclear	AUC_{0-4} > 1755 mg h/L AUC_{0-12} > 3014 mg h/L C_{min} ≥ 2 mg/L	C_{min} > 2.3 mg/L[b]

AUC = area under the concentration–time curve; AUC_{0-4} = the ratio of the area under the concentration–time curve during a 4-h period; AUC_{0-12} = the ratio of the area under the concentration–time curve during a 12-h period; C_{min} = trough drug concentration; PK/PD = pharmacokinetic/pharmacodynamic; Prop = prophylaxis

[a] Whilst in vitro concentrations at which viral replication is inhibited by 50% (i.e. EC_{50} representing antiviral activity) have been widely determined, there are no/limited data which correlate these values with in vivo pharmacokinetic parameters (e.g. AUC) to describe magnitudes required for pre-clinical efficacy

[b] Mostly related to anaemia

AUC-based monitoring with at least two time points collected combined with Bayesian dose adaptation best predicts aminoglycoside dosing requirements [38–40]. TDM-guided dosing with Bayesian dose adaptation has led to a shorter length of hospital stay and a reduced incidence of nephrotoxicity in patients receiving gentamicin for Gram-negative infections [39].

Bioanalytical assay

Commercial immunoassays are available for amikacin, gentamicin and tobramycin TDM. For other aminoglycosides (e.g. kanamycin and plazomicin), modified immunoassays or chromatographic assays need to be established.

Beta-lactam antibacterials

Pharmacokinetics

Beta-lactam antibacterials are generally hydrophilic, demonstrate low V_d and are predominantly cleared via renal elimination. Most beta-lactams have a moderate (30–70%) to low (< 30%) degrees of protein binding. Significant V_d and CL alterations are common, and these PK

Table 4 Recommendations for therapeutic drug monitoring (TDM) for antibiotics, antifungals and antivirals in critically ill patients[a]

Antibacterials	TDM recommendation, suggested TDM sampling and targets in critically ill patients	
	Recommendation and suggested sampling scheme/strategy	Target
Aminoglycosides	TDM recommendation by Panel: "YES"	
	AUC-based monitoring Two samples[b] One taken 30 min after the end of infusion and the other one taken between 6 and 22 h post-infusion	AUC: 80–120 mg h/L
	C_{max}/MIC monitoring One sample 30 min after the end of infusion	C_{max}/MIC ≥ 8–10
	C_{min} monitoring[c] One sample 30 min or just before the next dosing	C_{min} Amikacin < 2.5 mg/L Gentamicin/tobramycin < 0.5 mg/L
Beta-lactams	TDM recommendation by Panel: "YES"	
	C_{min} monitoring One sample 30 min or just before the next dosing Sampling should occur 24–48 h post-initiation of therapy	100% $fT_{>MIC}$
	C_{ss} monitoring for continuous infusion One sample at any time point during the infusion	C_{ss} > MIC
Co-trimoxazole	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Daptomycin	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
	AUC/MIC-based monitoring Two samples One taken between 1.5 and 3 h post-dosing and the other one taken within 1 h of the next infusion	AUC/MIC > 666
	C_{min} monitoring One sample Within 1 h of the next infusion Sampling should occur 72 h post-initiation of therapy	C_{min} < 24 mg/L
Fluoroquinolones	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
	AUC/MIC-based monitoring Two samples[b] One taken 2 h post-dosing and the other one taken 6 h post-dosing	$fAUC_{0-24}$/MIC ≥ 80
	C_{max}/MIC monitoring One sample 30 min after the end of infusion	C_{max}/MIC ≥ 8–12
Glycopeptides		
Teicoplanin	TDM recommendation by Panel: "YES"	
	C_{min} monitoring One sample 30 min or just before the next dosing	C_{min} ≥ 15–30 mg/L
Vancomycin	TDM recommendation by Panel: "YES"	
	AUC/MIC-based monitoring Two samples[b] One taken 1 h after the end of infusion and the other one taken within 1–2 h of the next infusion	AUC_{0-24}/MIC ≥ 400
	C_{min} monitoring for intermittent infusion One sample 30 min or just before the next dosing	C_{min} > 10 mg/L C_{min} ≥ 15–20 mg/L (severe infections)
	C_{ss} monitoring for continuous infusion One sample at any time point during the infusion	C_{ss}: 20–25 mg/L
Linezolid	TDM recommendation by Panel: "YES"	
	C_{min} monitoring One sample 30 min or just before the next dosing Sampling should occur 48 h post-initiation of therapy	C_{min}: 2–7 mg/L

Table 4 (continued)

Antibacterials	TDM recommendation, suggested TDM sampling and targets in critically ill patients	
	Recommendation and suggested sampling scheme/strategy	**Target**
Polymyxins		
Colistin	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
	C_{min} monitoring One sample Just before the next infusion Sampling should occur 48–72 h post-initiation of therapy	C_{min}: 2 mg/L
Polymyxin B	TDM recommendation: "NEITHER RECOMMEND NOR DISCOURAGE"	
	AUC-based monitoring At least one sample Sampling should occur 12–24 h post-initiation of therapy	AUC_{0-24}: 50–100 mg h/L
Antifungals	**Suggested sampling scheme/strategy**	**Target**
Echinocandins	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Fluconazole	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Flucytosine	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
	C_{max} monitoring One sample 2 h post-dose Sampling should occur 48 h post-initiation of therapy	$C_{max} < 100$ mg/L
	C_{min} monitoring One sample 30 min or just before the next dosing Sampling should occur 72 h post-initiation of therapy	$C_{min} \geq 25$ mg/L[d]
Isavuconazole	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Itraconazole	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE" C_{min} monitoring One sample 30 min or just before the next dosing Sampling should occur within 5–7 days post-initiation of therapy	$C_{min} > 0.5$–1 mg/L
Posaconazole	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
	C_{min} monitoring One sample 30 min or just before the next dosing Sampling should occur after 7 days of initiation of therapy	$C_{min} > 0.5$–0.7 mg/L (prophylaxis) $C_{min} > 1$ mg/L (treatment)
Voriconazole	TDM recommendation by Panel: "YES"	
	C_{min} monitoring One sample 30 min or just before the next dosing Sampling should occur between 2 and 5 days of initiation of therapy	C_{min}: 2–6 mg/L (prophylaxis or treatment)
Antivirals	**Suggested sampling scheme/strategy**	**Target**
Aciclovir/valaciclovir	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Foscarnet	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Ganciclovir/valganciclovir	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Oseltamivir	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	
Ribavirin	TDM recommendation by Panel: "NEITHER RECOMMEND NOR DISCOURAGE"	

AUC = area under the concentration–time curve; AUC_{0-24}/MIC = the ratio of the area under the concentration–time curve during a 24-hour period to minimum inhibitory concentration; CI = continuous infusion; C_{max}/MIC = the ratio of maximum drug concentration to minimum inhibitory concentration; C_{min} = trough drug concentration; C_{ss} = average steady-state drug concentration; $fT_{>MIC}$ = the duration of time that the free drug concentration remains above the MIC during a dosing interval; II = intermittent infusion

[a] Although consensus may not have been achieved for some of these antimicrobials/antimicrobial classes, suggested sampling strategies and targets for TDM are presented for those antimicrobials/antimicrobial classes where TDM data/experience have been reported

[b] Only one sample is needed with Bayesian dose adaptation/adaptive feedback control

[c] Only for treatment of more than 3 days

[d] Concentrations preventing resistance development based on in vitro pharmacokinetic model

Table 5 Comparative studies highlighting clinical benefits of performing therapeutic drug monitoring for gentamicin, voriconazole and ribavirin

Study/country/population	Patients	Study design	Clinical outcomes[a]	TDM	Non-TDM
Van Lent-Evers (1999)	Total: 232	Multi-centre, non-randomised, before-and-after trial	Dose changes (%)*	48.6	80.4
Netherlands	TDM: 105	TDM: Bayesian-guided dosing	Duration of therapy (days)*	5.9 ± 2.9	8.0 ± 4.9
Gentamicin	Non-TDM: 127	Non-TDM: standard or nomogram	Length of stay (days)*	20.0 ± 13.7	26.3 ± 31.5
Gram-negative sepsis			Mortality (%) Nephrotoxicity (%)* Total costs (in DFL)*	9 (8.6%) 3 (2.8) 13,125 ± 9,267	18 (14.2) 17 (13.4) 16,862 ± 17,721
Park (2012)	Total: 110	Single-centre, assessor-blinded, randomised controlled trial	Adverse events (%)	23 (42)	22 (42)[b]
South Korea	TDM: 55	TDM: concentration-controlled[c]	Drug discontinuation (%)*	2 (4)	9 (17)[b]
Voriconazole	Non-TDM: 55	Non-TDM: standard therapy	Treatment response (%)*,[d]	30 (81)[e]	20 (59)[f]
Invasive fungal infections					
Stickel (2013)[g]	Total: 16	Multi-centre, open-labelled, randomised controlled trial	Sustained virological response (%)[h]	10 (62.5)	6 (37.3)
Switzerland	TDM: 16	TDM: concentration-controlled[i]	Mean haemoglobin (g/L)*	99.6	106.3
Ribavirin	Non-TDM: 16	Non-TDM: weight-based dosing			
Chronic hepatitis C					

DFL = Dutch florin, i.e. the currency of Netherlands up to 2002; TDM = therapeutic drug monitoring

[a] An asterisk indicates a significant difference between TDM and non-TDM groups

[b] Only 53 patients were included

[c] Target trough concentration of 1.0–5.5 mg/L

[d] Included either complete or partial response

[e] Only 37 patients were included

[f] Only 34 patients were included

[g] Reported in a research letter

[h] Cumulative ribavirin exposure above 224.3 mg/L was significantly associated with sustained virological response

[i] Target concentration of 3.7 mg/L

alterations may lead to inadequate beta-lactam concentrations particularly in the earlier phase of critical illness. Hypoalbuminemia has been associated with an increase in the free fraction (non-protein bound) of highly protein-bound beta-lactams (e.g. ceftriaxone, ertapenem and semisynthetic penicillins such as flucloxacillin, oxacillin and temocillin) and low unbound concentrations towards the end of the dosing interval [8].

Pharmacodynamics

The PK/PD index associated with optimal beta-lactam activity is the % $fT_{>MIC}$ (40–70%). Critically ill patients data suggest that patients may benefit from longer (e.g. 100% $fT_{>MIC}$) [41–43] and higher (e.g. 2–5 × MIC) [42–44] beta-lactam exposures than those previously described. Although the beta-lactams generally have a wide therapeutic index, high exposures have been associated with neurotoxicity. Although myelosuppression is well-known toxicity for the beta-lactams [45], no toxicity thresholds have been well established to date.

Dosing in critically ill patients

An initial loading dose (LD) followed by prolonged beta-lactam infusion (continuous or extended infusion) maximises PK/PD target attainment and is likely to improve clinical outcomes in critically ill patients [46].

TDM in critically ill patients

The Panel recommends that TDM be routinely performed when beta-lactam antibiotics are used in critically ill patients.

The collateral damage of more aggressive beta-lactam dosing to account for altered drug PK, i.e. excessive drug exposure, has been increasingly reported over the last 10 years, although it is probably still under-reported. TDM of beta-lactam antibiotics in critically ill patients is, therefore, becoming more common to optimise dosing whilst minimising the likelihood of toxicity [5, 47]. C_{min} samples at steady state are widely used, although the use of dosing software could enable even earlier sampling and dose optimisation [48].

Bioanalytical assay

Several high-performance liquid chromatography with ultraviolet detection (HPLC–UV) and liquid chromatography–tandem mass spectrometry (LC–MS/MS) assays have been applied to beta-lactam TDM.

Co-trimoxazole

Pharmacokinetics

Co-trimoxazole consists of a combination of sulfamethoxazole and trimethoprim in a 5:1 ratio. Both drugs are predominantly cleared by renal elimination and are moderately bound to plasma proteins. Although the impact of critical illness on its PK has been scarcely reported, significant PK variability has been observed with weight-based dosing of co-trimoxazole in older studies [49, 50].

Pharmacodynamics

C_{max} and $fAUC_{0-24}$/MIC ratios have been linked with optimal sulfamethoxazole/trimethoprim activity. Higher doses and exposures may likely increase the likelihood of adverse events such as hyperkalemia and metabolic acidosis.

Dosing in critically ill patients

There are insufficient clinical data to support altering co-trimoxazole dosing for maximal outcomes in critically ill patients. Weight-based dosing depending on the pathogen is appropriate.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine sulfamethoxazole (as the representative drug in co-trimoxazole) TDM in critically ill patients.

Bioanalytical assay

No commercial assays are currently available, and a chromatographic assay is required to facilitate TDM.

Daptomycin

Pharmacokinetics

Daptomycin demonstrates a low V_d and is predominantly cleared via renal elimination. V_d and CL alterations are common, leading to variable and low drug exposure. It is a highly protein-bound drug (92–94%) and the free fraction increases in critically ill patients.

Pharmacodynamics

AUC_{0-24}/MIC ratios of $\geq$ 666 mg/L have been described for daptomycin efficacy in critically ill patients [51]. More recently, a C_{min} of < 3.2 mg/L has been linked to poor clinical outcomes in hospitalised patients with various Gram-positive infections [52]. A C_{min} of $\geq$ 24.3 mg/L is associated with an increased likelihood of creatine phosphokinase (CPK) elevation by > 30-fold [53].

Dosing in critically ill patients

Current data suggest that optimal AUC_{0-24}/MIC ratios can easily be achieved with a Product Information dose of 6 mg/kg but only for pathogens with an MIC of 0.1 mg/L. With increasing MICs, higher doses (10–12 mg/kg/day) are probably required to achieve these targets [51, 54, 55].

TDM in critically ill patients

The Panel neither recommends, nor discourages routine daptomycin TDM in critically ill patients.

As daptomycin presents highly variable and unpredictable PK, several centres have performed TDM and have reported their clinical experience [52, 56, 57]. Previous work has aimed for C_{min} < 24 mg/L at steady-state [52, 57]. AUC-based monitoring, via LSS, can also be applied to guide daptomycin dosing to achieve AUC_{0-24}/MIC ratios of $\geq$ 666 [58].

Bioanalytical assay

HPLC–UV and LC–MS/MS assays have been published for daptomycin TDM.

Fluoroquinolones

Pharmacokinetics

Fluoroquinolones are moderately lipophilic with V_d generally unaffected by critical illness, with the exception of levofloxacin. Most fluoroquinolones have a moderate to low degree of protein binding, and some are cleared, at least to some degree, by renal elimination.

Pharmacodynamics

Fluoroquinolones exhibit "concentration-dependent" bactericidal activity, and the AUC_{0-24}/MIC ratio best predicts clinical efficacy. Higher C_{max}/MIC ratios (> 8–20) may also be required for optimal bactericidal activity [59, 60]. AUC_{0-24}/MIC ratios of 25–30 may suffice against the Gram-positive organisms, but higher values ($\geq$ 125) are needed against the Gram-negative organisms [61, 62]. Several studies have also suggested that a ratio of > 100–200 may suppress the emergence of resistance against Gram-negative organisms. Although increasing reports of fluoroquinolones-associated seizures have emerged [63–65], no toxicity thresholds have been established and causality is debated [66].

Dosing in critically ill patients

A quinolone dosing regimen that maximises the AUC_{0-24}/MIC (e.g. LD with higher maintenance doses) should be considered in critically ill patients.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine fluoroquinolone TDM in critically ill patients.

Given the inter-individual PK variability reported in critically ill patients and the high propensity for emergence of resistance against quinolones, TDM may be useful, particularly where pathogens have MICs close to the susceptibility breakpoint.

Bioanalytical assay

HPLC and LC–MS/MS assays have been published for fluoroquinolones TDM.

Glycopeptides

Teicoplanin

Pharmacokinetics

Teicoplanin is hydrophilic, with a V_d of 0.7–1.4 L/kg, and is predominantly cleared via renal elimination. It has a long elimination half-life ($t_{½}$) due to its high plasma protein binding (≥ 90%). Variability of teicoplanin exposure is significant in critically ill patients [67–69].

Pharmacodynamics

A C_{min} of ≥ 10–20 mg/L has been associated with favourable clinical response in uncomplicated infection [70, 71], but higher concentrations (≥ 20–30 mg/L) are advocated for severe *Staphylococcal* infections including endocarditis and osteomyelitis. However, the clinical data supporting these higher concentrations are sparse. More recent data suggested that the $AUC_{0–24}$/MIC ratio (≥ 750) may better predict teicoplanin activity in serious methicillin-resistant *S. aureus* (MRSA) infections [72, 73]. Unpublished studies reported that a C_{min} of > 60 mg/L increased the likelihood of nephrotoxicity.

Dosing in critically ill patients

Teicoplanin has a long $t_{½}$ (150 h) with the use of LD essential to reduce the time to reach therapeutic exposures.

TDM in critically ill patients

The Panel recommends that TDM be routinely performed when teicoplanin is used in critically ill patients.

Bioanalytical assay

HPLC–UV, LC–MS/MS and immunoassays have been published for teicoplanin TDM.

Vancomycin

Pharmacokinetics

Vancomycin is hydrophilic, demonstrates a low V_d and is predominantly cleared via renal elimination. Critical illness alters the V_d and CL of vancomycin leading to variable and low drug exposure.

Pharmacodynamics

$AUC_{0–24}$/MIC ratios of ≥ 400 are recommended against *Staphylococcus aureus* infection, whereas higher exposures are advocated when treating critically ill patients with septic shock [74–76]. Prolonged (≥ 7 days) and high vancomycin exposures are associated with nephrotoxicity.

Dosing in critically ill patients

Safely attaining optimal $AUC_{0–24}$/MIC ratios when treating pathogens with MICs of > 1 mg/L is highly challenging with vancomycin [77]. LD of 25–30 mg/kg, followed by 15–20 mg/kg every 8–12 h should be considered in critically ill patients without renal impairment. Continuous vancomycin infusion has been associated with a lower nephrotoxicity risk [78, 79], but clinical superiority has yet to be demonstrated over intermittent dosing. For practical reasons and ease of TDM, however, continuous vancomycin infusion is sometimes preferred and has been increasingly used in some centres.

TDM in critically ill patients

The Panel recommends that TDM be routinely performed when vancomycin is used in critically ill patients.

Monitoring C_{min} (15–20 mg/L for intermittent infusion) or average steady-state concentration (C_{ss}, 20–25 mg/L for continuous infusion) for pathogens with MIC ≤ 1 mg/L has been widely used as a surrogate for the $AUC_{0–24}$/MIC target. However, current data have demonstrated that C_{min} is a poor surrogate for $AUC_{0–24}$ and may tend to underestimate the actual vancomycin exposure [31, 80–83]. AUC-based monitoring with Bayesian dose adaptation may likely be a better tool to guide vancomycin treatment in critically ill patients. Although the contemporary $AUC_{0–24}$/MIC target has always been approximated as ≥ 400 for vancomycin, this index was derived from BMD MIC, and the E-test equivalence to this might only be 226 [84].

Bioanalytical assay

Immunoassays are commercially available for vancomycin TDM.

Linezolid

Pharmacokinetics

Linezolid is moderately lipophilic, demonstrates a V_d that approximates the total volume of total body water, is predominantly cleared via non-renal elimination and demonstrates significant intra- and inter-patient PK variability leading to variable linezolid exposure.

Pharmacodynamics

Maximum efficacy is demonstrated at % $T_{>MIC}$ of ≥ 85% and AUC_{0-24}/MIC ratio of 80–120 [85]. Linezolid-induced thrombocytopenia has been reported at C_{min} and AUC_{0-24} of > 7–10 and > 300–350, respectively.

Dosing in critically ill patients

Critically ill patients may benefit from higher linezolid doses and/or altered dosing approaches (e.g. front-loaded dosing regimen and continuous infusion) although these approaches should be supported with TDM if available. Subgroups of patients who may likely require higher-than-standard linezolid doses include those who are obese, those with acute respiratory distress syndrome and ARC, as well as those who are infected with pathogens with MIC ≥ 2 mg/L [54, 86].

TDM in critically ill patients

The Panel recommends that TDM be routinely performed when linezolid is used in critically ill patients.

Using an epidemiological MIC distribution, a C_{min} target of > 2 mg/L is well correlated with an AUC_{0-24}/MIC ratio of ≥ 80 [87]. Therefore, maintaining linezolid C_{min} between 2 and 7 mg/L is recommended for optimal drug exposure whilst minimising haematological toxicity [88]. Alternatively, TDM via LSS can be used [89].

Bioanalytical assay

HPLC–UV, LC–MS/MS and immunoassays have been published, but these assays are currently sparsely implemented for routine TDM.

Colistin

Pharmacokinetics

Colistin is administered parenterally as the prodrug colistin methanesulfonate (CMS). CMS and colistin demonstrate a low V_d and have mixed elimination routes. The V_d and CL of colistin may be altered in critically ill patients, potentially affecting colistin exposure. Colistin protein binding in critically ill patients was reported as 59–74% and was concentration dependent [90].

Pharmacodynamics

Colistin demonstrates "concentration-dependent" bactericidal activity, and both in vitro and in vivo data have suggested that the free AUC_{0-24}/MIC ($fAUC_{0-24}$/MIC) ratio best predicts its activity. $fAUC_{0-24}$/MIC ratios of 10.9–13.7 and 3.5–9.0 have been described for optimal killing against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, respectively [91]. Prolonged high exposures are associated with neuro- and nephrotoxicity [92–95]. A C_{min} of > 2.4 mg/L increases the likelihood of colistin-induced nephrotoxicity [92, 96, 97].

Dosing in critically ill patients

A LD is recommended to compensate for the enlarged V_d in critically ill patients with the CMS dosing regimen also adapted to renal function. The variability in conversion from prodrug to active compound, particularly in patients with ARC, makes dosing highly challenging in this patient group, and as such, leading studies on colistin dosing define a singular dose for all creatinine clearance values > 90 mL/min [98].

TDM in critically ill patients

The Panel neither recommends, nor discourages routine colistin TDM in critically ill patients.

The therapeutic index for colistin is exceptionally narrow—if TDM is performed, due to the ongoing conversion of CMS to colistin, it is recommended to collect C_{min} samples when CMS concentrations and conversion are at the lowest (i.e. samples to be drawn just before the next dose or C_{min} monitoring), and these samples should be processed immediately. It has been suggested that an average steady-state concentration (C_{ss}) of 2 mg/L predicts colistin efficacy whilst limiting the likelihood of nephrotoxicity [98, 99]. This target concentration should achieve an $fAUC_{0-24}$/MIC ratio of ~ 12 for pathogens with an MIC of ≤ 2 mg/L, which corresponds to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint for susceptibility. As colistin concentrations are relatively constant with little fluctuations at steady state, this target concentration can also be applied for C_{min} monitoring. However, this target concentration has not been correlated with clinical outcomes.

Bioanalytical assay

High-performance liquid chromatography with fluorescence detection (HPLC-FL) and LC–MS/MS assays have been published for colistin TDM.

Polymyxin B

Pharmacokinetics

Polymyxin B demonstrates a low V_d and is predominantly cleared via non-renal elimination. Protein binding was high and hugely variable in critically ill patients and was reported as 58–98.4%. Although the PK of polymyxin B is relatively favourable when compared to colistin, current Product Information dosing recommendations may likely lead to sub-optimal drug exposure in critically ill patients.

Pharmacodynamics

Polymyxin B demonstrates "concentration-dependent" kill characteristics, and both in vitro and in vivo data

have suggested that the $fAUC_{0-24}$/MIC ratio best predicts its activity. $fAUC_{0-24}$/MIC ratios of 3.7–28.0 correlated best with *Klebsiella pneumoniae* killing [100], and these indices are in line with those reported for colistin against *P. aeruginosa* and *A. baumannii* (3.5–13.9) [91]. A steady-state AUC_{0-24} of 100 mg h/L has been proposed as the nephrotoxicity threshold [101].

Dosing in critically ill patients

Current data suggest that LD of 2.5 mg/kg followed by 1.5–2.5 mg/kg/day (in two divided doses) may be appropriate for pathogens with an MIC of ≤ 1 mg/L [102, 103]. Higher daily doses (up to 3 mg/kg/day), preceded by LD, should be considered for pathogens with an MIC of > 1–2 mg/L. Although it has been generally accepted that IV polymyxin B is best dosed by total body weight, emerging data have since disputed this approach [104].

TDM in critically ill patients

The Panel neither recommends, nor discourages routine polymyxin B TDM in critically ill patients.

The therapeutic index for polymyxin B is exceptionally narrow—if performed, AUC-based TDM (50–100 mg h/L) with at least one sample collected (concentrations at 12–24 h post-initiation of therapy) combined with Bayesian dose adaptation has been suggested to optimise polymyxin B dosing in critically ill patients [101, 102].

Bioanalytical assay

LC–MS/MS assays have been published for polymyxin B TDM.

Antifungals

Echinocandins

Pharmacokinetics

The echinocandin antifungals include anidulafungin, caspofungin and micafungin, which are only available for parenteral use. The echinocandins have high plasma protein binding (≥ 97–99%). Exposure in critically ill patients is generally lower and more variable compared to healthy volunteers, but the clinical implication of this is unclear due to the heterogeneous case mix and small sample sizes in these studies.

Pharmacodynamics

Echinocandin exposures relating to optimal clinical outcomes and toxicity occurrence have not been identified thus far. However, optimal mycological response for micafungin against *Candida* spp. has been observed in patients with AUC_{0-24}/MIC ratios of > 3000 [105].

Dosing in critically ill patients

Although echinocandins are presumed to be clinically comparable with each other, subtle dosing differences exist, e.g. the need for a loading dose, metabolic route and drug–drug interactions. Higher body weight may require higher dosing [106–108]. Echinocandin exposure can be influenced in patients with severe hepatic impairment, particularly for caspofungin. Lower exposure, as well as higher exposure, has been observed in these patients [109–111].

TDM in critically ill patients

The Panel neither recommends, nor discourages routine echinocandin TDM in critically ill patients.

Bioanalytical assay

LC–MS/MS assays have been published but are sparsely implemented for routine TDM.

Fluconazole

Pharmacokinetics

Fluconazole is available for parenteral and oral administration, is well absorbed from the gastrointestinal tract and displays linear PK. It is moderately lipophilic, demonstrates a V_d of around 1 L/kg and is predominantly cleared via renal elimination. Significant inter-individual PK variability has been observed in critically ill patients.

Pharmacodynamics

Maximal clinical efficacy in patients with candidemia has been described with AUC_{0-24}/MIC ratios of ≥ 55.2–100 [112, 113]. As the dose can be used as a surrogate for fluconazole AUC [114], the ratio of dose to MIC (dose/MIC) has also been used to describe clinical outcomes [112, 113, 115]. Higher dosing may likely lead to hepatotoxicity and seizures [116].

Dosing in critically ill patients

LD of 12 mg/kg IV followed by a maintenance dose (MD) of 6 or 12 mg/kg/day IV is advocated to achieve either the low (AUC_{0-24}/MIC ratio of 25) or high (AUC_{0-24}/MIC ratio of 100) PK/PD target, respectively, in critically ill patients with normal renal function [117].

TDM in critically ill patients

The Panel neither recommends, nor discourages routine fluconazole TDM in critically ill patients.

Bioanalytical assay

Several chromatographic assays have been published for fluconazole TDM.

Flucytosine

Pharmacokinetics

Flucytosine's V_d ranges from 0.6 to 0.9 L/kg and is predominantly cleared via renal elimination. Significant inter-patient PK variability has been observed, leading to variable flucytosine concentrations.

Pharmacodynamics

A C_{max} of > 100 mg/L has been associated with hepatotoxicity and myelosuppression in several clinical studies [118–121]. Concentrations of < 25 mg/L may selectively amplify resistant *C. albicans* mutants [122].

Dosing in critically ill patients

There are insufficient clinical data to support altering flucytosine dosing for maximal outcomes in critically ill patients. Standard, weight-based dosing, adapted to renal function, is appropriate.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine flucytosine TDM in critically ill patients.

TDM-guided dosing to optimise flucytosine efficacy remains poorly described as opposed to prevention of toxicity. If TDM is performed, a C_{max} of < 100 mg/L and C_{min} of ≥ 25 mg/L can be used to prevent flucytosine toxicity and resistance, respectively.

Bioanalytical assay

Several chromatographic assays have been published for flucytosine TDM.

Isavuconazole

Pharmacokinetics

Isavuconazole is available in oral (capsule) and IV formulations, and switching between these formulations is acceptable. It has a large V_d, and its CL is highly dependent on hepatic metabolism. Plasma protein binding is high (> 99%). It displays linear and favourable PK compared to the other triazoles. Exposures in real-world clinical settings are very similar to those described in clinical trials with > 90% of patients receiving standard isavuconazole dosing expected to achieve a proposed therapeutic concentration of 1 mg/L [123, 124].

Pharmacodynamics

Current data do not identify any significant relationship between isavuconazole exposure with clinical efficacy and safety end points.

Dosing in critically ill patients

LD of 200 mg IV 8 hourly for six doses (or 48 h) followed by MD of 200 mg IV once daily is recommended to achieve an effective C_{ss} by day 3 of treatment.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine isavuconazole TDM in critically ill patients.

Bioanalytical assay

HPLC–UV and LC/MS–MS assays have been published for isavuconazole monitoring.

Itraconazole

Pharmacokinetics

Itraconazole is available in oral (capsule/tablet and oral solution) and IV formulations. It has 30% higher bioavailability as an oral solution and is more preferred to capsule/tablet formulations. It is lipophilic, demonstrates a large V_d and is predominantly cleared via hepatic metabolism. Plasma protein binding is high (> 99%). Itraconazole displays variable and nonlinear PK. There are few data available concerning the use of itraconazole in critically ill patients, although continuous haemodiafiltration results in increased itraconazole elimination [125].

Pharmacodynamics

Higher itraconazole C_{min} has been associated with clinical outcome benefits in *Aspergillus* spp. [126], *Cryptococcus neoformans* [127, 128] and *Histoplasma capsulatum* infections [129]. During itraconazole prophylaxis, breakthrough infections and mortality are more likely in neutropenic patients with a C_{min} of < 0.25–0.5 mg/L [130–132]. Oropharyngeal and oesophageal candidiasis patients demonstrated better clinical responses when itraconazole concentrations are > 0.6–1 mg/L [133, 134]. An average concentration of ≥ 17.1 mg/L has been linked with itraconazole toxicity [135, 136].

Dosing in critically ill patients

LD of 200 mg IV 8 hourly for nine doses (or 72 h) followed by MD of 200 mg IV once or twice daily is recommended to achieve target concentrations within the first few days of therapy.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine itraconazole TDM in critically ill patients.

Apart from demonstrating nonlinear PK [137], its high variability in bioavailability and hepatic metabolism together with a less favourable safety profile when compared to other azoles traditionally support itraconazole TDM. A C_{min} target between 0.5 and 1 mg/L is used to

guide both prophylaxis and treatment of invasive fungal infections.

Bioanalytical assay

Several LC–MS/MS assays have been published for itraconazole TDM.

Posaconazole

Pharmacokinetics

Posaconazole is available as an oral suspension, tablet and IV formulations. It is lipophilic, demonstrates a large V_d and is predominantly cleared via hepatic glucuronidation. Plasma protein binding is high (> 98%). Extreme inter- and intra-individual PK variability and, consequently, sub-optimal exposures are typically seen with the oral suspension [138–142].

Pharmacodynamics

Higher C_{min} (> 0.5–0.7 mg/L) has been associated with reduced breakthrough infections in patients receiving posaconazole prophylaxis [143–150]. Patients with invasive aspergillosis demonstrated improved clinical response with an average posaconazole concentration of > 1 mg/L [151, 152]. Exposure-related toxicity has not been described for posaconazole although the European Medicines Agency (EMA), and most clinical studies have suggested a putative C_{min} threshold of > 3.75–4 mg/L [153], which has yet to be validated clinically.

Dosing in critically ill patients

LD of 300 mg IV every 12 hourly on day 1 followed by MD of 300 mg IV once daily is recommended for invasive fungal infections.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine posaconazole TDM in critically ill patients.

Although extensive PK variability has been previously described, the newer delayed-release oral tablets and IV formulations increase the likelihood therapeutic targets will be achieved [138, 154–156]. However, recent data still report highly variable PK in critically ill patients, even with IV posaconazole [157], and therefore TDM may still be useful in this population. Because of the long half-life of the drug (16–35 h) [158], a concentration obtained at a random time with respect to the previous dose, including a C_{min}, is approximately representative of the average daily concentration (C_{ave}) and is accepted as a surrogate for AUC. If TDM is performed, a steady-state C_{ave} target of > 0.5–0.7 mg/L and > 1 mg/L can be used to guide posaconazole prophylaxis and treatment of invasive fungal infections, respectively, particularly when oral suspension is used.

Bioanalytical assay

Several chromatographic assays have been published for posaconazole TDM.

Voriconazole

Pharmacokinetics

Voriconazole is lipophilic, demonstrates a large V_d and is predominantly cleared via hepatic metabolism. Plasma protein binding is 58%. Voriconazole displays nonlinear PK in adults and exhibits extensive inter-individual PK variability in all patient populations.

Pharmacodynamics

A C_{min} of ≥ 1 [159–165] or ≥ 2 mg/L [166–168], as well as a C_{min} to MIC (C_{min}/MIC) ratio of 2–5 [169], has been associated with improved clinical outcomes in the treatment of invasive fungal infections. Although no clear exposure–response relationship has been established for voriconazole prophylaxis, breakthrough fungal infections are reported to be more likely with a C_{min} of ≤ 1.5–2 mg/L [170, 171]. C_{min} of ≥ 4.5–6 mg/L has been linked with voriconazole-associated hepatotoxicity and neurotoxicity [161, 165, 167, 172–175].

Dosing in critically ill patients

LD of 6 mg/kg IV every 12 hourly for two doses followed by 3–4 mg/kg IV 12-hourly is recommended for invasive fungal infections.

TDM in critically ill patients

The Panel recommends that TDM be routinely performed when voriconazole is used in critically ill patients.

TDM-guided voriconazole dosing in the treatment of invasive fungal infections has been shown to improve clinical response and reduce voriconazole discontinuation due to adverse events [163]. Limited data are available in critically ill patients, but sub-optimal exposures and negative clinical outcomes have been observed in these patients with standard voriconazole dosing [160]. Also, recent publications reported the significant role of the inflammatory response in the unpredictable PK of voriconazole with a 0.015 mg/L rise in the C_{min} for every 1 mg/L increase in C-reactive protein (CRP) [176–178]. As inflammation is common in critically ill patients, this could have a significant impact on the incidence of voriconazole toxicities. A C_{min} target between 2 and 6 mg/L is recommended to guide voriconazole dosing.

Bioanalytical assay

Several chromatographic assays have been published for voriconazole TDM.

Antivirals

Aciclovir/valaciclovir

Pharmacokinetics

Valaciclovir is the orally administered prodrug of aciclovir, which is moderately lipophilic, demonstrates a large V_d and is predominantly cleared via renal elimination.

Pharmacodynamics

Limited data exist linking aciclovir exposures with clinical efficacy and toxicity. Although the efficacy of aciclovir/valaciclovir in the treatment of herpes simplex virus (HSV) infection has been associated with AUC and the time that the drug remains above the 50% inhibitory concentration (EC_{50}; $T > EC_{50}$) [179–183], these indices require further investigations. Higher concentrations, particularly in patients with renal impairment, have been linked with the likelihood of gastrointestinal and neurological adverse events [184–187].

Dosing in critically ill patients

A standard dose of 10–15 mg/kg IV 8 hourly is recommended for severe viral infections in immunocompetent patients.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine aciclovir TDM in critically ill patients.

Few reports are available on aciclovir TDM, and most of them included patients with encephalitis [188, 189]. A C_{min} of 2–4 mg/L can be recommended if TDM is performed.

Bioanalytical assay

Several HPLC–UV and LCMS-MS assays have been published for aciclovir TDM.

Foscarnet

Pharmacokinetics

Significant inter- and intra-individual PK variability has been reported, and it may be challenging to estimate foscarnet concentrations over time in an individual patient accurately.

Pharmacodynamics

No clear relationship has been established so far between its concentration and clinical efficacy. Most investigators have suggested maintaining plasma concentrations between an arbitrary range of 300–500 µmol/L to ensure that effective antiviral activity is achieved and sustained. Although several small-scale clinical studies have reported that clinical response (e.g. progression of CMV retinitis in HIV patients) and nephrotoxicity can be predicted by the AUC [190–194], the therapeutic exposure range of foscarnet remains undefined.

Dosing in critically ill patients

There are insufficient clinical data to support altering foscarnet dosing for maximal outcomes in critically ill patients. Standard, weight-based dosing, adapted to renal function, depending on the indication is appropriate.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine foscarnet TDM in critically ill patients.

Bioanalytical assay

Several HPLC–UV methods have been published to determine foscarnet concentration in biological fluids.

Ganciclovir/valganciclovir

Pharmacokinetics

Valganciclovir is the prodrug of ganciclovir, which is hydrophilic, demonstrates a low V_d (0.7 L/kg) and is predominantly cleared via renal elimination. The PK of ganciclovir/valganciclovir appears to be predictable with minimal unexplained inter-patient variability in solid organ transplant recipients. There is concern that plasma PK exposures may not be an accurate surrogate marker for intracellular concentrations to predict clinical response and toxicity [195, 196].

Pharmacodynamics

No clear relationship has been established between ganciclovir exposures with clinical efficacy and toxicity. AUC_{0-24} has been associated with ganciclovir antiviral activity with values of $\geq$ 40–60 mg h/L advocated for CMV prophylaxis [197–201]. C_{min} has also been used to predict ganciclovir activity, but the optimal cut-off value remains poorly defined [202–207]. No clearly defined toxicity thresholds have been described for ganciclovir, but higher C_{min} and AUC_{0-24} values are likely to increase the risk of haematological and neurological toxicity [199, 208].

Dosing in critically ill patients

In the treatment of CMV infections in immunocompromised patients, the usual dose of ganciclovir for induction therapy is 5 mg/kg IV every 12 hourly which is then followed by 5 mg/kg as a single daily infusion for maintenance therapy.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine ganciclovir/valganciclovir TDM in critically ill patients.

Several centres have reported their experience with ganciclovir/valganciclovir TDM [208, 209], even though changes in immunological markers have been reported to predict clinical outcomes reliably [210, 211]. A C_{min} of > 2 mg/L or AUC_{0-24} of > 40 mg h/L can be applied if TDM is performed. A clinically applicable LSS to estimate ganciclovir/valganciclovir AUC_{0-24} has been described [24] and combined with Bayesian dose adaptation; this approach demonstrated superior PK/PD outcomes and trends towards patient benefits when compared to standard dosing recommendations [208].

Bioanalytical assay

Several HPLC–UV and LC/MS–MS assays have been published for ganciclovir/valganciclovir TDM.

Oseltamivir

Pharmacokinetics

Oseltamivir is hydrophilic, demonstrates a large V_d and is predominantly cleared via renal elimination. Its active metabolite, oseltamivir carboxylate (OC), displays minimal inter- and intra-individual PK.

Pharmacodynamics

No clear relationship has been established between oseltamivir and OC exposures with either clinical efficacy or toxicity. Although the efficacy of oseltamivir in animal models of influenza appears to be dose dependent, no formal exposure–response relationships have been established [212–214]. It has been suggested that the AUC_{0-24} or AUC_{0-24}/EC_{50} might be suitable indices to guide therapy, but further studies are warranted to validate the clinical relevance of these findings [215, 216]. Higher AUC_{0-12} OC exposures have been associated with mild-to-moderate adverse events [217]. The PK of OC appears to be predictable, although this has been mostly determined in healthy volunteers where PK variability is known to be low [217, 218].

Dosing in critically ill patients

A dose of 75 mg PO once or twice daily is currently recommended for prophylaxis and treatment of influenza in critically ill patients.

TDM in critically ill patients

The Panel neither recommends, nor discourages routine oseltamivir TDM in critically ill patients.

Although there are limited clinical data to support oseltamivir TDM, French investigators have recently described the utility of paracetamol absorption test to predict OC absorption and likely plasma concentrations in critically ill patients [219].

Bioanalytical assay

Several HPLC–UV and LC/MS–MS assays have been published for oseltamivir TDM.

Ribavirin

Pharmacokinetics

Ribavirin demonstrates a large V_d (≥ 18 L/kg) and is predominantly cleared via renal elimination. Wide inter-individual PK variability, including bioavailability, has been reported with this drug.

Pharmacodynamics

Inconsistent data have been reported on the relationship between ribavirin exposure and efficacy, as well as toxicity occurrence. Although higher C_{min} [220–226] and AUC [225, 227, 228] values have been associated with eradication of hepatitis C virus (HCV) or sustained virological response in some studies, it is important to note that numerous studies have also shown no association between these parameters and sustained virological response. It has been suggested that the AUC_{0-4} (1.76 mg h/L) and AUC_{0-12} (3.01 mg h/L) after the first dose may be a better sustained virological response predictor when compared to C_{min} or any single time point [228]. Although haemolytic anaemia has been linked with a C_{min} of > 2.3–3.5 [224, 229, 230], some studies have found no significant correlation. Additionally, other studies indicated that other factors (e.g. pegIFN-alpha-2a levels) may have a greater impact on the outcome than ribavirin concentrations [231].

TDM in critically ill patients

The Panel neither recommends, nor discourages routine ribavirin TDM in critically ill patients.

Ribavirin TDM has been controversially discussed for at least a decade since hepatitis C is no longer treated as a pathogenic entity but rather according to different genotypes, and old combination partners are no longer state of the art. Furthermore, there is currently conflicting data regarding the relationship between ribavirin exposures with therapeutic or toxic effects. However, it is important to note that as opposed to weight-based dosing, TDM-guided ribavirin dosing has been shown to significantly improve sustained virological response in patients with chronic hepatitis C genotype 1 [227]. Although anaemia was more severe in the TDM group, it was well managed with erythropoietin beta. More recently, TDM has been suggested as a useful tool to guide ribavirin treatment in lung transplant recipients with paramyxovirus infection [232].

Bioanalytical assay

Several HPLC–UV and LC/MS–MS assays have been published for ribavirin TDM.

Main areas for future investigations

Optimal antimicrobial exposures and PK/PD targets in the treatment of sepsis and septic shock in ICU

Optimal intravenous antimicrobial therapy needs to be administered as soon as possible, preferably within the first hour of sepsis and septic shock recognition [233]. Empirical antimicrobial therapy should attempt to provide coverage against all likely pathogens (bacterial, fungal and/or viral) and effective exposures are needed in the interstitial fluid of tissues presumed to be the source of infection. As extreme pathophysiological changes are likely to affect antimicrobial exposures, factors associated with PK/PD alterations need to be determined and considered in critically ill patients with sepsis and septic shock. Optimal antimicrobial exposures and PK/PD targets for patient benefits need to be further elucidated before appropriate dosing regimens and strategies can be improved in this population. The role of biomarkers as a surrogate for an antimicrobial response should be investigated as an earlier therapeutic intervention can be made rather than relying on clinical signs and symptoms [234, 235]. More data on plasma and target-site tissue PK of antimicrobials, particularly in the first 24 h of therapy, are needed to evaluate the appropriateness of the current dosing regimen in this patient population.

Optimal antimicrobial exposures for reducing resistance development in ICU

Most of the Panel's treatment goals have been focused on maximising clinical and microbiological outcomes and not including resistance suppression. However, for most antimicrobials, clinical data are urgently needed to define thresholds that can minimise resistance emergence and whether they are safe for patients.

Impact of TDM in personalised antimicrobial dosing in critically ill patients

Only a few studies have attempted to compare the clinical outcomes of TDM-guided antimicrobial dosing versus outcomes without this intervention [39, 163, 227]. Currently, most data were obtained from small-scale and uncontrolled studies, which are not of itself, sufficient to support a global practice shift towards routine antimicrobial TDM in ICU. Therefore, well-designed and controlled studies focusing on patient-centred outcomes should be performed in this population to evaluate the real benefits of incorporating TDM into daily ICU practice.

The tools and essentials for TDM

Routine antimicrobial TDM in critically ill patients is currently hampered by slow turnaround times, and even in expert centres, antimicrobial concentrations may only be available after 6–8 h of blood collection, potentially leading to delayed dosing improvements. Furthermore, in most ICUs, TDM is probably not available for all important antimicrobials and certainly, not for 24 h and 7 days a week [5, 6]. An easy-to-use chromatography-based method that enables rapid and reliable simultaneous determination of antimicrobial concentrations in plasma and tissues can be developed, and some are now being used routinely in clinical settings. Although concentration measurements are usually performed in blood matrices (e.g. plasma or serum), several alternative sampling strategies (e.g. dried blood spots and volumetric absorptive microsamples), which are minimally or non-invasive approaches, need to be further investigated and validated for routine TDM in critically ill patients. Importantly, these "patient-friendly" strategies may play an important role in the establishment of TDM centres in remote and resource-limited settings.

Conclusion

Although alternative dosing strategies can improve antimicrobial exposure in critically ill patients, the extreme PK variability in this patient population means that some may still receive sub-optimal antibiotic exposure leading to unpredictable clinical outcomes. TDM-guided dosing is the only safe and effective way to ensure that all critically ill patients achieve therapeutic antimicrobial exposures. TDM-guided dosing has been shown to be clinically beneficial for aminoglycosides, voriconazole and ribavirin. For most common antibiotics and antifungals in the ICU, a clear therapeutic range has been established and for these agents, routine TDM in critically ill patients may be useful. Specifically, we recommend routine TDM when one of these antibiotics or antifungals is used in critically ill patients: aminoglycosides, beta-lactam antibiotics, linezolid, teicoplanin, vancomycin and voriconazole. For the antivirals, urgent research is needed to identify therapeutic targets for patient benefits and to also ascertain whether antiviral TDM is indeed meritorious in this patient population. Although we believe that TDM should be the standard of care for most antimicrobials in every ICU, important barriers, such as the availability of bioanalytical experts and TDM equipments in an institution, need to be addressed before routine TDM can be widely employed worldwide.

Electronic supplementary material

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Compliance with ethical standards

Conflicts of interest
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