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Expert Review of Clinical Pharmacology

ISSN: 1751-2433 (Print) 1751-2441 (Online) Journal homepage: http://www.tandfonline.com/loi/ierj20

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To cite this article: Nynke G. L. Jager, Reinier M. van Hest, Jeffrey Lipman, Fabio S. Taccone & Jason A. Roberts (2016) Therapeutic drug monitoring of anti-infective agents in critically ill patients, Expert Review of Clinical Pharmacology, 9:7, 961-979, DOI: 10.1586/17512433.2016.1172209

To link to this article: https://doi.org/10.1586/17512433.2016.1172209

Accepted author version posted online: 28 Mar 2016.
Published online: 15 Apr 2016.

EXPERT REVIEW OF CLINICAL PHARMACOLOGY, 2016
VOL. 9, NO. 7, 961–979
http://dx.doi.org/10.1586/17512433.2016.1172209

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REVIEW

Therapeutic drug monitoring of anti-infective agents in critically ill patients

Nynke G. L. Jager[a], Reinier M. van Hest[a], Jeffrey Lipman[b,c], Fabio S. Taccone[d] and Jason A. Roberts[b,c,e]

[a]Department of Pharmacy, Academic Medical Center, Amsterdam, The Netherlands; [b]Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia; [c]Departments of Pharmacy and Intensive Care, Royal Brisbane and Women's Hospital, Brisbane, Australia; [d]Department of Intensive Care, Hopital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium; [e]School of Pharmacy, The University of Queensland, Brisbane, Australia

ABSTRACT

Initial adequate anti-infective therapy is associated with significantly improved clinical outcomes for patients with severe infections. However, in critically ill patients, several pathophysiological and/or iatrogenic factors may affect the pharmacokinetics of anti-infective agents leading to suboptimal drug exposure, in particular during the early phase of therapy. Therapeutic drug monitoring (TDM) may assist to overcome this problem. We discuss the available evidence on the use of TDM in critically ill patient populations for a number of anti-infective agents, including aminoglycosides, β-lactams, glycopeptides, antifungals and antivirals. Also, we present the available evidence on the practices of anti-infective TDM and describe the potential utility of TDM to improve treatment outcome in critically ill patients with severe infections. For aminoglycosides, glycopeptides and voriconazole, beneficial effects of TDM have been established on both drug effectiveness and potential side effects. However, for other drugs, therapeutic ranges need to be further defined to optimize treatment prescription in this setting.

ARTICLE HISTORY
Received 4 February 2016
Accepted 26 March 2016
Published online
15 April 2016

KEYWORDS
Anti-infectives; antibiotics; antifungals; antivirals; therapeutic drug monitoring; pharmacokinetic; critically ill; intensive care

Introduction

Severe infection is recognized as an important determinant of outcome for patients at intensive care units (ICU) [1]. Moreover, the incidence of severe sepsis, defined as an infection associated with the occurrence of organ dysfunction, is reported to be increasing [2–4]. Initial appropriate anti-infective therapy is associated with significantly improved clinical outcomes [5–7]. Whilst appropriate anti-infective therapy is mostly defined in terms of timely commencement of treatment with a spectrum appropriate for the pathogen, adequate exposure also appears to be highly important [8]. However, achieving these exposures is challenging, particularly when using standard dosing regimens that have usually been derived in healthy volunteers or noncritically ill patients. Extrapolating these to critically ill patients may result in suboptimal exposure, since a variety of pathophysiological changes, which may significantly influence serum drug concentrations, can occur in this population [9].

In view of the diverse and unique pharmacokinetic (PK) profile of drugs in critically ill patients and the severity of the illness in these patients, there is a strong rationale to individualize anti-infective dosing in critically ill patients by use of therapeutic drug monitoring (TDM). In this article, we aim to critically review the available evidence supporting anti-infective TDM and to describe how TDM can be utilized to potentially improve treatment outcome in critically ill patients with severe infections.

Search strategy

A structured literature search was performed on PubMed (until January 2016), using the following search MeSH terms: ('antibacterial agents' OR 'antifungal agents' OR antiviral) AND ('therapeutic drug monitoring' OR PK OR pharmacodynamic [PD]) AND ('critical care' OR 'critical illness' OR 'care unit, intensive').

Also, a separate search was performed for each drug or drug class, for example aminoglycoside AND (PK OR 'therapeutic drug monitoring') AND ('critically ill' OR 'intensive care'). Papers written in English were reviewed, as well as the references listed in the relevant articles. The search was limited to data on adult patients. Studies were deemed eligible when presenting a clinical investigation on adult, critically ill patients where PK and drug exposures of anti-infective agents were evaluated, in order to reach a predefined target concentration. This structured research yielded 213 articles for aminoglycosides (n = 7 eligible), 117 articles for glycopeptides (n = 6 eligible), 284 articles for β-lactams (n = 11 eligible), 77 articles for fluoroquinolones (n = 10 eligible), 40 articles for colistin (n = 2 eligible), 45 articles for linezolid (n = 6 were eligible), 18 articles for daptomycin (n = 3 eligible), 34 articles for fluconazole (n = 3 eligible), 9 articles for itraconazole (n = 1 eligible), 9 articles for posaconazole (n = 1 eligible), 21 articles for voriconazole (n = 3 eligible), 10 articles for flucytosine 10 (n = 0 eligible), 6 articles for aciclovir (n = 0 eligible), 3 articles for ganciclovir (n = 1 eligible), and 9 articles for oseltamivir (n = 1 eligible).

PK changes in critically ill patients

Underpinning the need for TDM in critically ill patients is the variable, and usually suboptimal, anti-infective drug exposure that can occur in these patients. Indeed, there are several pathophysiological and/or iatrogenic factors that may affect the PK of anti-infectives in critically ill patients, summarized in Figure 1.

CONTACT Jason A. Roberts j.roberts2@uq.edu.au

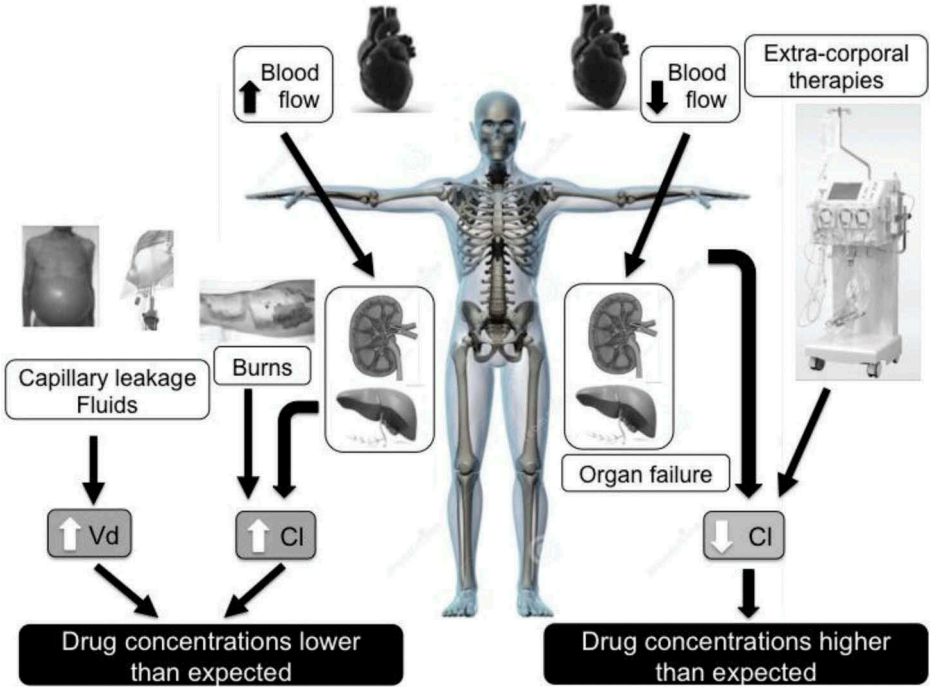

Figure 1. Pharmacokinetic changes during critical illness.
Cl = clearance; Vd = volume of distribution.

Impaired drug absorption

The absorption of orally administered drugs into the systemic circulation is expected to be low in critically ill patients. This is mainly due to decreased gut motility and poor blood perfusion of the gastrointestinal tract. Also, decreased blood flow to the peripheries impairs the systemic absorption of intramuscularly and subcutaneously administered drugs [9,10]. This common occurrence supports use of intravenous (IV) administration of anti-infective agents in most scenarios, particularly where there is uncertainty about gut function.

Changes in volume of distribution

The pathogenesis of infections in critically ill patients appears highly complex and involves the release of endotoxins and exotoxins from bacteria or fungi. These agents may stimulate the production of various endogenous mediators, which may cause maldistribution of blood flow, endothelial damage, and increased capillary permeability. This capillary leakage results in fluid shifts from the intravascular compartment to the interstitial space; a phenomenon called third spacing [9,11]. As a result, high volumes of resuscitative fluids and catecholamines may have to be administered in order to maintain adequate blood volume and systemic blood pressure [12]. This significant expansion of extracellular fluid volume may lead to an increase in the apparent volume of distribution (Vd) of some drugs, and thus a lower maximum plasma drug concentration in a dosing interval. Moreover, the Vd may also be increased in the presence of mechanical ventilation, extracorporeal circuits, or in patients with significant burn injuries [13]. The importance of an increased Vd differs between hydrophilic and lipophilic drugs. Hydrophilic agents (e.g. aminoglycosides, glycopeptides, and β-lactams) are distributed exclusively in the extracellular compartment and the above-mentioned changes can significantly increase Vd [14]. Lipophilic agents (e.g. fluoroquinolones) on the other hand, typically have a larger baseline Vd because of partitioning intracellularly and/or into adipose tissue, and as such their Vd is not largely influenced by the fluid shifts described above [9,14].

Changes in protein binding

The free or unbound drug is both the pharmacological active component as well as the component available for elimination. In general, total concentration of a drug is measured and published protein binding values can be used to predict the unbound drug concentration. However, in approximately 40% of critically ill patients, hypoalbuminemia occurs [15]. For drugs highly bound to albumin, such as ceftriaxone, flucloxacillin, and daptomycin, this may result in a significantly increased unbound fraction which means that a subtherapeutic total concentration not necessarily indicates a subtherapeutic unbound concentration. In patients with adequate or even augmented clearance, normal respective to low unbound concentrations may be expected. In most cases, the measured total concentration will not serve as an adequate surrogate for the free concentration anymore [16].

Changes in drug clearance

During critical illness, there is commonly an increased blood flow to major organs, due to the effect of fluid loading, use of vasoactive agents, and the underlying inflammatory response. As a result, augmented renal clearance (ARC), defined as a creatinine clearance >130 mL/min, has been reported to occur

in 15–65% of the patients in the ICU [17–19]. Younger patients with multitrauma, sepsis, traumatic brain injury, and burns are especially susceptible to ARC [20–22]. On the other hand, with progression of sepsis, myocardial depression can occur, which leads to a decrease in organ perfusion and failure of the microvascular circulation [23]. As a result, abrupt loss of kidney function, termed acute kidney injury (AKI), can occur. Moreover, nephrotoxic drugs such as vancomycin, aminoglycosides, and furosemide can also decrease renal function [8]. Of note, renal function in critically ill patients can change significantly, even over a brief period of hours.

Alterations in blood flow also affect hepatic drug metabolism; increased blood flow will lead to increased hepatic metabolism and myocardial depression results in decreased hepatic metabolism of some drugs. Moreover, hepatic dysfunction can be caused by infection-related cholestasis, hepatocellular injury, and liver cirrhosis. Liver failure will not only result in lower hepatic metabolism and clearance, but will also lead to decreased protein binding, due to a decreased production of albumin [24–26].

Extracorporeal clearance

Renal replacement therapy (RRT) is associated with an increased Vd and clearance of several drugs [27]. For most hydrophilic agents, which exhibit a low Vd and high clearance in healthy volunteers, the application of RRT will markedly increase the extent of elimination, compared with the elimination observed in moderate to severe AKI. On the contrary, most lipophilic agents, which usually exhibit a high Vd and low clearance in healthy volunteers, are expected to be poorly or moderately cleared by RRT. This is caused by the fact that only a small fraction of these drugs is present in plasma [28]. However, the impact of extracorporeal clearance on the patients' PK varies markedly between patients, since there are large differences in RRT modalities and settings used between institutions, and the extent of extracorporeal clearance depends on multiple factors, such as the RRT blood flow rate, ultrafiltration flow rate, filter or dialyzer material, and/or surface area [29]. Extracorporeal membrane oxygenation (ECMO) is a highly invasive intervention that assists critically ill patients with severe lung and/or heart dysfunction. In *ex vivo* studies and neonatal reports, ECMO is described to possibly cause an increased Vd for certain drugs, and several drugs can adsorb onto the ECMO tubing and/or oxygenator [30,31]. However, as with RRT, also the variable characteristics of ECMO procedures result in large differences in the impact of ECMO on patients' PK [32].

Minimum inhibitory concentration

The minimum inhibitory concentration (MIC) of a pathogen is the minimum concentration of the anti-infective agent that prevents growth of the pathogen over a 24-h interval; the lower the MIC, the higher is the susceptibility of the pathogen. The MIC is a critical factor of the PK/PD relationship that defines the drug exposure necessary to ensure the optimal drug effectiveness; indeed, the MIC is the denominator for the potential PK/PD targets and should ideally be measured. However, when it is not available, local antibiograms, EUCAST (European Committee on Antimicrobial Susceptibility Testing) or CLSI (Clinical and Laboratory Standards Institute) breakpoints can be used as surrogates for the actual MIC. The observation that MICs of pathogens causing infections in the ICU are usually higher compared with other clinical settings, underpins the need for individualized drug dosing to achieve PK/PD targets [33–35].

TDM

TDM aims at improving clinical outcome by individually adjusting the dose of a drug based on measured drug concentrations in biological fluids (e.g. plasma, serum, urine, saliva, etc.). Several criteria have been defined for rational, selective TDM. The first step is to consider whether the patient is on the best drug for his/her disease state and indication. When the right treatment is chosen for the patient, there are several criteria to be considered to be able to rationally perform TDM [36]. Four of these criteria will be discussed in this paper, that is (1) a good relationship between drug concentration and pharmacological response, (2) a defined target concentration range, (3) availability of an accurate and selective bioanalytical assay with a rapid turnaround time, and (4) large interindividual variability in PK.

Large interindividual differences in PK of critically ill patients have been reported for aminoglycosides [37–41], glycopeptides [42–46], β-lactams [47,48], fluoroquinolones [49–52], colistin [53,54], linezolid [49,55–59], daptomycin [60], fluconazole [61,62], itraconazole [63], posaconazole [64], voriconazole [65–67], and oseltamivir [68–70]. For flucytosine, aciclovir, and ganciclovir, no data on PK in critically ill patients have been reported in the literature. However, for these agents, the PK in noncritically ill patients have been described and shown to be highly variable [71–74]. Large interindividual differences in PK mean that after a one-size-fits-all dose of the anti-infective drug, a range of exposures is observed that is wider than the defined target range for that agent, thus causing underexposure in some critically ill patients, while the same dose causes overexposure in others.

The other three TDM criteria will be discussed for each of the anti-infective agents included in this article separately. Figure 2 shows the PK/PD targets for the different anti-infective agents. Clinical studies providing relevant data on dose individualization of anti-infective agents based on drug concentration monitoring in critically ill adult patients are shown in Table 1. Where available, potential TDM target concentrations are provided in Table 2.

Antibiotic agents

Aminoglycosides

Relationship between drug concentration and pharmacological response

Several *in vitro* studies have shown that the rate and extent of bactericidal activity of aminoglycosides is dependent on the magnitude of aminoglycoside peak concentration (C_{max}) to which a pathogen is exposed, rather than the duration of

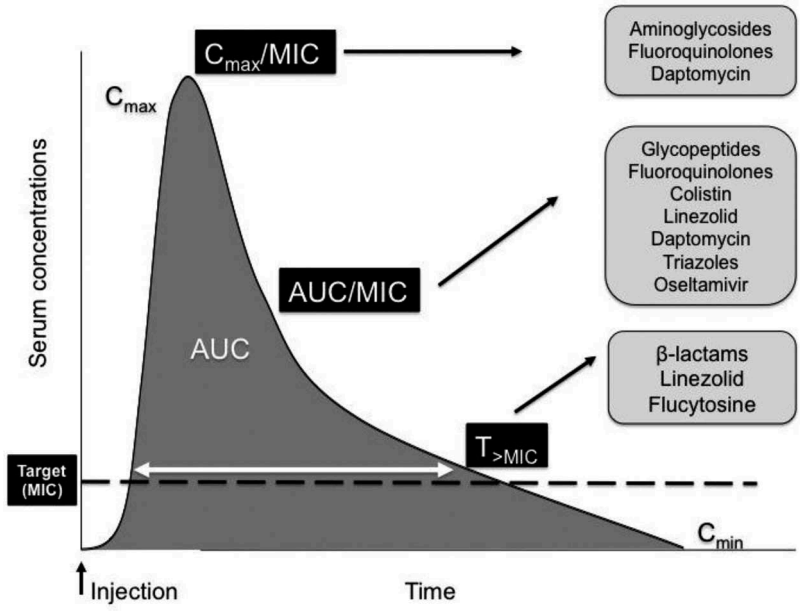

Figure 2. Pharmacokinetic/pharmacodynamics indices of anti-infective agents.
AUC = area under the serum concentration time curve; MIC = minimum inhibitory concentration; T = time.

aminoglycoside exposure. In contrast to bactericidal activity, aminoglycoside-associated nephrotoxicity and ototoxicity are dependent on the duration of exposure, not the absolute concentration [98–100]. Further to this, several studies have suggested that the area under the aminoglycoside serum concentration–time curve (AUC) is associated with efficacy and toxicity [98,101].

Defined therapeutic concentration range

Clinical studies have demonstrated a C_{max}/MIC ≥ 8–10 to be associated with a shorter time to clinical response and a greater probability of clinical cure [77,102,103]. Toxicity is related to the aminoglycoside trough concentration (C_{min}), thus dosing intervals should be at least 24 h, to allow for gentamicin and tobramycin concentrations to be <1 mg/L and amikacin concentrations to be <5 mg/L [38,77,99,100,104]. Also, for tobramycin and gentamicin, an AUC_{0-24} between 70 and 120 mg L/h has been reported to increase efficacy with minimal toxicity [101].

Availability of a bioanalytical assay

Immunoassays, for the rapid measurement of aminoglycosides are commercially available, have been validated and are appropriate for routine daily clinical practice [105].

Use of TDM to potentially improve treatment outcome in critically ill patients

Aminoglycosides are hydrophilic compounds, and a higher apparent Vd and altered renal clearance in critically ill patients have been widely described in the literature [38–41,75–77]. Moreover, a therapeutic range has been defined and TDM has been shown to benefit treatment outcome [50–52]. AUC targeted TDM using Bayesian adaptive feedback could possibly be best practice, although is yet to be shown to provide superior outcomes compared with monitoring peak and trough drug concentrations. With Bayesian feedback, a priori PK parameters of a population model are combined with the patient's measured drug concentrations, in order to optimize dosing. At this time, measurement of peak (target ≥ 8–10 × MIC) and trough (target < 1 mg/L for gentamicin and tobramycin and <5 mg/L for amikacin) concentrations of aminoglycosides in critically ill patients is advised, starting from the first dose.

Glycopeptides

Relationship between drug concentration and pharmacological response

The AUC/MIC is suggested in clinical studies to be the PK–PD index correlating with the efficacy of vancomycin [106,107]. Also, several reports showed a relation between vancomycin trough concentrations and nephrotoxicity [108–110]. For teicoplanin, the optimal PK–PD has not been defined yet, although several clinical studies showed a relation between trough levels and efficacy [111–115].

Defined therapeutic concentration range

For vancomycin, several clinical studies have demonstrated that a target AUC/MIC ≥ 400–450 is desired to obtain optimal efficacy [116,117]. Trough levels of 10–15 mg/L have been suggested to be a surrogate for the AUC/MIC target of 400–450 for the majority of severe infections, although trough concentrations of 15–20 mg/L are suggested to be needed for infections caused by a pathogen with a higher MIC, such as methicillin susceptible *Staphylococcus aureus* (MRSA) [107]. Also, decreased emergence of vancomycin resistant organisms has been described when trough concentrations are maintained above 10 mg/L [118]. However, AUC > 700 mg L/h [109] or AUC > 1300 mg L/h [110] are reported to increase the potential for toxicity. Also, trough concentrations ≥ 15 mg/L during intermittent infusion [108,119,120] and

Table 1. Clinical studies providing relevant data on individualization of dosing anti-infective agents based on drug level monitoring in critically ill adult patients.

Reference	Drug	PK target	Patient population	*n*	PK changes	TDM required?	Suggested sampling time	Suggested dosing	Suggested TDM target
Rea [75]	Gentamicin Tobramycin	C_{max}/MIC ≥ 10	MICU	102	Vd higher Cl lower	Yes	C_{max}	7 mg/kg od	C_{max}/MIC ≥ 10
Buijk [76]	Gentamicin Tobramycin	C_{max}/MIC ≥ 10 C_{min}	Critically ill patients	89	Vd higher Cl lower	Yes	C_{max}, C_{min}	7 mg/kg od	C_{max}/MIC ≥ 10 C_{min} < 0.5 mg/L
Conil [38]	Tobramycin	AUC_{0-24}/MIC 80–125 C_{max}/MIC ≥ 10 C_{min}	ICU patients	49	Vd higher Cl lower	Yes	C_{max}, C_{min}	5 mg/kg od	C_{max} > 10 mg/L C_{min} ≤ 1 mg/L
Taccone [39]	Amikacin	C_{max}/MIC 8–10	Patients with severe sepsis and shock	74	Vd higher	Yes	C_{max}	LD ≥ 25 mg/kg	C_{max}/MIC 8–10
Petejova [40]	Gentamicin	C_{max}/MIC 8–10 C_{min}	Septic patients with AKI on CVVH	7	Vd higher Cl lower	Yes	C_{max}, C_{min}	LD 240 mg	C_{max}/MIC 8–10 C_{min} < 2 mg/L
Roberts AAC [41]	Gentamicin	C_{max}/MIC ≥ 10 AUC_{0-24}/MIC 70–120 C_{min}	Critically ill patients with AKI on EDD-f	14	Vd higher Cl lower	Yes	C_{max}, C_{min}	6 mg/kg/48 h	C_{max} ≥ 10 mg/L AUC_{0-24} 70–120 mg h/L C_{min} < 1 mg/L
Duszynska [77]	Amikacin	C_{max}/MIC 8–12 C_{min}	Critically ill patients	63	Vd higher Cl lower	Yes	C_{max}, C_{min}	nm	C_{max}/MIC 8–12 C_{min} < 5 mg/L
Van de Vijsel [42]	Vancomycin	AUC_{0-24}/MIC ≥ 400 C_{min}	Critically ill patients undergoing CVVHD	24	Vd higher Cl lower	Yes	nm	CI: 1.5 g LD, 1–1.5 g/24 h II: 20 mg/kg LD, 15 mg/kg od	C_{min} 15–20 mg/L
Roberts [43]	Vancomycin	AUC_{0-24}/MIC > 350 C_{min}	Critically ill patients with AKI	10	nm	Yes	C_{min}	nm	C_{min} ≥ 15 mg/L
Jeurissen [44]	Vancomycin	AUC/MIC ≥ 400	Critically ill patients	20	nm	Yes	Random	LD 1000 mg, 3000 mg/24 h	C_{ss} 25 mg/L
Roberts [45]	Teicoplanin	C_{min}	Critically ill patients	13	nm	Yes	C_{min}	6 mg/kg/day	C_{min} 10–20 mg/L
Pea [78]	Teicoplanin	C_{min}	Critically ill patients	202	nm	Yes	C_{min}	LD 6 mg/kg/12 h 3×	C_{min} ≥ 10 mg/L
Bellmann [79]	Teicoplanin	C_{min}	Critically ill patients on CVVH	11	nm	Yes	C_{min}	nm	C_{min} 15–25 mg/L
Roberts [43]	Meropenem	100%$T_{>MIC}$	Critically ill patients with AKI	17	nm	Yes	C_{min}	nm	C_{min} > 2 mg/L
Lheureux [26]	Meropenem	≥40%$T_{>4-8\times MIC}$	Critically ill patients	22	nm	Yes	C_{max}, C_{min}	nm	≥40%*T* 8–16 mg/L
Beumier [80]	Meropenem	≥40%$T_{>4-8\times MIC}$	Septic patients on CRRT	32	nm	Yes	C_{max}, C_{min}	1 g tid	≥40%*T* > 8 mg/L
Goncalves-Pereira [81]	Meropenem	100%$T_{>MIC}$	Septic critically ill patients	15	Similar to healthy patients	Yes	C_{min}	1 g tid	C_{min} > 2 mg/L
Roberts [43]	Piperacillin	100%$T_{>MIC}$	Critically ill patients with AKI	6	nm	Yes	C_{min}	nm	C_{min} > 16 mg/L
Lheureux [26]	Piperacillin	50%$T_{>4-8\times MIC}$	Critically ill patients with cirrosis	16	nm	Yes	C_{max}, C_{min}	nm	50%*T* 64–128 mg/L
Sime [82]	Piperacillin	100%$fT_{>MIC}$ C_{min}/MIC 1–10	Febrile neutropenia patients	32	nm	Yes	C_{min}	nm	C_{min} 16–160 mg/L
Beumier [80]	Piperacillin	≥50%$T_{>4-8\times MIC}$	Septic patients undergoing CRRT	16	nm	Yes	C_{max}, C_{min}	4 g 4dd	≥50%*T* > 64 mg/L
Bauer [83]	Piperacillin	>50%$T_{>4\times MIC}$	ICU patients with CRRT	42	Vd higher	Yes	C_{max}, C_{min}	>9 g/day	>50%*T* > 64 mg/L
Beumier [80]	Ceftazidime or cefepim	≥70%$T_{>4-8\times MIC}$	Septic patients undergoing CRRT	7	nm	Yes	C_{max}, C_{min}	2 g tid	≥70%*T* > 32 mg/L
Chapuis [84]	Cefepime	≥50%$T_{>MIC}$	ICU patients	21	Cl lower	Yes	nm	2 g bid	≥50%*T* > 4 mg/L
Spooner [85]	Ciprofloxacin	AUC_{0-24}/MIC ≥ 100 C_{max}/MIC ≥ 10	Critically ill septic patients on CVVHDF	7	Cl lower	No	–	400 mg bid	–
Pea [86]	Ciprofloxacin	AUC_{0-24}/MIC ≥ 125 C_{max}/MIC ≥ 10	Severely ill patients	89	Cl higher	Yes	C_{max}, C_{min}	>bid 400 mg	AUC_{0-24} ≥ 125 mg h/L C_{max} ≥ 10 mg/L
Szalek [87]	Ciprofloxacin	AUC_{0-24}/MIC > 125 C_{max}/MIC > 10	Critically ill patients	20	Vd higher Cl higher	Yes	C_{max}	LD 600 mg	C_{max}>5 mg/L
Lipman [88]	Ciprofloxacin	AUC/MIC > 100 C_{max}/MIC ≥ 8	Severely septic patients	16	nm	No	–	400 mg tid	–
Furhmann [89]	Moxifloxacin	AUC_{0-24}/MIC > 30 C_{max}/MIC > 10	Patients on CVVHDF	9	Comparable to healthy subjects	No	–	400 mg od	–
Roberts [43]	Ciprofloxacin	AUC_{0-24}/MIC ≥ 125 C_{min}/MIC > 1	Critically ill patients with AKI	6	nm	Yes	C_{min}	nm	C_{min} > 2 mg/L
Conil [90]	Ciprofloxacin	AUC_{0-24}/MIC > 100 C_{max} > MIC 8–12	ICU patients with sepsis	70	Vd lower	Yes	C_{max}	nm	C_{max} > 5 mg/L
Pea [46]	Levofloxacin	AUC/MIC > 125 C_{max}/MIC > 12.2	ICU patients with VAP	10	Cl higher	No	–	500 mg 2dd	–

(*Continued*)

Table 1. (Continued).

Reference	Drug	PK target	Patient population	*n*	PK changes	TDM required?	Suggested sampling time	Suggested dosing	Suggested TDM target
Rebuck [91]	Levofloxacin	AUC/MIC > 125–250 C_{max}/MIC > 10–12	Critically ill patients	28	Cl lower	No	–	500 mg 1dd	–
Roberts [92]	Levofloxacin	AUC/MIC > 80	Critically ill patients	18	Comparable to noncritically ill patients	No	–	nm	–
Karnik [54]	Colistin	C_{max}/MIC > 8	Critically ill patients	15	Nm	No	–	nm	–
Markou [53]	Colistin	C_{max}/MIC 8–10	Critically ill patients	14	Cl lower	No	–	>225 mg bid/tid	–
Luque [56]	Linezolid	AUC_{0-24}/MIC 80–120	Neurosurgical critically ill patients	11	nm	Yes	C_{min}	>600 mg bid	AUC_{0-24} ≥ 80 mg h/L
Zoller [55]	Linezolid	AUC_{0-24}/MIC 80–120 100%$T_{>MIC}$	Medical-surgical critically ill patients	30	nm	Yes	C_{min}	nm	AUC_{0-24} 200–400 mg h/L C_{min} 2–10 mg/L
Swoboda [57]	Linezolid	AUC_{0-24}/MIC > 100 85%$T_{>MIC}$	Septic patients	15	Vd higher Cl higher	Yes	nm	nm	85%T > 4 mg/L AUC_{0-24} > 400 mg h/L
Roger [49]	Linezolid	AUC_{0-24}/MIC ≥ 80	Critically ill patients on CVVHD or CVVHDF	13	nm	Yes	nm	>600 mg bid	AUC_{0-24} ≥ 160 mg h/L
Dong [59]	Linezolid	85%$T_{>MIC}$ AUC_{0-24}/MIC 80–120	Severely ill ICU patients	8	nm	Yes	nm	600 mg bid	85%$T_{>MIC}$ AUC_{0-24}/MIC 80–120
Whitehouse [93]	Linezolid	85%$T_{>MIC}$ AUC_{0-24}/MIC > 100	ICU patients	28	nm	No	nm	600 mg bid	85%T > 4 mg/L AUC_{0-24} > 400 mg h/L
Reiber [60]	Daptomycin	C_{min}	ICU patients	86	nm	Yes	C_{min}	nm	C_{min} < 25 mg/L
Wenisch [94]	Daptomycin	C_{min} C_{max}	Critically ill patients on CVVHDF	9	nm	Yes	C_{max}, C_{min}	8 mg/kg/48 h	C_{min} < 25 mg/L C_{max} > 100 mg/L
Vilay [95]	Daptomycin	C_{min} < 10 mg/L C_{max} > 100 mg/L AUC_{0-24} 500 mg h/L	Critically ill patients on CVVHDF	8	Vd higher	No	–	8 mg/kg/48 h	–
Yagasaki [96]	Fluconazole	100%$T_{>MIC}$ C_{min} > 10 mg/L	Critically ill patients on CHDF	4	Cl higher	No	–	500–600 mg bid	–
Buijk [61]	Fluconazole	AUC/MIC 12–25	Critically ill patients with GI surgery	14	Cl lower	No	–	400 mg od	–
Sinnollareddy [62]	Fluconazole	$fAUC_{0-24}$/MIC ≥ 100	ICU patients	15	nm	No	–	nm	–
Hagihara [63]	Itraconazole	AUC_{0-24}/MIC ≥ 25 C_{min} ≥ 0.5 mg/L	ICU patients	10	nm	Yes	C_{min}	200 mg/24 h	AUC_{0-24}/MIC ≥ 25
Ray [64]	Posaconazole	C_{min}	Critically ill patients	27	Absorption lower	Yes	C_{min}	nm	C_{min} > 0.25 mg/L (prophylaxis) C_{min} > 0.7 mg/L (treatment)
Myrianthefs [65]	Voriconazole	100%$T_{>MIC}$	Critically ill patients	18	nm	Yes	C_{min}	nm	C_{min} 1–5.5 mg/L
Radej [66]	Voriconazole	C_{min}	Critically ill patients on CVVH	6	nm	Yes	C_{min}	4 mg/kg/12 h	C_{min} 1–5.5 mg/L
Wang [67]	Voriconazole	C_{min}	Patients with invasive fungal infections	15	nm	Yes	C_{min}	nm	C_{min} 1–5 mg/L
Horvatits [73]	Ganciclovir	AUC 50 mg h/L C_{min} 2 mg/L	Critically ill patients on CVVHDF	9	nm	No	–	2.5 mg/kg	–
Lemaitre [97]	Oseltamivir	C_{min}	Critically ill patients on ECMO and/or CVVHDF	7	ECMO: comparable to healthy subjects CVVHDF: lower Cl	Yes	C_{min}	150 mg bid	C_{min} 100–200 mg/L

AKI: Acute kidney injury; AUC: area under the plasma concentration–time curve; BID: two times a day; CAPD: continuous ambulatory peritoneal dialysis; C_{max}: maximum plasma drug concentration; C_{min}: minimum plasma drug concentration; CHDF: continuous hemodiafiltration; Cl: clearance; CVVHD: continuous venovenous hemodialysis; CVVHDF: continuous venovenous hemodiafiltration; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; EDD-f: extended daily diafiltration; GI: gastro-intestinal; HD: hemodialysis; ICU: intensive care unit; nm: not mentioned; OD: once daily; TID: three times a day; VAP: ventilator-associated pneumonia; Vd: volume of distribution; QID: four times a day; MIC: minimum inhibitory concentration.

concentrations above 25–28 mg/L during continuous infusion [121,122] are shown to be related to a higher risk of nephrotoxicity. For teicoplanin, trough concentrations of >10 mg/L are suggested to be associated with efficacy for the majority of severe infections, although trough concentrations > 20 mg/L are considered to be needed for MRSA endocarditis and osteomyelitis [111–115].

Table 2. Summary of PK/PD indices associated with efficacy and toxicity and suggested targets for therapeutic drug monitoring.

Anti-infective	PK/PD index	PK/PD threshold for effectiveness	PK/PD threshold for toxicity	Analytical assay
Aminoglycosides	C_{max}/MIC	C_{max}/MIC ≥ 8–10	Gentamicin, tobramycin: C_{min} > 1 mg/L Amikacin: C_{min} > 5 mg/L	Immunoassay
Glycopeptides	AUC/MIC	Vancomycin: AUC/MIC ≥ 400 II: C_{min} 10–15 mg/L II, higher MICs: C_{min} 15–20 mg/L CI: C = 20–25 mg/L Teicoplanin: II: C_{min} > 10 mg/L II, higher MICs: C_{min} > 20 mg/L	Vancomycin: II: C_{min} > 20 mg/L CI: C > 25 mg/L	Immunoassay
β-lactams	$T_{>MIC}$	100%$fT_{>MIC}$	Not clearly defined	LC–MS/MS
Fluoroquinolones	AUC/MIC C_{max}/MIC	Ciprofloxacin: C_{max}/MIC 8–10 Levofloxacin: C_{max}/MIC ≥ 12	Not clearly defined	HPLC–UV
Colistin	AUC/MIC	Not clearly defined	C_{min} > 2.4 mg/L	LC–MS/MS
Linezolid	AUC/MIC $T_{>MIC}$	C_{min} > 2 mg/L	C_{min} > 6 mg/L	HPLC–UV LC–MS/MS
Daptomycin	AUC/MIC C_{max}/MIC	C_{max} > 100 mg/L	C_{min} > 25 mg/L	HPLC–UV LC–MS/MS
Fluconazole	AUC/MIC	Not clearly defined	Not clearly defined	HPLC–UV LC–MS/MS
Itraconazole	AUC/MIC	Prophylaxis: C_{min} > 0.5 mg/L Treatment: C_{min} > 1.0 mg/L	Not clearly defined	HPLC–UV LC–MS/MS
Posaconazole	AUC/MIC	Prophylaxis: C_{min} > 0.7 mg/L Treatment: C_{min} > 1.0 mg/L	Not clearly defined	HPLC–UV LC–MS/MS
Voriconazole	AUC/MIC	C_{min} > 2 mg/L	C_{min} > 6 mg/L	HPLC–UV LC–MS/MS
Flucytosine	$T_{>MIC}$	II: C_{min} > 25 mg/L CI: C = 50 mg/L	II: C_{max} 50–100 mg/L CI: C = 50 mg/L	HPLC–UV
Aciclovir	Not clearly defined	Not clearly defined	Not clearly defined	Immunoassay HPLC–UV LC–MS/MS
Ganciclovir	Not clearly defined	Not clearly defined	Not clearly defined	Immunoassay HPLC–UV LC–MS/MS
Oseltamivir	AUC/MIC	Not clearly defined	Not clearly defined	HPLC–UV LC–MS/MS

II: Intermittent infusion; CI: continuous infusion; *C*: concentration; C_{max}: peak concentration; C_{min}: trough concentration.

Availability of a bioanalytical assay

Immunoassays are commercially available, have been validated, and are found to be suitable for daily clinical TDM [123].

Use of TDM to potentially improve treatment outcome in critically ill patients

Glycopeptides are hydrophilic compounds, and a higher apparent Vd and altered renal clearance in critically ill patients have been described in the literature [42]. Moreover, for vancomycin, TDM has been shown to benefit treatment outcome [124]. Individual dosing based on measured trough concentrations as a practical surrogate marker for AUC can be applied in critically ill patients, although AUC estimation (target AUC/MIC ≥ 400) with the aid of Bayesian feedback may be preferable [125]. Target for intermittent dosing is C_{min} 10–15 mg/L for vancomycin and C_{min} > 10 mg/L for teicoplanin, although when higher MICs are expected or observed, such as MRSA, the C_{min} target is 15–20 mg/L for vancomycin and >20 mg/L for teicoplanin. For continuous infusion, the target concentration for vancomycin is 15–25 mg/L. A loading dose should be given to critically ill patients, and samples should be taken from the first maintenance dose. Sampling should be repeated frequently (at least twice a week), especially when changes in organ function occur.

β-lactams

Relationship between drug concentration and pharmacological response

The effectiveness of β-lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams) in clinical studies is suggested to be time dependent: it depends mainly on the duration of the presence of the agent at a concentration superior to the target pathogen's MIC, $T_{>MIC}$, or the concentration of the unbound drug over MIC, $fT_{>MIC}$ [47,126,127].

Defined therapeutic concentration range

In vitro and *in vivo* animal studies have demonstrated that the β-lactam concentration should be maintained above the MIC between 40% and 70% of the dosing interval [128]. However, several studies in critically ill patients showed higher targets for clinical response; 75%$T_{>MIC}$ for meropenem [129], 100%$T_{>MIC}$ for cefepime and ceftazidime [130], and 100%$fT_{>MIC}$ for amoxicillin, ampicillin, cefazolin, cefepime, ceftriaxone, doripenem, meropenem, and piperacillin [47,131]. For meropenem, piperacillin, ceftazidime, and cefepime, C_{min}/MIC > 8 was associated with neurological deterioration in one retrospective study in critically ill septic patients [132].

Availability of a bioanalytical assay

Available assays for the measurement of β-lactams include bioassay, HPLC–UV, and LC–MS/MS [105,128,133].

Use of TDM to potentially improve treatment outcome in critically ill patients

β-lactams are hydrophilic compounds, and a higher Vd in critically ill patients compared to healthy subjects has been described in the literature [47,83,134]. Also, ARC [135,136] and decreased renal and hepatic clearance [84,132] of β-lactams is described in critically ill patients. Some β-lactams (e.g. ceftriaxone and flucloxacillin) are highly protein bound (>80%), so for these agents the free concentration rather than the total concentration should be measured. TDM should be applied in critically ill patients treated with β-lactams, where 100% $fT_{>MIC}$ should be used as a target. Trough serum samples should be obtained 24–48 h after onset of treatment, unless Bayesian adaptive feedback is available, in which case sampling from the first dosing interval can be performed in most cases.

Fluoroquinolones

Relationship between drug concentration and pharmacological response

Fluoroquinolones display concentration-dependent kill characteristics [137]. For ciprofloxacin and levofloxacin, C_{max}/MIC and AUC/MIC have been associated with clinical and microbiological cure in critically ill patients [138,139].

Defined therapeutic concentration range

Several clinical studies have suggested that achieving a C_{max}/MIC ≥ 8–10 or AUC_{0-24}/MIC > 125–250 for ciprofloxacin is associated with a successful clinical treatment of infections caused by Gram-negative pathogens [103,139,140]. Also, suboptimal drug exposure of ciprofloxacin; AUC_{0-24}/MIC < 100, is associated with development of antimicrobial resistance of Gram-negative pathogens [141]. For infections caused by Gram-positive pathogens, AUC_{0-24}/MIC > 30–40 is suggested as a target [142]. The need to reduce ciprofloxacin dose to avoid toxicity is still under debate [127]. For levofloxacin, achieving C_{max}/MIC ≥ 12 has been shown to be associated with successful clinical and microbiological outcomes [143].

Availability of a bioanalytical assay

Several laboratories have developed and validated HPLC–UV assays for fluoroquinolone TDM [105].

Use of TDM to potentially improve treatment outcome in critically ill patients

Fluoroquinolones are lipophilic agents and fluid shifts in critically ill patients will have minimal effect on the Vd of these agents [92]. However, since PK of ciprofloxacin are shown to be difficult to predict in critically ill patients and there is a substantial risk of resistance, TDM should be applied in critically ill patients treated with ciprofloxacin. AUC targeted TDM using Bayesian adaptive feedback is likely to be best practice, although is yet to be shown to provide superior outcomes compared with monitoring peak drug concentrations. Therefore, at this time, it is advised to measure peak serum concentrations after 24 h, with a target of C_{max}/MIC 8–10. For levofloxacin, PK of critically ill patients are shown to be comparable to PK in noncritically ill patients. Renal clearance was shown to be the most important descriptor of levofloxacin clearance and can therefore be used to individualize levofloxacin dosing [92].

Colistin

Relationship between drug concentration and pharmacological response

Colistin is thought to have predominantly concentration-dependent bactericidal activity [144,145]. A prospective clinical trial has identified trough concentrations to be predictive of nephrotoxicity [146].

Defined therapeutic concentration range

In vitro studies have correlated AUC_{0-24}/MIC > 7–23 with maximum bacterial killing [144,145,147]. No clinical studies investigating a therapeutic range have been published yet. Trough levels above 2.4 mg/L were associated with a higher risk of AKI [146].

Availability of a bioanalytical assay

Colistin is a complex mixture of at least 30 different components. Available assays for the measurement of colistin include bioassay, HPLC–UV, and LC–MS/MS, although these assays don't all measure the same components of the colistin mixture (usually colistin A and B), complicating the exchange of measured concentrations [148].

Use of TDM to potentially improve treatment outcome in critically ill patients

Colistin is hydrophilic and therefore there may be a substantial effect of possible changes in Vd and augmented or decreased renal clearance on drug concentrations in critically ill patients. Given the PK variability of colistin, TDM may be beneficial, although it is difficult to make strong recommendations before a clear target exposure is defined and validated. Until then, individual dose recommendations could be based on creatinine clearance [54,149].

Linezolid

Relationship between drug concentration and pharmacological response

In human studies, clinical and microbiological cure is associated with AUC/MIC and $T_{>MIC}$ [58].

Defined therapeutic concentration range

In seriously ill patients, higher efficacy rates were observed when the $T_{>MIC}$ was ≥85% and the AUC_{0-24}/MIC was in the range of 80–120 [58]. Furthermore, maintaining C_{min} between 2 and 6 mg/L is suggested to be helpful in retaining appropriate efficacy and avoiding the associated thrombocytopenia [150,151].

Availability of a bioanalytical assay

There is no commercially available assay for the quantification of linezolid. Only a few laboratories use custom-made HPLC–UV or LC–MS/MS methods [55].

Use of TDM to potentially improve treatment outcome in critically ill patients

Linezolid is a hydrophilic compound, and therefore, there may be an increased Vd and augmented or decreased clearance on drug concentrations in critically ill patients. Indeed, unpredictable PK have been described for linezolid in critically ill patients. It seems reasonable to perform TDM in patients with a high risk of altered PK, such as critically ill patients with sepsis, burns, organ failure or critically ill patients using concomitant medication known to influence the linezolid concentration, such as rifampicin. For practical reasons, the suggested sampling time is after approximately 3 days, just before the next dose (target C_{min} 2–6 mg/L), although a Bayesian adaptive feedback approach could allow earlier measurement and dose optimization.

Daptomycin

Relationship between drug concentration and pharmacological response

In preclinical studies, the bactericidal effect of daptomycin is associated with AUC/MIC and C_{max}/MIC [152,153].

Defined therapeutic concentration range

Preclinical studies have shown that bactericidal activity was established at AUC_{0-24}/MIC 38–442 [152,154], a small patient cohort study reported a higher efficacy when AUC_{0-24}/MIC > 666 [155]. *In vitro*, AUC_{0-24}/MIC ≥ 200 was related with resistance suppression [156]. Also, an *in vitro* C_{max}/MIC of 12–94 was suggested to be associated with an optimal bacteriostatic effect [152]. A clinical trial demonstrated that a trough concentration of >24.3 mg/L was associated with an increased probability of creatine phosphokinase elevation [157].

Availability of a bioanalytical assay

There is no commercially available assay for the quantification of daptomycin; however, several HPLC–UV and LC–MS/MS assays have been published for quantification of daptomycin [158–160].

Use of TDM to potentially improve treatment outcome in critically ill patients

Daptomycin is a hydrophilic compound, and a higher Vd in critically ill patients compared to healthy subjects has been described in the literature [161]. Also, augmented or decreased renal clearance of daptomycin is to be expected in critically ill patients. Given the PK variability of daptomycin, TDM may be beneficial, although it is difficult to make strong recommendations before a clear target exposure is defined and validated. However, it seems reasonable to perform TDM in patients at high risk of altered PK, such as critically ill patients with sepsis, burns, or organ failure. The suggested sampling times are C_{max} (target > 100 mg/L, this is the C_{max} observed in noncritically ill patients treated with 6 mg/kg daptomycin [95]) and C_{min} (target < 25 mg/L), starting after the first dose.

Since daptomycin is highly protein bound (90%), the unbound fraction in patients with hypoalbuminemia will be substantially higher, meaning that a subtherapeutic total concentration not necessarily indicates a subtherapeutic unbound concentration.

Antifungal agents

Fluconazole

Relationship between drug concentration and pharmacological response

Animal studies have shown that fluconazole exhibits concentration- and time-dependent antifungal activity. In line with this, the AUC/MIC is considered the predictive PK/PD index associated with maximal fungal killing [162,163].

Defined therapeutic concentration range

An AUC_{0-24}/MIC near 25 has been shown to be associated with optimal cure rate in animal models of invasive candidiasis [163]. In clinical studies, an AUC_{0-24}/MIC between 11.5 and 55 was shown to be associated with decreased patient mortality [164,165]. Moreover, the AUC is shown to be highly correlated to dose and dose/MIC > 100 was suggested to be associated with clinical outcome [166].

Availability of a bioanalytical assay

There are several microbiological as well as chromatographic methods described in the literature [167]. However, the results of a 5-year international proficiency program showed that 12% of the analyses lie outside the predefined acceptable range for accuracy. These results emphasize the need to further improve the analytical methods for antifungal TDM in clinical care [168].

Use of TDM to potentially improve treatment outcome in critically ill patients

Fluconazole is a hydrophilic compound, and an increased Vd of fluconazole in critically ill patients has been described in the literature [169]. Also, augmented as well as decreased renal clearance of fluconazole has been demonstrated in critically ill patients [61,96]. Given the wide therapeutic index and safety profile of fluconazole, routine TDM is not recommended at this time. However, dosing should be adapted to renal function.

Itraconazole

Relationship between drug concentration and pharmacological response

Several *in vitro* studies have demonstrated that itraconazole exhibits concentration-dependent antifungal activity [170,171]. An animal model of invasive pulmonary aspergillosis demonstrated a significant PD relationship between itraconazole peak plasma concentrations and antifungal activity [172].

A clinical trial performed in neutropenic patients showed a relationship between itraconazole trough levels and prophylactic effect [173].

Defined therapeutic concentration range

A trough concentration of ≥0.25–0.5 mg/L is associated with effective antifungal prophylaxis in neutropenic patients [173,174].

Availability of a bioanalytical assay

Itraconazole can be analyzed by microbiological as well as chromatographic methods [167,175]. However, the results of these assays are demonstrated to be discordant, since the bioassay simultaneously detects itraconazole and its active metabolite resulting in a 2–10 times higher analyzed itraconazole level than those obtained by chromatographic methods [176]. Moreover, the results of a 5-year international proficiency program showed that 22% of the analyses lie outside the predefined acceptable range for accuracy. These results emphasize the need to further improve the analytical methods for antifungal TDM in clinical care [168].

Use of TDM to potentially improve treatment outcome in critically ill patients

Itraconazole is a lipophilic compound; no alterations in Vd are expected in critically ill patients. The optimal PK/PD target for itraconazole is not determined yet; however, trough concentrations are suggested to be related to efficacy. Therefore, it seems reasonable to perform TDM in critically ill patients, especially when concomitant medication known to influence the itraconazole concentration, such as CYP3A4 inhibitors or inducers, is administered. Target trough concentrations are >0.5 mg/L for prophylaxis and >1 mg/L for treatment. This concentration should be analyzed using a chromatographic method. Since itraconazole is highly protein bound (99%), the altered unbound fraction in patients with hypoalbuminemia should be considered when interpreting measured total concentrations.

Posaconazole

Relationship between drug concentration and pharmacological response

Several *in vitro* and animal studies have shown that AUC/MIC is the PK/PD index related to the fungistatic effect of posaconazole [177]. Also, several clinical trials have demonstrated a relationship between posaconazole trough concentrations and efficacy of prophylaxis and treatment of invasive fungal infections [178–182].

Defined therapeutic concentration range

Several clinical studies have reported a concentration–response relationship between posaconazole plasma trough concentrations and the risk of breakthrough infections, where C_{min} > 0.5 or 0.7 mg/L is suggested to result in optimal prophylactic efficacy [178–182]. For the treatment of invasive aspergillosis, a target trough concentration of >1 mg/L is suggested [178,183]. There appears to be no relationship between posaconazole concentrations and toxicity [178].

Availability of a bioanalytical assay

There are several microbiological as well as chromatographic methods described in the literature [167,175]. However, the results of a 5-year international proficiency program showed that 25% of the analyses lie outside the predefined acceptable range. These results emphasize the need to further improve the analytical methods for antifungal TDM in clinical care [168].

Use of TDM to potentially improve treatment outcome in critically ill patients

Posaconazole is a lipophilic compound and therefore no alterations in Vd are expected in critically ill patients. Routine TDM is advised during treatment and also prophylaxis of critically ill patients with posaconazole, in order to improve efficacy, since exposure–response relationships have been demonstrated, fixed dose regimens have shown to result in suboptimal exposure and fungal infections can be life-threatening, especially for critically ill patients. Target trough concentrations are >0.7 mg/L for prophylaxis and >1 mg/L for treatment. Since posaconazole is highly protein bound (98%), the altered unbound fraction in patients with hypoalbuminemia should be considered when interpreting measured total concentrations. Trough samples should be taken after about 5–7 days, which might have implications for the timely optimization of therapy. An alternative would be to obtain a trough sample after 2 days of treatment, using 0.35 mg/L as an interim target [178]. The recent availability of tablet and IV formulations, which provide far superior bioavailability compared with the liquid formulation, suggests that underdosing will be less common with the new formulations.

Voriconazole

Relationship between drug concentration and pharmacological response

Several *in vitro* and animal studies have shown that AUC/MIC is the PK/PD index related to the fungistatic effect of voriconazole [177]. Also, several retrospective studies have identified a relationship between voriconazole trough concentrations and clinical outcome during prophylaxis [184] and treatment [185–188]. Moreover, several prospective clinical trials showed an association between plasma trough concentrations and efficacy and toxicity during treatment of invasive fungal infections [189–191].

Defined therapeutic concentration range

Retrospective clinical studies have shown that trough concentrations ≥ 1.7–2.0 mg/L were associated with optimal clinical response in treatment of invasive fungal infections [185–188,192]. Prospective studies have identified plasma trough concentrations ≥ 1.0–1.5 mg/L to be associated with a higher probability of a favorable response [189–191]. A retrospective clinical trial showed that patients on prophylactic therapy with voriconazole who had voriconazole concentrations > 2 mg/L had a lower risk of obtaining an invasive fungal infection [184]. Trough concentrations ≥ 4.5–6 mg/L have been associated with higher risk of voriconazole-associated neurotoxicity

(visual and auditory hallucinations, encephalopathy) and elevation of hepatic enzymes [185,187,189–192].

Availability of a bioanalytical assay

There are several microbiological as well as chromatographic methods described in the literature [167,175]. However, the results of a 5-year international proficiency program showed that 14% of the analyses lie outside the predefined acceptable range. These results emphasize the need to further improve the analytical methods for antifungal TDM in clinical care [168].

Use of TDM to potentially improve treatment outcome in critically ill patients

Voriconazole is a lipophilic compound and PK of voriconazole in critically ill patients have been shown to be comparable to the PK of voriconazole in healthy subjects [193]. However, voriconazole PK have been shown to be unpredictable in all populations. A prospective clinical trial demonstrated the added value of TDM during voriconazole treatment by showing a more favorable response in the TDM-group, compared to the non-TDM group [194]. Therefore, TDM is advised during treatment and also prophylaxis of critically ill patients with voriconazole. Trough samples should be taken after about 2 days, and a range of 2–6 mg/L should be used as a reference [192,195]. Nonlinear PK have been described for voriconazole; this should be taken into account when the voriconazole dose is adjusted based on observed patient concentrations [196].

Flucytosine

Relationship between drug concentration and pharmacological response

An animal study showed that $T_{>MIC}$ is the PK/PD index related to the pharmacologic effect of flucytosine [197]. Several retrospective preclinical as well as clinical studies in noncritically ill patients have identified a relationship between flucytosine concentrations and toxicity [198–200] and flucytosine concentrations and prevention of resistance [201].

Defined therapeutic concentration range

A small clinical trial demonstrated an association between trough concentrations of flucytosine and bone marrow depression, where concentrations > 125 mg/L were associated with reversible leukopenia [200]. Several other clinical studies showed an association between a higher risk of developing thrombocytopenia, leukopenia, and liver toxicity and flucytosine trough concentrations > 100 mg/L [198,199,202]. Furthermore, an *in vitro* study showed that development of resistance most frequently occurs at drug concentrations < 25 mg/L [201].

Availability of a bioanalytical assay

Available assays for the measurement of flucytosine include bioassay and HPLC–UV [203]. However, the results of a 5-year international proficiency program showed that 23% of the analyses lie outside the predefined acceptable range. These results emphasize the need to further improve the analytical methods for antifungal TDM in clinical care [168].

Use of TDM to potentially improve treatment outcome in critically ill patients

Flucytosine is a hydrophilic compound, and an increased Vd of flucytosine has been demonstrated in critically ill patients [204]. Also, a substantial effect of augmented or decreased renal clearance on the PK in critically ill patients is to be expected. Although no data on critically ill patients are available for flucytosine, TDM to avoid resistance and prevent toxicity is advised. Trough concentrations should be >25 mg/L to avoid resistance, and peak concentrations should be 50–100 mg/L to minimize the risk of toxicity. In patients treated with continuous flucytosine infusion, a serum concentration of 50 mg/L is recommended.

Antiviral agents

(val)Aciclovir

Relationship between drug concentration and pharmacological response

No study showing an association between aciclovir plasma concentrations and efficacy has been found in the literature. However, several case reports describing a relationship between high aciclovir concentrations and toxicity, especially neurotoxicity (tremor, myoclonus, confusion, agitation, lethargy, hallucination, extrapyramidal symptoms, impairment of consciousness), have been published [205–208].

Defined therapeutic concentration range

No therapeutic range for plasma aciclovir concentrations has been defined. Several case reports associate adverse events with high plasma peak concentrations: >10 [205], >18 [208], >25 [206], and >51 mg/L [207]. Several clinical studies have reported plasma concentrations of aciclovir in noncritically ill patients; however, no relationship with efficacy was described.

Availability of a bioanalytical assay

Available assays for the measurement of aciclovir include bioassay, HPLC–UV, and LC–MS/MS [72,209].

Use of TDM to potentially improve treatment outcome in critically ill patients

Aciclovir is a hydrophilic compound, and therefore there may be an effect of increased Vd and augmented or decreased renal clearance in critically ill patients. In critically ill patients, dosing could be individualized based on creatinine clearance [72]. Also, it seems reasonable to perform TDM in patients with a high risk of altered PK, such as critically ill patients with sepsis, burns, organ failure or critically ill patients using concomitant medication known to influence the aciclovir concentration, such as mycofenolic acid. The suggested target concentrations are those observed in healthy subjects using aciclovir: C_{min} around 0.5–0.7 mg/L and C_{max} around 5–10 mg/L [72].

(val)Ganciclovir

Relationship between drug concentration and pharmacological response

No clear relationship between ganciclovir and pharmacological response has been established. Several (small) studies have investigated a possible relationship between ganciclovir concentrations and outcome, where some have demonstrated an association between concentrations and viremia suppression [210]. Other authors have not been able to correlate drug concentrations with clinical or virological efficacy [211–214]. Likewise, toxicity has not been clearly associated with drug concentrations, where some have found an association [215] and others did not find an association [74,212,214].

Defined therapeutic concentration range

No therapeutic range for plasma ganciclovir concentrations has been clearly defined. An AUC_{0-24} of 45 mg h/L was shown to cause a lower risk of developing *Cytomegalovirus* viremia during prophylactic therapy of ganciclovir [210]. In a small clinical study, neutropenia has been associated with C_{min} > 2.5 mg/L and C_{max} > 12.8 mg/L [215]. Other studies have reported patient plasma concentrations, although no relationship with clinical outcome was described.

Availability of a bioanalytical assay

Available assays for the measurement of ganciclovir include immunoassay, HPLC–UV, and LC–MS/MS [74].

Use of TDM to potentially improve treatment outcome in critically ill patients

Ganciclovir is a hydrophilic compound, and therefore there may be an effect of increased Vd and augmented or decreased renal clearance in critically ill patients. Routine TDM for ganciclovir and its prodrug valganciclovir is not advised, since no clear relationship between drug concentrations and efficacy or toxicity has been established and no clear therapeutic range has been obtained. Moreover, ganciclovir therapy could be assessed by other techniques, such as antigenemia and PCR-DNA, for which a clearer relationship with clinical outcome has been established [74]. In critically ill patients, dosing could be adjusted to creatinine clearance. Also, it seems reasonable to perform TDM in patients with a high risk of altered PK, such as critically ill patients with sepsis, burns, organ failure or critically ill patients using concomitant medication known to influence the ganciclovir concentration, such as mycofenolic acid. C_{max} and C_{min} are shown to be significantly correlated with AUC and can therefore be used as an indicator for AUC [216]. Target concentrations are the concentrations observed in subjects with normal renal function using ganciclovir: C_{max} between 4.75 and 9.5 mg/L and C_{min} between 0.25 and 1.2 mg/L [211,217,218].

Oseltamivir

Relationship between drug concentration and pharmacological response

No clear relationship has been established between oseltamivir, its active metabolite oseltamivir carboxylate, and pharmacological response. An *in vitro* study showed an association between AUC of oseltamivir carboxylate and efficacy against influenza [219]. An inoculation study with healthy volunteers showed an association between oseltamivir carboxylate AUC and efficacy for oseltamivir against influenza [220]. A clinical study in healthy volunteers showed a relationship between oseltamivir carboxylate AUC and side effects (p = 0.006) [221].

Defined therapeutic concentration range

There are no clinical data defining a therapeutic concentration range of oseltamivir carboxylate described in the literature.

Availability of a bioanalytical assay

Available assays for the measurement of oseltamivir and oseltamivir carboxylate include HPLC–UV and LC–MS/MS [222].

Use of TDM to potentially improve treatment outcome in critically ill patients

Oseltamivir is a hydrophilic compound, and therefore there may be an effect of increased Vd and augmented or decreased renal clearance in critically ill patients [223]. Routine TDM for oseltamivir is not advised, since no clear relationship between drug concentrations and efficacy or toxicity has been established and no therapeutic range has been obtained. In critically ill patients, dosing could be adjusted based on creatinine clearance [222]. Also, it seems reasonable to perform TDM in patients with a high risk of altered PK, such as critically ill patients with sepsis, burns, or organ failure. Target concentrations are the concentrations observed in noncritically ill patients using oseltamivir; C_{max} around 0.34 mg/L, C_{min} around 0.17 mg/L, and AUC_{0-24} of 6.1 mg h/L for a dosing regimen of 75 mg 12-hourly [222].

Conclusions

TDM of anti-infectives is of increasing interest for optimizing treatment of infections in critically ill patients. For many anti-infectives, especially the hydrophilic agents, there is strong evidence of altered PK in critically ill patients. Many studies have described a higher apparent Vd and a great effect of augmented or decreased renal clearance on concentrations of renally cleared compounds in critically ill patients. These data indicate that TDM could be useful in order to optimize treatment in this patient group. However, only for the aminoglycosides, glycopeptides, flucytosine, voriconazole, and posaconazole, a clear therapeutic range is defined. Moreover, only for aminoglycosides, glycopeptides, and voriconazole, a beneficial effect of TDM on clinical outcome has been established. For other compounds, no therapeutic range has been established yet. However, for treatment of critically ill patients with β-lactams, fluoroquinolones, and itraconazole, we also advise to perform TDM, since there are several reports suggesting a therapeutic target range and PK of these agents are shown to be difficult to predict in critically ill patients leading to a substantial risk of suboptimal exposure.

Expert commentary and 5-year view

Three factors form the cornerstone of adequate treatment with anti-infective agents in critically ill patients; the host, the causative pathogen, and the anti-infective agent. There is strong evidence that the PK of critically ill patients can be highly altered between and also within patients, although standard dosing regimens usually obtained from healthy subjects are used in this patient group. These dosing regimens will in many cases lead to suboptimal exposure. Second, PK/PD targets are usually expressed in relation to the MIC of the pathogen, highlighting that accurate and timely determination of the MIC of the pathogen causing the infection is of high importance to help define the PK exposure necessary for optimal effects. However, especially at the beginning of treatment, these values will not be available and local antibiograms, EUCAST, or CLSI breakpoints should be used as surrogates for the actual MIC at that time. Third, knowledge of the characteristics of the anti-infective agent (e.g. hydrophilicity, toxicity) is of high importance.

Adequate anti-infective treatment is of high relevance in critically ill patients, since this could be life saving for this patient group. Therefore, a shift toward individualized anti-infective treatment of critically ill patients using TDM is inevitable.

The first step would be to develop accurate and sensitive assays, where assay development and validation should be rigorous, to ensure accurate results are consistently obtained. In some cases, the measurement of unbound drug concentrations is advocated; appropriate processes should be developed and validated for each individual drug. Also, turnaround time of the analytical assay should be taken into account when developing a method for TDM. Since the condition of critically ill patients can change rapidly, results should be known at least the same day. Although LC–MS/MS is usually the most accurate and sensitive method to determine patient plasma concentrations, the necessity of a short turnaround time will result in more single assays instead of batch processing, which will lead to substantially higher costs. Randomized cost-effectiveness trials of TDM in critically ill patients are necessary to prove whether this form of TDM will not only provide clinical, but also financial benefit. At this time, there are many laboratories developing their own methods, while it would be much better to have a robust and validated method to be used in different laboratories, so cross validation can be performed and quality of the assay can be assured. For drugs exhibiting high protein binding, measurement of unbound concentrations is preferred over the calculation of unbound concentrations from published protein binding values, because such calculations may not reflect the unbound anti-infective concentration in a critically ill patient. The second step will be to identify therapeutic targets. Until now, possible target concentrations are usually derived from very small studies. To truly establish therapeutic ranges of anti-infectives, large multicenter studies are suggested. When these ranges have been established, a well-designed randomized controlled trial (TDM arm vs. conventional dosing arm), where drug concentrations and MICs are measured, should be performed to quantify the beneficial effect of TDM-guided dosing in critically ill patients.

Key issues

- Pathophysiological changes in critically ill patients result in altered pharmacokinetics of anti-infectives, especially for hydrophilic agents.
- Therapeutic drug monitoring (TDM) is recommended for all critically ill patients treated with aminoglycosides, glycopeptides, β-lactams, fluoroquinolones, flucytosine, itraconazole, voriconazole, and posaconazole.
- For renally cleared anti-infectives, dosing should be adjusted to renal function and monitoring of plasma concentrations performed in patients with a high risk of deviating pharmacokinetics, such as critically ill patients with sepsis, burns, organ failure or in patients using concomitant medication known to influence concentrations of the anti-infective agent.
- There is a lack of data on therapeutic concentration ranges for many anti-infectives.
- Randomized controlled trials investigating TDM versus non-TDM are warranted to quantify the value of TDM.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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